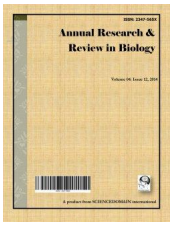

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Gold Nanomaterials as Drug Delivery System against Diseases

Ardhendu Kumar Mandal[1*]

[1]Infectious Diseases and Immunology Division, CSIR-Indian Institute of Chemical Biology, India.

Author's contribution

Author AM wrote the first draft of the manuscript. Author AM collected the literature searches, read and approved the final manuscript.

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ABSTRACT

Owing to the growing of diseases caused by infectious pathogens as well as toxicants, it is needed to develop targeted nanotechnology-based system in order to treat specific diseases. The treatments with conventional antimicrobial and anticarcinogenic agents against diseases have associated the development of multi drug resistance, high toxic side effects, inadequate therapeutic index and low bioavailability of drugs. In this concern, site- specific drug delivery may be an important arena of research to enhance drug-efficacy and reduce adverse side effects to host cells while antimicrobial and anticarcinogenic nanosized gold materials have emerged as potent drug delivery vehicles against various diseases due to their unique size dependent physico-chemical and optical properties, ease of surface modification and high surface-to-volume ratio associated active functional groups, and bio- compatibility. This review focussed on mainly gold nanoparticles (AuNPs), along with their mechanism of actions, biodistribution, pharmacokinetics, toxicities, host-immune response, and their potential applications against a lot of diseases. The review also demonstrated on the development of AuNPs coated drugs, ligands such as chitosan, polyethylene glycol (PEG) / polyethylene imine (PEI) with / without sugars, peptides, proteins, antibodies and genes as drug delivery carriers for targeting small molecules and drugs to diseased sites.

**Corresponding author: E-mail: ardhendu_mandal@yahoo.co.in;*

Keywords: Infectious diseases; cancer; multi drug resistance; gold nanomaterials; drug delivery system.

ABBREVIATIONS

AuNPs : Gold nanoparticles
ROS : Reactive oxygen species
PEG : Poly ethylene glycol
PEI : Poly ethylenimine
$HAuCl_4$: Tetrachloroauric acid
$NaBH_4$: Sodium borohydride

1. INTRODUCTION

When infectious agents enter into the body, innate immune responses become initiated through activation of phagocytic cells such as macrophages as a first line of defence against any spread of infections through proteolytic damages of the organisms in phagolysosome. The adaptive immune system becomes functional to check the development of diseases inducing specific reactions to infectious agents for their eradication mediated by lymphokines and cytokines, specially, macrophages [1].

During the spread of diseases micro-organisms proliferate in the phagolysosomal compartments of the host macrophages overcoming lysosomal proteolysis and protective host immunity. In this regard, intracellular or extracellular infectious diseases as well as cancer caused by different pathogens or toxicants have raised world-wide human health hazards causing millions of mortalities each year. Most of the pathogens commonly colonize and infect host cells via biofilm formation and invasion weakening host immune defences. Many infectious diseases and cancer have been treated with antimicrobial and anticarcinogenic drugs against life-threatening microbial infections and carcinogenesis [2,3]. Currently, treatments are limited to surgery, chemotherapy and radiation. Owing to several clinical procedures and inadequate therapies for overcoming multi-drug resistance, it is vital to select and develop new antibiotics and chemical modifications of existing drugs as well as new drug delivery technologies to treat dreadful diseases enhancing therapeutic efficacies with no side effects. In this concern, particularly, gold AuNPs having optical, electronic and molecular recognition properties are noble compared to other metallic nanoparticles. These nanoparticles are not only inert, nanosized, surface-hydrophobic, and not easily oxidized to the exposure of oxygen or highly acidic environments [4] but also highly stable, sensitive, less toxic and consistent for targeting to the effected sites passively due to electrostatic attractions with the targeted cells against diseases as drug delivery system. Furthermore, AuNPs may be used as promising antipathogenic agents against targeted cells by disrupting the cell membrane directly or forming free radicals while pathogens may not develop resistance. The nanosized (~2nm) AuNPs with different surface cationic functionalities featuring different chain length, aromatic and non aromatic characteristics make them unique for damaging targeted cell membrane [5].

Moreover, to prevent aggregation of NPs, stabilizing agents are required during or after their synthesis. During the synthesis of AuNPs, sodium citrate acts as reducing agent and is absorbed onto the NPs-surface. Poly ethylene glycol (PEG) is one of the most commonly used stabilizer molecules and is able to increase half-life circulation of NPs and obviously, cellular uptake with reduced immunogenicity [6]. Bifunctional PEG can be conjugated with a thiol molecule in one extremity and a different functional group on the other extremity such as biotin, amine, azide, carboxylic for use to allow other functionalization with different biomolecules against diseases.

The functional biocompatible ligands with drug on nanoparticle surface can provide multivalent interactions to biological molecules allowing AuNPs to be drug targeting agents in combating various diseases [7,5,8]. Moreover, active biological components such as sugars, proteins, peptides and genes can be conjugated to the AuNPs for active targeting to the specific site of interest against diseases. Therefore, the developed platform should facilitate a combination of various effector molecules such as therapeutic agent, stabilized and targeting moieties for maximal therapeutic efficacies [9,10].

