Molecular toxicity mechanism of nanosilver

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Abstract
Silver is an ancient antibiotic that has found many new uses due to its unique properties on the nanoscale. Due to its presence in many consumer products, the toxicity of nanosilver has become a hot topic. This review summarizes recent advances, particularly the molecular mechanism of nanosilver toxicity. The surface of nanosilver can easily be oxidized by O₂ and other molecules in the environmental and biological systems leading to the release of Ag⁺, a known toxic ion. Therefore, nanosilver toxicity is closely related to the release of Ag⁺. In fact, it is difficult to determine what portion of the toxicity is from the nano-form and what is from the ionic form. The surface oxidation rate is closely related to the nanosilver surface coating, coexisting molecules, especially thiol-containing compounds, lighting conditions, and the interaction of nanosilver with nucleic acids, lipid molecules, and proteins in a biological system. Nanosilver has been shown to penetrate the cell and become internalized. Thus, nanosilver often acts as a source of Ag⁺ inside the cell.

One of the main mechanisms of toxicity is that it causes oxidative stress through the generation of reactive oxygen species and causes damage to cellular components including DNA damage, activation of antioxidant enzymes, depletion of antioxidant molecules (e.g., glutathione), binding and disabling of proteins, and damage to the cell membrane. Several major questions remain to be answered: (1) the toxic contribution from the ionic form versus the nano-form; (2) key enzymes and signaling pathways responsible for the toxicity; and (3) effect of coexisting molecules on the toxicity and its relationship to surface coating.

1. Introduction
Colloidal silver, silver nanoparticles, and nanosilver are some of the names used for silver particles of 1–100 nm in at least one of the dimensions. For convenience, we will use the expression “nanosilver” throughout this paper for silver nanoparticles of different shapes, sizes, and surface coatings. Having been used as an antibiotic since ancient times, silver has found many more applications in medicine, optics, sensing, painting, and cosmetics, due to the discovery of its many properties in the nanometer-sized form [1–4]. As of today, the Project on Emerging Nanotechnologies at the Woodrow Wilson International Center for Scholars has found a list of more than 400 consumer products that claim to contain nanosilver [5]. Given the increasing use in commercial products, the potential for the release of nanosilver into the environment and its effects on environmental health are of increasing concern [3,6–14].

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One of the most widely known lesions caused by nanosilver is argyria, although the mechanism causing the lesion is still unknown [1,3,10,14–16]. People applying nanosilver developed bluish-colored skin. Other studies have widely investigated toxicities such as oxidative damage in cellular systems [17–26]. In the past 10 years, particularly the past 3 years, a great number of articles have been published in an attempt to understand various aspects of the toxicity of nanosilver. Several reviews have also dealt with the exposure, environmental fate, and in vivo and in vitro toxicities [1,3,9,10,13,14,16,27–29]. Nanosilver undergoes a variety of transformations in environmental and biological media [1,3,6–14,24,27,28,30–53]. The environmental fate, state of agglomeration or aggregation, and dissolution in environmental and biological media are dependent on how nanosilver is prepared, what types of surface coating are used, and the conditions under which they are used. As a result, environmental fate is highly variable within a range of surface functionalizations that can make the same material biocompatible or biohazardous. Also, a wide variety of test systems using bacteria, cells, aquatic species, or rodents have been used to test the toxicity of nanosilver.

This review does not intend to provide details about the toxicity of silver nanomaterials, but will summarize some of the more recent findings and raise questions for future research on what is important for the understanding of the molecular toxicity mechanism of nanosilver.

