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Target Organ Toxicity by Nanoparticles – A Short Review

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ABSTRACT

Nanotechnology is the term given to those areas of science and engineering where the phenomena take place at nano-scale dimensions. Nanotechnology deals with particles sized between 1 to 100 nanometers in at least one dimension and it involves developing or modifying materials or devices within that size. Nanoparticles have different physical, chemical, electrical and optical properties than those that occur in bulk samples of the same material. All aspects of life will benefit from the revolution in nanotechnology. Engineered nanoparticles are increasingly produced for use in a wide range of industrial and consumer products. Hundreds of tons of nanoparticles already enter in the environment annually, but still very little is known of their interactions with biological systems. The challenge for toxicologists is to identify key factors that can be used to predict the toxicity, permit targeted screening, safe and sustained development and use of nanoparticles. In order to gain a sustained development, new technology always needs a good balance between benefit and risk. The aim of this paper is to summarize the target organ toxicity of nanoparticles in different biological systems.

Keywords: Nanotechnology, Nano-scale, Nanoparticles, Nano-meter and Engineered nanoparticles.

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INTRODUCTION

Physicist Richard P. Feynman was first who introduced concept of nanoscience in 1959 in his key lecture at the annual meeting of the American Physical Society, and the term nanotechnology was coined in 1974 by a Japanese researcher Nario Taniguichi to mean “precision machining with tolerance of a micrometer or less”. It refers to engineering on the molecular and atomic basis.

Every new technology brings with it new risks and for nanotechnology, the potential risks to workers and consumers are paramount. They can arise from exposure to nanomaterials either at work or through consumer products. With the fast development of nanotechnology, industries are currently involved in nanotechnology-related activities, among which the manufactured nanoscale materials or engineered nanoparticles are being used in a wide range of products. The estimated economic impact of nanoparticles will be 1 trillion US dollars by 2015 and will increase because of abundant use of nanoparticles in industrial, consumer and medical products¹. A growing public debate is emerging on whether the environmental and social costs of nanotechnology outweigh its many benefits²⁻⁵. The questions about the side effects of products of nanotechnologies are pertinent, since the potential for exposure to nanoparticles will increase as the quantity and types of nanoparticles used in the society grow.

From the fact that the sizes of the nanoparticles (<100nm) and biological molecules are comparable, one easily bethinks of such a consequence that the nanoparticle may easily invade the natural defense system of human body or other species and easily enter into the cells to affect cellular functions. With an enormous exposure risk and demand, it would be fundamental to obtain knowledge about toxic effects of nanoparticles on different (pulmonary, hepatic, central nervous, cardiovascular and developmental) target organs.

TARGET ORGAN TOXICITY BY NANOPARTICLES

As different tissues and organs have different chemical compositions, structures and functions, toxic responses are mostly different once nanoparticles enter different organs. Skin, respiratory tract and gastrointestinal tract are always in direct contact with environmental nanoparticles. On the other hand, other physiological systems such as cardiovascular and central nervous systems may have chances to interact with exogenous nanoparticles circulated or transported from the above exposure routes. So, they may also be a specific target for any type of nanoparticle entered into the body.

Lung

The representative studies of pulmonary inflammation and fibrosis induced by nanoparticles in experimental animal model was first reported by Lam and Warheit, who demonstrated that intratracheal instillation of single-walled carbon nano-tubes (SWCNTs) and multi-walled carbon nano-tubes (MWCNTs) induced pulmonary granuloma formation and some interstitial inflammation⁶⁻⁷. Further study indicated that both SWCNTs and MWCNTs could induce alteration of cell structures⁸. Free radical or oxidative activity of nanoparticles has been found to be predominant factor in ability to cause lung inflammation⁹⁻¹⁰.

The epidemiological studies have found a correlation between exposure to respirable airborne particulate matter and increased mortality and adverse respiratory health effects, including the development of emphysema, chronic bronchitis and asthma¹¹⁻¹². When inhaled nanoparticles deposit dispersedly upon the alveolar surface, which likely leads to a chemo-attractant signal, resulting in lower recognition and alveolar macrophage responses¹³.

Since the lung is a major portal of entry for nanoparticles into the body, there is a need to understand the mechanisms relating nanoparticle physico-chemical characteristics to the pulmonary defense and adverse effects for better risk assessment of pulmonary exposure to nanoparticles.

Liver

For blood borne particles the Kuffer cells remain a key clearance system with subsequent potential for accumulation of dose in liver. The Kuffer cells are known to be affected by oxidative stress from nanoparticles to produce inflammatory mediators like $TNF\alpha$ ¹⁴. The consequences of nanoparticle injury to the liver could be inflammation or alterations in the hepatic production of clotting factors that could contribute systemic thrombosis¹⁵.

Administration of 120 nm ZnO nanoparticles at different doses in mice had a positive dose-response relationship and caused fatty degeneration of hepatocytes around the central vein, whereas, 20 nm ZnO nanoparticles displayed negative dose-effect damage¹⁶.

Cardio-vascular system

Statistically significant associations between particulate air pollution and ischemic heart disease, arrhythmia and heart failure have been reported in animal studies exposed to ambient air particles and increasing incidences of peripheral thrombosis and atherosclerotic lesion formation¹⁷. Much less is known about the impact of nanoparticles on the cardiovascular system. However, besides the factor of size, other physico-chemical properties such as shape, crystal structure, solubility, surface area, surface charge and surface coating also play an important role in systemic circulation following lung administration¹⁸.

