

Progress in research on gold nanoparticles in cancer management

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Abstract

Introduction: The rapid advancement of nanotechnology in recent years has fuelled burgeoning interest in the field of nanoparticle research, particularly its application in cancer management. At present, there seems to be heightened interest in the application of gold nanoparticles (AuNPs) to the management of cancer, encompassing diagnosis, monitoring, and treatment. AuNPs could be used as drug delivery agents that target cancer cells or in gene therapy. These efforts are undertaken in the hope of revolutionizing current methods and strategies for cancer treatment. This review will focus on the current applications of AuNPs in cancer management.

Objectives, data sources, study appraisal and synthesis methods, results: objectives, data sources, study eligibility criteria, participants, and interventions, study appraisal and synthesis methods, results are not required, as the study will be a literature review. Just introduction, ethics and dissemination, and conclusion are applicable.

Ethics and dissemination: Ethical approval and informed consent are not required, as the study is a literature review and does not involve direct contact with patients or alterations to patient care.

Conclusion: AuNPs have many properties that are of great value for the diagnosis and treatment of tumors. AuNPs are small in size and can penetrate widely and deposit on the tumor site, bind to many proteins and drugs, target delivery drugs, and have good biocompatibility. The application of AuNPs in the diagnosis and treatment of tumors is very considerable. In the near future, AuNPs will certainly play an important role in the treatment of tumors.

Abbreviations: AuNCs = gold nanoclusters, AuNPs = gold nanoparticles, AuNRs = gold nanorods, AuNSs = gold nanoshells, CTAB = cetyltrimethylammonium bromide, EGFR = epidermal growth factor receptor, EpCAM = epithelial cell adhesion molecule, HER-2 = human epidermal growth factor receptor-2, MTX = methotrexate, PEG = polyethylene glycol, PET = positron emission tomography.

Keywords: cancer management, gold nanoparticles (AuNPs), research progress

The rapid advancement of nanotechnology in recent years has fuelled burgeoning interest in the field of nanoparticle research, particularly its application in medicine. A constantly expanding knowledge base derived from a better understanding of the properties of gold nanoparticles (AuNPs) coupled with rigorous experimentation means that the frontiers of nanotechnology are

constantly being challenged. At present, there seems to be heightened interest in the application of AuNPs to the management of cancer, encompassing diagnosis, monitoring, and treatment. These efforts are undertaken in the hope of revolutionizing current methods and strategies for cancer treatment. This review will focus on the current applications of AuNPs in cancer management.

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1. Introduction

According to the World Health Organization (WHO), cancer accounted for millions of deaths in 2017, making it the leading cause of death in the world. Deaths from cancer worldwide are expected to increase, with an estimated 12 million deaths in 2030.^[1] Therefore, it is a constant challenge to advance effective means of cancer diagnosis, monitoring, and treatment. Current therapies employed for the treatment of cancer include surgery, chemotherapy, and radiation therapy, among others.^[2] While these methods have been accepted and practiced for decades, they have their drawbacks and side effects. For example, surgical removal of tumors is restricted mainly to large, resectable and accessible tumors. Chemotherapeutic drugs only target rapidly dividing cells and thus not only kill cancer cells but also destroy normal cells such as bone marrow cells.^[3] Radiation therapy such as gamma rays inevitably causes deleterious effects to healthy tissues along the radiation path. In light of the shortcomings of current treatment modalities, a critical thrust towards improving

cancer therapy is to specifically target therapeutic agents to tumour cells while sparing healthy tissues from tumors.^[4]

In recent years, nanomaterials and nanotechnology have increasingly entered the stage of clinical application.^[5] AuNPs have unique physical and chemical properties, mainly manifested in the following aspects: AuNPs are relatively safe, stable and easy to prepare, and they have many unique characteristics, such as small size effects, surface effects, quantum size effects, electrical effects, and optical effects.^[6–8] AuNPs have better penetration ability than traditional drugs and a lower risk of application in treatment and diagnosis.^[9,10] Therefore, AuNPs can be widely used in biomedicine, especially in cancer therapy.

