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Review article

Strategies and knowledge gaps for improving nanomaterial biocompatibility

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ABSTRACT

With rapid development of nanotechnology and nanomaterials, nanosafety has attracted wide attention in all fields related to nanotechnology. As well known, a grand challenge in nanomaterial applications is their biocompatibility. It is urgent to explore effective strategies to control the unintentional effects. Although many novel methods for the synthesis of biocompatible and biodegradable nanomaterials are reported, the control strategy of nanotoxicity remains in its infancy. It is urgent to review the archived strategies for improving nanomaterial biocompatibility to clarify what we have done and where we should be. In this review, the achievements and challenges in nanomaterial structure/surface modifications and size/shape controls were analyzed. Moreover, the chemical and biological strategies to make nanomaterial more biocompatible and biodegradable were compared. Finally, the concerns that have not been studied well were prospected, involving unintended releases, lifecycle, occupational exposure and methodology.

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1. Introduction

Nanomaterials with novel properties and functionalities have been widely used in various fields, for example, drug delivery, medical image, catalytic materials, chemical sensor, energy storage and contamination treatments (Cheng et al., 2017; Perreault et al., 2014; Delplace and Nicolas, 2015; Hwang et al., 2015). The numbers of published paper were 63,167 and 162,093 in 2006 and 2016, respectively, based on Web of Science (search date was 25th-Feb-2017; search topic was "nano*"; years published were set as 2006 and 2016, respectively). The development and use of nanomaterials have raised safety concerns, as their small size facilitates accumulation in and interaction with biological tissues (Mu et al., 2016; Minetto et al., 2014; Ding et al., 2017; Oomen et al., 2014). In recent years, many reports have indicated possible negative effects of various nanomaterials and their potential to

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provoke oxidative stress, inflammation, genetic damage and long-term pathological effects on biology (Ren et al., 2016; Bussy et al., 2013). "Nanotoxicology" becomes an important topic of nanomaterial safety, and the number of publications linking to nanomaterials has increased quickly over recent decades (Maynard et al., 2006). The numbers of published paper were 1066 and 8959 in 2006 and 2016, respectively, based on Web of Science (search date was 25th-Feb-2017; search topics were "nano*" and "toxic*"; years published were set as 2006 and 2016, respectively). Human could contact nanomaterials by the intentional use (e.g., nanomedicine) and unintentional exposure (e.g., dermal penetration and inhalation of released nanomaterials from nanodevices during application and disposal, and occupational exposure during nanomaterial manufacturing) (Nowack et al., 2013; Pujalté et al., 2017; Wang et al., 2013; Chiappini et al., 2015). Therefore, the biocompatibility and biodegradation of nanomaterials need to be thoroughly control before they can be safely applied.

Currently, researchers from chemical, biological, medical and environmental fields have paid much attention to the investigation and control of adverse effects of nanomaterials. To control nanotoxicity, some novel methods (e.g., chemical chain modification, biosynthesis and biomaterials inspired from nature) were used to synthesize biocompatible and biodegradable nanomaterials with various functions, sizes and shapes (e.g., nanocrystals, quantum dots and nanowires, nanotubes and nanoporous) (Wang et al., 2006; Xue et al., 2015). The numbers of published paper were 1127 and 5079 in 2006 and 2016, respectively, based on Web of Science (search date was 25th-Feb-2017; search topics were "nano*" and "biocompatib*"; years published were set as 2006 and 2016, respectively). These new discoveries call for a re-evaluation of previous works with the scope of this recently acquired knowledge. Unlike common toxicological researches and chemical synthesis, the control strategy of nanotoxicity or nanomaterial risks remains in its infancy. Compared with polymer nanoparticles (NPs), methods relating to the degradability of other types of nanomaterial are rare. Recently, it was reported that magnetic nanoparticles were metabolized into ferritin iron, as proofed by animal, stem cell and endosome models (Ruiz et al., 2015; Mazuel et al., 2016). However, the systemic methodology for nanotoxicity regulation is still imperfect. It is well known that nanomaterial sizes, shapes and surface groups affect the biocompatibility, while these properties may be changed by the active components (e.g., nonspecific binding to proteins and catalysis by enzymes) in vivo, which should be further understood. As a result, biocompatibility become once again unknown and the byproducts will be more likely to undergo unintentional translocations (Hu et al., 2016a, 2016b). Many knowledge gaps and misunderstandings still remain to improve biocompatibility of nanomaterials, for example, biomaterial stability and high quantity in large scale, unintentional risks of NPs releasing in the life cycles of materials and biology, tracking nanomaterial in situ and in vivo for a long term and category control to face the blooming nanomaterials.

