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Potential Risk of Nanotechnology Radioactive Materials for Diagnostics

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ABSTRACT

The manufacture of personalized, real time, specific, and sensitive diagnostic tools continue to be of importance as the need for rapid diagnosis and monitoring of disease persists. In many health conditions like cancer and Covid-19 infection timely diagnosis of diseases can affect chances of survival. The accurate and timely diagnosis of diseases is enhanced by the unique optical, fluorescent, and magnetic properties of nanoscale elements. However, ultra-fine Nano particles unintentionally released into the air through human activities like combustion have been linked to respiratory and cardiovascular diseases. This makes it important for Nano engineered devices to be assessed for safety and toxicity concerns. Toxicity studies on the bulk material of the nanoscale elements used in diagnosis does not suffice as Nano materials due to their small size have unique interactions with biological membranes. Radioactive functionalized nanoparticles have been employed in several diagnostic imaging techniques such as Positron Emission Tomography, Magnetic Resonance Imaging, Computed Tomography, and Optical Imaging. These radioactive nanoparticles provide many benefits over conventional contrast agents including their theranostic ability. Spherical gold nanoparticles used in vivo for CT imaging have shown a 3-fold higher X ray attenuation than an iodine-based contrast agent. The tremendous benefits associated with use of radioactive functionalized nanoparticles calls for study of the risks associated with them as more and more radioactive nanotechnology-based products are employed in health care. Radioactive functionalized nanoparticles should be assessed for safety in both their radionucleotide component and nanomaterial component. Recent studies of nanoparticles have shown that they can lead to DNA damage by generation of Reactive Oxygen Species (ROS). Some of the discovered factors that play a key role in the generation of ROS include size, composition, surface charge, and shape. Understanding of the method of different radio nucleotide nanoparticle toxicity, the extent to which it causes toxic effects, and factors involved in its toxicity can help manufacturers reduce or eliminate their toxic profile while maximizing their benefits.

Keywords

Nano devices, Radio nucleotides, Imaging, Diagnostics, Nano-materials, Toxicity of nanoparticles, radioactive functionalized nanoparticles, Nanotechnology.

Introduction

Late, inaccurate diagnosis and poor monitoring has contributed to high mortality rate globally. The implementation of innovative nanotechnology devices in the diagnosis of diseases and its use in monitoring of diseases has resulted in a reduction in mortality rate of various diseases. Despite the goal of nanotechnology to create advancements in image-based detection and targeted delivery these nano scale devices might possess toxic properties due to their unique optical, fluorescent and magnetic properties. Because of these properties the term nano-toxicology was coined and defined as the science of dealing with the effects of nano-devices and nanostructures in living organisms. Nanoparticles have innate toxicity profiles, and this toxicity can be due to properties such as their particle size, surface area, shape/structure, surface charge, and surface coatings.

Over the past decades, nano-theranostic nanoparticles (TNPs) that simultaneously transmit diagnostic information and monitor the therapy process *in situ* have been developed mainly in nano-oncology realm [1].

These TNPs dispose of unique physical and chemical properties to target desired cells and tissues producing therapeutic and imaging action against the disease [2].

Multiple imaging approaches were used such as optical imaging, ultrasound (US), magnetic resonance imaging (MRI), computed tomography (CT), single-photon computed tomography (SPECT) and positron emission tomography (PET).

Unmet needs in conventional diagnostics

Nano devices, such as cantilevers, have been integrated into high-sensitivity disease marker diagnostic detectors and devices, are stable over long periods of time, and display reliable performance properties. In cancer research, application of these nanodevices has provided hope within the scientific community for the development of novel cancer therapeutic strategies. Tremendous efforts have been made toward the development of novel diagnostic and therapeutic methods for improving patient quality of life and lengthening survival. Advances in image-based detection, targeted drug delivery, and metastases ablation could go a long way to improve patient outcome. Classical approaches generally do not meet patients' expectations due to a lack of specificity and poor patient stratification. More highly targeted and customized treatments are needed. Toward this goal, nanotechnologies and nanodevices have been explored for their potential utilities in advancing targeted therapeutic approaches.

The goal of nanotechnology is to create advancements in image-based detection and targeted delivery, but these nano scale devices might possess toxic properties due to their unique optical, fluorescent, and magnetic properties.