Multifunctional nanoparticles are a hot research topic and are being developed for cancer diagnosis and treatment.^[11] For example, AuNPs can be used for MRI detection, and coupled with polyethylene glycol (PEG) molecules to increase the circulating time of nanoparticles *in vivo*, and so on.^[12] In the adenocarcinoma mouse model, tumor-specific F3 peptides can be used as targeted transport, and adriamycin transport carriers have been proven to be effective.^[13]

A better understanding of nanomaterials, especially AuNPs, would almost certainly improve the management of cancer. Here, we provide a review of the studies that have been conducted on AuNPs over the past decade, describe the research progress of AuNPs in cancer management, and discuss the possible molecular mechanisms underlying cancer.

2. Characteristics of AuNPs

AuNPs exhibit unique physical and chemical properties due to their different shapes and sizes.^[14] First, the gold core of AuNPs is essentially inert and non-toxic. Second, the synthesis of AuNPs is relatively easy, and the diameter range is relatively controllable, usually from 1 to 150 nm. Third, AuNPs can be good drug carriers, because different features and sizes can control the release of drugs in different locations.^[15]

Various shapes of AuNPs have been developed to address different therapeutic needs. AuNPs mainly used for imaging and radiation sensitization are produced by the reduction of chloroauric acid with a diameter ranging from 1 to more than 100 nm.^[16] The gold nanoshell (AuNS) is a spherical structure consisting of a core of silica and a thin gold shell with diameters ranging from 50 to 150 nm. The optical properties of AuNSs can be adjusted by changing the core diameter and shell wall thickness. Gold nanorods (AuNRs) are usually synthesized by reacting chloroauric acid on gold seeds with cetyltrimethylammonium bromide (CTAB) as a stabilizer.^[17,18] The absorption wavelength of AuNRs has 2 peaks depending on the plasmon resonance of light in its longitudinal and lateral directions. AuNRs are typically 25 to 200 nm in size and can be changed by the length-to-diameter ratio (i.e., aspect ratio) of these particles. There are also other forms of AuNPs, such as nanocage and hollow gold nanospheres.^[19,20]

3. AuNPs and cytotoxicity

As the utility of AuNPs largely depends on the degree of inherent toxicity, studies on the toxicological profile are discussed preceding their usage in cancer management. It has been proven that the cytotoxicity of AuNPs is closely related to nanoparticle size, surface charge, and functional groups.^[21] In the literature, AuNPs have been reported to lack the ability to induce adverse

and acute toxicity and are thus deemed to be biocompatible entities for use in biomedical applications.^[22] However, recent studies have shown that there could be more to AuNP toxicity than already surmised and that the extent of toxicity response is closely associated with the size of the AuNPs.^[19,23] Investigations have revealed that decreasing the size of NPs correlated with more widespread tissue distribution, heightened potential to deeper penetration within certain tissues, more effective internalization by cells, and increased toxic effects.^[24] In terms of surface functionality, studies have shown that modification of the AuNP surface affects its uptake, interactions with cellular constituents and cytotoxicity.^[25]

3.1. Nanoparticle size and cytotoxicity

For AuNPs, the nanoparticle size (D_{core}) is the basic parameter determining cytotoxicity. Studies have shown that AuNPs ($D_{\text{core}} < 2.0$ nm) have significant cytotoxicity due to their ability to enter the nucleus; when the D_{core} of AuNPs is more than 10 nm, cytotoxicity is weak and increases slightly with D_{core} .^[26] In 2007, Pan et al demonstrated the dependence of cytotoxicity on the particle size of AuNPs with different particle sizes ($D_{\text{core}} = 0.8, 1.2, 1.4, 1.8,$ and 15 nm). They found that the cytotoxicity of gold nanoclusters (AuNCs) is significantly stronger than that of AuNPs when the D_{core} is greater than 10 nm. The different sizes of AuNCs obtained by the MTF method ($D_{\text{core}} = 0.8, 1.2, 1.4,$ and 1.8 nm) have variant IC50 values for different cell lines, indicating that cytotoxicity is also related to cell type.^[27] Vetten et al found that AuNPs with a particle size of 20 nm was slightly more toxic to Chinese hamster ovary cells than the size of 14 nm.^[28]

