Editorial

Research perspectives: gold nanoparticles in cancer theranostics

Junjie Li[1], Sanjay Gupta[2], Chun Li[1]

[1]Department of Cancer Systems Imaging, [2]Department of Diagnostic Radiology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Corresponding to: Chun Li, Ph.D., Professor. Department of Cancer Systems Imaging–Unit 59, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Houston, Texas 77030, USA. Email: cli@mdanderson.org.

Abstract: High recurrence rates after surgical resection remain a formidable challenge in many cancers. Although chemo- and/or radiotherapy are often applied following surgery to prevent tumor relapse, these treatments are generally accompanied by serious side effects and challenges in their delivery that limit their effectiveness. Gold nanoparticles (AuNPs), which possess unique physicochemical properties, have the potential to enhance the efficacy of these conventional treatment modalities. In this review, we briefly describe the current state of AuNP research in the area of cancer theranostics. Recent studies have investigated AuNPs' use as photothermal converters, drug carriers, radiosensitizers, and imaging probes in a wide range of applications for cancer diagnosis and therapy. AuNPs have promise in minimally invasive thermal ablation therapy, diagnostic imaging, intraoperative tumor margin delineation, and multimodal anticancer therapy. The successful translation of AuNPs into the clinic will have significant impact on the care of cancer patients using image-guided, minimally invasive approaches.

Keywords: Cancer theranostics; gold nanoparticles (AuNPs); image-guided intervention

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Introduction

For patients with focal solid tumors, surgical removal of localized cancer often offers the only chance at a cure. Because recurrence after surgical resection is a formidable challenge in many cancers, surgery is often used in combination with chemo- and/or radiotherapy. However, the efficacy of chemotherapy is often limited by mutational heterogeneity, genomic instability, multidrug resistance, poor drug penetration into tumor tissue, and serious side effects (1,2). The efficacy of radiotherapy, on the other hand, is limited by the radioresistance of the tumor cells and the challenges of developing advanced, highly precise image-guided treatment plans to deliver high radiation doses to a defined treatment volume without damaging the surrounding normal tissues (3,4). Cancer theranostics, a proposed process of tailoring a treatment to individual patients based on image guidance, have a great potential in improving the therapeutic efficacy with reduced damage to normal tissues.

One emerging field with enormous potential in image-guided anticancer therapy is medical nanotechnology. Researchers are increasingly investigating the potential roles of nanoscale structures in preclinical research and clinical applications taking advantage of the fact that multiple functions can be integrated into a single nanostructure. Of these structures, gold nanoparticles (AuNPs) have been actively investigated as photothermal converters, drug carriers, radiosensitizers, and imaging probes in a wide range of applications in cancer diagnosis and therapy (5-10). In this perspective, we briefly review recent advances in the application of AuNPs in cancer theranostics, with an emphasis on their potential use in image-guided interventions.

Physicochemical properties

AuNPs are classified into different subtypes, including nanospheres, nanorods, nanoshells, nanocages, and surface-enhanced Raman scattering (SERS) nanoparticles, based on

their size, shape, and physicochemical properties (11-14). Despite their differences, different types of AuNPs have several unique properties that make them ideally suited to certain applications in cancer theranostics. AuNPS are biocompatible, have strong surface plasmon resonance (SPR) peak tunable from visible to near-infrared (NIR) region, and can be readily functionalized by attaching a variety of molecules to their surfaces.

One property of AuNPs that makes them suited to applications in cancer theranostics is their versatile and straightforward chemistry, which makes it relatively easy to attach various biomolecules to their surfaces. For example, AuNPs can be coated with polyethylene glycol chains via Au-S bonds to reduce their uptake by the liver and spleen and prolong their half-life in blood (15). Other biomolecules such as peptides (16-18), small-molecular-weight compounds (19,20), aptamers (21-23), and monoclonal antibodies (24-26) have also been attached to the surface of AuNPs to increase the particles' tumor-targeting potential. Another property of AuNPs is SPR, which is an optical phenomenon arising from the interaction between an electromagnetic wave and the conduction electrons in a metal (27,28). When exposed to light, the conduction electrons in a metal nanostructure collectively oscillate at a resonance frequency. At this resonance frequency, the incident light is absorbed by the nanostructure. For spherical solid AuNPs, the plasmon resonance varies only weakly with the particle size, shifting to longer wavelength as the particle size increases. For core-shell structured spherical AuNPs, the plasmon resonance depends on the size and thickness of the metallic shell layer. SPR absorption in AuNPs is followed by energy relaxation through nonradioactive decay channels. This results in an increase in kinetic energy, leading to overheating of the local environment around the light-absorbing species. This phenomenon of rapid conversion of absorbed light into heat, known as the photothermal effect, has been applied to thermal ablation therapy of solid tumors.

