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Comparative analysis of redox and inflammatory properties of pristine nanomaterials and commonly used semiconductor manufacturing nano-abrasives

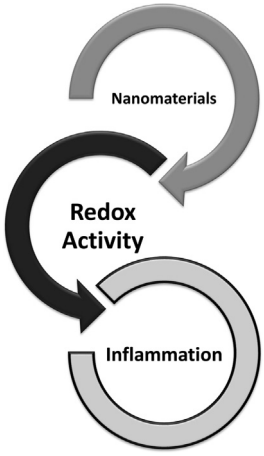
Nicole L. Flaherty[1], Akshaya Chandrasekaran[1], Maria del Pilar Sosa Peña, Gary A. Roth, Sara A. Brenner, Thomas J. Begley, J. Andrés Melendez*

SUNY Polytechnic Institute, Colleges of Nanoscale Science and Engineering, 257 Fuller Road, Albany, NY 12203, United States

HIGHLIGHTS

- Pristine nanomaterials cannot be used as a surrogate for commercially used slurries in determining their effects *in vitro* or *in vivo* as the results do not always coincide.
- 8-isoprostane levels likely serve as a potential indicator of the inflammatory potential of a particular nanomaterial.
- ROS measurements must be properly monitored and redox-sensing fluorophores may be used, but only provide a snap shot of the cellular redox milieu in response to nanomaterials.
- SiO_2 nanomaterials induce both oxidation and inflammation.

GRAPHICAL ABSTRACT



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ABSTRACT

Continued expansion of the nanotechnology industry has necessitated the self-assessment of manufacturing processes, specifically in regards to understanding the health related aspects following exposure to nanomaterials. There exists a growing concern over potential occupational exposure in the semiconductor industry where Al_2O_3, CeO_2 and SiO_2 nanoparticles are commonly featured as part of the chemical mechanical planarization (CMP) process. Chronic exposure to toxicants can result not only in acute cytotoxicity but also initiation of a chronic inflammatory state associated with diverse pathologies. In the current investigation, pristine nanoparticles and CMP slurry formulations of Al_2O_3, SiO_2 and CeO_2 were employed to assess their ability to induce cytotoxicity, inflammatory responses and reactive oxygen species in a mouse alveolar macrophage cell model. The pristine nanoparticles and slurries were not intrinsically cytotoxic and did not generate free radicals but were found to act as scavengers in the presence of an oxidant stimulant. Al_2O_3 and SiO_2 nanoparticles increased levels of pro-inflammatory cytokines while pristine SiO_2 nanoparticles induced generation of F_2-Isoprostanes. In co-treatment

* Corresponding author at: SUNY Polytechnic Institute, Colleges of Nanoscale Science and Engineering, 257 Fuller Road, NFE-4313, Albany, NY 12203, United States. Fax: +1 518 437 8687.
E-mail address: jmelendez@sunypoly.edu (J. A. Melendez).
[1] These authors contributed equally to this work.

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Inflammation
Redox activity

studies, the pristine nanomaterials modulated the response to the inflammatory stimulant lipopolysaccharide. The studies have established that pristine nanoparticles and slurries do not impact the cells in a similar way indicating that they should not be used as slurry substitutes in toxicity evaluations. Further, we have defined how an alveolar cell line, which would likely be the first challenged upon nanomaterial aerosolization, responds to diverse mixtures of nanomaterials. Moreover, our findings reinforce the importance of using multiple analytic methods to define the redox state of the cell following exposure to commonly used industrial nanomaterials and toxicants.

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1. Introduction

Nanomaterials have found their way into numerous day to day applications and the magnitude of their use in semiconductor manufacturing has generated concern owing to risk of worker exposure. Despite the widespread use of nanomaterials in numerous industrial and commercial applications, the risk associated with exposure to these materials has not been completely investigated. In semiconductor fabrication, nanoparticles are both used as a tool and generated as waste in multiple manufacturing processes creating multiple exposure points.