The irregularity of AuNP morphology and its colloidal stability in biological media can affect the phagocytosis of AuNPs by cells and the physiological functions of cell membranes and organelles in different morphologies and different dispersed states of AuNPs.^[29] Therefore, physical properties such as the shape and dispersion state of AuNPs can also affect their cytotoxicity. Wang et al found that AuNRs had the highest cytotoxicity, while nano hexapods showed no significant cytotoxicity even at relatively high concentrations (200 mg/L), indicating different morphologies of AuNPs with different cytotoxicities.^[30] Recently, Wang et al found that the aggregation/assembly of AuNPs in the cells prolongs the residence time and increases the reactive oxygen species generated by the cells, thereby affecting cell function.^[31]

3.2. Surface charge and cytotoxicity

The surface charge of AuNPs determines the amount of phagocytosis of AuNPs and its distribution in cells. Hauck et al found that changing the surface charge of AuNPs by electrolyte coatings can control the phagocytosis of AuNPs by mammalian cells.^[32] Although many studies have shown that the cytotoxicity of the positively charged AuNPs is greater than that of the electrically neutral and negatively charged AuNPs, the relationship between the surface charge and biocompatibility remains unclear.^[33] Pillai et al found that positively charged AuNPs are easily phagocytosed by cells and have high cytotoxicity, indicating that the amount of phagocytosis of AuNPs by cells depends on the net charge (Q_{net}) of AuNPs.^[34] Goodman et al. examined AuNCs with different charges and showed that the cytotoxicity of positively charged AuNCs was

greater than that of neutral and negatively charged AuNCs.^[35] In contrast to these results, Schaeublin et al found through studies of the interaction of AuNCs ($D_{\text{core}} = 1.5 \text{ nm}$) with HaCaT cells that both positively and negatively charged AuNCs are cytotoxic, that negatively charged AuNCs are more toxic, and that electrically neutral AuNCs are less toxic than charged AuNCs. This phenomenon indicates that the cytotoxicity of AuNPs with similar surface charge and size is also closely related to cell types.^[36] This belief was confirmed by studying the interaction of different particle diameter ($D_{\text{core}} = 16$ and 58 nm) AuNPs with cells.^[37]

In addition, the combined effects of both particle size and surface charge on the engulfment cytotoxicity are considered. Jiang et al examined the phagocytosis of AuNPs of HeLa cells with different particle sizes and found that the phagocytosis of electrically neutral or negatively charged AuNPs was correlated with particle size, while the phagocytosis of the positively charged AuNPs increased with increasing particle size.^[38]

3.3. Surface modification and cytotoxicity

Surface modification with ligands/stabilizers of AuNPs allows for a certain degree of targeting, and the type of ligands can also affect the cytotoxicity of AuNPs.^[39] AuNRs modified by CTAB can significantly reduce PC-3 cell proliferation, while the polypeptide YSA-modified AuNRs have a weaker effect on cell proliferation. Biocompatible ligands are generally capable of reducing the cytotoxicity of AuNPs, and as shown by Deol et al, grafting of further dendrimers onto the surface of glutathione-modified AuNPs can improve their cell toxicity.^[40]

4. AuNPs in cancer management

4.1. AuNPs as drug delivery agents targeting cancer cells

AuNPs as drug delivery agents can increase the pharmacokinetics of the drug, thereby reducing non-specific side effects and achieving higher doses of targeted drug delivery. A prominent application of AuNPs is using them as vehicles for delivery of molecules into cells. The payload can be a small molecule drug or a large biomolecule such as a protein, DNA or RNA.^[41] However, various factors need to be considered in designing an effective drug delivery system. The properties of AuNPs, such as their size, charge, and surface chemistry, have been shown to affect their uptake, as well as their subsequent intracellular fate.^[42]

