Ecotoxicology and Environmental Safety 166 (2018) 294–300

Contents lists available at ScienceDirect

Ecotoxicology and Environmental Safety

journal homepage: www.elsevier.com/locate/ecoenv

Current approaches for safer design of engineered nanomaterials

Ruth Hwang[a,1], Vahid Mirshafiee[b,c,1], Yifang Zhu[a], Tian Xia[b,c,*]

[a] Fielding School of Public Health, Department of Environmental Health Science, University of California Los Angeles, Center for Health Sciences, 650 Charles E. Young Dr. South, Los Angeles, CA 90095, United States

[b] Center for Environmental Implications of Nanotechnology, California NanoSystems Institute, University of California Los Angeles, 570 Westwood Plaza, Los Angeles, CA 90095, United States

[c] Division of NanoMedicine, Department of Medicine, University of California Los Angeles, 10833 Le Conte Ave., Los Angeles, CA 90095, United States

ARTICLE INFO

Keywords:
Engineered nanomaterials
Safer design
Doping
Coating
Surface chemistry
Aspect ratio

ABSTRACT

The surge of applications for engineered nanomaterials (ENMs) across multiple industries raises safety concerns regarding human health and environmental impacts. ENMs can be hazardous through various mechanisms, including, particle dissolution and shedding of toxic metal ions, surface reactivity and perturbation of cellular membranes, lysosomal membrane damage, activation of inflammation pathways (*e.g.*, NLRP3 inflammasome), *etc*. The aim of this review is therefore to discuss practical approaches for the safer design of ENMs through modification of their physicochemical properties that can lead to acute and/or chronic toxicity. This is premised on our understanding of how different ENMs induce toxicity within various biological systems. We will summarize studies that have investigated nanomaterial toxicity both *in vitro* and *in vivo* to understand the underlying mechanisms by which nanoparticles can cause inflammation, fibrosis, and cell death. With this knowledge, researchers have identified several design strategies to counter these mechanisms of toxicity. In particular, we will discuss how metal doping, surface coating and covalent functionalization, and adjustment of surface oxidation state and aspect ratio of ENMs could reduce their potential adverse effects. While these strategies might be effective under certain experimental and exposure scenarios, more research is required to fully apply this knowledge in real life applications of nanomaterials.

1. Introduction

Engineered nanomaterials (ENMs) are increasingly used in different scientific and industrial disciplines, including, but not limited to, medicine, transportation, electronics, agriculture, food, and cosmetics (Ji et al., 2012; Stark et al., 2015; Vance et al., 2015). For therapeutic and diagnostic purposes, ENMs have emerged as great candidates for targeted drug delivery and bioimaging.(Zhang et al., 2007; Yildirimer et al., 2011). The electrical and waste water treatment industries utilize nanomaterials to improve sensing and conduction properties of materials and improve water quality, respectively (Contreras et al., 2017; Devi and Ahmaruzzaman, 2017; J. Hou et al., 2017; C. Hou et al., 2017). However, this growing application of nanomaterials in consumer products and various technologies could increase the possibility of ENMs entering into human bodies and the environment, and raise major safety concerns with regard to their potential adverse impacts. In fact, numerous studies have previously explored toxicological effects of ENMs on different biological species, and found some of these nanomaterials to be toxic towards mammalian cells, plants, and aquatic organisms (Jiang et al., 2015; Jiang et al., 2017; Li et al., 2014; R. Li et al., 2015; X. Li et al., 2015; Mirshafiee et al., 2017; Nel et al., 2006; Nel et al., 2013; Sun et al., 2015; Osborne et al., 2015; Osborne et al., 2017; Wang et al., 2013). Moreover, some of these investigations were able to correlate the adverse biological outcomes of these cytotoxic nanomaterials to their physical or chemical characteristics (*e.g.*, size, surface charge, and aspect ratio) and identify the key factors that make them toxic to the biological organisms. These correlations between nanomaterial's physicochemical properties and its cytotoxicity (*i.e.*, structure-activity relationships) have been derived by preparing combinatorial libraries of nanomaterials with various, but well-defined, physicochemical properties such as size, surface chemistry, and shape, and their mechanistic toxicological profiling in tissue culture cell and animal models (Nel et al., 2013; Zhang et al., 2012a; Mirshafiee et al., 2018. For example, comprehensive analysis of highly soluble metal

