REVIEW

Biomedical applications of gold nanorod-based multifunctional nano-carriers

Xin Wang · Mingqian Shao · Song Zhang · Xinli Liu

Abstract Due to the good biocompatibility, ease of modification and unique optical properties, gold nanorods (AuNRs) have attracted more and more attentions in biomedical fields. In particular, through surface functionalization, AuNRs can be used as nano-carriers for drugs, probes, nucleic acids, and proteins in cancer treatment. In this review, we summarize the latest progress in biomedical applications of AuNRs-based nano-carriers including those in detection, biocatalysis, imaging, drug, and gene delivery. We also discuss the bioeffects of AuNRs such as in vivo distribution, translocation, localization, metabolism, and toxicity. Finally, we highlight some challenges in future biomedical applications of AuNRs-based nano-carriers.

Keywords Gold nanorods · Nano-carrier · Nano-biomedical application · Multifunctional platform · Biological effects

Xin Wang and Mingqian Shao contributed equally to this study.

X. Wang · M. Shao · S. Zhang · X. Liu (✉)
Shandong Provincial Key Laboratory of Microbial Engineering, QiLu University of Technology, Daxue Road, Changqing District, Jinan 250353, Shandong, People's Republic of China
e-mail: vip.lxl@163.com

Introduction

With the rapid development of imaging technology, the perspectives of biomedical research have turned from subcellular structures in micro-scale (chromosomes, organelles, cytoskeleton, etc.) to biomolecules in nano-scale (nucleic acids, proteins, etc.). Studies on how biomacromolecules assemble, coordinate, transmit signals, and execute function are very meaningful and important, because they can facilitate the research on nano-biointeractions and promote the progress in biological detection, diagnosis and treatment techniques. Nano-biomedicine mainly focuses on the bioeffects of nanomaterial and nanotechnology in biomedical applications, specifically, researching on the interaction between nanomaterial and biosystems, designing, and developing new type of nanomaterial according to its structure and property. The nanomaterial can be used as carriers of agents and information in the fields of biocatalysis, imaging and diagnosis, etc. Nano-carriers have many advantages when compared with traditional biological carriers, such as small size, large aspect ratio, ease to be modified with multiple functional molecules. They could significantly improve tissue and cell targeting, extend the circulation time and realize controllable release of biomolecules (DNA, siRNA) or drugs (Kim et al. 2012).

AuNRs are new precious metal nanomaterial with ease of preparation, controllable shape and size. They also have unique physical and chemical properties,

such as surface-enhanced Raman scattering (SERS), surface plasmon resonance (SPR), two-photon luminescence (TPL), enhanced penetration and retention (EPR) effects, photothermal effects. Through surface modification, the multifunctional nano-complex can further expand applications of AuNRs in the fields of sensing and detection (le Tuyen et al. 2012; Sivashanmugan et al. 2013; Osberg et al. 2012; Hu et al. 2012; Komathi et al. 2013; Truong et al. 2012), biocatalysis (Zhou et al. 2012; Blankschien et al. 2012), imaging (Gui and Cui 2012; Dreaden and El-Sayed 2012; Ng et al. 2013; Zhu et al. 2012a; Zhang et al. 2012; Ju et al. 2013), drug and gene delivery (Tucker-Schwartz et al. 2012; Ramos and Rege 2012; Chu et al. 2013; Chakravarthy et al. 2010; Alkilany et al. 2012), hyperthermia (Gui and Cui 2012; Dreaden and El-Sayed 2012; Chakravarthy et al. 2010; Dreaden et al. 2012a, b) and multifunctional diagnose platform (Zhang et al. 2012; Ren et al. 2013). Various applications of AuNRs in biomedical fields are illustrated in Fig. 1. Herein, we will elaborate the functionalization, biomedical applications, and bio-effects of AuNRs-based nano-carriers,

and discuss some difficulties and challenges in the future applications of AuNRs.

Modification and functionalization of AuNRs

AuNRs have been synthesized for several decades, and the seeded growth syntheses have attracted much attention in AuNRs optical properties and applications (Lohse and Murphy 2013). Surface modification of AuNRs is very essential to its stability and cytotoxicity (Kim et al. 2013). AuNRs synthesized in laboratory often have a layer of CTAB molecules on the surface, and the high concentration of salts in the biosystems could induce CTAB molecules to shed off, leading to aggregation. Surface functionalization could dramatically change the situation, it could alter surface properties of AuNRs, increase AuNRs stability in solution and improve the transmission of AuNRs in biosystems. Three general surface functionalization methods for AuNRs are presented in Fig. 2. For example, to modify AuNRs with compounds-containing mercapto group, for instance mercapto group-

Fig. 1 Schematic representation of biomedical applications of AuNRs-based nano-carriers
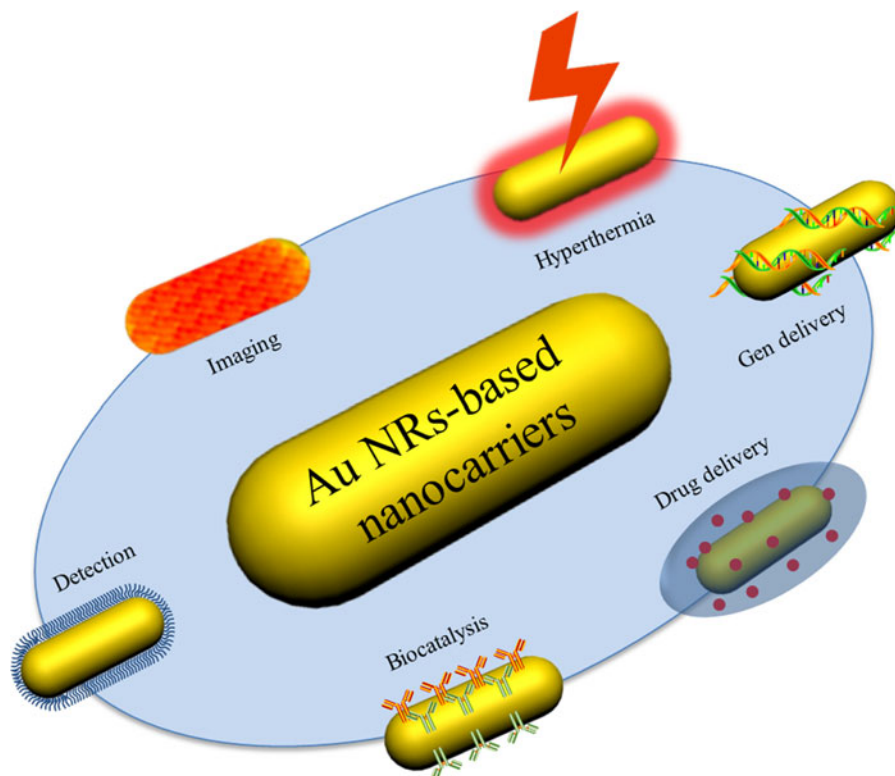
terminated poly(ethylene glycol) (PEG-SH), could form stable gold–sulfur ligand bond. It can effectively prevent the reunion of AuNRs, against non-specific adsorption of proteins. As a result, prolongs the circulation time in vivo and increases the accumulation of AuNRs at tumor site. Kim et al. (2010) studied on the plasmonic properties of 6-nm gold nanoparticles in 4-cyano-4-*n*-pentylbiphenyl (5CB), they found that the solubility was obviously enhanced after the surface capping material was changed to ligands that chemically resemble the liquid crystal molecules.