The present review provides an overview of the most recent achievements relating to the strategies to improve nanomaterial biocompatibility. However, we neither list the global literature nor show all the related knowledge. The key issues and main strategies are highlighted, and the major challenges are discussed to reduce the scientific "blind spots". First, the achievements and challenges in nanomaterial structure/surface modifications and size/shape controls were analyzed. And then, the chemical and biological strategies to make nanomaterial more biocompatible and biodegradable were compared. Afterwards, the evaluation and control of occupational exposure were elucidated. Finally, concerns that have not been studied well were prospected, involving unintended releases, life-cycle, occupational exposure and methodology.

2. Structure modifications and unintended byproducts

Biodegradability is a key issue in nanomaterial synthesis. Biodegradable materials are those that can transform from an initial, stable structure into soluble products that can be resorbed or processed by the body (Tibbitt et al., 2015). The ideal nanomaterials that achieved by optimization of synthesis is biodegradable and the degraded products can easily excrete from biological body. Nanomaterial structure or framework is closely related to the degradability and subsequent toxicity in human bodies, especially for polymeric nanomaterials. In this section, first, effects of polymeric nanomaterial sequence modifications on degradation were discussed. And then, the strategy of introducing labile units and trigger-responsive units to nanomaterial main or side chains and their action as chain linkers were highlighted. Finally, the concerns of biodegraded byproducts were discussed.

2.1. Structure modifications for biodegradation

It is well known that more crystalline stereoregular polymers exhibit slower degradation profiles than atactic ones. In addition to the stereostructure, the distribution of monomer units in a copolymer chain is also related to the degradation rate. As a result, control of nanomaterial sequences should be taken into account prior to introducing nanomaterials to environment and human health related applications. Specifically, sequenced poly(lactic-co-glycolic acid) has been shown to degrade into more homogeneous and ordered products with a gradual degradation rate, while random poly(lactic-co-glycolic acid) has been shown to rapidly degrade into heterogeneous and ill-defined products (Thomas and Lutz, 2011). The initial weight loss of sequenced polymers was observed to be less than that of randomly constructed polymers. Subsequently, the nearly linear molecular weight loss profile and uniform thermal behavior throughout the course of the hydrolysis were observed for sequenced polymers (Li et al., 2011). This mechanism can be attributed to the different cleavage site patterns; random polymers contain cleavage sites that are greater in number and disorder compared with their sequenced counterparts. The degradation process of sequenced copolymers and random copolymers is described in Fig. 1a. Ordered arrays of silver nanoparticles on peptide nanofibers exhibited limited toxicity to eukaryotic cells, where cell viabilities were >90% and <20% at 50 μM ordered silver nanoparticles and 50 μM $AgNO_3$ exposures, respectively (Pazos et al., 2016). As sequenced nanostructures are more biocompatible than random ones, the former nanoparticles may be eco-friendly.

To promote the in vivo biodegradation process of nanomaterials, scientists have presented several approaches, involving the introduction of labile units into the polymer backbones or side chains and the connection of polymer chains via degradable or reversible linkages. The aforementioned methods are illustrated in Fig. 1b–d. Introducing labile units into polymer backbones leads to either partial or complete degradation since the 80s, depending on the number and type of cleavable units (Delplace and Nicolas, 2015). Inserting labile units into the side chains can alter polymeric material properties such as hydrophilicity, which leads to the improved water solubility as well as faster excretion rates (a commonly accepted renal excretion limit is approximately 40–60 kDa) (Delplace and Nicolas, 2015). Droumaguet et al. developed novel polymeric NPs containing a biodegradable poly(alkyl cyanoacrylate) (PACA) core (Le Droumaguet et al., 2012). Instead of introducing labile units into the backbones or side chains of polymers, connecting polymer chains with a degradable linkage is also an effective approach. Cho et al. used poly-(ethylene glycol) methyl ether methacrylate (PEGMA) as hydrophilic arms, and the combination of 2-(dimethylamino)ethyl methacrylate (DMAEMA) and disulfide dimethacrylate cross-linkers as degradable cores (Cho et al., 2011). These polymers were biocompatible, with >80% cell viability after 48 h incubation even at high concentration (800 μg/mL) (Cho et al., 2011). Overall, introducing labile units into nanomaterials is certainly helpful in the respect of controllable effectiveness and subsequent biodegradation in vivo. However, it is still a tough work to balance biodegradability and stability for specific applications, which require materials degraded at the right time and in the right place.