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Review Article

Cellular pathways involved in silica nanoparticles induced apoptosis: A systematic review of *in vitro* studies

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ABSTRACT

Silica nanoparticles (SiNPs) have been found to pass through biological barriers and get distributed in the human body. They induce cell apoptosis via various mechanisms in body organs. To understand these mechanisms, we carried out systematic review of *in vitro* studies on SiNPs-induced cell apoptosis. Office of Health Assessment and Translation approach for Systematic Review and Evidence Integration was used to identify 14 studies dating from the year 2000 to current. Four studies showed an increase in DNA damage, cell cycle arrest, proapoptotic factors and decrease in antiapoptotic factors resulting to apoptosis. Eight studies showed induction of mitochondrial dysfunction, Bax upregulation, Bcl-2 downregulation, and caspase-3, −7, −9 activities increase. Increase in FADD, TNFR1 and Bid proteins was observed in one study, while the other NO production and caspase-3 activity was increased. These studies found the potency of SiNPs to induce cell apoptosis through DNA damage, mitochondrial, tumor necrosis factor, and nitric oxide related pathways.

1. Background

Nanomaterials (NMs), particles with less than 100 nm diameter, are rapidly applied in technical and medicinal fields due to their unique physiochemical properties and tunable characteristics. One of the most important members NMs is silica nanoparticles (SiNPs), which have extensive applications in biomedical and biotechnological fields, such as drug carrier, gene therapy, and molecular imaging (Tan et al., 2004; Luo et al., 2004; Lu et al., 2007). This is because of their unique properties, such as ease of synthesis, relatively low cost, and availability of sites for surface modifications (Barik et al., 2008; Fadeel and Garcia-Bennett, 2010). Thus, possible health impact of SiNPs upon introduction into the body is of great concern.

SiNPs have been found to enter the human body via inhalation, ingestion, dermal contact and injection, and distribute in nearly all organs through blood stream (Fruijtier-Pölloth, 2012; Xie et al., 2010; Nishimori et al., 2009). They induce cell death resulting to tissue dysfunction and organ injuries (Yu et al., 2013). Numerous in vitro studies have investigated cytotoxicity that leads to cell death in different cell lines after SiNPs exposure (Napierska et al., 2009; Bauer et al., 2011; Ahamed, 2013). Cell death may occur by two distinct mechanisms; apoptosis or necrosis. SiNPs have been reported to induce cell apoptosis in several human cell lines (Ahamed, 2013; Lankoff et al., 2013; Yang et al., 2014).

Apoptosis is an active and physiological mode of cell death with characteristics such as cell shrinkage, chromatin condensation, DNA fragmentation, plasma membrane blebbing, and formation of apoptotic bodies (Chen et al., 2005). It is considered a vital component of various processes in the cell including chemical-induced cell death (Elmore, 2007). There are two main apoptotic pathways: the extrinsic or death receptor pathway and the intrinsic or mitochondrial pathway.

The extrinsic pathways involve expression of Fas or TNF receptors that can lead to apoptosis via ligand binding and protein cross-linking. The receptors FasR and TNFR1 play critical role in transmitting the death signal from the cell surface to the intracellular signaling pathways (Elmore, 2007). Fas ligand (FasL) binds to its receptor that leads to the formation of a death-inducing complex by recruiting the adaptor molecule, Fas-associated death domain (FADD) and procaspase-8, while binding of TNF ligand to TNF receptor results in the binding of the adapter protein TRADD with recruitment of FADD and RIP. FADD associate with procapase-8 resulting to activation of procaspase-8 to caspase-8 which is required for cell death (Chen et al., 2005; Elmore, 2007).

The intrinsic pathways involve stimuli that produce intracellular signals acting directly on targets within the cell and are mitochondrial-initiated events (Elmore, 2007). The stimuli cause changes in the inner mitochondrial membrane resulting to opening of the mitochondrial permeability transition (MPT) pore, loss of the mitochondrial

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transmembrane potential and release of cytochrome c into the cytosol (Saelens et al., 2004). The release of cytochrome C to cytosol triggers the downstream caspases and induces the intrinsic apoptosis. So mitochondria have the ability to control the intrinsic apoptosis pathway through either cytochrome C, calcium, morphology changes (fission/fusion) or some membrane proteins expression imbalance (Bcl-2) (Hongmei, 2012). The extrisic and intrinsic apoptosis pathways converge at the activation of caspase-3, which, in turn, induced downstream caspases leading to apoptosis. Between these two pathways a crosstalk is offered by Bid (a proapoptotic protein) (Chen et al., 2005).

Therefore, it is important to have a comprehensive understanding of various mechanisms involved in SiNP induced apoptosis. Thus, this systematic review summarizes the apoptosis signal pathways and some ligands involved in SiNPs induced apoptosis, and provides the current evidences of SiNPs induced apoptosis mechanisms.

