Chapter 14
Toxicocinetic and Mechanisms of Action of Nanoparticles

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ABSTRACT

Human exposure to nanoparticles has been dramatically increased in the past 25 years as a result of the rapidly developing field of nanotechnology. Many have recognized the importance of identifying potential effects on human health associated with the manufacture and use of these important technology. Many questions remain unanswered regarding the short- and long-term effect, systemic toxicity, and carcinogenicity. Engineered nanoparticles can be taken up by the human body via inhalation, ingestion, dermal uptake, and injection. They can reach the bloodstream and ultimately affect multiple body organs such as liver and spleen or even transcend the blood-brain barrier. Because of the huge diversity of materials used and the wide range in size of nanoparticles, these effects will vary a lot. Local and systemic adverse effects consist of primarily inflammatory reactions. Other observed effects include generation of reactive oxygen species and subsequent oxidative stress, disruption of proteins, DNA, mitochondria and membrane structures, as well as changes in cell signaling pathways.

INTRODUCTION

Human being has been exposed to nanoparticles (NP) throughout its evolution via inhalation of ultrafine particles (UFP) produced by fires, volcanic action and other natural phenomena. This exposure has been dramatically increased in the past 25 years as a result of the tremendous development of nanotechnology, which has produced large numbers of synthetic nano-sized particles. With nanomaterials (NM) becoming an integral part of the economy and a relevant component of consumer products, many have recognized the importance of prospectively identifying the human health and environmental risks associated with the manufacture and use of these materials. As NM based products enter the market, there is an urgent need of advanced researches in order to prevent dramatic consequences of any health issues caused by nanotechnology-driven products. Entire populations are at high risk for NM exposure due to the wide availability of these new products and many questions remain unanswered regarding the short- and long-

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term effects of NM on several living organisms. These synthetic particles can be taken up by different routes such as inhalation, ingestion, dermal uptake and injection (Jain, 2017).

Inhalational toxicity is to be expected, given the known effects of inhaled fine particulate matter. It has been proposed that dermal exposure will be the most relevant route of exposure, but there is considerably less literature regarding dermal effects and absorption (Curtis, Greenberg, Kester, Phillips, & Krieger, 2006). The ability of NP to penetrate beyond the epidermal and/or dermal layers is important to consider, along with their subsequent bioaccumulation and systemic effects. Data on NP toxicity often conflict when comparing in vitro and in vivo studies and less defined still are the potential effects of nanoproducts on fetal development and the environment.

There are still many unanswered questions about the fate of engineered NP in human being. They can reach the bloodstream and ultimately affect multiple organs. Biodistribution, movement through tissues, phagocytosis, opsonization and endocytosis of NP are all likely to have an impact on potential toxicity. Because of the huge diversity of materials used and the wide range in size of NP, these effects vary a lot. The main concern is about smaller particles that can easily enter cells. The interaction of NP with biological systems is affected by other factors such as shape, chemical composition, surface chemistry, surface charge and aggregation state. These parameters can modify cellular uptake, protein binding, translocation from portal of entry to the target site and the possibility of causing tissue injury.

One of the most important fact about NP is their remarkable surface reactivity, a characteristic that may result in toxicity effects. Evidence from the literature states that our understanding of NP properties is incomplete and toxicity as well as biodistribution to specific targets occur for NP with particular characteristics. Some NP exhibit the ability to translocate into different type of cells and organs such as liver, spleen, kidneys, etc or even transcend the blood-brain barrier (BBB).

Local and systemic adverse effects consist usually of inflammatory reactions. Some deleterious effects, including inflammatory reactions and pulmonary tissue injury, have been demonstrated following inhalational exposure to nano-sized TiO_2. These inflammatory reactions may result in fibrosis and granulomatous reactions.

Other observed pathological effects include generation of reactive oxygen species (ROS) and subsequent oxidative stress, disruption of proteins, DNA, mitochondria and membrane structures as well as changes in cell signaling pathways such as calcium and cytokine pathways.

To date, we have barely scratched the lessons to learn and to comprehend the effects of these tiny molecules on cells, tissues and whole organisms. It is clear that additional studies using human subjects must be undertaken in order to adequately predict short and long-term effects of NP. This chapter focuses on the current knowledge of nanotoxicity, highlights areas where new information is available and suggests directions for additional and future research. The results of early cytotoxicity studies are reviewed by mechanism pathways.

TOXICOCINETIC OF NANOPARTICLES

Absorption

NP can enter human body and penetrate some important organs such as lungs, intestine and skin. Their penetration depends mainly on two parameters; size and surface characteristics. These parameters usually modify protein binding, cellular uptake, translocation from portal of entry to the target site.

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