2. Behavior of nanosilver in biological and environmental media

The main changes that nanosilver undergoes in environmental and biological media are as follows. (1) Losing and displacing of the surface-coating agent. Nanosilver surface-coating agents, such as citric acid, amino acids, cetyl trimethylammonium bromide, and sodium dodecyl sulfate, are noncovalently attached to nanosilver particles, with some being more tightly bound than others. These surface-attached coating agents are in an equilibrium state with the free ligand molecules in solution. Dispersion of nanosilver in a biological or environmental medium will cause the surface-coating agents to re-establish equilibrium by mostly losing some of the coating molecules. Some will be displaced by other available molecules such as biological macromolecules, inorganic and organic ions, or the nanosilver particles become partially uncoated due to the lack of proper coating agents present. As a result, nanosilver becomes unstable in these media. (2) Aggregation and agglomeration. Due to displacement of the coating agents by other molecules such as water or inorganic ions, nanosilver may no longer be stable by itself, but undergo aggregation. This has been observed and reported in many publications [12,20,31,32,36,43,54]. (3) Surface oxidation and release of Ag⁺. Silver atoms (Ag⁰) on the surface of nanosilver, when interacting with molecular oxygen, can be oxidized to silver oxide [9,12,26,30,35,37,52,54–60]. It may also interact with other redox-active compounds to yield ionic silver. The silver oxide can interact with the media to release Ag⁺. The oxidation to silver oxide and release of silver ions can occur in the environmental media, biological media, as well as inside the cell. Thus, nanosilver, whether as individual particles or as agglomerates/aggregates, can also be viewed as a source of Ag⁺ through the slow-release process. These phenomena are summarized in Fig. 1.

Levard et al [7] have recently reviewed the environmental fate and transformation of nanosilver. They have proposed a mechanism for the transformation of nanosilver in the environment (Fig. 2). Other studies have also pointed out that the transformation of nanosilver in environmental and biological media is strongly influenced by the concentration of sulfur ions (S²⁻ and SH⁻) and sulfur-containing compounds, dissolved oxygen, Cl⁻, biological macromolecules (DNA and protein), other organic compounds that have strong affinity for either atomic or ionic silver, and lighting conditions [6–8,10,33,38,52,54,61–66]. Among SO₄²⁻, S²⁻, PO₄³⁻, and EDTA, sulfide ligands are the most effective to reduce nanosilver toxicity by formation of Ag₂S. Liu et al [64] have found that nanosilver forms Ag₂S by reacting with dissolved sulfide species (H₂S, HS⁻) under relevant, but controlled laboratory conditions. The reaction kinetics and mechanism are dependent on dissolved oxygen, pH, lighting conditions, other organic matters, as well as the high or low concentrations of sulfide. Exposure to light can also alter the toxicity of nanosilver, presumably by light-induced transformation of nanosilver [32,68].

3. Mechanism of toxicity

The toxicity of nanosilver is closely related to its transformation in biological and environmental media, including surface oxidation, release of silver ions, and interaction with biological macromolecules [3,9,10,13,14,27,28]. There is always a challenge to distinguish precisely what portion of the toxicity is from the ionic form and what portion is from the nano-form of silver [26,57,69,70]. AshaRani et al [71,72] have
studied the antiproliferative activity of nanosilver and proposed a mechanism of toxicity (Fig. 3). Nanosilver particles can interact with membrane proteins and activate signaling pathways, leading to inhibition of cell proliferation [23,73,74]. The nanosilver particles can also enter the cell through diffusion or endocytosis to cause mitochondrial dysfunction, generation of reactive oxygen species (ROS), leading to damage to proteins and nucleic acids inside the cell, and finally...
inhibition of cell proliferation [19,20,23,24,54,75–82]. Oxidative stress occurs when the generation of ROS exceeds the capacity of the cellular antioxidant defense system. Depletion of glutathione and protein-bound sulphydryl groups and changes in the activity of various antioxidant enzymes have been implicated in oxidative damage [17,19,20,24,82–85]. An important toxicity mechanism for nanosilver is the interaction of both the ionic and nano-form of silver with sulfur-containing macromolecules such as proteins, due to the strong affinity of silver for sulfur [38,55,62,64,67,71,86–93].