Electrostatic adsorption or layer-by-layer polyelectrolyte assembly is commonly used to functionalize AuNRs. Firstly, to adsorb anionic polyelectrolyte polystyrene sulfonate sodium (PSS) on positive-charged CTAB molecules, followed by adsorption with poly (diallyldimethyl ammonium chloride, PDDAC) (Chakravarthy et al. 2010). Compared with CTAB modification, PDDAC modification can obviously reduce toxicity of AuNRs, and increase cellular uptake of AuNRs remarkably (Qiu et al. 2010). Vigderman et al. functionalized AuNRs by complete exchange of CTAB with its thiolated analog (16-mercaptohexadecyl) trimethylammonium bromide (MTAB). Inductively coupled plasma-optical emission spectrometry (ICP-OES) showed that breast cancer cells (MCF-7) could uptake extremely large number of AuNRs (Vigderman et al. 2012). AuNRs

can also be modified with specific surface groups and covalently linked with nucleic acids, proteins or other targeting ligands, such as RGD peptide (Oyelere et al. 2007; Xiao et al. 2012a), folic acid (FA) (Huang et al. 2011), delta enkephalin (Black et al. 2008), these modifications can also be further used in gene therapy (Yamashita et al. 2011).

Another strategy often used to functionalize AuNRs is physical modification by forming shell structure of mesoporous silica around AuNRs. Gorelikov and Matsuura (2008) reported the one-step synthesis they coated one thin layer of mesoporous silica around AuNRs. In the process of synthesis reaction, the CTAB molecule on the surface of AuNRs can be used as 3D polymerization reaction templates of tetraethyl orthosilicate (TEOS), which could contribute to the formation of mesoporous structure. High aspect ratio, large pore size, excellent biocompatibility, superior chemical and thermal stability, all of these features make mesoporous silica-coated AuNRs superior carriers for drug and gene delivery (Slowing et al. 2008; Xu et al. 2012). The layer of silicon dioxide could improve the dispersibility of AuNRs and reduce toxicity by shielding unstable and toxic CTAB molecules. So far, mesoporous silica-coated AuNRs have already been applied in biological imaging (Huang et al. 2011), hyperthermia (Chen et al. 2010a), drug and gene delivery (Chen et al. 2010b).

Fig. 2 Schematic representation of three general surface functionalization methods for AuNRs
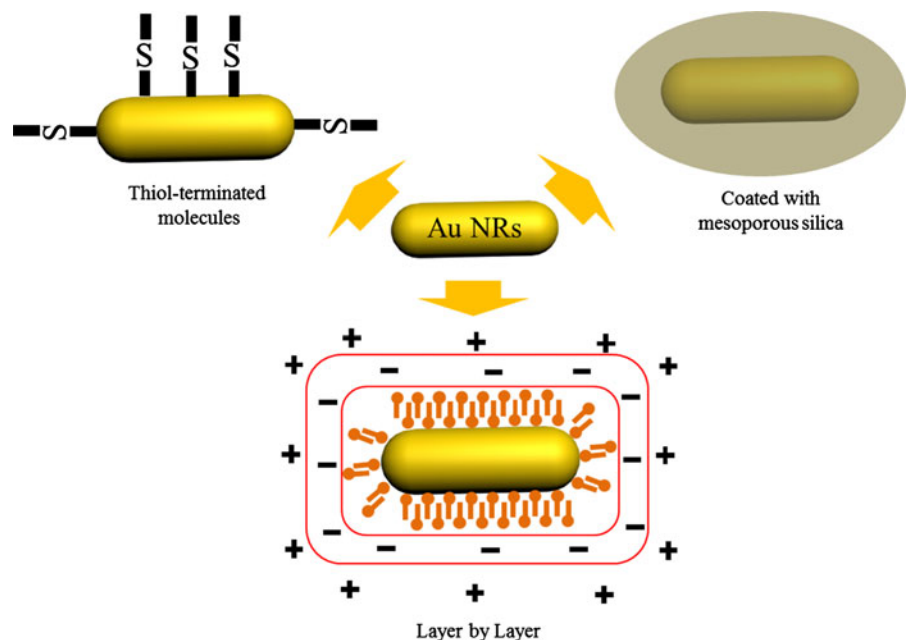
Biomedical applications of AuNRs-based nano-carriers

In recent years, development of new formulations of drugs and biological products based on nano-carriers has become an important trend in current research in nano-biomedical fields. Nanoparticles could carry and transport a variety of biomolecules and drugs including nucleic acids, polypeptides, proteins, radioactive substances, chemotherapeutic drugs, fluorescent probes, photosensitizers (Vigderman and Zubarev 2012), which show great prospects in early diagnosis and treatment (Dreaden et al. 2012a, b). Various biomedical applications of AuNRs-based nano-carriers are presented in Table 1. Meanwhile, AuNRs could achieve efficient drug loading, controllable drug release by stimulus of microenvironment or external physical stimulus (light, magnetism, ultrasound, heat, electricity) (Table 2). For example, sensitive response to acidic pH of tumor tissue or protease of organisms and the light-mediated remote control of drug release corresponding to dose and time show great value in future cancer therapy.