* Corresponding author at: Center for Environmental Implications of Nanotechnology, California NanoSystems Institute, University of California Los Angeles, 570 Westwood Plaza, Los Angeles, CA 90095, United States.
E-mail address: txia@ucla.edu (T. Xia).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.ecoenv.2018.09.077
Received 9 May 2018; Received in revised form 14 September 2018; Accepted 18 September 2018

oxides particles such as ZnO and CuO has shown that these nanoparticles induce significant cytotoxicity in mammalian cells and living animals because of their dissolution and release of toxic metal ions (George et al., 2010; Xia et al., 2008; Xia et al., 2011; Naatz et al., 2017). Another example is silver nanoparticle that has been demonstrated to display a size-dependent cytotoxicity due to its dissolution and release of silver ions (Osborne et al., 2015; Wang et al., 2013; C. Hou et al., 2017; J. Hou et al., 2017). Comprehensive toxicological profiling of ENMs and development of structure-activity relationships not only helps to identify the key physical or chemical characteristics of ENMs that render them toxic, but also helps to develop safer design strategies that minimize nanomaterials toxicity by optimizing their physicochemical properties (Li et al., 2014; Sun et al., 2015; George et al., 2010; Naatz et al., 2017). Thus, we aim to discuss exemplary studies in this review article that explored the underlying mechanisms linking nanomaterial toxicity to their physicochemical properties and proposed strategies to design safer ENMs premised on these correlations. While there might be various safer design techniques to develop less toxic nanomaterials, we will specifically summarize example approaches, including, doping, surface coating, adjustments of surface chemistry and charge, and modification of shape and aspect ratio.

2. Examples of safer design approaches

2.1. Doping

Several studies have identified doping as an effective strategy to reduce the cytotoxicity of industrially important ENMs such as ZnO, CuO, and SiO_2 nanoparticles. Doping is a facile yet effective method that is used to modify a material's crystal structure by addition of impurities in order to achieve improved catalytic, electro-optical, magnetic, chemical, and physical properties (Babu et al., 2014). Dopants such as iron (Fe), titanium (Ti), and aluminum (Al) are typically evenly incorporated into the host lattice to change the binding energy of metal ions to oxygen, or reduce the density of reactive chemical groups on the particle surface (Sun et al., 2015; George et al., 2010). The working mechanisms of doping in reduction of ENM cytotoxicity is premised on changing nanoparticle's physicochemical properties, which involves either decrease in nanoparticle dissolution and release of toxic ions, modification of reactive surfaces to reduce generation of reactive oxygen species (ROS), or perturbation of the cellular membrane that leads to inflammation and cell death (Sun et al., 2015; George et al., 2010; Xia et al., 2011; Naatz et al., 2017).

Flame spray pyrolysis (FSP) is a well-established technique for the doping of nanomaterials, which employs rapid combustion during the synthesis procedure (Teoh et al., 2010). Through a liquid precursor, a self-sustaining flame with high local temperature and large temperature gradient allows for the formation of homogenous crystalline nanoscale materials from droplet or gas to particle (Teoh et al., 2010). This process is well-suited for industrial applications because of the facile one-step synthesis process and potential to scale-up the production of doped nanomaterials. Here we will give several examples of the FSP approach to reduce toxicity of nanomaterials.

