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Nanoparticle-Induced Biochemical Changes in Biological Systems

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Abstract

Nanoparticles (NPs) are currently used in the diagnosis and treatment of many human diseases, including autoimmune diseases and cancer. However, cytotoxic effects of NPs on normal cells and living organs is a severe limiting factor that hinders their use in medicine. As nanotechnology continues to evolve, the widespread application of NPs in medicine, environmental science, and industry raises concerns about their interactions with living organisms. There are various mechanisms through which NPs alter cellular functions, including oxidative stress, inflammatory responses, and genetic damage. The review highlights how physicochemical properties such as size, shape, and surface charge influence NP behavior and toxicity within biological environments. Key mechanisms of NPs toxicity, including oxidative stress, inflammatory responses, and alterations in gene expression, are discussed, emphasizing the complex interplay between NP physicochemical characteristics and biological interactions. This review emphasizes the need for comprehensive toxicological assessments and standardized evaluation models to better understand NP-induced biochemical alterations and their implications for human health and safety. Insights gained from this analysis will inform future research directions and the development of safer nanomaterials.

Keywords: Nanoparticles, Nanotechnology, Cytotoxicity, Biochemical alteration

* Introduction

Nanotechnology, a recently developed field of science, has various practical uses, including energy production, industrial processes, and biomedical

applications. Its significant application lies in the field of biology and biomedical research. Nanoparticles (NPs) can be designed to have distinct composition and functionalities, offering innovative tools and methods previously unavailable in biomedical research. (Wang and Wang, 2014; Altammar, 2023).

Nanomaterials play a significant role in medicine for creating sophisticated drug delivery systems that offer control over drug loading effectiveness, biodistribution, cell/tissue targeting, therapeutic effects, cytotoxicity, selectivity, imaging capabilities, blood circulation duration, half-life, and excretion. Many believe that these characteristics are primarily associated with the surface chemistry of nanomaterials, their overall surface area, hydrodynamic size, and the drug they carry (Kladko et al., 2021).

The use of nanotechnology in personalized medicine presents a unique opportunity to enhance the treatment of numerous illnesses. Nanomaterials have various advantages as tools for diagnosis and therapy due to their adaptable design, small dimensions, high surface-to-volume ratio, and the ability to easily modify their surfaces with multivalent ligands to enhance their affinity for target molecules. Nanomaterials can be customized through engineering to engage with particular biological components, allowing them to benefit from the insights offered by personalized medicine techniques. There exists an intricate connection between the physicochemical properties of nanomaterials (such as size, charge, and surface properties) and their interactions within biological systems. Even small alterations in size, charge, surface modification, and chemical composition can result in significantly different interactions with living systems (Zhang et al., 2012).

The medical field has seen increasing use of nanotechnology, with a variety of applications (Wagner et al., 2006). Nanotechnology utilizes (NPs) and nanoscale technology for disease prevention, diagnosis, and treatment through diagnostic tools, delivery systems, and drug treatments (Xuan et al., 2023).

Nanoparticles (NPs) have garnered significant attention in scientific research over the past few decades. Despite numerous study reports, there remains a gap, particularly in health toxicology studies, underlying mechanisms, and

related evaluation models for a comprehensive understanding of the effects of NPs. The small size of NPs provides various properties, expanding their applications. Their small size and uneven electron distribution enable a wider range of applications for their magnetic properties and their suspensions (Reiss and Hütten, 2005), including data storage (Duong et al., 2014), drug transport (Dong et al., 2011), and environmental purification. NPs possess properties such as small size and large surface area, which facilitate their interaction with molecules at the target site and mediate a range of toxicity mechanisms. These NP properties are closely linked to the severity of organism response and toxicity. While NP-based techniques have advanced technology across various fields, their use can significantly impact health due to their extremely small size and very high surface/volume ratio, making them highly reactive (Arora et al., 2012). This characteristic can lead to their toxicity upon contact with biological systems (Lasalvia et al., 2019).

Living organisms react differently to various types of nanomaterials, and the interaction results in biochemical changes depending on the dose of received nanomaterials. At average doses, nanoparticles cause toxicity and may induce oxidative stress by altering the oxidoreduction equilibrium. At relatively low doses, nanoparticles can be beneficial in nanomedicine for addressing deficiencies of essential elements (Hamdi and Hidouri, 2024).