However, AuNPs are not without properties that potentially limit their use in cancer theranostics. AuNPs can be retained in the body for a long time, and this long-term retention is a major concern when considering *in vivo* applications of AuNPs. One approach to increase the clearance of AuNPs from the body is to use nanoparticles of less than 5 nm in size, which can be readily excreted through the renal system (29). Another approach is to synthesize nanoclusters that eventually disintegrate into individual AuNPs less than 5 nm in size, which can then be efficiently cleared from the body (30).

Applications in anticancer therapy

Drug delivery

Because of their tremendous surface area, AuNPs are capable of carrying a large amount of drugs and thus can serve as efficient drug carriers. Targeted drug delivery enhances the tumor's uptake of the drug, reduces the distribution of the drug to normal organs, and thereby increases the drug's therapeutic window. You *et al.* (31) reported that up to 60% of a doxorubicin payload could be loaded onto hollow gold nanospheres because the drug molecules were adsorbed to both the inner and the outer surfaces of the hollow gold nanospheres via electrostatic attraction. Owing to the strong SPR absorption of novel gold nanostructures, drug release can be activated by NIR light (31,32). Researchers are also investigating AuNPs as carriers for the delivery of siRNAs, microRNAs, and oligodeoxynucleotide (19,33-35). Interestingly, AuNPs loaded with doxorubicin have been shown to be able to reverse cancer cells' resistance to the drug (36). AuNP-mediated photothermal effect could improve blood perfusion and increase delivery of macromolecular drugs to the tumor when these agents were injected at the time of phototherapy (37).

Photothermal ablation

AuNPs, in particular those have SPR peak in the NIR region (700-1,064 nm), have been investigated for the photothermal ablation (PTA) of cancer cells. Although not as popular as radiofrequency ablation, laser-induced PTA has been used to ablate liver tumors (38-43). However, as with patients treated with other percutaneous interventions, such as radiofrequency ablation, patients treated with PTA—even those with small- to medium-sized lesions—frequently have local recurrence (44,45). Thus, novel photothermal conducting agents that can efficiently convert optical energy to thermal energy are needed to achieve better local tumor control. These agents are expected to increase the efficiency of PTA, reducing the required energy dose of laser light and thereby lowering the potential for damage to surrounding normal tissues. To date, most photothermal conducting agents have been based on various AuNPs, including nanoshells, nanorods, and nanocages (11-13). Of particular interest are hollow gold nanospheres

(HAuNS) with outer diameter of 40 nm (16,19,26). The size of nanoparticles is the most important physicochemical factor influencing the tumor targeting efficiency. It was shown that smaller AuNPs (20-40 nm) coated with PEG had longer blood circulation time than larger gold nanoparticles (80 nm). The 20-nm AuNPs exhibited the lowest uptake by reticuloendothelial cells and the slowest clearance from the body (15). Moreover, smaller particles have a better chance of extravasating from blood vessels into extravascular fluid space. In certain tumors, such as glioma and ovarian cancer, pore cutoff size was between 7-100 nm (46,47). Therefore, to improve targeted delivery of AuNPs, it is desirable that their size be less than 80 nm.

Melancon *et al.* (26) conjugated C225, an antibody directed at epidermal growth factor receptor (EGFR), to the surface of HAuNS and evaluated their distribution to EGFR-overexpressing A431 human squamous carcinoma in mice. Radiotracer counting for tumor showed that C225-HAuNS had a higher uptake value in the A431 tumors than did control IgG-conjugated HAuNS at 24 h after injection. There was an increase greater than threefold in the number of HAuNS and their aggregates per field observed under dark-field microscope in the perivascular area of the tumor in mice injected with C225-HAuNS than in mice injected with IgG-HAuNS, suggesting that the interaction between C225-HAuNS and EGFR may have facilitated extravasation of HAuNS into the interstitial space. The efficacy of PTA mediated by intravenously injected C225-HAuNS has also been assessed in A431 tumor-bearing mice (37). Magnetic resonance thermal imaging of mice bearing A431 tumors injected with anti-EGFR antibody-coated HAuNS revealed that at 2 mm depth from the surface, exposure to low doses of NIR light (808 nm, 4 W/cm^2) resulted in average maximum temperatures of 65.2±0.10 ℃. In contrast, the control mice (saline plus laser) had an average maximum temperature of 47.0±0.33 ℃ after 3 min of laser treatment. The maximum temperature increase occurs on the surface of the tumor and the temperature decreased going deeper into the tumor. Validation with histology showed that tumors in mice injected with anti-EGFR-coated HAuNS and treated with laser induced significantly larger necrotic areas than tumors in mice treated with saline plus laser, indicating that intravenously injected HAuNS in combination with NIR laser could mediate effective PTA therapy.