Mitochondria appear to be the sensitive targets for nanosilver. Bressan et al [76] have studied the interaction of nanosilver with human dermal fibroblasts. They have found that nanosilver particles accumulate outside the mitochondria, cause direct mitochondrial damage, and disturb the function of the respiratory chain, resulting in ROS generation and oxidative stress. AshaRani et al [94] have suggested that the disruption of the mitochondrial respiratory chain by nanosilver increases ROS production and interruption of ATP synthesis, thus leading to DNA damage. Hsin et al [88] have studied the toxicity mechanism of nanosilver in NIH3T3 fibroblasts. They have found that treatment with nanosilver induces the release of cytochrome c into the cytosol and translocation of Bax to the mitochondria, indicating that nanosilver acts through ROS and C-Jun N-terminal kinase to induce apoptosis via the mitochondrial pathway. Interaction of nanosilver with DNA also leads to cell cycle arrest at the G2/M phase. Park et al [87] have found that nanosilver induces G1 arrest and completely blocks the S phase, therefore inducing apoptosis.

4. Interaction and damage to cell membranes

Nanosilver can interact with cellular membranes and cause toxicity. In particular, nanosilver can interact with bacterial membranes and this is considered to be the main mechanism for the antimicrobial effect of nanosilver [16,34,36,95–97]. Khan et al [95,96] have studied the interaction of nanosilver with five types of bacteria. They have found that the adsorption of nanosilver on the bacterial surface, or interaction with extracellular proteins, is dependent on pH, ζ potential, and NaCl concentration. El Badawy et al [34] have found that surface charge is the most important factor for nanosilver–bacteria interaction. Joshi et al [36] have demonstrated that production of the extracellular polymeric substance, colanic acid by Escherichia coli, protects the bacteria against nanosilver toxicity. Wigginton et al [92] have found that the binding of nanosilver to bacterial proteins inhibits enzyme activities, and the binding is dependent on surface modifications. Grigor’Eva et al [98] have found that nanosilver particles are adsorbed on the outer membrane of Gram-negative Salmonella typhimurium and the cell wall of Gram-positive Staphylococcus aureus, and penetrate and accumulate in cells without aggregation and damage of neighboring cytoplasm. In S. aureus, nanosilver binds to DNA fibers. Cell responses to nanosilver differ morphologically in S. typhimurium and S. aureus, and mainly are presented by damage of cell structures. It is evident that nanosilver directly interacts with macromolecular structures of living cells and exerts an active influence on their metabolism.

Nanosilver interaction with mammalian cells in vitro may cause membrane damage including altering membrane permeability. Cheng et al [83] have found that nanosilver disrupts cell membranes and causes apoptosis through oxidative damage. The damage in fibroblast membranes allows calcium influx and induces intracellular calcium overload, and further causes ROS overproduction and mitochondrial membrane potential variation [83]. Baruwati et al [18] have studied “green” synthesized nanosilver and found that exposure to these particles alters the membrane permeability of barrier cells (intestinal and brain endothelial) and stimulates oxidative stress pathways in neurons. George et al [35] have found cell membrane lysis in RT-W1 cells, as well as red blood cells, upon exposure to nanosilver. Chairungkitti et al [78] have found that nanosilver (< 100 nm) causes ROS formation in A549 cells, and reduces cell viability and mitochondrial membrane potential.

5. Cellular uptake

Nanosilver can be taken up by many different cells and become internalized [19,20,28,43,45,79,84,99–102]. Lu et al [99] have reported that nanosilver uptake by human skin keratinocytes is dependent on the size and shape of the nanoparticles and incubation time. Both spherical and rod-formed nanosilver can penetrate the cell and the cellular uptake is dependent on incubation time (Fig. 4). Recent studies conducted by Kruszewski et al [28,103] have investigated the influence of nanosilver on three mammalian cell lines: human hepatocellular liver carcinoma (HepG2), human lung carcinoma (A549), and human colorectal adenocarcinoma (HT-29). All cells were treated with 20-nm or 200-nm nanosilver for 2 hours or 24 hours at 10 μg/mL, 50 μg/mL, and 100 μg/mL, respectively. It has been revealed that nanosilver uptake corresponds to the formation of ROS. Nanosilver uptake in HT29 is lower than in A540 and HepG2 cells, indicating increased ROS production in cells with higher nanosilver uptake. This group believes that possible production of mucin by HT29 cells might prevent the nanosilver uptake.

