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Review Article

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 O_2 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 (Ag^0) 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 (S^{2-} 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 SO_4^{2-}, S^{2-}, Cl^-, PO_4^{3-}, and EDTA, sulfide ligands are the most effective to reduce nanosilver toxicity by formation of Ag_xS_y [67]. Liu et al [64] have found that nanosilver forms Ag_2S by reacting with dissolved sulfide species (H_2S, 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

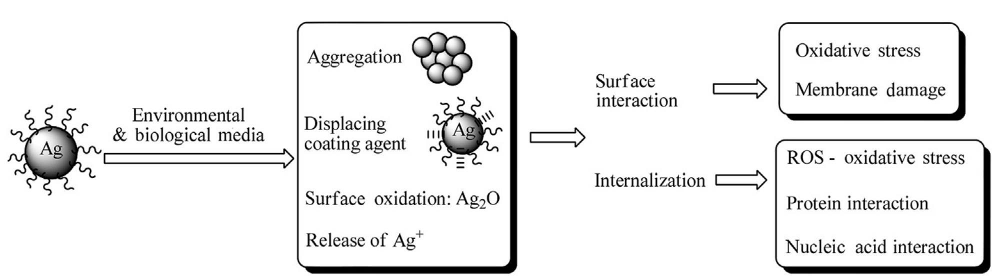

Fig. 1 – Fate and toxicity of nanosilver in biological and environmental media.