Carriers for biological detection

Based on the properties of SERS and SPR, AuNRs can be used as carriers for detection of proteins, nucleic acids and other molecules (Fig. 3). Lu et al. (2012) used the photoluminescence of plasmonic AuNRs to detect biotin–streptavidin-binding efficiency, the results indicated that the photoluminescence can provide an alternative way for label-free plasmonic sensing and the detection sensitivity was improved to a large extent. Zhu et al. (2013) investigated the spectroscopic-sensing of RNA folding, they found that the length of the RNA, AuNRs aspect ratio, large dielectric constant (DC) difference between RNA shell and environmental media were important factors affecting the sensitivity of detection. Spadavecchia et al. (2013) studied the detection of DNA hybridization using the plasmonic properties of AuNRs, the amplification results in a significant decrease of the limit of detection from 40 nM as observed for unlabeled DNA to 0.2 nM for labeled DNA molecules. Sun et al. (2012) used glucose oxidase (GOx)-modified AuNRs as label to study the sensitive

electrochemical immunosensor for the detection of protein biomarker tumor necrosis factor α (TNF-α), the results showed that the immunosensor had higher sensitivity, wide linear range (0.005–10 ng/mL) and upstanding selectivity. Kim et al. designed a material strategy for a type of bio-interfaced system which relied on ultrathin electronics supported by bioresorbable substrates of silk fibroin. These concepts showed important opportunities for diagnosing and treating disease and for improving brain/machine interfaces (Kim et al. 2010).

However, owing to the complexity of biosystems, AuNRs confronts a lot of limitations in the fields of in vivo detection. SERS could detect a variety of spectral information which is very difficult to analyze. The repeat sequences of biomolecules could also lead to overlapping of information in SERS spectrum. In addition, because of the weak signal intensity of SERS, it usually takes long-point scan time to get better results. Therefore, it needs detailed analysis when detecting biomolecules (Willets 2009).

Carriers for biocatalysis

Insufficient coordination of surface atoms could lead to high surface energy and increase surface active sites, these characteristics are basic conditions for AuNRs as superior catalyst. Blankschien et al. reported the fabrication of light-responsive and thermophilic enzyme-photothermal AuNRs complex. They found that the enzyme can significantly improve the efficiency of glucose decomposition under light activation. The encapsulated nanocomplex turned out to be reusable and stable for several days, which makes AuNRs useful in industry and in the research on biochemical pathways (Blankschien et al. 2012). He et al. formed Au@Pt nanostructure by depositing Pt dots on the surface of AuNRs by transporting oxygen to the solution, and the Au@Pt could lead to the oxidation of vitamin C quickly. Because of the similar activity to oxidase, peroxidase, catalase, the nanocomplex can also be used as catalyst in reduction reaction as well as decomposition reaction (He et al. 2011). The properties of low cost, high stability, small affect by reaction condition, adjustable enzyme activity (Fig. 3) make AuNRs very suitable for catalytic reaction especially for oxidation–reduction reaction.

Table 1 Biomedical application of AuNRs-based nano-carriers and division according to its function

Function	Modification	Targeting ligand	Cell line/ tumor model	Achievements	References
Detection	4-ATP	Microcystin-LR-ovalbumin	N/A	Linear detection range is from 0.01 to 5 ng mL^{-1}	Zhu et al. (2012b)
	Silica OTMS, DSPE-PEG	DTTC	Tumor-bearing mice	Achieve multimodal tumor detection and photodynamic therapy	Zhang et al. (2013b)
	GO	Transferrin antibody	N/A	Permit 32 times enhancement in sensitivity	Zhang et al. (2013a)
Biocatalysis	CTAB	Tthermophilic enzyme *Aeropyrum pernix* glucokinase	N/A	Decomposition rate of glucose is 60 % under light irradiation	Blankschien et al. (2012)
	Shell structure	Pt	N/A	Lead to the oxidation of vitamin C quickly	He et al. (2011)
Gene delivery	Poly(amino ether)	Plasmid DNA	PC3/PC3-PSMA cells	Exhibit higher transgene expression and lower cytotoxicity	Ramos and Rege (2012)
	Positive charged	ssRNA	Type A influenza virus, A549 cells	Inhibit viral replication effectively through activation of immune response	Chakravarthy et al. (2010)
	MHA	Two different DNA oligonucleotides	N/A	Release is efficient and released oligonucleotides are still functional	Wijaya et al. (2008)
Drug delivery	Carboxyl group	Folate, DOX	KB cells	Achieve monitoring the drug and vehicle by multi-photon microscopy	Book Newell et al. (2012)
	PEG	Folate, DNA, DOX	KB/HeLa-Luc cells	Selectively deliver upon NIR irradiation	Xiao et al. (2012b)
	PEG	Platinum prodrug	A549, A549R cells	Overcome cellular resistance associated with deactivation	Min et al. (2012)
	Silica	Kanamycin	*E. coli* BL21	Obvious synergistic effect are achieved	Hu et al. (2013)
Hyperthermia	Mesoporous silica	DOX	A549 cells	Multifunctional theranostic platform with hyperthermia, imaging, chemotherapy is established	Zhang et al. (2012)
	PEG, 11-mercaptoundecanoic acid	Paclitaxel	KB-3-1/ A549 cells	Have the potential of preventing tumor reoccurrence and metastasis	Ren et al. (2013)
	Chitosan	Cisplatin	HeLa/H22, tumor-bearing mice	The hyperthermia could increase the sensitivity of cancer cells to chemotherapeutic drugs	Chen et al. (2013b)
Imaging	PEG	N/A	U2OS/HeLa cells	Individual nanorods in live U2OS cells could be followed in 3 dimensions for over 30 min	van Noort et al. (2013)

Table 1 continued

Function	Modification	Targeting ligand	Cell line/ tumor model	Achievements	References
	Silica	N/A	MSC cells	Achieve lower background values and high spatial and temporal resolution	Jokerst et al. (2012)

A549 human pulmonary adenocarcinoma cells, *A549R* cisplatin-resistant A549 cells, *DSPE* 1,2-distearoyl-sn-glycero-3-phosphoethanolamine, *DTTC* 3,3′-diethylthiatricarbocyanine iodide *E. coli*, *BL21* an *E. coli* B strain that lacking Lon and ompT protease, *HeLa* human cervical carcinoma cells, *H22* murine hepatic cells, *KB-3-1* a derivative of HeLa (DSM ACC 57), *MHA* mercaptohexanoic acid, *MSC* mesenchymal stem cells, *NIR* near-infrared, *OTMS* octadecyltrimethoxysilane, *PEG* poly(ethyleneglycol), *PC3* human prostate cancer cells, *U2OS* human osteosarcoma cells, *4-ATP* 4-amino thiophenol