In experiments conducted by Monteiro-Riviere et al [104], human epidermal keratinocytes (HEKs) were used to study uptake of nanosilver and silica-coated nanosilver complexed to albumin, immunoglobulin G (IgG), and transferrin human serum proteins. Uptake of nanosilver in HEKs was < 4.1% of the applied dose. The presence of proteins suppressed citrate, but not silica-coated nanosilver uptake. Exposure to IgG reduced 110-nm citrate nanosilver uptake. In contrast, the greatest uptake of 20-nm silica nanosilver was seen with IgG, whereas 110-nm-silica-coated nanosilver was seen with IgG.
based cloud point extraction method to quantify nanosilver versus Ag⁺ uptake in HepG2 cells. They found that ~10.3% of the silver taken up by the cells was in ionic form. Miao et al [84] have reported that nanosilver can be taken up by the freshwater alga *Ochromonas danica*, and they have suggested that the internalization of nanosilver is an alternative mechanism of toxicity in algae. Meyer et al [43] have observed that nanosilver can be taken up by *Caenorhabditis elegans*, and the resulting toxicity due to exposure to nanosilver is from both the internalized nanosilver particles and the ionic silver formed outside the organism. Choi and Hu [79] have found that the smaller 5-nm nanosilver is more toxic to the nitrifying bacteria than the larger particles. They have suggested that the observed toxicity is due to easy penetration and internalization of the smaller nanoparticles.

6. ROS production and cytotoxicity

Cytotoxicity of nanosilver is closely related to cellular uptake, production of ROS, and triggering of the cellular antioxidant mechanisms [17–26,28,35,42,43,45,82–85,100–103,105,106]. Most of these studies used mammalian cells in culture [19,83,85,103,106], but some used aquatic species [24,25,35,42] and organisms [20–23,26,43,45]. One in vivo study by Ahmadi et al [82] using chickens exposed to nanosilver found that nanosilver has significant effect on the activity of oxidative stress enzymes.

In vitro studies with various primary cells and cell lines are the most used methods. Arora et al [107] have studied the toxicity of nanosilver in primary fibroblast and liver cells, and found that nanosilver is present in the mitochondria and triggers the antioxidant mechanisms. Braydich-Stolle et al [73] used mouse stem cells and found that smaller nanosilver particles are more likely to produce ROS and cause apoptosis. Trickler et al [108] have found that the cytotoxicity of polyvinylpyrrolidone (PVP)-coated nanosilver in rat brain cells is size- and shape-dependent and causes proinflammatory effects. Hussain et al [105] have evaluated in vitro toxicity of several nanoparticles, including nanosilver (15 nm and 100 nm) in a rat liver-derived cell line (BRL 3A). Following 24 hours of incubation after exposure, the mitochondrial
function and membrane integrity (measured as lactate dehydrogenase leakage) were significantly decreased at 5 mg/mL and 10 mg/mL. Lactate dehydrogenase leakage was dose-dependent and more severe with the 100-nm than with the 15-nm nanosilver. Several publications suggest that a strong correlation between ROS levels and mitochondria damage exists [14,19,20,54,69,78,109,110].

7. Interaction with and damage to cellular proteins

It is well known that silver, both nanosilver and Ag⁺, can interact with proteins and amino acids. Amino acids like cysteine have been widely used as surface-coating agents for nanosilver [35,78]. The interaction of nanosilver with proteins is believed to be an important mechanism of toxicity for nanosilver [9,19,23,24,29,50,78,86,90–92,96,106,110–121]. As proposed by Saptarshi et al [118], nanosilver can cause the formation of protein corona, protein unfolding, and altered protein function (Fig. 5).

Shannahan et al [119] have investigated the formation of protein corona by incubating Dulbecco’s Modified Eagle’s Medium supplemented with 10% fetal bovine serum and 20 nm or 110 nm citrate and PVP stabilized nanosilver for 24 hours. They found that albumin, apolipoproteins, keratins, and other serum proteins interacted with nanosilver. Citrate- and PVP-stabilized larger nanosilver (110 nm) showed greater binding ability to proteins compared to smaller nanoparticles, suggesting changes in nanoparticle size cause different protein corona formation. Corona formation found on 20 nm nanosilver implies binding of more hydrophobic proteins compared to larger 110 nm particles.