One particular example is Fe-doped ZnO nanoparticles. ZnO is an important ENM that has wide industrial applications such as in cosmetics (*e.g.*, sunscreens) and electronics (Vance et al., 2015). However, there are clinical reports on ZnO-induced pulmonary inflammation in humans called metal fume fever that occurs when welders are exposed to metal fumes containing high concentrations of ZnO (Liu et al., 2016). This indicates that assessment of ZnO nanoparticle toxicity is highly relevant to human health. ZnO dissolution to Zn^{2+} ions has been known to play a major role in its induction of toxicity and inflammation, thus reduction of dissolution could potentially decrease its adverse effects (Wang et al., 2016). In order to explore the effect of doping on dissolution and toxicity of ZnO nanoparticles, George et al. (2010) prepared Fe-doped ZnO nanoparticles by FSP and assessed their cytotoxicity in RAW 264.7 and BEAS-2B mammalian cells. Characterization of particle dissolution indicated Fe-doped ZnO nanoparticles are less soluble than pure ZnO particles, which is attributed to the higher binding energy of iron to oxygen than zinc (George et al., 2010). The reduced dissolution further led to a decrease in cytotoxicity, which was reflected by the decrease in number of cells positively stained by propidium iodide (PI), and preservation of mitochondrial membrane potential at even the lowest Fe-doping level of 1.02% (atomic percentage of Fe content) (George et al., 2010). These *in vitro* data were also validated *in vivo* by examining the toxicity of Fe-doped ZnO nanoparticles in zebrafish embryos and rodent lungs (Xia et al., 2011). While ZnO nanoparticle exposure adversely interfered with embryo hatching, which ultimately caused starvation and death, hatching rate significantly improved upon exposure to Fe-doped ZnO nanoparticles. When rodents including mice and rats were exposed to Fe-doped ZnO nanoparticles, polymorphonuclear cell count, lactate dehydrogenase (LDH) release, and cytokine (IL-6) production in bronchoalveolar lavage (BAL) fluid were reduced compared to levels in rodents exposed to the un-doped ZnO controls. Heme-oxygenase-1 (HO-1) expression, an oxidative stress biomarker for inflammation, was also reduced in animals exposed to Fe-doped ZnO. These results demonstrate that doping partially inhibits cytokine production and can lessen the inflammatory response (Xia et al., 2011). While these two studies provide information about toxicity of Fe-doped and un-doped ZnO nanoparticles towards mammalian cells, another study assessed the viability of bacteria, including, *B. subtilis*, *P. putida,* and *E. coli*, in the presence of these nanoparticles (Li et al., 2011). Interestingly, it was found that Fe-doping does not impact the IC_{50} values of these nanoparticles and bacteria viability (Li et al., 2011). The difference behind these findings can be explained by variations with experimental cell type, exposure environment, and dose of ZnO nanoparticles. In fact, tannic acid that was added to the exposure media in order to mimic the natural aquatic environment increased the IC_{50} values of ZnO nanoparticles by uptake and chelating of Zn^{2+} ions. Therefore, ZnO nanoparticle toxicity was ameliorated by Zn^{2+} chelating action of tannic acid rather than Fe-doping (Fig. 1).

Another example is CuO nanoparticles doped with iron *via* FSP. CuO nanoparticles are employed in large-scale production for semiconductors, antifouling paints, and sensors (Naatz et al., 2017). Similar to ZnO nanoparticles, CuO nanoparticles are hazardous due to dissolution and shedding of toxic Cu^{2+} ions that generate ROS and induce inflammation (Naatz et al., 2017). Copper can cause oxidative stress injury leading to inflammation (Zhang et al., 2012a), cellular DNA damage, (Toduka et al., 2012) and reduced reproductive capacity in aquatic organisms such as *Daphnia magna* (Adam et al., 2015). The dissolution of un-doped and Fe-doped CuO nanoparticles in various

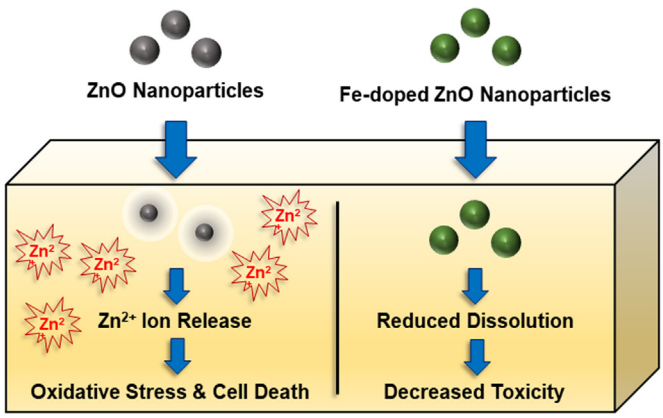

Fig. 1. Effect of Fe doping on cytotoxicity of ZnO nanoparticles. Doping ZnO particles with iron decreases their dissolution and shedding of toxic Zn^{2+} ions that further reduces their induced oxidative stress and cell death.