Radioisotopes and radiolabeled nanomaterials

Radioisotopes are a crucial component in nano medicine. Radiolabeling is a well-established and useful technique for quantitative *in vivo* assessment of the biological uptake and pharmacokinetics of synthetic nanomaterials [3]. Several γ-ray-emitting radionuclides including positron emitters (β + decay) have been extensively used for developing nanomaterial-based diagnostic agents for positron emission tomography (PET) or single-photon emission computed tomography (SPECT) [4]. These radiolabeled materials can be used to visualize tumor tissues in living subjects as well as other important biological phenomena. In recent years, therapeutic radionuclides (α- and β-emitters) have also been used in clinical applications, and some of these trials have shown significant impacts on tumor treatment [5]. Therefore, there is increasing interest in using a combination of therapeutic radioisotopes and nanosized materials for developing promising candidates for new radiopharmaceuticals.

Table 1: Some β ray emitting radioisotopes used for preparing radiolabeled nanomaterials for efficient cancer therapy owing to their availability and relative low production cost. These radioisotopes have a good tissue penetration ability [16].

Radioisotope	Decay Product	Decay Half life	Mean Penetration Range in Tissue mm
^{131}I	^{131} Xe	8.02 days	0.4
^{67}Cu	^{67} Xn	2.60 days	0.19
^{90}Y	^{90} Zr	2.67 days	2.5
^{166}Ho	^{166} Er	1.12 days	0.84
^{177}Lu	^{177}Hf	6.73 days	0.16
^{186}Re	^{186}Os	3.72 days	0.43
^{188}Re	^{188} Os	17.0h	0.98
^{198}Au	^{198} Hg	2.70 days	0.38

Radioactive functionalized nanoparticles show more favorable properties *in vivo* compared to bare radio nucleotide. One advantage of radioactive functionalized nanoparticles is their ability to carry multivalent radio nucleotide element in a single carrier. Multivalent incorporation of radionuclides in a nanoparticle enables transporting numerous α- or β-emitters to cells. Moreover, nanomaterials can be designed to conjugate with various functional molecules such as chemotherapeutic drugs, contrast agents, or cancer-targeting molecules (e.g., antibodies, peptides, and small-molecule ligands). The nanomaterial carrier can control the pharmacokinetic property of the functional molecule and radio nucleotide.

Toxicity evaluation of Nanoparticles

Nanoparticles have innate toxicity profiles, and this toxicity can be due to properties such as their particle size, surface area, shape/structure, surface charge, and surface coatings. For example, small particle size is associated with a large surface area per unit mass, and large surface area is associated with a higher biological reactivity. The formation of free radicals such as hydroxyl radical and superoxide anion are increased with a larger surface area. Oxidative stress might play an important role in nanoparticle's toxicity especially in metal nanoparticles. This free radical formation has been proposed as a reason for inflammatory responses associated with nanoparticles. Research on dose-effect relationship of specific nanoparticles, human and environmental exposure via inhalation, oral, and dermal will be important to elucidate the risks of nanoparticles to both humans and environment. The importance of biometrics, dose, and dose metric will help in the safety evaluation of engineered nanoparticles.

A common route of entry of nanoparticles is via inhalation and *in vivo* studies have shown lung inflammation because of nanoparticles. There has been report of systemic bio distribution of nanoparticles in bloodstream and lymphatic pathways. Another common route of exposure is via topical either accidentally or by application of cosmetics containing nanomaterials. However, the outer layer of the epidermis, the stratum corneum, protects against environmental injury. Still titanium dioxide has been found to penetrate the stratum corneum and even hair follicles. Penetration of Titanium dioxide into the skin and its interaction with the body's immune system has been described [6].

In a different investigation of silver nanoparticles with human fibro sarcoma and human/skin carcinoma (A43 cells) were undertaken. When the cells were challenged with silver nanoparticles of dose 6.25ug/ml signs of oxidative stress such as decrease in oxyradical scavengers, reduced glutathione and super oxide dismutase concentration, and increase in lipid peroxidation were observed. It was suggested that the signs of oxidative stress following exposure from silver nanoparticles was due to formation of per oxyradicals [7].