Table 2 Summary of response mode of AuNRs-based nano-carriers

| Mode	Modification	Activator	Cell line	Principle	References
Temperature	CTAB	Poly (*N*-isopropylacrylamide)	Tumor-bearing mice	High temperature could change the size of PNIPAM-coated AuNRs	Kawano et al. (2009)
pH	PEG	cRGD, NOTA	U87MG cells	Hydrazone bond could be broken at lower pH environment	Xiao et al. (2012a)
Enzyme	Peptide sequence	Lectin	HeLa cells, SCC-7 tumor-bearing mice	Matrix metalloproteinase could decompose the peptide, thus induce fluorescent dye releasing after NIR irradiation	Yi et al. (2010)
Light	Poly(vinyl-pyrrolidone)	*N*-methyl-2-pyrrolidone	N/A	UV irradiation could promote cross-linking of PVP chains on the surface of adjacent particles	Grzelczak et al. (2011)
Magnetism	Fe_3O_4, PEG	MR signal	SK-BR-3, MCF-7 cells	Inducing magnetic coupling between Fe_3O_4 nanoparticles	Wang et al. (2009)
Microenvironment	PEG, ScFv peptide, ATF peptide, RGD peptide	EGFR, uPAR, $a_v b_3$ integrin receptor	A549 cells	Antigen–antibody binding	Huang et al. (2010)

ATF amino terminal fragment, *cRGD* cy-clo(Arg-Gly-Asp-ᴅ-Phe-Cys) peptides, *EGFR* epidermal growth factor receptor, *NMR* nuclear magnetic resonance, *NOTA* 1,4,7-triazacyclononane-N,N′,N″-triacetic acid, *PNIPAM* poly(N-isopropylacrylamide), *RGD* arginine-glycine-aspartate, *SK-BR-3* human breast adenocarcinoma cell line, *MR* magnetic resonance, *ScFv* single-chain variable fragment, *U87MG* human glioblastoma cells, *uPAR* urokinase plasminogen activator receptor

Carriers for imaging

Various kinds of imaging can be achieved due to the superior properties of AuNRs (Fig. 4), including intracellular imaging, small animal imaging, and even unmarked imaging. Here, we expound applications of AuNRs-based nano-carriers with different imaging techniques.
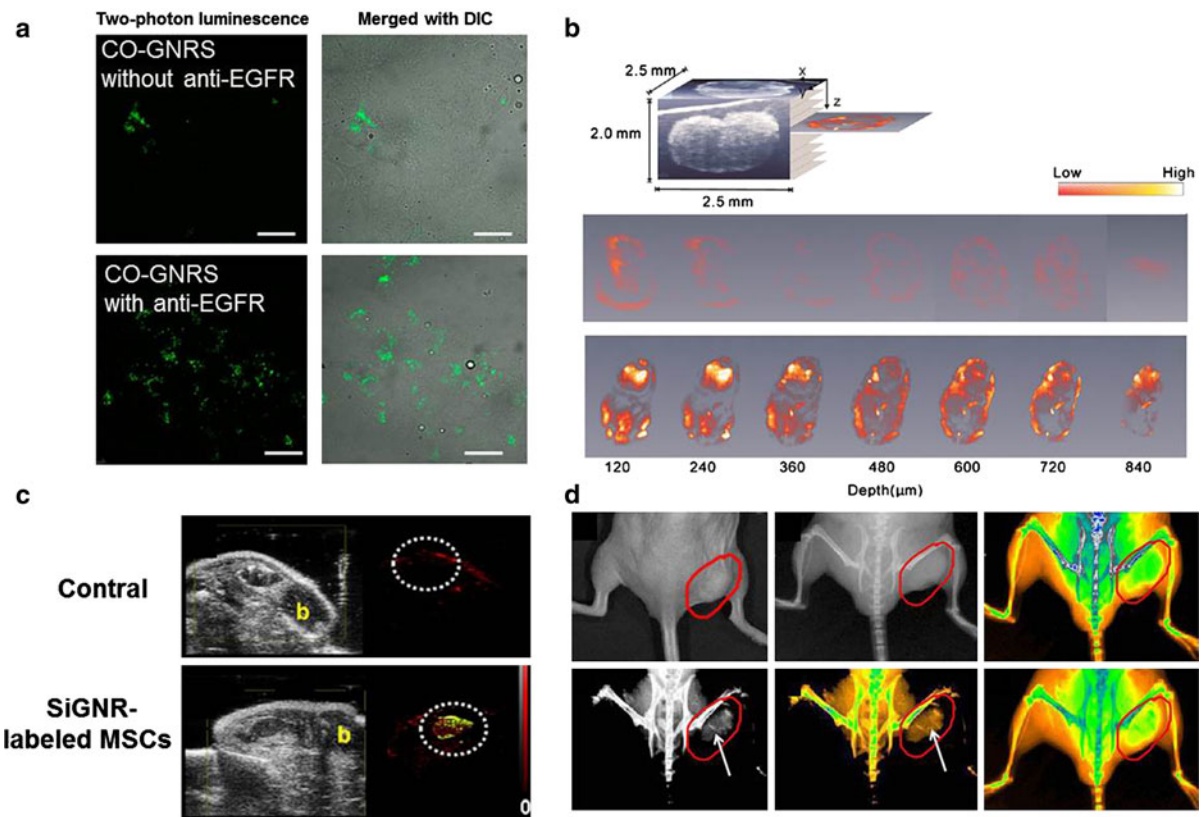
Two-photon luminescence

The TPL imaging of AuNRs have been widely used in the imaging of cells, tissues, vicinal blood vessels of epidermis. Wang et al. used femtosecond pulse laser to irradiate AuNRs at wavelength of 830 nm. They found that the two-photon fluorescence intensity produced by AuNRs was 58 times higher than that produced by
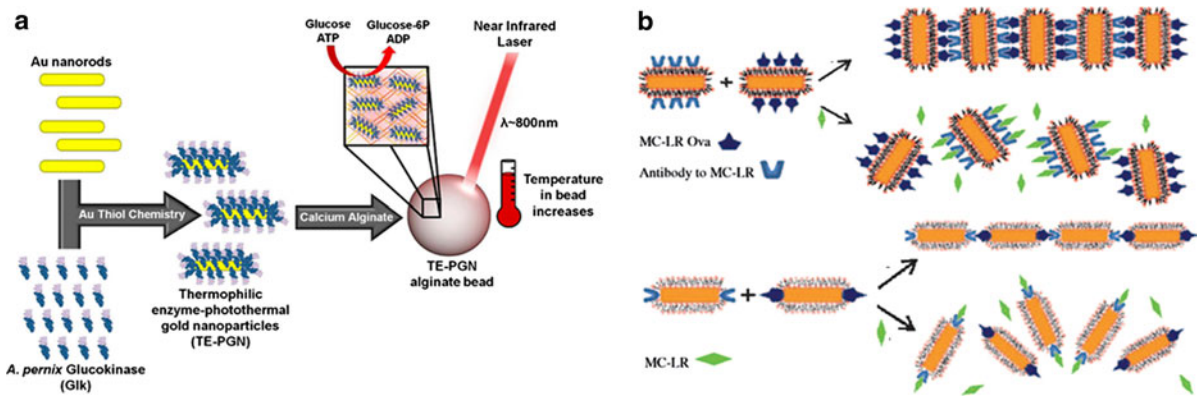
Fig. 3 Schematic illustration of biomedical applications of AuNRs in biocatalysis and biological detection: **a** thermophilic enzyme-photothermal AuNRs (TE-PGNs) synthesis and laser-induced activation. Reproduced with permission from Blankschien et al. (2012), **b** toxin detection method with nanorods assemblies. Reproduced with permission from Wang et al. (2010b)