2. Methodology

2.1. Literature search and review

We performed a comprehensive literature search in order to identify studies describing mechanism of SiNPs induced cell apoptosis based on Office of Health Assessment and Translation (OHAT) approach for systematic review and evidence integration (DHHS, January 9, 2015). We searched all the articles published and indexed from the year 2000 to date. Electronic searches were performed in Web of Science (https://webofknowledge.com/), PubMed (http://www.ncbi.nlm.nih.gov/pubmed), EMBASE (https://www.embase.com/login) and CNKI (http://www.cnki.com.cn) using search strategy ((Cytotoxicity and SiNPs) or (Apoptosis and SiNPs) or (SiNPs and DNA or Mitochondrial damage)). Our search flow diagram is summarized in Fig. 1. For inclusion, the studies had to be primary literature and assess any *in vitro* SiO_2NP induced cell apoptosis. We excluded the duplicated articles, meeting abstracts and reviews without specific data. Two independent reviewers (M.A.A. and S.A) screened all titles and abstracts for relevancy, using Distiller SR® software (Evidence Partners), and resolved any conflicts or discrepancies. Data from the studies were extracted, and were cross-checked by the two reviewers. For assessing the quality of the studies, we used guideline for assessing quality of *in vitro* studies as described by Samuel et al. (2016), since OHAT protocol could only assess quality of *in vivo* and observational studies only. Briefly, quality in study methodology was assessed by answering 11 questions. The questions covered scientific background description; study purpose and objective; study model justification; study design description; experimental outcome description; cell maintenance condition; measurement of precision and variability description; dose/concentration response consideration; result interpretation and discussion; research funding. Studies were rated on percentage based on the 11 questions, the study was considered of good quality if it had above 80% rating.

3. Results

3.1. Search results and characteristics of SiNPs induced cell apoptosis studies

Out of 584 studies identified by our search, 14 met the inclusion criteria as shown in Fig. 1. The studies had good quality rating as shown in Appendix A. Human HepG2 hepatoma cells, human vascular endothelial (HUVECs) cells, human L-02 hepatic cells, human epidermal keratinocyte (HaCaT) cells, human lung epithelial (A549) cells, Human skin epithelial (A431) cells, human normal liver (HL-7702) cells, rat normal liver (BRL) cells and mouse leukaemic monocyte macrophage (RAW 264. 7) cells were used for the experiments. Most (69.2%) studies had 24 h SiNP exposure time, the particle concentration ranged from 2.5 to 1000 μg/mL and the size varied from 6 nm to 86 nm. The apoptotic rate was detected by the FITC-annexin binding and DNA fragments (Table 1).

3.2. Mechanisms of SiNPs induced cell apoptosis

Fifteen experiments from 14 articles about mechanisms of cell apoptosis induced by SiNPs are listed in Tables 2–5. There were four apoptotic pathways, namely DNA damage related pathway, mitochondrial apoptotic pathway, death receptor mediated pathway, and nitric oxide related pathway.

3.2.1. DNA damage related pathway

All the 4 studies were included as shown in Table 2. SiNPs induced cell

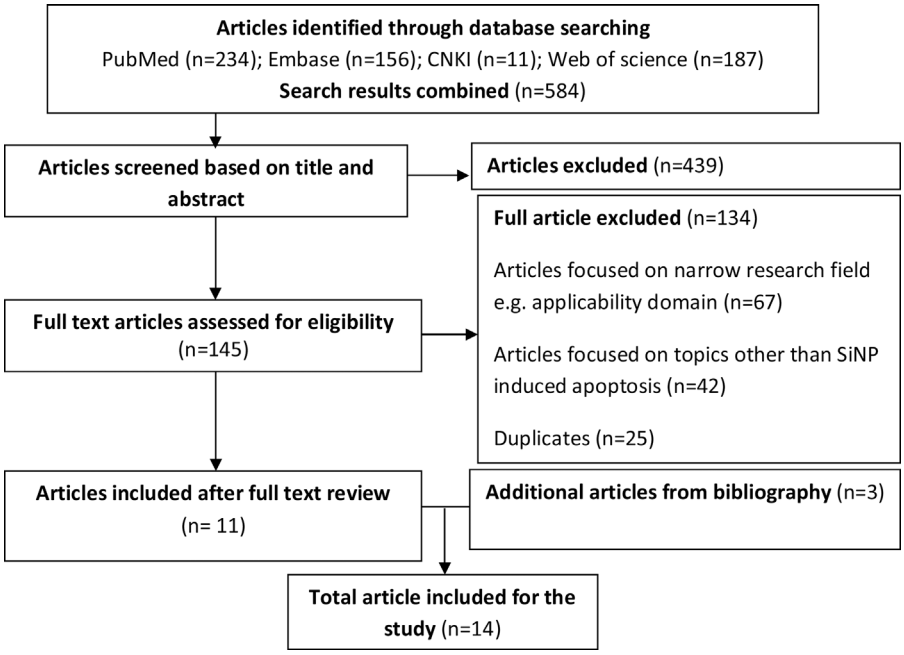

Fig. 1. Flow chart of studies included.