A different investigation by Chol et al. supported this, where apoptosis was induced by silver nanoparticles in the liver of adult Zebrafish by exposure to silver nanoparticles. Reports shows that level of malondialdehyde, a substrate of lipid peroxidation, and increased level of glutathione after treatment with silver nanoparticles. While the MRNA level of the oxyradical scavenging enzyme Catalase and glutathione peroxidase were reduced in tissues. The Authors concluded that the increased level of hepatic malondialdehyde shows silver nanoparticles induced oxyradicals in the liver. Also, the stimulation of glutathione suggests that the liver responds in a defensive manner to the production of oxyradicals, the elevated oxidative stress can damage lipids, carbohydrates and proteins.

An investigation into oxidative stress associated with gold nanoparticles was also launched in human lung fibroblast cells. It was observed that cells exposed to gold nanoparticles developed more lipid hyper oxides, an indicator of lipid peroxidation compared to control cells. Malonaldehyde reacts with proteins and DNA forming adducts that are genotoxic. In this study, malondialdehyde modified protein adducts were quantified by western blotting to confirm lipid peroxidation and the result showed that the amount of protein alkylated by malonaldehyde was more in the gold nanoparticles treated samples than in control cells.

Mechanism of Induced Toxicity

Oxidative Stress

From Research, we have found that nanoparticles exposure increases reactive oxygen species production. A phenomenon known as oxidative stress. Knaapen et al. suggests there are three main causes of reactive oxygen species release, one is the active redox cycling on the surface of nanoparticles particularly the surface of metal-based nanoparticles, second is, oxidative groups functionalized on nanoparticles, and lastly, particle cell interactions especially in areas where there is a rich pool of reactive oxygen species producers like the lungs where there is inflammatory phagocytes, macrophages, and neutrophils. Overproduction of reactive oxygen species activates cytokines and upregulates interlukin1, kinases, and tumor necrosis factor as an indicator of proinflammatory signaling processes as counter reaction to oxidative stress.

Miura et al. reported that well-known oxidative stress related genes ho-1 and mt 2a were upregulated when silver nanoparticle was given. Hussain et al. investigated the role of oxidative stress as the potential mechanism of silver nanoparticle toxicity [8]. In the study ROS generation following 6h of exposure to Ag (15, 100 nm) at 0, 5, 10, 25 and 50g/ml was investigated. The level of ROS in cells increased in a concentration dependent manner and was statistically increased from 10g/ml concentration Ag (15, 100nm) treatment at 25 and 50g/ml resulted in an approximately 10-fold increase in ROS generation over control levels.

Despite the widespread development of nanotechnology and nanomaterials throughout the last 10–20 years, only recently has their potential toxicological effect on humans, animals, and the environment received some attention. Moreover, although the original intended use of nano medicine was to improve human health, NPs can be purposely misused for other intentions as many researchers have been reporting due to soiling or maximizing the toxicity of the NPs.[4,5] Too often, as well, NP or nanomaterial (such as carbon nanotubes [CNTs]) synthesis techniques involve toxic materials. In order to decrease the cost of nanodrug delivery vehicles, make them more effective in the body, promote a healthy environment, and reduce unintended use, new approaches and design principles are clearly needed for this field.

Table 2: Showing some of the toxicological effects of Nanoparticles [17].

Description of finding, *in vivo*	**Particle type**
NPs cause pulmonary inflammation in the rat.	All PSP
Later studies show that inflammation is mediated by surface area dose.	SWCNT, MWCNT
NPs cause more lung tumors than fine particles in rat chronic	PSP only.
Studies. Effect is surface area mediated.	
NPs cause progression of plague formation (ApoE-/-mice)	SWCNT, PM2.5
NPs affect immune response to common allergens.	Polystyrene, CB, DEP
NPs can have access to systemic circulation upon inhalation and instillation.	Specific NP, dependent on surface coating.
Description of finding, *in vitro*	
NPs cause oxidative stress *in vivo* and *in vitro*, by inflammatory action and generation of surface radicals.	PSP, NP general, CNT
NPs inhibit macrophage phagocytosis, mobility and killing.	CB, TiO_2
NPs cause platelet aggregation.	PM, SWCNT, fullerenes, latex-COOH surface
NPs exposure adversely affects cardiac function and vascular homeostasis.	PM, SWCNT
NPs interfere with Ca-transport and cause increased binding of pro-inflammatory transcription factor NF-kB.	CB (<100 nm), ROFA, PM2.5
NPs can affect mitochondrial function.	Ambient NP
NPs can translocate to the brain from the nose.	MnO_2, Au, carbon
NPs do affect rolling in hepatic tissue.	CB