In addition to applications in PTA, AuNPs are also being investigated as mediators to generate heat through their interaction with radiowaves to facilitate radiofrequency ablation of cancer cells (48,49).

Radiosensitization

The notion of using AuNPs to enhance radiation therapy has attracted significant attention since Herold *et al.* (50) first demonstrated the potential of gold microspheres to enhance effective radiation dose. The authors attributed this enhancement to electrons that were produced and scattered from irradiated gold particles. Herold *et al.* further postulated that with the increasing use of interstitial brachytherapy with isotopes that produce low-energy photons, high-Z particles such as AuNPs might have a role in improving the therapeutic ratio. Theoretical work by Roeske *et al.* (51) and Cho *et al.* (52) showed that low-energy X-rays would provide the highest degree of dose enhancement with high-Z materials, including AuNPs, and that a brachytherapy approach appears to be highly feasible and promising. Ngwa *et al.* (53) calculated that ablative dose enhancement to tumor endothelial cells could be achieved by applying tumor vasculature-targeting AuNPs as adjuvants to brachytherapy using lower energy sources. Many studies have shown that AuNPs can enhance radiotherapy in preclinical animal studies (8,9,54-56). Some researchers have proposed that in addition to physical dose enhancement, radiobiological effects may also play a role in the radiosensitization effect of AuNPs (57,58).

Applications in image-guided therapy

By exploiting AuNPs' unique physicochemical properties, researchers have developed AuNP-based imaging probes for optical imaging, photoacoustic (PA) imaging, magnetic resonance imaging (MRI), X-ray imaging (29,59), single-photon emission computed tomography (SPECT), and positron emission tomography (PET). Targeting AuNPs to tumors provides not only molecular information but also visual guidance for selective thermal ablation or accurate surgical removal. Because surgery is the most effective and widely used procedure in treating cancer, any improvement in accurately identifying residual lesions intraoperatively represents a major opportunity to improve patient care.

PA and SERS imaging

AuNPs' tunable absorption and scattering properties make them useful for various optical imaging techniques, including PA imaging and SERS imaging. In PA imaging,

the transient heating and thermal expansion caused by a short light pulse induce a pressure wave on the target tissue, permitting acoustic detection using ultrasonography. Various AuNPs with SPR absorption in the NIR region have been used for PA imaging. For example, hollow gold nanospheres have been used to enhance the imaging contrast of the cerebral cortex vasculature in mice (60). In addition, cyclic peptide cyclo (Arg-Gly-Asp-phe-Lys) [c(RGDfK)]-conjugated HAuNS have been used to image integrin αvβ3 in human glioma U87 cells in the brains of nude mice (61). In that study, specific tumor targeting visualized by PA imaging was verified by PET and immunofluorescence staining of the excised tumors. Moreover, the tumor deposition of the AuNPs was used to guide subsequent PTA therapy (61). Other gold nanostructures with NIR absorption, including silica-cored gold nanoshells (62), nanorods (63), nanocages (64), nanobeacons (65), and nanoclusters (66), have also been evaluated for PA imaging applications.

AuNPs can amplify the Raman scattering efficiencies of adsorbed molecules by as much as 10^{15}-fold, enabling researchers to spectroscopically identify single molecules at room temperature (67,68). SERS imaging exploits the SPR to enhance the Raman signal, making it possible to detect multiple biomarkers with extremely high sensitivity (67). AuNPs-based SERS agents can highlight tumor margins to help ensure the complete removal of residual disease and avoid surgical injury to normal tissues (69,70).

X-ray and MRI

Gold has higher absorption than iodine, less bone and tissue interference, and thus can achieve better contrast with lower X-ray dose as a contrast agent for X-ray (59). Sub-5 nm AuNPs showed low retention in liver and spleen with elimination by the kidneys, resulting in visualization of organs such as kidneys and tumor with high spatial resolution and high clarity (29). Unlike its application as a contrast agent for X-ray, AuNPs do not possess intrinsic property that permits their use for MRI. To facilitate the MRI-based visualization of plasmonic AuNPs, Ji *et al.* (71) synthesized nanoparticles composed of a super-paramagnetic iron oxide (SPIO) core and a gold shell (SPIO@AuNS). T2- and T2-weighted MRI with these nanoparticles demonstrated significant contrast enhancement in both agar phantoms and tumor models. NIR laser irradiation at increasing concentrations and power resulted in the linear increase in the temperature of the nanoparticles. Murph *et al.* (72) developed a manganese—AuNP positive contrast agent that could be used for site-specific T1-weighted molecular imaging *in vivo* and *in vitro*. Chen *et al.* (7) synthesized and characterized folic acid (FA)-modified dendrimer-entrapped AuNPs loaded with gadolinium, which could specifically target FA receptor-expressing cancer cells via a receptor-mediated pathway and showed high X-ray attenuation intensity and reasonable T1 relaxivity suitable for both CT and T1-weighted MRI. Both *in vitro* cell imaging and *in vivo* tumor imaging with these AuNPs demonstrated significantly improved contrast ratios, indicating that targeted dual-mode CT/MRI could be used to detect cancer cells overexpressing FA receptors. In addition, magnetic resonance temperature imaging can be used to monitor the temperature profile during AuNP-mediated PTA therapy and compare it with the theoretical predictions. These image-guided computational modeling and real-time monitoring tools are important for planning individualized PTA-chemotherapy.