Fig. 4 Schematic representation of applications of AuNRs in cell imaging: **a** two-photon luminescence and merged image with DIC of CO-GNRS with and without anti-EGFR conjugation in Cal 27 cells. *Scale bar* 10 μm. Reproduced with permission from Charan et al. (2012), **b** cross-sectional PT-OCT images obtained at different depths (120, 240, 360, 480, 600, 720, and 840 μm) below the surface by slicing the 3D data cube. Reproduced with permission from Jung et al. (2011), **c** in vivo presents both B-mode (*gray scale*) and PA (*red*) images of the intramuscular injection of negative control and SiGNR-labeled MSCs. Reproduced with permission from Jokerst et al. (2012), **d** real-time in vivo X-ray images after intravenous injection of AuNRs–SiO$_2$–FA in nude mice at different time points. Reproduced with permission from Huang et al. (2011). (Color figure online)

rhodamine. After injection of mice via the tail vein, the fluorescence intensity of AuNRs in the bloodstream was three times higher than the autofluorescence of blood vessels and tissues. These results suggested that AuNRs were very suitable for shallow tissue imaging with the good contrast (Wang et al. 2005). Durr et al. modified AuNRs with surface-specific adsorption of targeted antibodies, they successfully identified the surface receptor molecules of tumor cell and realized three-dimensional imaging of marked tumor cell (Durr et al. 2007). Zhang et al. developed a multi-mode optical imaging microscope, combined with the NIR irradiation, it could induce second harmonic generation (SHG), TPL, linear resonance light scattering with imaging of human skin cancer cells (Cao et al. 2012).

X-ray computed tomography

The X-ray CT is based on the difference of X-ray absorption coefficient at different parts of organism. As the conventional angiography molecule, iodine has high atomic weight and X-ray absorption coefficient, which is often used as contrast agent. However, such contrast agent can cause renal toxicity and could be excreted rapidly by the kidney, making scan time allowed very limited. AuNRs have higher absorption coefficient than iodine, super for bone and soft tissue imaging, can significantly reduce radiation dose and mitigate radiation damage to organism. AuNRs modified with PEG-SH have longer circulation time than iodine which could achieve visualization at molecular level by decorating AuNRs with targeting ligand against the biomarkers of specific diseases. Luo et al. reported that $Au@SiO_2$ loaded with indocyanine green (ICG) could realize dual function of X-ray scanning and fluorescence imaging. $Au@SiO_2$ could enhance the intensity of CT contrast agent and could help to obtain higher contrast images (Luo et al. 2011). Huang et al. synthesized FA-coated $Au@SiO_2$ nanocomplex, they located the tumor using X-ray tomography and established the integrated treatment platform with imaging and hyperthermia (Huang et al. 2011).

Photoacoustic tomography

PTA, similar to ultrasound imaging, is characterized by non-invasive optical imaging. PTA could also achieve deeper tissues detection than TPL. AuNRs have high optical absorption efficiency at wavelength near LSPR, after absorption of laser energy, acoustic shock generated by instantaneous high thermal and thermoelasticity expansion can be detected and converted into information in graphical form through scanning transducer. Wang et al. used AuNRs as photoacoustic imaging probes, by using the enhanced difference photoacoustic microscopy (PAM), they observed the spatial structure of blood–brain barrier in rat model (Wang et al. 2012). Neus et al. synthesized the liposome–AuNRs hybrids consisted of lipid-bilayer-associated AuNRs, they accomplished deep tissue detection, therapy and monitored the distribution in living animals (Lozano et al. 2012). Yang et al. observed the dynamic changes of intracellular AuNRs through optoacoustic imaging, the results demonstrated an successful application of PAM for complements to imaging of non-fluorescent nanoparticles (Yang et al. 2012).

Optical coherent tomography

OCT utilizes the technology of section scanning, and has similar principle with ultrasound imaging. When irradiate the spot at detection site, the phase difference of reflected wave in micro-structure at different depth can be measured by interferometer. The signal–noise ratio of traditional OCT is usually not high enough to achieve high-quality imaging, so researchers designed the core–shell structure of AuNRs to improve it (Zhang et al. 2012; Zhu et al. 2012a; Ng et al. 2013). Ju et al. recently investigated the photoacoustic cavitation for a broad range of ultrasound pressures and nanoparticle concentrations of AuNRs illuminated at wavelength of 724 nm. Results showed that photoacoustic cavitation can be produced at depth in biological tissue without exceeding the safety limits for ultrasound or laser radiation at tissue surface (Ju et al. 2013).

Carriers for hyperthermia

Traditional cancer treatments can cause damage to both normal and tumor cells along with liver and kidney toxicity, inducing hair loss, nausea, and loss of heart function. In general, radiation therapy could kill cancer cells effectively, but it can also cause damage

to normal cells inevitably, inducing bone marrow suppression. The LSPR of AuNRs can be adjusted to near-infrared region, after irradiation by femtosecond pulse laser, the light energy absorbed by AuNRs can be rapidly converted into heat, and the large amount of heat are too late to release while causing AuNRs melting and deformation, and resulting in tumor cell membrane blebbing, enhancement of cell membrane permeability, denaturation of intracellular protein, loss of mitochondrial function, and eventually lead cancer cells to necrosis. Hyperthermia is usually achieved by the physical methods (microwave, electromagnetic field, ultrasound, water bath, hot perfusion) by changing local tumor microenvironment and organelle structure (Shen et al. 2013; Leung et al. 2013). In contrast, moderate hyperthermia can ease negative effects of traditional cancer treatments. Huang et al. conjugated AuNRs to anti-epidermal growth factor receptor (anti-EGFR) monoclonal antibodies. When exposed to continuous red laser at wavelength of 800 nm, both efficient cancer cells diagnostics and selective photothermal therapy could be achieved at the same time (Huang et al. 2006).