Genotoxicity

Nano genotoxicity was coined to represent the growing trend of research into nanoparticle induced genotoxicity and carcinogenesis. Although there is still no exact, correlation between NP induced genotoxicity, lung cancer it is pointed out in literature that long-term inflammation, and oxidative stress present in tissue can eventually induce DNA damage in cells and tissues. Continuous Reactive oxygen species production in the cell can lead to gene mutations/deletions leading to mutagenesis, carcinogenicity, and subsequently development of tumors and cancer. Particularly the metal-based NPs like Ag Nps, Au Nps, and TiO nanoparticles are important for that kind of ROS production and genetic damage. Because of DNA damage induced by NPS, single strand DNA breaks, double-strand breaks, DNA deletions and genomic instability in the form of increase in 8-hydroxy-2-deoxyguanosine levels are formed.

The genotoxicity of zinc oxide nanoparticles, widely used in cosmetics and sunscreens, was evaluated in some studies. Sharma et al. investigated the genotoxicity of these nanoparticles in primary human epidermal keratinocytes using comet assay. Results showed a significant induction in DNA damage in cells exposed to 8 and 14 ug/ml ZnO NPs for 6 hours comparing to control group. Finding demonstrated that ZNO NPs are assimilated by the human epidermal keratinocytes and induce cytotoxic and genotoxic responses.

Zinc oxide (ZnO) nanoparticles are widely used in cosmetics and sunscreens. Human epidermal keratinocytes may serve as the first portal of entry for these nanoparticles either directly through topically applied cosmetics or indirectly through any breaches in the skin integrity. Therefore, the objective of the present study was to assess the biological interactions of ZnO nanoparticles in primary human epidermal keratinocytes (HEK) as they are the most abundant cell type in the human epidermis. Cellular uptake of nanoparticles was investigated by scanning electron microscopy using back scattered electrons imaging as well as transmission electron microscopy. The electron microscopy revealed the internalization of ZnO nanoparticles in primary HEK after 6 h exposure at 14 microg/ml concentration. ZnO nanoparticles exhibited a time (6-24 h) as well as concentration (8-20 microg/ml) dependent inhibition of mitochondrial activity as evident by the MTT assay. A significant ($p < 0.05$) induction in DNA damage was observed in cells exposed to ZnO nanoparticles for 6 h at 8 and 14 microg/ml concentrations compared to control as evident in the Comet assay. This is the first study providing information on biological interactions of ZnO nanoparticles with primary human epidermal keratinocytes. Our findings demonstrate that ZnO nanoparticles are internalized by the human epidermal keratinocytes and elicit a cytotoxic and genotoxic response. Therefore, caution should be taken while using consumer products containing nanoparticles as any perturbation in the skin barrier could expose the underlying cells to nanoparticles [9].

Benefits of Radio labeled Nano systems and their stabilization

Radionucleotides

The marriage of radionuclides and nanoparticles has emerged in numerous biomedical applications, especially for personalized medicine [10]. In diagnostics, the combination of radionuclide imaging, using gamma or positron emitters, with CL-based optical imaging permits whole-body disease mapping with high overall sensitivity and simultaneous high-resolution local scrutiny of the lesions for image-guided surgery. Another important finding described in the review is that the interaction of radionuclides with nanoparticles containing heavy atoms generates X-ray emission, which can be exploited to perform single photon emission tomography (SPECT) for nanoparticle localization. Since the energy of the X-rays deriving from different materials varies, multiplex imaging can be achieved to further delineate the distribution of a single component in a mixture of nanoparticles. To demonstrate clinical relevance, the authors mix the Food and Drug Administration-approved glass microspheres Thera spheres, which contain Y and are commonly used by radiologists, with bismuth or europium NPs. Due to its pure β– emission, Y falls into the category of radionuclides considered unsuitable for imaging. The author's show that Thera spheres can be clearly visualized using SPECT with the europium or bismuth energy windows under focus. This strategy could be further improved by incorporating NPs into Y-labelled microspheres for more precise and direct localization. In addition to *in vivo* imaging, the findings in their study also shed light on *in vitro* detection and measurement of Y and other pure β– emitters. For example, a highly efficient nanoparticle detection system can be developed based on the photons or X-rays emitted from the interaction between radionuclides and NPs for convenient radioactivity quantification in bio samples. Since some dye molecules and polymers also show the property of scintillation, characterizing the interaction of radionuclides with NPs composed of organic materials, which usually have better biocompatibility than metallic NPs, would also be interesting [11].