Gold nanoconjugated cetuximab and gemcitabine have been shown to be highly targeted in pancreatic cancer cells with high epidermal growth factor receptor (EGFR) expression.^[43] Jiang et al prepared AuNPs with diameters from 2 to 100 nm and coupled them with trastuzumab using a citric acid reduction method. The results suggest that they target human epidermal growth factor receptor-2 (HER-2)-positive SK-BR-3 breast cancer cells. Better targeting is achieved, and cells have an obvious endocytosis effect on AuNPs with a diameter of 40 to 50 nm, while small diameter AuNPs tend to separate from the cell membrane.^[44] Chen et al used AuNPs of approximately 14 nm as the carrier linking with methotrexate (MTX) to study adverse reactions in vitro and anticancer effects in vivo. The results showed that compared with MTX alone, the coupling MTX of AuNPs can be rapidly and efficiently concentrated in tumor cells which significantly reduces the dose-dependent effect of efficacy.^[45] Goel et al also conducted a similar study and found that

AuNPs can not only deliver drugs but also specifically infrared photothermal damage of tumor cells, which can be combined with near-infrared rays.^[46]

4.2. AuNP application in tumor imaging

The most effective way to improve the prognosis of tumors is early diagnosis. In precision, intensity modulated radiation therapy, such as 3-dimensional conformal radiation therapy and image-guided radiation therapy, accurate and clear images are important for the delineation of tumor target areas.^[47] In recent years, many studies have attempted to use functional imaging to develop tumour radiotherapy plans. Although single photon emission computed tomography (SPECT) and positron emission tomography (PET) have higher sensitivity and specificity in distinguishing tumors from normal tissues, their spatial resolution is poor.^[48,49] High spatial resolution is important in improving the tumor treatment ratio. The commonly used contrast agents are iodine agents, which have a short half-life in the blood ($<10 \text{ min}$) and are less tumor-specific. With the rapid development of nanotechnology, the application of multifunctional nanoparticles in medical imaging has become important, such as iron oxide nanoparticles, carbon nanorods, GNPs, and so on.^[50] Among these nanomaterials, AuNPs have received increasing attention due to their mature synthesis, stability and especially high X-ray absorption capacity.^[51]

AuNPs are characterized by small size, good biocompatibility, and high atomic number, which mean that AuNPs are potentially good contrast agents. At present, there are 2 ways in which AuNPs can target tumor cells: passive or active. Passive targeting uses only the osmotic tension effect (EPR) to converge in tumor tissue to form enhanced imaging.^[51,52] Active targeting is the coupling of AuNPs with tumor-specific targeting agents, such as EGFR monoclonal antibodies, to achieve active targeting of tumor cells by GNP. When the energy exceeds 80 keV, the mass decay of gold is higher than that of iodine, which indicates that gold-nano is more advantageous in development.^[53] Rand et al used mixed AuNPs with liver cancer cells and X-ray imaging and found that the liver cancer cell clusters in the gold-nano-mixed group were significantly more potent than the simple liver cancer cells. Using this new technology, tumors with a few millimetres diameter in vivo can be detected, which is of great significance for early diagnosis.^[54]

4.3. AuNP application in tumor radio sensitization

The distribution of AuNPs in tissues depends on their own parameters, such as size and ability to inactivate tumor cells. Radiation therapy is widely used in almost all types of tumours, such as breast cancer.^[55] The rays include X-rays, gamma rays, and high-energy particles. However, radiation therapy is indistinguishable between cancerous and normal tissues. Therefore, reducing normal tissue damage remains a limiting factor in radiation therapy.^[56] Herold et al injected 1.9 nm AuNPs into breast cancer model mice and found that the tumor volume was reduced dramatically and the 1-year survival rate was higher after 2 minutes irradiation (30 Gy).^[57] Stern et al injected AuNPs into the tumor site with radiotherapy and found that the tumor volume was significantly smaller and did not significantly expand with time.^[58]

