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Research review paper

Toxicity of inorganic nanomaterials in biomedical imaging

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ABSTRACT

Inorganic nanoparticles have shown promising potentials as novel biomedical imaging agents with high sensitivity, high spatial and temporal resolution. To translate the laboratory innovations into clinical applications, their potential toxicities are highly concerned and have to be evaluated comprehensively both in vitro and in vivo before their clinical applications. In this review, we first summarized the in vivo and in vitro toxicities of the representative inorganic nanoparticles used in biomedical imagings. Then we further discuss the origin of nanotoxicity of inorganic nanomaterials, including ROS generation and oxidative stress, chemical instability, chemical composition, the surface modification, dissolution of nanoparticles to release excess free ions of metals, metal redox state, and left-over chemicals from synthesis, etc. We intend to provide the readers a better understanding of the toxicology aspects of inorganic nanomaterials and knowledge for achieving optimized designs of safer inorganic nanomaterials for clinical applications.

Contents

1. Introduction

In the 21st century, many new concepts have been proposed and introduced in medical sciences, such as theranosis, preventive medicine, individualized medicine, multimode imagings, etc. All these require supports from the multifunctional platform of excellent performance (e.g., high sensitivity, high specificity, high resolution and high accuracy). Nanomaterials and nanoscale particles, because of their unique nano-characteristics and novel physicochemical properties, provide promising multifunctional platforms that suffice the requirements of the above medical diagnosis and/or therapy. For example, early diagnosis that can

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detect diseases before health is deteriorated largely depends on the development of smart diagnostic agents, in which the nanostructured and nanoscale materials play important roles (Bharali and Mousa, 2010). With the rapid accumulation of advanced knowledge on the distinctive properties and unique functions of nanomaterials, utilization of nanoparticle characteristics for medical purposes has shown great promising potentials of building smart nanomedicines for the development of theranosis, preventive medicine, individualized medicine, multimode imagings, etc. Nanomedicine, defined as the applications of nanotechnology for diagnosis, monitoring, therapy and the control of the biological systems, is becoming a hotspot in the research fields of chemistry, materials sciences, medical sciences and clinical translation medicines, etc. (Zhang et al., 2008). The current nanomedicine mainly includes the nanoparticle-based nanovehicles for the targeted drug delivery, diagnostic nanoparticle platforms for the biomedical imagings and the therapeutic nanoparticle platforms for treating clinical diseases (Bharali and Mousa, 2010; Lin and Datar, 2006).

The changed physicochemical properties of nanoparticles play crucial roles in the excellent performance of nanoparticle-based medicines (Chen et al., 2005; Cho et al., 2010; Kang et al., 2012; Liang et al., 2010). The first is due to the nanoscale size which makes the physicochemical properties of the nanoparticles different from that of the bulk counterparts. For instance, when the size is scaled down to the range of nanometer sizes, iron oxide nanoparticles are endowed with superhigh magnetic susceptibility (Pouliquen et al., 1992). The second is that the small-sized nanoparticles easily penetrate into the tissue and even cells, allowing the clinicians or researchers to track and detect the histopathological, cellular and even molecular changes during the disease treatment or diagnosis with nanomedicines (Chen et al., 2008). The third is the large surface-to-volume ratio and size-related surface activity. They make the nanoparticles apt to various surface chemical modifications to improve their biocompatibility and to enhance the active targeting by conjugating with disease-related biomarkers (Byrne et al., 2008). The fourth is the nanostructure which can be assembled or constructed layer by layer or shell by shell to contain different payloads for realizing multifunctions-at-one-platform in biomedical applications. Nowadays, the noninvasive in vivo imagings include magnetic resonance imaging (MRI), fluorescence imaging (FI), positron emission tomography (PET) and near-infrared fluorescence imaging (NIRFI), etc. However, given that the limitations for each technology in application, multimodal nanoprobes have been advocated for simultaneous imagings to improve efficiency (Lee et al., 2012). Multifunction-at-one-platform is the key to actualize the human dreams of multi-mode imagings, theranosis, individualized therapy, etc. (Sun et al., 2011; Wang et al., 2012). For instance, we developed an integrated multimodal assembly strategy and assembled two gold nanoclusters at the ferroxidase active sites of ferritin heavy chain. The obtained gold–ferritin nanostructure not only retained the imaging properties of gold nanoparticles, but also enhanced fluorescent intensity and possessed tunable emissions from green to far-red owning to the coupling interaction between the paired gold clusters within the ferritin shell. The far-red gold–ferritin nanostructure simultaneously achieved ferritin receptor-mediated targeting and biomedical imaging both in vitro and in vivo and showed great potential as a novel biomedical imaging agent (Sun et al., 2011). Additionally, we innovatively designed a bifunctional peptide which could target cell nuclei and meanwhile biomineralize and capture gold clusters, thus acting as a specific probe for nuclei (Wang et al., 2012). So far, many nanoparticles have shown enormous potentials of building an effective multifunctions-at-one-platform. Among them, gold nanoparticles, quantum dots, iron oxide nanoparticles, the recently-emerging upconversion nanoparticles, PET imaging nanoprobes, etc. are representative ones with promising applications (Fig. 1) (Taylor et al., 2012).