Chemical-mechanical planarization (CMP) is a process frequently used in the semiconductor industry to achieve planar surfaces between layers of interconnects which are necessary for achieving high performance. This process involves the elimination of excess materials through a combination of chemical and abrasive action facilitated by a slurry solution (Krishnan et al., 2010). Due to the wide range of materials needed to create a functional semiconductor chip, there are a multitude of slurry formulations that are applied throughout manufacturing. Major variations include the pH of the solution as well as the size and composition of the micro- or nano-abrasive. Metal oxides such as SiO_2, CeO_2, and Al_2O_3 are examples of three commonly used nano-abrasives in slurries. A growing body of literature on the inflammatory potential of nanoparticles illustrates that cellular responses are quite variable and highly depend on the size, dosage and physicochemical properties of the nanomaterial in question as well as the media it is delivered in (Alexis et al., 2008; Meissner et al., 2009; Nel et al., 2009; Maiorano et al., 2010; Sohaebuddin et al., 2010; Pavlin and Bregar, 2012). Additionally, several groups have demonstrated that the biomechanical environment of the cell greatly impacts not only their capacity to take up particles but also inflammatory response to said particles (Patel et al., 2012; Patel and Kwon, 2012, 2013). Furthermore, certain nanomaterials used in industries have been found to catalyze the generation of reactive oxygen species (ROS) which have potent effects on host cell signaling.

Aberrant ROS production has been linked to chronic inflammation; progressively leading to increased risk of cancer, neurological disorders, cardiovascular diseases, metabolic disorders etc. (Festa et al., 2000; Xu et al., 2003; Clevers, 2004; Berg and Scherer, 2005; Federico et al., 2007; Freund et al., 2010). Nanomaterials have the potential directly redox-cycle, alter antioxidant function and augment the production of reactive oxygen species. ROS are key signal transduction molecules with the capacity to modulate kinase and phosphatase cascades involved in inflammatory signaling. Chronic inflammation is at the heart of many disease processes and in this fashion the inflammatory potential of any particular nanomaterial is directly linked to their redox activity as delineated here.

While occupational exposure studies in relation to the CMP process are underway, additional data and study sites are needed (Shepard and Brenner, 2014a, 2014b). Manufactured nanomaterials have been shown to be proinflammatory, therefore it is critical to determine whether CMP slurries containing various nanoparticles are also inducers of inflammation (Onuma et al., 2009; Könczöl et al., 2012). This will allow better assessment of potential occupational hazards in the current and future manufacturing processes.

Much is still not known regarding their inflammatory potential, we focused our investigation on nanoparticles of high prevalence in the semiconductor industry: Al_2O_3, SiO_2 and CeO_2. These nanoparticles were assayed for their ability to induce cytotoxicity, inflammatory cytokine production and ability to induce ROS production in murine alveolar macrophages. In addition to pristine nanoparticles, we investigated the toxicity and inflammatory potential of several commercial slurries containing the aforementioned nanoparticles as abrasives. This allowed us to determine whether the base abrasive nanoparticles alone can be used as a surrogate for future toxicity or exposure studies.

2. Methods

2.1. Nanoparticle characterization

Al_2O_3, CeO_2 and SiO_2 nanoparticles were purchased from Sigma–Aldrich. Nanoparticles were diluted to a concentration of 100 μg/ml in water, PBS or RPMI (containing 10% fetal bovine serum, penicillin/streptomycin and β-mercaptoethanol) for size distribution measurements and in water for zeta potential measurements. After sonication to create a homogenous suspension, the size distribution and zeta potential were determined using a Malvern Zetasizer (Dispersion Technology Software, Malvern Instruments Version 5.03). Commercial CMP slurries were characterized in a similar manner to obtain size distribution results in water and RPMI, and zeta potential measurements in water. All formulations were assayed for the presence of endotoxin using Thermo Scientific Pierce LAL Chromogenic Endotoxin Quantitation (Fisher Scientific PI88282). Neither the pristine nanomaterials nor the commercial slurries contained endotoxin. All results are reported as the mean ± SEM of three independent measurements.

2.2. Scanning electron microscopy

Nanoparticles were diluted to a concentration of 0.1% w/v in water and RPMI containing fetal bovine serum. After removing the top layer *via* the scotch tape method, 5 μl of each sample was placed onto a highly ordered pyrolytic graphite stub. Samples imaged using InLens detector of LEO 1550 SEM at 5 kV and a working distance of 5 nm.

2.3. Cell culture and treatment

Mouse alveolar macrophage cells (ATCC® CRL-2019), MH-S cells, were cultured in RPMI (Sigma) supplemented with 10% fetal bovine serum (Fisher) in a 37 °C humidified incubator maintained with 5% CO_2. Prior to treatment, 1×10^6 MH-S cells were plated in 6-well plates and incubated for 24 h at 37 °C. Cells were treated with indicated doses of nanoparticles or slurry and incubated for

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