Targeting AuNPs is a hotspot of present research. By coupling chemical drugs or some biomacromolecules with AuNPs through

chemical methods, it can play a role in reducing toxicity and increasing efficiency by changing the volume, mass, and charge of AuNPs.^[59] Zhang et al constructed PEG-GNP conjugates from PEG using different diameters of AuNPs.^[60] By co-culturing with HeLa cells, Zhang et al found that the amount of the conjugates entering cells was much higher than that of pure AuNPs.^[61] Khoshgard et al synthesized folate and AuNPs to construct FA-GNP conjugates and co-cultured with HeLa cells with high expression of folate receptors and found that the uptake of FA-GNPs by cells was much higher.^[11] Khoshgard et al found that the DEF (dose enhancement factor) co-cultured with FA-GNPs was 1.23 ± 0.09 times that of the simple irradiation group.^[46] The results showed that the main uptake site was the cytoplasm, while the uptake of C225-GNPs was much higher.^[62]

There is currently no clear conclusion about the mechanism of radio-sensitization of AuNPs. Jain et al co-cultured breast cancer cells with AuNPs under hypoxic, normoxic and aerobic conditions and irradiated them. The uptake of AuNPs by cells under hypoxic conditions was higher than that under aerobic conditions. Under hypoxic conditions, the proliferation of breast cancer cells is also significantly reduced.^[63] AuNPs showed better sensitizing effects under normoxia and moderate hypoxia. However, under the condition of a lack of oxygen, there is no significant sensitization. Yasui et al concluded that AuNPs are mainly deposited in the cytoplasm and increase the expression of endoplasmic reticulum stress-related proteins by downregulating DNA repair by inhibiting the expression of DNA repair-related proteins and promoting apoptosis.^[64,65]

4.4. AuNP application in tumor hyperthermia

The thermo-therapeutic mechanism involves the initiation of heat stress in cells at 42 to 47°C, resulting in the activation of cells and/or initiation of intracellular and extracellular degradation mechanisms. The effects of hyperthermia on intracellular and extracellular processes include changes in signal transduction, induction of apoptosis, reduction of perfusion and tumor oxygenation and so on.^[40] AuNRs or AuNSs have significant advantages for the absorption and scattering of near-infrared light (wavelengths from 650 to 900 nm). When exposed to electromagnetic radiation, especially near-infrared light, AuNPs can generate heat through surface plasmon resonance effects. Since the absorption peak of AuNPs is in the visible range (450–600 nm), the absorption of near-infrared light by normal tissues is extremely small.^[42] Stimulation of AuNPs by near-infrared laser irradiation induces hyperthermia and minimally damages normal tissues. Therefore, gold nano mediated thermo-therapeutics have the advantages of specificity and small trauma compared with traditional methods. In a mouse model of colon cancer, the researchers injected PEG-conjugated AuNPs into mice, and AuNPs were deposited on the tumor site and irradiated with near-infrared light at 800 nm. This treatment significantly prolonged the survival of the mice.^[66] Moreover, the skin reaction in the normal part of the body was not different from that in the control group and only in the tumor site. Stuchinskaya et al found that AuNPs linked to anti-HER-2 antibodies can selectively target the killing of HER-2 over-expressing breast cancer cells after laser irradiation, indicating that AuNPs linked to antibodies are a kind of photothermal therapy and effective medium.^[67] Huang et al found that the anti-EGFR antibody AuNRs can kill tumor cells at a lower laser power without causing normal cells to be damaged

by high heat.^[68] Hainfeld et al found that the tumor was completely ablated and that normal tissues were almost intact, in the photothermal treatment of rat tumors with modified cetuximab AuNPs.^[69] Wang et al covalently bound the nucleic acid aptamer CSC13 to the surface of AuNRs and targeted killed prostate cancer DU-145 cells and cancer stem cells under near-infrared light.^[70]

AuNPs absorb near-infrared rays, which accelerates the tumor temperature rise, and can also be used to enhance tumor absorption of X-ray doses. The combination of hyperthermia and radiation therapy is synergistic. When the tumor was heated to 43.5°C with X-ray irradiation for 2 hours, the heat enhancement ratio is 8:1, making hyperthermia one of the most effective radio-sensitizers.^[71] However, tumor hyperthermia has certain limitations, such as poor specificity, difficulty in reaching deep tumors, and heat tolerance in the early stages.^[72]