Though they possess new medical functions with high efficacy, the safety concern of inorganic nanoparticles is a key determinant factor in their clinical applications. It is imperative to establish structure–activity relationship (SARs) and to develop the risk reduction strategies. The interactions of these engineered nanoparticles with biological systems and the consequent toxicity change with not only materials themselves but also nano-characteristics. For example, the particle size and the nanosurface properties can largely govern the bioavailability, transport, biotransformation, cellular uptake and the triggered biological responses (Zhu et al., 2012a). Herein, the safe implementation of nanoparticles goes beyond conventional hazard, exposure and risk assessment strategies of the classic materials (Nel et al., 2013). In the past decade, many engineered nanoparticles for biomedical applications have undergone the toxicological studies in vitro or in vivo, however, their pharmacokinetics, namely, the processes of absorption, distribution, metabolism and excretion of these inorganic nanoparticles in vivo, has been less systemically understood so far (Ritschel and Kearns, 2004). After the nanoparticles are administrated into the body in biomedical applications, whatever the entry routes (oral, injection, etc.), interactions between nanoparticles and the biological systems (such as proteins, cells, tissues and organs) are inevitable until the nanoparticles are carried to its effective sites via the bloodstream. The pharmacokinetics of the nanoparticles in vivo and their toxicity that might arise have been described in Fig. 2. First, the exogenous nanoparticles can enter into the bloodstream in contact with various serum proteins. The interaction of nanoparticles with serum proteins mostly leads to the formation of protein layers on the nanosurfaces, called as “protein corona”. The physicochemical parameters of nanoparticles have been found to be critical determinants affecting nanoparticle–protein interactions (Tenzer et al., 2011). In turn, protein corona influences the particle biodistribution, biocompatibility and even therapeutic efficacy (Aggarwal et al., 2009). Therefore, the interaction of the exogenous nanoparticles with serum proteins, after they enter into the blood, has to be carefully investigated in the toxicity assessment.

Then, with the bloodstream, different nanoparticles distribute into different organs and tissues to different extents depending on both the physio-anatomical features of the vasculature in these tissue and organs and the physicochemical properties of nanoparticles (Almeida et al., 2011; Wang et al., 2013). Due to the small size of the nanoparticles, the blood can transport them via the circulation to many organs and tissues. In some tissues (i.e., liver and spleen), nanoparticles enter the tissues by size-dependent cellular uptake or endocytosis by macrophages or Kupffer cells so that they are selectively and specifically removed from the blood, which is called tissue-specific extravasation (Wang et al., 2013). Afterwards, these nanoparticles are internalized into cells, offering the basis for executing their diagnostic or therapeutic functions in vivo. Therefore, cellular uptake, intracellular trafficking of nanoparticles and cell fate have to be assessed with the physicochemical properties of nanoparticles being taken into account (Zhao et al., 2011). In some organs, extravasation of the nanoparticles may be restricted by the existence of natural barriers formed by the tight junctions between the endothelial cells. However, the penetration of these barriers (blood–brain barrier, the placenta barrier, etc.) is observed in vivo studies where the undesirable effects (neurotoxicity, reproductive and developmental toxicity, etc.) are likely to be induced in some cases.

Following biodistribution, nanoparticles then undergo metabolic processes. The activity of cytochrome P450 enzymes, the main redox enzymes involved in metabolic transformations, is likely to be affected (Fröhlich et al., 2010; Sereemaspun et al., 2008). Finally, the nanoparticles can be excreted from the body via the kidneys or/and in the feces (Chen et al., 2008). But in some cases, parts of the nanoparticles are retained in the body for the long-term period due to the uncompleted excretion and consequently they may disturb the normal functions of the organs or tissues and induce chronic organ toxicity, metabolic toxicity, immunotoxicity or even genotoxicity. Therefore, to minimize and even abolish the possible health risks, the potential toxicity of these nanoparticles has to be scientifically assessed in depth before they are used in the clinic (Fadeel and Garcia-Bennett, 2010).