Aljabali et al. (2023) noted that (NPs) can have both positive and negative health impacts, acting as a "double-edged sword" depending on their physical composition. The physical-chemical properties, including structural composition, surface charge, shape, crystallinity, surface area, zeta potential (surface charge), solubility, and surface functionalities, are factors that influence NP toxicity. The biosynthesis of nanomaterials presents advantages over chemical methods by utilizing non-toxic agents and yielding higher efficiency, thereby reducing health and environmental concerns (Basheer et al., 2023; Karunakaran et al., 2023).

Nanoparticles can induce a range of biochemical changes in biological systems, impacting cellular processes and functions including: -

1- Cellular Uptake and Distribution: Nanoparticles (NPs) have the ability to influence the destiny of cells, either by triggering or preventing

mutations, initiating communication between cells, and affecting the structure of cells. These effects are primarily determined by interactions at the interface between nanomaterials and biological entities. The intracellular behavior of NPs is crucial for their effectiveness, as these carriers are designed to transport specific molecules (such as genes, drugs, and contrast agents) to the cytosol, nucleus, or other specific intracellular locations. However, the efficient and controlled entry and movement of NPs into cells pose significant challenges. In addition to their interactions with cell membranes, a comprehensive understanding of the mechanisms involved in the cellular uptake and movement of NPs is essential for the development of effective and safe nanomedicines through the precise adjustment of the physicochemical properties of NPs to optimize their targeting, uptake, and movement within cells (Mitchell et al., 2021).

Upon reaching the outer membrane of a cell, NPs can interact with components of the plasma membrane or the extracellular matrix and enter the cell, primarily through a process called endocytosis. Endocytosis involves the engulfment of NPs in membrane invaginations, followed by their separation and release to form endocytic vesicles, which are then transported to specialized intracellular sorting and movement compartments. Researchers have focused on the interaction between nanoparticles (NPs) and biological systems to gain insights into how NPs alter downstream cell signaling pathways. NPs can drive specific biological responses or enhance the uptake and movement within cells to deliver therapeutic and diagnostic payloads. The uptake of NPs by cells involves highly regulated mechanisms that can be categorized into pathways based on endocytosis and direct entry of NPs into cells. Endocytosis is a complex process that includes the binding of specific ligands to cell surface receptors to form a ligand-receptor complex, the involvement of cytosolic proteins in the formation of a coated pit, the invagination of the plasma membrane, the separation of the invagination to form an intracellular vesicle, and the release and recovery of endocytic proteins from the vesicle (Donahue et al., 2019; Sabourian et al., 2020).

Direct cellular entry refers to the ability of NPs to cross the cell plasma membrane through biochemical or physical means, which includes: (a) Direct translocation, where NPs disrupt the

cell plasma membrane and enter the cell, bypassing endosomal entrapment and energy-dependent transport. (b) Lipid fusion, where lipid bilayer-coated NPs fuse with the cell membrane, delivering the cargo directly to the cytoplasm. (c) Electroporation, which involves the formation of pores through electrical pulses, allowing NPs to be internalized. (d) Microinjection, which involves the injection of NPs into the cytoplasm (Donahue et al., 2019).

When NPs are recognized and not tolerated, they can affect cellular pathways, leading to cellular dysfunction. Several factors can promote an intolerable response, including non-biocompatible size or shape, excessive homo- or hetero-aggregation, chemical transformations, corrosion, and the release of ions or soluble compounds by NPs (Ernst et al., 2021).

2- Oxidative Stress: The primary mechanism of NPs' toxicity involves the production of reactive oxygen species (ROS) and nitrogen species (RNS) (Ray et al., 2021). ROS and RNS cause oxidative and nitrosative stress, leading to damage in DNA, lipids, and proteins. Additional mechanisms include disturbed calcium balance, impaired mitochondrial function, compromised cell membrane integrity, disruption of protein interactions, unfolded proteins, ER stress, and genotoxicity (Kumar et al., 2017; Mohammadinejad et al., 2019; Toscano and Torres-Arias, 2023; Ji et al., 2024).

NP-mediated toxicity is associated with paradigms such as oxidative stress, inflammation, genetic damage, and the inhibition of cell division and cell death (Johnston et al., 2010). Previous research has consistently indicated that NP toxicity is often linked to the generation of ROS, which can have both protective and harmful effects during biological interactions. The physicochemical properties of NPs, including particle size, surface charge, and chemical composition, are crucial factors in determining the ROS response and NP-induced injury, as many of these intrinsic properties can catalyze ROS production (Manke et al., 2013). The generation of ROS can lead to oxidative stress, causing the oxidation of biomolecules such as proteins, phospholipids, and DNA, ultimately resulting in cell death and inflammation (Pondman et al., 2023).