2. SYNTHESIS OF GOLD NANO-COMPOSITES

AuNPs may be synthesized by reducing tetrachloroauric acid ($HAuCl_4$) to Au^o with two methods. One is followed with apple extract [11]

while 2ml $HAuCl_4$ solution (10 nM in distilled water) are mixed with 50 ml filtered apple extract and shaken with 160 rpm at 80°C for 12 h. Then AuNPs are harvested by spinning at 12000 rpm for 10 min, washed with alcohol, and dried at room temperature.

The other synthesized method is chemical reduction of $HAuCl_4$ by dissolved trisodium citrate [12]. Briefly, aqueous $HAuCl_4.2H_2O$ is boiled under reflux during stirring. The color of the solution is changed from yellow to deep red after quick addition of 10 ml 1% trisodium citrate signifying the formation of mono-dispersed spherical AuNPs (~13 nm diameter). The solution is then allowed to cool to room temperature after an additional 15 min reflux, andfiltered through a 0.45 µm acetate filter and stored at 4°C for future use at a concentration of 1 mg / ml.

AuNPs are also synthesized by using sodium borohydride ($NaBH_4$) as a reducing agent [13]. Here, AuNPs are prepared by reduction of $HAuCl_4.3H_2O$ with $NaBH_4$ where the solution of $HAuCl_4.3H_2O$ (0.2 mM, 40 mL) are poured in a beaker and chilled solution of $NaBH_4$ (0.050M/0.075M, 0.02 mL) are added in it. The yellow color of gold chloride solution is immediately converted to brick red color indicating the formation of AuNPs.

Gold nanoparticles may also be synthetic, plant or animal originated or chemically modified natural products [14].

Chitosan-coated AuNPs are prepared while chitosan acts as reducing and stabilizing agent [15]. Briefly, chitosan flakes are dissolved at 65°C under stirring in 0.1M acetic acid for obtaining a 1% (W/V) concentration. Chitosan solution is then heated at 60°C, and gold chloride solution (1 / 2 mM, CS:$HAuCl_4$ (V/V) =5:2) is added drop-wise. The synthesis is conducted under heating and stirring within 4 h.

For the preparation of PEG- or poly ethylenimine (PEI)- coated AuNPs, the synthesized AuNPs are dissolved in distilled water to a concentration of 5000 rpm. PEG (Mw = 3350) or PEI (Mw = 10000) is then added to adjust the solution to 1.0 mg / ml. The mixtures are incubated at 30°C with gentle shaking for 24 h and then spun at 12000 rpm for 10 min. The pellets are washed with distilled water for 3 times and preserved in 1 mM NaCl for further use.

AuNPs may also be conjugated with antibiotics or drugs as combination therapy against infection [16] and modified to incorporate a diverse array of functionalized ligands [17]. The binding of AuNPs with biological molecules such as sugars, peptides, genes can be made by the conjugation of nanoparticles' surface with proper biomolecules to target diseased cells [18-24].

3. MECHANISM OF ACTION OF GOLD NANOPARTICLES

Gold nanoparticles coated with ligands as well as drugs may enter into the host macrophage cells via electrostatic attraction or endocytosis through passive targeting, followed by endosomal release while AuNPs conjugated with peptide, sugar, DNA may enter into the cytoplasm or cellular matrix directly through the cell membrane by active targeting. Due to smaller sizes (~2-15 nm) of the AuNPs, they can also extravasate through enlarged pores of capillary endothelium in tumor sites.

AuNPs exert their antimicrobial activities mainly in two ways. Firstly, they change the membrane potential and reduce adenosine triphosphate synthase activities reducing the cellular metabolism. Secondly, they decline the subunit of the ribosome for t-RNA binding, collapsing its biological mechanism. AuNPs with a small size and enhanced surface area produce some beneficial electronic effects for increasing surface reactivity to cause cell death. They basically react with phosphorus-or sulphur-containing DNA molecules or proteins respectively. They bind to thiol group nicotinamide adenine dinucleotide dehydrogenases and disrupt their respiratory chains inducing oxidative stress with the release of reactive oxygen species (ROS), responsive to damage the cell structure leading to cell death [25].

Though AuNPs are generally regarded as non microbicidal owing to their biological inertness, their surface modifications make them highly efficient in acquisition of microbicidal capability even against multi-drug resistance [26]. Due to having higher surface to volume ratio and enhanced number of active atoms at the outer surfaces [27] of the ultra small sized AuNPs, cationic metal ions are slowly released from metal oxide and absorbed through the cell membrane following direct interactions with the functional groups of nucleic acids and

proteins resulting damage of the associated cells.