4.5. AuNP application in tumor gene therapy

Gene therapy is a new treatment that began in the late 20th century and provides an ideal way to treat cancer.^[73] The targeted introduction of nucleic acids into tumor cells is a key process in gene therapy. Efficient transfection reagents must protect nucleic acids from nuclease degradation, and nucleic acids are released by cells and act in activated and released forms within the nucleus. AuNPs protect the surface of DNA from DNase I degradation.^[74] On the one hand, due to steric hindrance, the enzyme cannot bind to the DNA on the surface of the particles and is not degraded by the enzyme.^[75] On the other hand, a highly concentrated ion concentration around the DNA inhibits the activity of the enzyme. A synthetic non-viral nucleic acid delivery system such as a liposome has a low immunogenicity but in general has a problem of low delivery efficiency.^[76]

AuNPs have a large specific surface area and are easy to modify. They can be used as an ideal transfection reagent by loading a large amount of nucleic acid while regulating surface charge and enhancing water disposability, improving transfection efficiency and reducing toxicity.^[77] Mitra et al used epithelial cell adhesion molecule (EPCAM) monoclonal antibody as a targeting ligand and bound it to PEI-modified AuNPs. The results showed that siRNA-loaded AuNPs successfully entered RB cells and significantly reduced their viability.^[78] At the same time, control experiments showed that targeted siRNA-AuNPs significantly downregulated the expression of the EPCAM gene in RB cells compared to non-antibody-modified siRNA-AuNPs.

Ghosh et al used cysteamine-modified AuNP-miRNAs, which are 10 to 20 times more efficient than liposomes and can effectively release miRNAs and downregulate the expression of genes.^[79] Since the nucleic acid aptamer has a targeting function, it has become a hot spot for anti-tumor research. Ryou et al used AuNPs to deliver RNA ligands specific for β -catenin (which acts as a transcription factor in the nucleus) into HepG2 cells with higher transfection efficiency than liposomes.^[80] The results showed that the transcriptional activity of β -catenin in the nucleus was almost completely inhibited, and the mRNA levels of cyclin D and oncogene c-myc were decreased. In addition, they also ligated the RNA aptamer targeting the transcription factor NF- κ B p50 to AuNPs. The results indicated that AuNPs could load aptamers into human lung cancer A549 cells and effectively induce apoptosis.

4.6. Other applications of AuNPs in tumor management

AuNPs can also be used as a stabilizer for other drug carriers, such as liposomes, and at the same time improves their delivery efficiency. The drug is susceptible to leakage in the plasma and other organs and limits its use.^[81] Wang et al examined the adsorption of phospholipids by nanoparticles and demonstrated that nanoparticles can induce gelation at the liposome adsorption site. Since 25% of the outer surface of the lipid is occupied by the nanoparticles, the nanoparticle-modified liposome has no obvious leakage within 50 days of the solution.^[82]

Yang et al used AuNPs as stabilizers for oil-in-water emulsion droplets. They prepared a net negatively charged oil-in-water emulsion droplet with a particle size below 100 nm. The positively charged AuNPs bind to it via electrostatic interaction and then as a “bridge” to shield the strong repulsion between AuNPs and force. The results showed that the interaction between the AuNP-emulsion and AuNP-transferrin significantly improved the stability of the emulsion droplets.^[83,84]

In addition, AuNPs can also be used to promote the release of drugs. An et al embedded AuNPs in the middle of the bilayer of the liposome and used its photothermal effect to cause phase transition of the liposome bilayer to achieve drug release.^[85]

5. Conclusions

AuNPs have many properties that are of great value for the diagnosis and treatment of tumors. AuNPs are small in size; can penetrate widely, deposit on the tumor site, bind to many proteins and drugs, and target delivery drugs; and have good biocompatibility. Although the tumor imaging and radiosensitization studies of AuNPs described in this paper are limited to cell experiments and animal experiments, they provide new strategies and new ideas for early diagnosis and precise radiation therapy. The research on AuNPs is still in its infancy, and many problems need to be solved urgently, such as how to reduce the biological toxicity while improving the biological stability and so on. The potential application of AuNPs in the diagnosis and treatment of tumours is very considerable. In the near future, AuNPs will certainly play an important role in the treatment of tumors.

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