In case of manufactured nanoparticles, a single intrapharyngeal instillation of SWCNTs can induce activation of hemeoxygenase-1 (HO-1), a marker of oxidative stress in lung, aorta and heart tissue in transgenic mice¹⁹. Furthermore, the C57BL/6 mice exposed to SWCNTs developed pathophysiological changes related to vascular diseases such as mitochondrial DNA damage, elevation of mitochondrial glutathione and protein carbonyl levels¹⁹ and old individuals are more sensitive to nanoparticle exposure than the young and adult individuals¹⁶.

Administration of 120 nm ZnO nanoparticles at different doses in mice had a positive dose-response relationship and caused fatty degeneration of cardiovascular cells, whereas, 20 nm ZnO nanoparticles displayed negative dose-effect damage²⁰.

Gastrointestinal system

The gastrointestinal tract is one of the largest immunological organs of the body, containing more lymphocytes and plasma cells than spleen, bone marrow and lymph nodes. Nanoparticles can be ingested directly via food, water, drugs or drug delivery systems. In addition, nanoparticles cleared from the respiratory tract via the mucociliary escalator can subsequently be ingested into the gastrointestinal tract. Thus gastrointestinal is considered as important target of nanoparticle exposure.

Oral administration of copper nanoparticles (23.5 nm) in mice produced alimentary canal function disorders such as loss of appetite, diarrhea and vomiting, etc. Further pathological examination revealed severe lesions in kidneys, liver and spleen, whereas, mice exposed to copper micro particles (17 nm) exhibited no such symptoms and toxicities²¹.

Central nervous system

Respiratory system is considered to be the main portal of entry for inhaled nanoparticles but extrapulmonary translocation after respiratory tract deposition is likely to happen via accidental or occupational acute exposure²². It is also possible that inhaled ultrafine particles, by virtue of their extremely small size may deposit in the olfactory mucosa and then translocate in CNS, which in turn might cause neurotoxicity. The inhaled ultrafine carbon (35 nm) and manganese oxide (30 nm) nanoparticles can translocate in the brain via olfactory neuronal pathway²³⁻²⁴.

Some investigations have indicated that inhaled or intranasally instillation of particles may trigger a pro-inflammatory response in nervous tissue. For instance, intranasally instilled ultrafine carbon black (14 nm) can induce inflammatory changes (interleukin-1 β , TNF α and chemokine mRNA) in the brain olfactory bulb²⁵ and it was also observed that potential damage of nanoparticles on CNS may be size dependent. For instance, pro-inflammatory responses were observed in brain olfactory bulb of the 14 nm carbon black treated mice but not in the 95 nm carbon black treated mice.

TiO₂ nanoparticles directly enter into brain via olfactory pathway and induce pathological changes in the olfactory bulb and hippocampus regions ²⁶.

Skin

Skin is the largest organ of the body and is composed of three layers- epidermis, dermis and subcutaneous tissue. The outer layer of epidermis, called stratum corneum is a 10 µm thick keratinized layer of dead cells.

Currently, there is lack of information on whether nanoparticles can be absorbed across skin's stratum corneum barrier or systemically administered particles can accumulate in dermal tissue. The tendency for nanoparticles to traverse the skin is a primary determinant of its dermatotoxic potential. That is, the nanoparticles must penetrate the upper most stratum corneum layer in order to gain entrance to the viable epidermis and exert toxicity in the lower cell layers.

Nanoparticles caused dermatotoxicity was reported in an animal model study, 0.5 and 1.0 µm beryllium particles could penetrate through the stratum corneum and develop hapten-specific, cell-mediated immune response ²⁷. In an *in vivo* study, Shevadova *et al.* (2003) reported that SWCNTs caused a significant dose-response reduction of cell viability and oxidative stress biomarkers (e.g. antioxidant reserve) and with significant increase in lipid peroxides in human epidermal keratinocytes (0, 0.06, 0.12 and 0.24 mg/mL of SWCNTs for 18 hours), suggesting an increase of cutaneous toxicity ²⁸.

Developmental effects

Individuals undergoing a spectrum of developmental changes as well as embryos and fetuses can get affected by nanoparticles. Entry of nanoparticles into the blood means that they are likely to flow through the placenta where foetal circulation comes close to maternal circulation. There is no actual mixing of blood but placenta allows passage of biological molecules so nanoparticles can also get transferred through it and may affect the normal developmental process in the fetus.

CONCLUSION

Nanotechnology is a double-edged sword, the same novel properties making nanoparticles attractive, makes them potentially toxic. Particular care must be taken in nanomedicine, since this area is where greater exposure would be present. Joint efforts by *in vivo* and *in vitro* tests and theoretical studies can help putting together all the pieces of the puzzle to investigate the cellular and molecular mechanisms underlying the observed association for a range of body systems (such as pulmonary, cardiovascular, hepatic systems etc.). There has to be a compromise between testing all the possible toxic scenarios for each nanoparticle, and creation of standards to unify tests. An

understanding of the relationship between the physical and chemical properties of the nanostructure and the *in vivo* behavior would provide a basis for assessing nanotoxicity and more importantly may lead to predictive models for nanotoxicity assessment. Exposure of nanoparticles of different physiochemical characteristics via inhalation, ingestion or dermal exposure is likely to lead to their distribution, beyond the portal of entry to other body systems. The cumulative dose in a target organ will eventually lead to an adverse response. There has to be incorporation of all the relevant data as a part of model construction and conduct uncertainty analysis as an extension of the traditional risk assessment paradigm to nanoparticles.

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