Carriers for gene and protein delivery

With the purpose of treating and correcting defects of gene, gene therapy is usually achieved by importing normal human genes or genes that have therapeutic function into target cells by a certain way. But exogenous gene or small interfering RNA has low transfection efficiency and is very easy to be degradation by nuclease in the physiological environment, leading the half-life shortened. Viral vectors have high transfection efficiency, but may cause immune response or even lead to mutation. Therefore, gene transfection need for a safe and low toxicity vector to carry exogenous genes into cells. In recent years, researches on Au NR-based nano-carriers involved transportation of nucleic acids and proteins have attracted much attention. Because DNA and proteins could be modified easily on the surface of AuNRs, and can still maintain the function even after release.

Ramos and Rege synthesized poly(amino ether)-functionalized nano-complex (PAE–AuNRs) using a layer-by-layer deposition approach, and then binded with plasmid DNA by means of electrostatic interaction. The results indicated that the stable and effective PAE–AuNRs assemblies were promising engineered platform for transgene delivery (Ramos and Rege 2012). Chakravarthy et al. used AuNRs to deliver an innate immune activator to against type A influenza virus. They found the GNR-5′PPP-ssRNA nano-complex could activate the retinoic acid-inducible gene I (RIG-I) pathogen recognition pathway. Results suggested that further evaluation of biocompatible nano-complex as unique antivirals for treatment of seasonal and pandemic influenza viruses was warranted (Chakravarthy et al. 2010). Mahajan et al. (2012) designed the nanocomplex by electrostatically binding AuNRs with MMP-9 siRNA, the uptake of nano-complex by BMVEC cells can result in suppression of matrix metalloproteinase-9 (MMP-9) expression, and the nano-complex could also prevent the damage to BBB disruption induced by neuroinflammation. Kah et al. conjugated coronas of serum proteins on AuNRs, and then loaded AuNRs with DNA oligonucleotides and doxorubicin. These coronas can hold small molecular drugs at a capacity much higher (5–10 times) than covalent conjugation strategies can achieve (Kah et al. 2012). Xu et al. (2012) prepared surface-engineered AuNRs, which were used as promising DNA vaccine adjuvants for HIV treatment, they found PDDAC- or PEI-modified AuNRs can significantly promote cellular and humoral immunity as well as T-cell proliferation. These findings shed lights on the rational design of low-toxic nanomaterial as a versatile platform for vaccine nanoadjuvants delivery systems (Fig. 5).

Carriers for drug delivery

Although chemotherapeutic drugs play an important role in cancer treatment, they still have many disadvantages, such as large demand, significant side effects, non-specific targeting, susceptible to be discharged or even causing multidrug resistance. These shortcomings significantly limit their clinical applications. AuNRs could be used as nano-carriers of drugs, and release of drugs can be remotely controlled by external stimuli. Due to its advantages in highly flexible control of dosage and time, the use of light as remote-activation stimuli is worth considering.

Book Newell et al. coupled AuNRs with a targeting ligand, FA and DOX, they utilized multi-photon fluorescence lifetime imaging to monitor the uptake
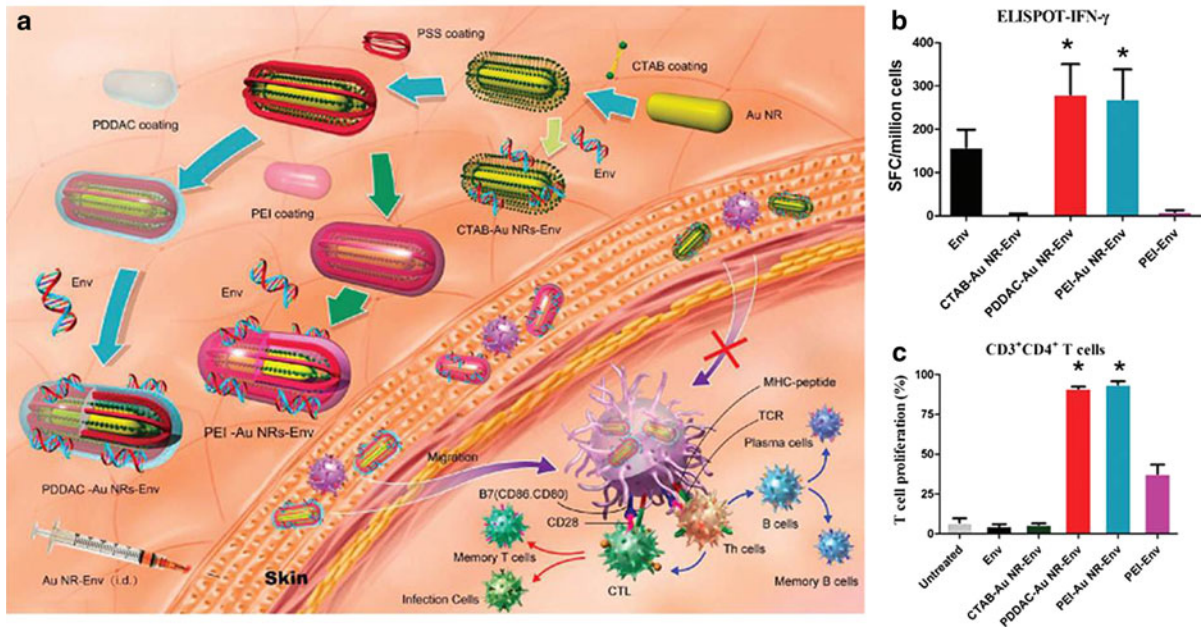
Fig. 5 The mechanism of AuNRs as vaccine adjuvants: **a** AuNRs with different surface coatings mixed with Env plasmid, the effects of AuNRs on the immune response and dendritic cell maturation, **b** IFN-γ analyzed by ELISPOT, **c** CD3$^+$CD8$^+$T cells proliferation. Reproduced with permission from (Xu et al. 2012)

of AuNRs, release of drug and localization of AuNRs in living cells (Book Newell et al. 2012). Min et al. (2010) conjugated PEGylated AuNRs with Pt(IV) prodrug as drug delivery system, it showed superior cytotoxicity to different types of cancer cells compared to cisplatin. Xiao et al. linked DOX onto PEGylated AuNRs via a hydrazone bond to achieve pH-sensitive drug release, and then conjugated tumor-targeting ligands (i.e., the cyclo(Arg-Gly-Asp-D-Phe-Cys) peptides, cRGD) and ^{64}Cu-chelators (i.e., 1,4,7-triazacy-clononane-N,N′,N″-triacetic acid (NOTA)) onto the distal ends of the PEG arms to achieve active tumor-targeting and PET imaging. The results suggested that the multifunctional AuNRs-based nanoplatform can be optimized for combined cancer therapies (chemotherapy and thermotherapy) and multimodality imaging (PET, optical, X-ray CT) (Xiao et al. 2012a).

