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Historical perspective

Perturbation of cellular mechanistic system by silver nanoparticle toxicity: Cytotoxic, genotoxic and epigenetic potentials

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ABSTRACT

Currently the applications of silver nanoparticles (Ag NPs) are gaining overwhelming response due to the advancement of nanotechnology. However, only limited information is available with regard to their toxicity mechanism in different species. It is very essential to understand the complete molecular mechanism to explore the functional and long term applications of Ag NPs. Ag NPs could be toxic at cellular, subcellular, biomolecular, and epigenetic levels. Toxicity effects induced by Ag NPs have been evaluated using numerous in vitro and in vivo models, but still there are contradictions in interpretations due to disparity in methodology, test endpoints and several other model parameters which needs to be considered. Thus, this review article focuses on the progressive elucidation of molecular mechanism of toxicity induced by Ag NPs in various in vitro and in vivo models. Apart from these, this review also highlights the various ignored factors which are to be considered during toxicity studies.

Contents

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1. Introduction

Nanotechnology has become a major scientific endeavor in the last decade and researchers world-wide are continuing to discover unique properties and applications of nanomaterials [1]. The benefits of nanomaterials are widely publicized and they have already found their commercial applications in various day-to-day products [2]. Nevertheless, the same properties which make nanoparticles (NPs) so attractive for their use in new products have also led to concerns that NPs may raise the risk for humans and environment [3]. Among the metal NPs, it is estimated that Ag NPs have the highest degree of commercialization due to its well known antimicrobial and anticancer properties [4–11]. Despite the fact that several antibiotics are prevalent, Ag NPs possess unique antibacterial properties, including bacteriostatic and bactericidal effects against different species of bacteria [12]. Ag NPs also have the advantage of being potent against multi-drug resistance (MDR) strains such as methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa* [13,14], ampicillin-resistant *Escherichia coli O157:H7* and erythromycin-resistant *staphylococcus pyogenes* (*S.pyogenes*) [15] where conventional antibiotics fail [16,17]. Due to its high antibacterial activity, Ag NPs have been widely used in various applications, such as water purification [18], food packaging [19], and in sunscreen cream and other cosmetic items [www.nanotechproject.org]. Hence the chances of exposure to the human body and the environment have also increased manifold. NPs have an innate capacity of toxicity by being smaller in size when compared to its parent bulk material [20]. It has been reported that sustained introduction of silver may get accumulated in the body in the form of argyrial depots (irreversible discolorations of eyes or skin) [21,22]. The fact that NPs can easily enter the human body and can accumulate in the environment has engrossed government sectors to form the fulcrum of support for research in "nanotoxicology". The Society of Toxicology addresses toxicology as "the study of the adverse effects of chemical, physical and biological agents on people, animals and the environment" (http://www.toxicology.org/index.asp). Several government bodies, such as the U.S. Environmental Protection Agency (USEPA) acknowledge the need for the risk assessment processes to potentiate the health and environment impacts of manufactured nanomaterials. The National Nanotechnology Initiative (NNI) has laid down the methods for toxicity evaluation of nanomaterials for health and environment [23,24]. The recent concern for nano-safety has drawn the attention of the eminent scientific community throughout the world, for example, the Nature Nanotechnology journal has started an initiative for discussion on this important subject of nanotoxicology (www.nature.com/nnano/focus/nanotoxicology). Nevertheless efforts are being made to explore the toxicity of these NPs, which is still vague and needs to be annotated [25,26,4].

2. Molecular mechanisms of toxicity of Ag NPs against microbes

Noticeably Ag NPs have received extensive consideration owing to their tenacious toxic potential against microbial cells, i.e., antimicrobial activity [27,28] including antibacterial as in Fig. 1 [29–31], antifungal [32,33] and antiviral [34,35] properties. Despite the fact that the exact antimicrobial mechanisms of Ag NPs are still anonymous, the conceivable mechanisms of Ag NPs have been prompted by assorted investigations intimated in Box 1 and also schematically represented in Fig. 2.

To understand whether the toxic effects of Ag NPs against bacterial cells are due to either Ag^+ ions or Ag NPs remained an enigma. However various reports have come up with certain conclusions. Some reports suggest that both Ag NPs and Ag^+ ions are effective against a broad-spectrum of microorganisms including antibiotic resistant bacteria [45]. Detailed analysis of literature shows conflicting interpretations of efficacy of the same NPs against several bacterial cells [46]. Hence it was conveyed that these differences might be inferred as distinct capacity of particular bacterial cells for the same particles or variation in bacterial cell membrane [47]. In the recent past, it was reported that the antibacterial effect of Ag NPs was solely due to Ag^+ release and not due to Ag NPs directly, thus Ag^+ ion is a definitive molecular toxicant [48].

2.1. Collective effect

Ag NPs possess therapeutic advantage over conventional and narrow targeting antibiotics, due to a rare chance for microbes to develop resistance against it [49]. Nevertheless, the collective effect of Ag NPs when incorporated with other antibacterial drugs promises enhanced bactericidal effects [50]. The apparent enhancement in activity could be the combined result of their differential mechanisms of inhibition [50]. The synergistic effects of Ag NPs have been proclaimed with many drugs [51]. Synergistic enhancement of the antibacterial effect of chitosan–Ag NP composite against *S. aureus* had been investigated in [52]. Another research group found that when ciprofloxacin, a broad-spectrum antibiotic (effective against both Gram-positive and Gram-negative bacteria), was impregnated with Ag NPs, it has shown enhanced antibacterial effect against a phytopathogen (*Pseudomonas* species) [53]. The mechanism behind this synergy would be the tiny size of Ag NPs which enables it to penetrate the cell wall and cell membrane easily, and also allows more Ag^+ ions to get in contact to solution which could then actively damage the bacterial cell. Wherein, ciprofloxacin targets DNA gyrase, a type II and IV topoisomerase enzyme, necessary for separation of bacterial DNA, thereby inhibiting bacterial growth [54,55]. The main advantage of this approach is that it reduces the requirement of higher doses of antibiotics and thereby brings in superfluous effects [53,56]. Additionally toxic effects of Ag NPs against viruses (antiviral properties) have been reported against several virus species including hepatitis B, herpes simplex virus (HSV), respiratory syncytial virus and monkey pox virus [57,58]. Few studies have indicated that Ag NPs act as a potent antiviral agent against human immunodeficiency virus (HIV-1) in vitro [59]. It was found convincing against a wide range of HIV-1 strains including the laboratory strains, clinical isolates, M and T tropic strains and anti-retroviral drug resistant strains [59]. The Ag NP mechanism of action lies in its ability to inhibit nucleocapsid binding with CD4 cells by competitively binding with HIV-1 GP-120 protein. Thus it inhibits the fusion followed by which, it also inhibits viral entry and infectivity [62]. Thus it displays assorted interference at several stages of the HIV-1 life cycle [59,17]

3. Perspective mechanisms of toxicity of Ag NPs against eukaryotes/eukaryotic in vitro models

Indiscriminate use of Ag NPs in consumer products, medicines, household appliances etc., makes Ag NP interaction common to the human body and environment. It may approach the human body by different exposure routes, such as dermal, inhalation, or ingestion, directly [60–62] or indirectly by virtue of its deposition in water bodies or plants [63–65]. It may also be carried into the body subcutaneously, intravenously or intraperitonally [66–68].