The optical properties of AuNPs are based upon the surface Plasmon resonance oscillations employed to provide photodynamic therapy to damage diseased tissues. One approach of this therapy is to utilize light absorbing dyes to generate ROS to kill the microbes or associated cells [28]. Another approach is to use AuNPs and laser energy to destruct the cells through photo thermal therapy [29] where upon getting exposure to resonating laser emission light, the kinetic energy of AuNPs enhances causing physical disruption of the exposed target cells through local heating.

4. BIODISTRIBUTION OF GOLD NANO-PARTICLES

To consider AuNPs as effective pharmaceutical, it is essential to get a firmed understanding about their biodistributions in living systems. The biodistributions of these nanoparticles depend on their size, surface charge, hydrodynamic radius, coated ligands and different routes of administration resulting different retention time [30-36]. These studies focussed that the 15 nm size among others such as 15 nm, 50 nm, 100 nm and 200 nm, of AuNP had the highest permeation coefficient while the larger particles demonstrated a lag time of 3 h to 6 h, respectively. After inductively coupled plasma analysis of the blood and the different organs, it was monitored that the majority of the AuNPs of various sizes were present in the liver, lung and spleen while 15 nm AuNPs seemed to get accumulated the most in blood, liver, lung, spleen, kidney, brain, stomach and heart. Their studies showed that 15 nm and 50 nm AuNPs were able to cross the blood brain barrier significantly while 200 nm nanoparticles revealed very minute presences in the brain tissues. The studies also showed that size and surface charge of AuNPs affect biodistribution with the smallest cationic nanoparticles accumulated in kidneys and larger ones in the spleen, liver, lungs and heart [37]. Other investigators analyzed the effect of size and ionic ligands of mono-disperse AuNPs (1.4 nm and 18 nm) by intra-tracheal instillation into the lungs and intravenous injection into tail vein of rats [38]. Their results implicated that the smaller sized nanoparticles translocated through the respiratory tract in contrast to bigger sized nanoparticles while the biodistribution patterns for the intravenous injection were different in the organs probably due to the modifications of the AuNPs by cells and proteins during their translocations.

For designing a biocompatible nanoparticle monolayer, PEG was used to passivate surfaces for resisting non specific interactions, specifically of biomolecules [39-41] where investigations on the biodistribution and the pharmacokinetics of different PEG-AuNPs in nude mice were accomplished [33]. It was monitored that 20 nm AuNPs coated with PEG5000 showed the lowest uptake in the reticulo endothelial system and obviously the longest half-life as well as significantly higher tumor extravasation compared to nanoparticle sizes of 40 nm and 80 nm.

5. TOXICITIES OF GOLD NANO-PARTICLES

Internalized AuNPs cause toxicity to the mammalian cells inducing ROS generation, DNA fragmentation and mitochondrial damage led to reduction in cell viability [42,43]. AuNPs display cytotoxicity by disrupting the cytoskeleton network through alterations of the tubulin and the actin filaments and cause cellular stress leading to decrement in cell differentiation and proliferation [44]. Though AuNPs indicate a significant toxic effect against many types of cell, the studies demonstrated that the effects on dendritic cells were not significant despite their enhanced concentration of administration implying their specific non immunogenic response [45]. In an in vivo experiment, normal mice treated with weekly intraperitoneal injection of AuNPs (8 mg/kg b wt; size 8 nm - 37 nm) exhibited lethal effect on the majority of the rats tested while no harmful effect for the nanoparticles-sizes of 3 nm, 5 nm, 50 nm and 100 nm [46]. On the other concern, cytotoxic effects of AuNPs against in vitro cancer cells have been depicted to be dependent on the morphology as well as surface chemistry of the nanoparticles where doses of 6.25 – 100 µg/mL of spherical 25 nm AuNPs showed the optimum cytotoxicity to the cancer cells [47].

Generally, the host immune system becomes activated by the stimulation of the interactions with the invasive pathogens leading to up-regulations of related genes. Earlier studies have indicated that peptide-conjugated AuNPs were recognized by the macrophages which subsequently activated immune responses by expressing immunity-related genes owing to the

strong interactions between AuNPs and immune receptors of the host cells [48].

6. CONCLUSIONS

Gold nanomaterials are considered to have microbicidal as well as anti carcinogenic features that may be regulated by their selective fabrications into the structural shapes and the sizes. Moreover, the increased surface to volume ratio of gold nanostructures allows golds' optical and thermal properties to function in combination with their anti microbial or anti carcinogenic activities. The enhanced aspect ratio of AuNPs also increases their nanostructure stability to attach ligands, sugars, proteins, peptides, antibodies, genes and conjugated molecules with drug for a range of biological applications including targeted nanoparticles-encapsulated vesicular drug delivery to get their greater biological efficiencies which require further investigations.

Generally, AuNPs, when administered into the body, get accumulated to reticulo- endothelial system and ultimately, a few are eliminated from the body through renal excretion. As the functional or physiologic pore size of glomerular capillary wall of kidney is about 4.5 – 5 nm in diameter, AuNPs should be modified ideally as spherical in shape, having less than 5 nm size [49], coated with ligands and / with vesicular drug [50] to avoid toxic side effect and to get renal clearance for their therapeutic use.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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