Combined function of AuNRs-based nano-carriers

Development theranostic systems in nano-scale for effective treatment of tumor have always been a popular trend in nano-biomedical research. By integrating diagnosis, imaging and treatment into one single nanoplatform, AuNRs could realize promising combined functions (Hu et al. 2013).

Carriers for imaging and hyperthermia

Charan et al. linked AuNRs with MUA (11-mercap-toundecanoic acid) and low-molecular-weight chitosan oligosaccharide ($M_w \sim 5,000$), and then conjugated with tumor targeting monoclonal antibody. The results demonstrated that CO–AuNRs could be a potential candidate for localized hyperthermia-based noninvasive imaging and photothermal-related therapies (Charan et al. 2012). Chen et al. (2013a) synthesized a novel nano-seaurchin structure through mesoporous silica-coated AuNRs, the nanoplatform provided stable photoacoustic signal and high efficient hyperthermia effect both in vitro and in vivo, and realize photoacoustic imaging and photothermal therapy simultaneously.

Carriers for hyperthermia and drug delivery

Combining hyperthermia with chemotherapeutic drugs could produce synergistic therapeutic effect

toward tumor cells or even multidrug resistant cancer cells. Ren et al. loaded AuNRs with paclitaxel with high density (2.0×10^4 paclitaxel per AuNRs) via nonspecific adsorption. The combined photothermal therapy and chemotherapy was shown to be highly effective in killing head and neck cancer cells and lung cancer cells (Ren et al. 2013). Chen et al. synthesized multifunctional chitosan nanospheres which co-carried AuNRs and cisplatin, results showed that the nano-complex could produce local hyperthermia to an average temperature of 49 °C in tumor tissue after NIR irradiation for 10 min. Compared with chemotherapy or photothermal treatment alone, the combined photothermal therapy and chemotherapy had a significantly synergistic effect and improved the therapeutic efficacy (Chen et al. 2013b).
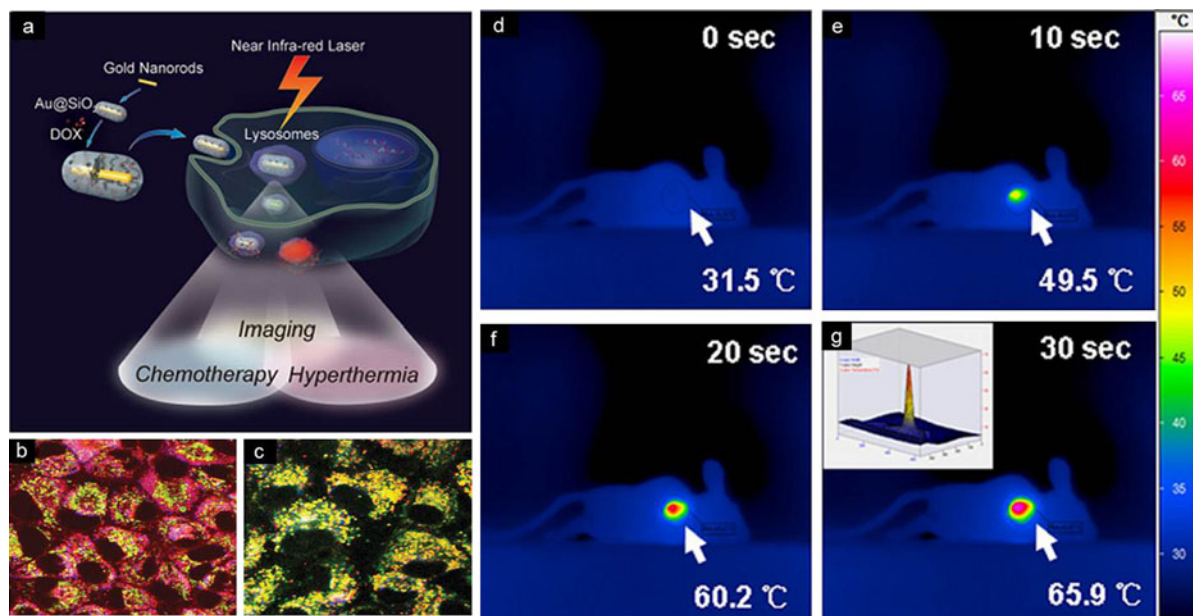
Carriers for imaging, hyperthermia, and drug delivery

In order to expand drug-loading capacity of AuNRs, surface modification such as modified with polymers or mesoporous structure usually be a good choice.

Zhang et al. synthesized the multifunctional nano-carrier (Au@SiO$_2$) loaded with DOX, they coated mesoporous silica structure around AuNRs, and the mesoporous silica can also be functioned as physical barrier to avoid AuNRs reunion. Owing to the controllable TPL imaging and unique LSPR property of AuNRs, it could realize imaging and hyperthermia through NIR irradiation, and the NIR irradiation could also be employed to control drug release. In the treatment options, NIR laser irradiation at a low intensity was used to realize imaging, and achieve temperature rising quickly to induce DOX release from Au@SiO$_2$-DOX. While at a relatively high intensity, it could realize both hyperthermia effect of killing cancer cells and releasing DOX (Fig. 6).