3- Inflammatory Responses: Exposure to nanoparticles can occur through inhalation, ingestion, skin contact, or direct administration into

the bloodstream. This is followed by interactions with biological systems, tissues, and cells. Specifically, the interactions with the immune system are extremely important. Nanoparticles can be recognized as foreign entities by immune cells in bodily fluids and tissues, such as monocytes, phagocytes, platelets, leukocytes, and dendritic cells. These cells will then engulf and remove the nanoparticles. Consequently, the immune system may react, leading to negative effects such as hypersensitivity reactions and inflammation at the tissue or body level (Zolnik et al., 2010; Ilinskaya and Dobrovolskaia, 2016). The majority of immune responses to nanoparticles are unwanted, so significant efforts have been made to evade detection by the immune system. However, through intelligent nanoparticle design, it is feasible to direct the immune response for our benefit, a strategy that can be leveraged for the development of vaccines and cancer immunotherapy. Cell-autonomous antimicrobial defense mechanisms, such as autophagy, can be harmful in the case of long-lasting nanoparticles and result in vesicle accumulation, thereby increasing cell death through mitochondrial dysregulation (Stern et al., 2012; Pondman et al., 2023).

Nanoparticles (NPs) have been found to potentially lead to mitochondrial damage by increasing inflammatory factors, as suggested by studies (Asharani et al., 2009; Nair et al., 2009; Premanathan et al., 2011). The toxicity of NPs has been linked by researchers to various parameters such as particle shape, size, dispersity, surface charge, and protein corona effects. Multiple research findings have pointed to the activation of oxidative stress and the expression of genes associated with inflammation by NPs (Guo et al., 2015; Cameron et al., 2022; Ajdary et al., 2018; Kang et al., 2008). According to Ajdary et al. (2018) the common mechanisms of nanoparticle cytotoxicity can be summarized as in Figure 1.

Certain NPs have demonstrated the ability to trigger inflammatory responses in cells, including macrophages and neutrophils. Upon encountering foreign entities like NPs, the immune system's initial responders are phagocytic cells. Multiple studies have documented adverse interactions between nanoparticles and the immune system, with immune stimulation potentially causing immunosuppression and leading to inflammatory or autoimmune conditions, thereby

increasing the likelihood of the body getting infected (Aljabali et al., 2023).

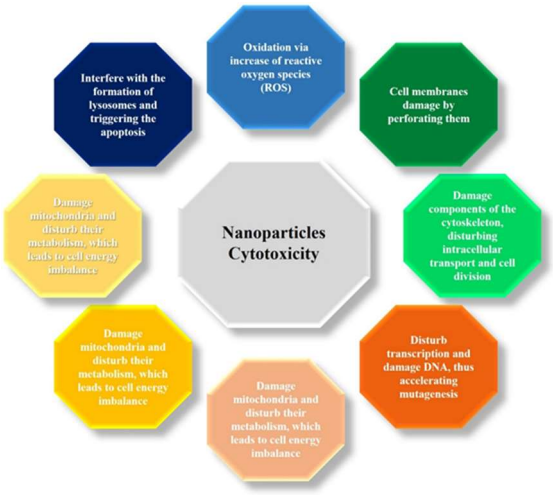

Figure 1: Common mechanisms of NP cytotoxicity

4- Gene Expression Changes: The presence of NPs might influence gene expression and its control. Being exposed to NPs in the workplace due to dental nanomaterials could cause shifts in gene expression linked to the harmful impacts of NPs on well-being. Depending on the particular characteristics of the NPs, these changes in the impacted molecular pathways could disturb cellular balance and add to pulmonary toxicity (Guadagnini et al., 2015; Simova et al., 2024).

The formation of hydroxy deoxyguanosine causes damage to the DNA strand through base changes. If the DNA is not repaired, it leads to cell cross-linking, which in turn contributes to the development and advancement of cancer. Following oxidative stress, different signaling pathways are activated, potentially resulting in cell death (Shang et al., 2014; Ajdary et al., 2018).