Interaction of nanosilver with protein molecules such as serum albumin [91,113], human blood protein hemoglobin (Hb) [65], and cytoskeletal proteins [121] has been studied using spectroscopic methods. All these proteins interact with nanosilver and, as a result, cause protein conformational changes or even protein damage. The interaction with protein is concentration dependent [86]. Nanosilver interaction with human serum albumin induces conformational changes [113]. The percent of α helices is reduced, whereas the percent of β sheets is increased in the human serum albumin secondary structures. This is possibly due to breaking of the hydrogen bonds between neighboring α helices and formation of sterically less-ordered hydrogen bonds between the α helices and the citrate-coated nanosilver. Due to the binding with bovine serum albumin (BSA), the effectiveness of nanosilver as an antimicrobial agent decreases [114]. Mahato et al [65] have reported findings on the interaction of nanosilver with hemoglobin (Hb). A time- and concentration-dependent nanosilver interaction with Hb has been observed. Nanosilver can bind and approach the heme, tryptophan, amide, and aromatic amine residues in the protein. As a result, Hb undergoes conformational changes and becomes unfolded by increasing the β-sheet structure. The nanosilver–Hb forms a charge-transfer complex in which the Hb heme, along with the nanosilver involved in the electron transfer mechanism, forms the Hb–nanosilver assembled structure. The electron transfer mechanism is dependent on the size of the silver particles. Da Silva Paula et al [122] have found that nanosilver in vitro inhibits creatine kinase from the brain and skeletal

![Fig. 5 – Schematic representation of nanoparticle surface induced unfolding of the interacting protein molecule and consequences. Note. From “Interaction of nanoparticles with proteins: relation to bio-reactivity of the nanoparticle,” by S.R. Saptarshi, L. Duschl, and A.L. Lopata, 2013, J Nanobiotec, 11, p. 26. Copyright 2013, BMC Central. Reproduced with permission.](image-url)
muscle cells, but not from heart cells. They have suggested that nanosilver inhibits this enzyme through interactions with thiol groups.

Mariam et al. [123] studied the interaction between nanosilver and BSA at physiological pH in an aqueous solution. Fluorescence spectroscopy was used because BSA has two fluorescent tryptophan residues. It showed that nanosilver had a strong ability to quench the intrinsic fluorescence of BSA by both static and dynamic quenching mechanisms. This indicates a complex formation between BSA and nanosilver and that spontaneous binding of BSA with nanosilver changes the microenvironment of the tryptophan residues in BSA.

Binding of nanosilver with bacterial proteins has also been studied. Wigginton et al. [92] have reported that binding of nanosilver to bacterial proteins is dependent upon surface modifications of nanosilver, and the nanosilver binding to the bacterial protein inhibits the enzymatic activity. Nanosilver interacts with the extracellular bacterial proteins following pseudo-second order kinetics [96]. Joshi et al. [36] have demonstrated that production of the extracellular polymeric substance, colanic acid by engineered E. coli protects the bacteria against silver nanoparticle toxicity.

8. Binding and damage to cellular DNA and DNA repair

Nanosilver is known to interact with DNA and cause DNA damage. Rahban et al. [124] have studied the interaction of nanosilver with calf thymus DNA and found that nanosilver can tightly bind DNA and alter DNA conformation. Recent in vitro studies have investigated the ability of nanosilver to induce DNA damage [125,126]. In the study by Hackenberg et al. [126], human mesenchymal stem cells were used to investigate DNA damage potential. Nanosilver was found to induce significant time-dependent DNA damage following short exposure and incubation of 24 hours. They concluded that, direct interaction of nanosilver may be an inducer of genotoxicity. Inflammatory cells (neutrophils and macrophages) exposed to nanoparticles elicit inflammation by forming ROS that generate oxidative DNA damage [76,127,128]. Molecular damage in normal lung fibroblasts (U251) and brain cancer glioblastoma (IMR-90) cells has been examined. Nanosilver binds to cytosolic proteins causing a corona and expresses genes involved in DNA damage. Increased ataxia telangiectasia mutated (ATM) and ATM-related levels in fibroblast cells indicate DNA double-strand breakage [129]. Piao et al. [85,117] have conducted a comparative study with nanosilver and AgNO3 in human Chang liver cells. They have found that nanosilver induces ROS generation, suppresses reduced glutathione, and causes DNA damage, protein carbonylation, and membrane oxidation.