SPECT and PET

AuNPs have been labeled with various radioisotopes, such as ^{64}Cu, and ^{111}In, to facilitate quantitative studies of their pharmacokinetics and *in vivo* biodistribution (17,19,61,70). Jang *et al.* (73) proposed using folate-conjugated, radioactive iodine—labeled gold nanorods for selective SPECT/CT imaging and subsequent thermal ablation of tumor cells overexpressing folate receptor. *In vitro* studies demonstrated that the uptake of the nanorods by folate receptor-positive human ovarian carcinoma SKOV3 cells was 2.7 times higher than that by folate receptor-negative human lung adenocarcinoma epithelial A549 cells. *In vivo* studies revealed that folate receptor-positive tumors in mice were clearly visible on SPECT with a good signal-to-noise ratio 24 hours after the nanorods were injected. Thus, these gold nanorods enable one to simultaneous apply photothermal therapy and monitor the nanoparticles' distribution in folate receptor-positive tumors.

Multimodal imaging

Multimodal AuNP-based imaging probes are designed to have integrated or complementary functions. For example, PA imaging provides tomographic image with high spatial resolution and deep penetration but has limited sensitivity, whereas SERS imaging produces highly sensitive and multiplexed images but has a poor depth of penetration.

Jokerst *et al.* (74) developed a gold nanorod-based PA/SERS imaging approach. The PA/SERS imaging nanorods had an obvious compensation effect for detecting early-stage ovarian cancer in mice, thereby showing promise in helping surgeons completely remove tumors. Kircher *et al.* also developed triple-modality AuNPs for MRI, PA imaging, and SERS imaging (75). In these AuNPs, a 60-nm gold core is covered with a thin SERS layer, which in turn is protected by a 30-nm silica coating that is functionalized with maleimide-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)-gadolinium for MRI. MRI and PA imaging were used to determine the position, size, and locoregional stage of the tumor before surgery, and SERS imaging was used intraoperatively to guide tumor resection. These triple-modality AuNPs accurately delineated the brain glioblastoma from normal tissue in mice both preoperatively and intraoperatively (75). The core-shell SPIO@AuNS nanoparticles were labeled with ^{111}In for quantifying their biodistribution and tumor uptake after intravenous injection. The SPIO component in the SPIO@AuNS not only permitted MRI visualization, it also directed the nanoparticles to the tumors with an external magnetic field gradient, whereas the gold nanoshells mediated efficient PTA of cancer cells (76,77). Yang M *et al.* (78) reported an affiibody-based trimodality nanoprobe for PET, MRI, and optical imaging of EGFR-positive tumors. The nanoprobe comprised a highly mono-dispersed hetero-nanostructure with two different functional nanomaterials, gold and iron oxide. The iron oxide component within the hetero-nanostructures offered T2 MRI contrast, and the AuNPs functioned as reporters for PET and optical imaging. In addition, the nano-platform allowed surface-specific modification with both a targeting molecule (anti-EGFR affibody protein) and a PET tracer (radiometal ^{64}Cu chelators) in a highly efficient and reliable manner. These types of multifunctional nanomaterials promise high sensitivity and specificity for the *in vivo* detection of human EGFR-expressing tumors, and permit image-guided PTA therapy.

Future perspectives

AuNPs have many potential applications in minimally invasive interventions and surgery. The successful translation of AuNP-mediated laser-induced PTA to the clinic will improve local tumor control and potentially reduce tumor recurrence. AuNP-based imaging probes, especially those used for PA and SERS imaging, have the potential to help surgeons delineate tumor margins and identify micro-metastases intraoperatively. Currently, clinical trials are investigating the use of AuNPs for the treatment of solid tumors, including tumor necrosis factor—bound AuNPs (Aurimune; for tumor necrosis factor delivery) and silica-cored gold nanoshells (AuroLase; for PTA). Given the multi-functionality of AuNPs, it is conceivable that future advances in AuNP-mediated cancer therapy will be in the form of multi-modality therapy, which could include chemo-PTA therapy and chemo-PTA-radiotherapy.

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