Exposure to these engineered nanomaterials (ENM) has the potential to cause changes in the patterns of DNA methylation within cells, as well as modifications to histones post-transcriptionally and the expression of non-coding ribonucleic acid (RNA). The effects of these changes depend on the dose of ENM and their physicochemical properties, including size, shape, and surface chemistry, as well as on the sensitivity of the cell or organism. The affected genes primarily play a role in controlling the epigenetic process, as well as in apoptosis, cell cycle regulation, DNA repair, and pathways associated with inflammation. Long-term changes to these pathways may contribute to the development or progression of specific diseases (Moreira et al., 2021). Nanoparticles have the potential to disrupt the normal progression of the cell cycle, potentially leading to cell cycle arrest or apoptosis (Encinas-Gimenez et al., 2024).

5- Protein Interactions

a- Protein corona formation: The challenge lies in the interaction of NPs with biological fluids. As NPs

enter the bloodstream, proteins cover their surface, forming a protein corona (PC) that influences the characteristics and behavior of NPs. The PC plays a crucial role in immune recognition by mononuclear phagocytic system (MPS) cells through opsonin binding, leading to rapid elimination from the circulation. Interestingly, dysopsonins, identified in the PC of several NPs, can impart stealth properties, prolonging circulation time and enhancing efficacy. Hence, maintaining the balance between opsonin and dysopsonin is crucial for predicting NPs' fate in vivo. The PC significantly impacts the toxicity and efficacy of NPs through various mechanisms; altering the biodistribution of nanostructures, leading to rapid liver elimination after uptake by MPS cells; shielding the interactions between ligands on NPs' surface and their targets (Mirshafiee et al., 2013); and potentially inducing NP degradation and drug leakage through the action of the C system. (Liu et al., 2020; Akhter et al., 2021; Panico et al., 2022; Mahmoudi et al., 2023).

The structure of PC can typically be split into two parts (Figure 2). The tightly bound proteins forming the inner layer, which has a longer lifespan, are known as the hard corona (HC), whereas the outer layer consisting of weakly bound proteins with a shorter lifespan is referred to as the soft corona (SC) (García-Álvarez and Vallet-Regí, 2021; Soliman et al., 2024).

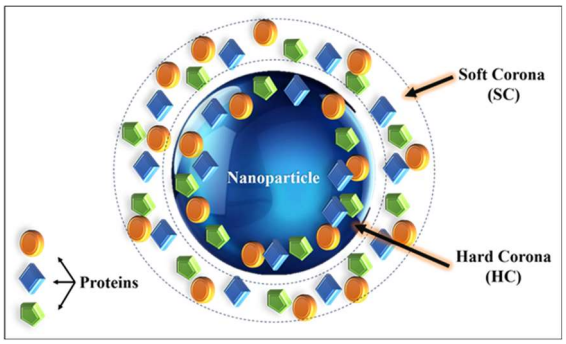

Figure 2: Illustration of hard corona and soft corona

b- Enzyme Inhibition or Activation: Nanoparticles have the ability to interact with enzymes, changing their activity and impacting metabolic pathways. NPs can modify the structure and function of an enzyme. The relationship between enzymes and NPs is determined by the fundamental characteristics of NPs, including structure, size, surface chemistry, charge, and surface shape (Wu et al., 2009; MacCormack et al., 2012).

Enzymes can attach to nanoparticles through simple adsorption or chemical linkages. Immobilization alters the catalytic activity of enzymes through various mechanisms, including the loss of dynamic properties, changes in conformational integrity, and reduced accessibility of the active site to

substrates (Arsalan and Younus, 2018; Anboo et al., 2022; Khafaga et al., 2024).

*** Conclusion**

In conclusion, nanotechnology presents a transformative approach in biomedical research, particularly through the development of NPs that can enhance drug delivery and personalized medicine. The unique physicochemical properties of NPs, such as their small size and high surface area, enable significant interactions with biological systems, leading to both therapeutic benefits and potential health risks. While NPs can facilitate targeted delivery and improve treatment efficacy, they also pose challenges, including toxicity and adverse biological responses due to oxidative stress, inflammatory reactions, and gene expression changes. A comprehensive understanding of these interactions is crucial for optimizing NP design to maximize therapeutic potential while minimizing health risks. Future research should focus on bridging the knowledge gaps in nanotoxicology and developing safer nanomaterials that can effectively navigate biological barriers without eliciting harmful effects. As nanotechnology continues to evolve, its responsible application in medicine holds the promise of advancing treatment modalities and improving patient outcomes.

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