Nowadays, emerging radiolabeled nano systems are revolutionizing medicine in terms of diagnostics, treatment, and theranostics. These radionuclides include polymeric nanoparticles (NPs), liposomal carriers, dendrimers, magnetic iron oxide NPs, silica NPs, carbon nanotubes, and inorganic metal-based nano formulations. Between these nano-platforms, polymeric NPs have gained attention in the biomedical field due to their excellent properties, such as their surface to mass ratio, quantum properties, biodegradability, low toxicity, and ability to absorb and carry other molecules. The use of nanoparticles as imaging probes has several advantages over conventional imaging agents. Loadability is one of the advantages where the concentration of the imaging agent can be controlled within each nanoparticle during the synthesis process. Another advantage is the tunability of the surface of the nanoparticles that can potentially extend the circulation time of the agent in the blood or target a specific location within the body. Finally, nanoparticles can act as multifunctional MI agents, since they have two or more properties that can be used simultaneously in multiple imaging techniques, and especially in MRI [12].

In addition, NPs can carry high payloads of radionuclides, which can be used for diagnostic, treatment, and theranostics depending on the radioactive material linked. The radiolabeling process of nanoparticles can be performed by direct or indirect labeling process. In both cases, the most appropriate must be selected in order to keep the targeting properties as preserved as possible. [13]

Physical radiation from radioactive species is responsible for the radioactive polymeric NP emission with beta (β) or alpha (α) emitters for therapy purposes while polymeric NPs with gamma (γ) or positron emitters are used for diagnostic targets [14]. The ideal radioactive polymeric NP should be able to target tissues and restrict radiation from spreading to other healthy tissue around the target. In addition, radioactive polymeric NPs should remain in the body for a short period of time to avoid prolonged patient exposure to radiation, but long enough to allow the acquisition and processing of images via computers and as well as release of therapeutic active agents [15].

A stable association between the radionuclide and the nanoparticle is essential for the successful implementation of radiolabeled nanoparticles in cancer diagnosis and therapy. Loss of the radionuclide can result in its accumulation in non-targeted tissues.

Knowledge gaps in the toxicity of radio functionalized nanoparticles

Lack of specific knowledge on the toxicity of radio functionalized nanoparticles leads to the perception that all radioactive nanomaterials are dangerous to human health. The chronic effects and exposure to these engineered radioactive nanoparticles are still largely unknown. Following extensive research in these devices, it will be possible to tell their exact toxicological risk to human health.

Identification of possible health risks is a prerequisite for assessing the safety of the new products that are being developed. Therefore, the area of nanotoxicology is gaining utmost significance with the increase in use of these devices. Safety studies on radioactive nanomaterials through toxicological research will provide information about their possible adverse effects.

Conclusion

Radioactive functionalized nanoparticles used for diagnosis of disease has the potential to fulfill the needs of targeted and personalized diagnosis in medicine. These radioactive functionalized nanoparticles confer many benefits over contrast agents in noninvasive imaging such as MRI, CT, PET, and SPECT. Their theranostics capabilities make them suitable for many treatment modalities. However, like any innovation it also has its risks, and these risks are worthy of extensive investigation due to their potential toxic side effects from *in vivo* studies. Due to the immense benefits associated with the radioactive functionalized nanoparticles there is a chance of overlooking the need to quantify and estimate risks associated with each radionucleotide, nanomaterial employed and effect of interaction when combined. Research which aims on gaining an understanding and establishing the method of different radionucleotide nanoparticle toxicity, the extent to which it causes toxic effects, and factors involved in its toxicity can help manufacturers reduce or eliminate their toxic profile while maximizing their benefits.

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