Distribution, transportation, metabolism, and toxicity of AuNRs

Studies on the physical and chemical properties of AuNRs and understanding the mechanism of bio-nano-interaction will help to exert its function more efficient and safe. The distribution, transportation,

Fig. 6 Multifunctional platform of imaging, hyperthermia and drug delivery: **a** TOC image of the report **b**, **c** Intracellular localization of DOX (*red*) and Au@SiO$_2$ (*blue*) with organelle-specific probes. Reproduced with permission from (Zhang et al. 2012) The infrared thermal image of tumor-bearing mouse (**d–g**) under an 808 nm NIR laser irradiation at 2 h post intravenous injection (i.v.) of pGNRs@mSiO$_2$-RGD with 3 W/cm^2 for 30 s (*inset* the 3-D temperature map). The *color bar* relates the relative temperature values in °C (*upper*). Reproduced with permission from (Shen et al. 2013). (Color figure online)

metabolism, and toxicity of AuNRs are the major aspects of safety evaluation. Cellular uptake and toxicity of AuNRs are closely related to surface modification, aspect ratio, and cell types. Chen and Irudayaraj, for the first time, quantified the localization and evaluated the diffusion time of herceptin-conjugated AuNRs in different cell organelles by fluorescence correlation spectroscopy (FCS). They found that herceptin-conjugated AuNRs had similar intracellular localization as herceptin ErbB2 complex had (Chen and Irudayaraj 2009). Wang et al. studied on the interaction between AuNRs and different cell lines. They observed that AuNRs had distinct effects on cell viability via killing cancer cells while posing negligible impact on normal cells. This differed in cellular uptake, intracellular trafficking, and susceptibility of lysosome to AuNRs by

different types of cells, which lead to the selective accumulation of AuNRs in the mitochondria of cancer cells (Wang et al. 2010a).

In addition, the removal of AuNRs also associated with its exposure pathways. AuNRs could easily be accumulated in the reticuloendothelial system through intravenous injection. However, AuNRs could be discharged in the form of feces when uptake of AuNRs by oral route. So researching on how to avoid being recognized by reticuloendothelial cells, decreasing non-specific accumulation while increasing the volume in target organs, are considerable challenges. When surface-modified AuNRs with PEG, it could reduce the non-specific adsorption of plasma proteins, prolong the circulation time in the blood. As a result, AuNRs accomplished its function through penetrating into the target tissues or cells by the EPR effect

Table 3 Procedures of researching on bioeffects of AuNRs

Research object	Focus	Methods
Microenvironment	1. The influence of corona and physiological microenvironment on the Au NRs property, such as pH, ionic strength, liquid fluidity, temperature	1. Spectroscopy and other conventional bioanalysis methods (CD, LC-MS, SDS-PAGE)
		2. Characterization (zeta potential, SEM, TEM, UV, etc.)
		3. Structure analysis methods (NMR, X-ray crystallography) and advanced nuclear technology (XAFS, XRF, SAS)
Cell	1. Cellular uptake, transportation, metabolism, secretion, and degradation	1. Quantitative analysis (ICP-MS, AES)
	2. Organelles targeting	2. Location and chemical state analysis (TEM, CLSM, XRF, XMCT)
	3. Cellular signal pathways and responses (proliferation, differentiation, apoptosis, immune activation, migration, and cell–cell interaction)	3. Conventional biochemical and cytological methods
Tissue, organ	1. Tissues and organs targeting property, non-specific enrichment	1. General tissue and pathological method (IHC)
	2. The physiological function of targeted tissues and organs (liver, lungs, kidneys, etc.)	2. Quantitative analysis method (ICP-MS)
	3. Structure and function of biological barriers	
	4. The long-term effects	
Individual level	1. Conventional toxicity indicators (blood and urine biochemistry, heart rate, genetic, and neurological toxicity)	1. Small animal imaging technology
		2. Quantitative analysis method (ICP-MS)
	2. Animal behaviors, breeding, and growth	
	3. The long-term effects	

AES atomic emission spectroscopy, *CD* circular dichrism, *CLSM* confocal laser scanning microscope, *ICP-MS* inductively coupled plasma mass spectrometry, *IHC* immunohistochemical, *LC–MS* liquid chromatograph–mass spectrometer, *SAS* small-angle scattering, *SDS-PAGE* sodium dodecyl sulfate polyacrylamide gel electrophoresis, *SEM* scanning electron microscope, *TEM* transmission electron microscope, *UV* ultraviolet, *XAFS* X-ray absorption fine structure, *XMCT* X-ray microscope-computed tomography, *XRF* X-ray fluorescence

(Walkey et al. 2012; Akiyama et al. 2009). Huang et al. conjugated AuNRs to three different ligands of solid tumors, and then studied the targeted delivery of AuNRs. The results suggested that these targeting ligands could only marginally improve the total gold accumulation in xenograft tumor models in comparison with non-targeted controls, but could greatly alter the intracellular and extracellular nanoparticle distributions (Huang et al. 2010).

When researching on the bio-effects of AuNRs, researchers need to pay attention to different aspects, such as biomolecules, microenvironment, cells, tissues, organs, and individual level (Table 3). The methods include conventional characterization, spectroscopic analysis, structural analysis, quantitative analysis, conventional molecular and cell biology techniques, organization and pathological techniques, small animal imaging techniques, etc. All these methods could also provide mirrors for the researches on bio-effects to other metal nanomaterials.

Conclusions

AuNRs could absorb proteins in biological systems, thus forming protein–AuNRs nano-complex. These proteins could probably block functions of molecules modified on the surface of AuNRs, which in turn decreases the sensitivity of biological detection. Therefore, how to design suitable modification methods and exposure pathways to reduce the non-specific adsorption of proteins, achieve long blood circulation time, and eventually be cleared by the body, are problems to be resolved.

The bio-effects of AuNRs are complex processes. Researchers need dynamically monitor the behavior of AuNRs in vivo and in vitro, and focus on the long-term effects before achieving comprehensive biomedical applications. However, relevant systematic researches are very limited. Therefore, it is very necessary to carry on multi-faceted evaluation on bio-effects of AuNRs. The focuses should be extended from conventional cytotoxicity to the influence on immune system, respiratory system, cardiovascular system, and reproductive system.

Owing to limited light penetration depth in tissue, the applications of optical imaging techniques are still limited for AuNRs. How to combine deep imaging techniques (X-ray tomography imaging, magnetic resonance imaging, and body-embedded optical fiber), while achieving imaging and therapy simultaneously are still worth exploring. High-throughput screening combined with metal genomics (metal characterization and analytical methods) and biological genomics (biochips, proteomics) could help to evaluate and predict structure, performance, functionality of AuNRs systematically (Li et al. 2008).

In summary, AuNRs-based nano-carriers have great potential in biomedical fields, such as biological monitoring, imaging, thermotherapy and multifunctional nano-complex diagnose, and all these bring ideas and hopes to the development of biomedicine. In connection with structure, property and bio-effects of AuNRs, developing real-time, sensitive, high-throughput detection, and analysis methods could be the important consults to rational design of AuNRs-based nano-carriers. Ultimately, through surface modification and functionalization, it could improve targeting of AuNRs, reduce immune response and other negative effects, these AuNRs-based multifunctional nano-carriers will play crucial role in future biocatalysis, disease diagnosis, imaging and therapy.

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