The main damage is the increased level of 8-oxoguanine (Fig. 6). Similar results have been noted in a comparative study of nanosilver and Ag+ on immortalized human T lymphocyte cells [130]. Jurkat T cells are highly sensitive to nanosilver in that they promptly increase levels of ROS during initial exposure. When compared to Ag+, nanosilver causes an increase in ROS formation after 24 hours, suggesting a slow release of silver ions to cause oxidative stress. Confirmation of oxidative stress was revealed by DNA damage signaling pathways, p39 mitogen-activated protein kinase, nuclear factor-E2-related factor-2, and nuclear factor-κB.

ROS are able to induce oxidative DNA damage and activate a wide variety of cellular events, therefore, our group has used both a direct DNA damage (alkaline comet assay) and an oxidative DNA damage (formamidopyrimidine glycosylase FPG – comet assay) method to study DNA damage and repair (Fig. 7). Time-dependent DNA repair in human cells damaged by nanosilver has not been reported. As shown in Fig. 7, both time- and concentration-dependent DNA damage were observed.

By exposing immortalized human keratinocyte cells (HaCaT) to 10μM or 50μM nanosilver (in Ag atoms) and with incubation times of 30 minutes, 4 hours, 8 hours, and 24 hours, a time-dependent increase of direct and oxidative DNA damages is observed (Fig. 7). The direct DNA damage increases and reaches a maximum at 8 hours of incubation followed by a
decrease at 24 hours incubation. However, the decrease did not reach the level of the controls (Fig. 7A). For oxidative DNA damage, it also increases and reaches a maximum at 8 hours, but decreases to the control level at 24 hours (Fig. 7B). We believe that complete DNA repair is not achievable for the direct damage because it is known that nanosilver can be internalized in the cell and slowly release Ag⁺, which can cause direct DNA damage [99,131]. This result is different from the DNA damage and repair results when the same cell is exposed to multiwalled carbon nanotubes (MWCNTs) as reported by the authors. We found that functionalized MWCNTs cause increased DNA damage of HaCaT cells at up to 4 hours (compared to 8 hours for nanosilver) [132]. Furthermore, the damaged DNA can be fully repaired after 24 hours incubation. This means that although both MWCNTs and nanosilver cause DNA damage and the damage can be repaired by the cellular repair system, the nanosilver-induced direct damage cannot be fully repaired due to the slow release of silver ions while inside the cells.

9. Outlook

As a result of the increased use of nanosilver in consumer products, the number of research articles on silver has been exponentially increasing. On the toxicity of nanosilver alone, there have been > 550 publications related to silver nanoparticle toxicity in 2011–2013, based on a search from Scopus.com (December 15, 2013) using silver nanoparticle toxicity. However, several key questions remain to be answered on the toxicity mechanism of nanosilver. (1) Toxicity contribution from the ionic form versus the nano-form of silver. Due to surface oxidation, other surface reactions, and dissolution of nanosilver in a biological or environmental medium, silver ions are slowly released. It must be considered that both contribute to the toxicity observed. It is also important to consider some secondary products of nanosilver, such as particles bound to protein and DNA, for their contribution to toxicity. (2) The interaction of nanosilver with protein, nucleic acid, and cell membrane all contributes to the toxicity of nanosilver. However, which one is the primary biological macromolecule that is involved in the toxicity of nanosilver? What are the key enzymes or signaling pathways that are involved? (3) Contribution to toxicity by coexisting molecules. In the biological and environmental systems, there are many coexisting molecules: inorganic ions, organic molecules, and biological macromolecules. What are their contributions to the toxicity of nanosilver? How does it relate to the surface coating materials used for nanosilver?

Fig. 7 – Direct (A) and oxidative (B) DNA damage and repair of HaCaT cells exposed to nanosilver after 30 minutes, 4 hours, 8 hours, and 24 hours of incubation.

Conflicts of interest

All authors declare no conflicts of interest.

Acknowledgments

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