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Review Article

Preparation, Modification, and Application of Hollow Gold Nanospheres

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Hollow gold nanospheres (HGNs) have great potential applications in biological sensing, biomedical imaging, photothermal therapy, and drug delivery due to their unique localized surface plasmon resonance (LSPR) feature, easy modification, good biocompatibility, and excellent photothermal conversion properties. In this review, the latest developments of HGNs in biosensing, bioimaging, photothermal therapy, and drug delivery are summarized, the synthesis methods, surface modification and bioconjugation of HGNs are also covered in this summary.

1. Introduction

As an important member of nanomaterials, gold nanomaterials have drawn wide attention in the biomedical field due to its numerous excellent properties [1, 2]. There are many types of gold nanomaterials, including gold nanospheres (GNSs) [3], gold nanorods (GNDs) [4], hollow gold nanospheres (HGNs) [5], gold nanostars [6], gold nanocages [7], and gold nanorings [8]. HGNs have attracted a lot of interest due to their excellent chemical/physical properties. First, compared with gold nanospheres whose absorption peaks are located in visible region, the absorption peaks of HGNs could be adjusted to the near-infrared region (700~900 nm) [9]. Near-infrared light has high penetration depth in biological tissue and fluids because these biological species lack absorbing groups in the infrared region of the spectra, which offers unparalleled advantage in photothermal treatment using near-infrared lasers. Second, HGNs have less toxicity than GNRs, because CTAB, which has biotoxicity, is not necessary in synthetic process of HGNs. In addition, hollow structure of HGNs generates minimum mass in the same size of gold nanostructures of different morphologies. The hollow structure makes them able to load medicines and other functional materials, which form significant advantages in drug delivery field. Furthermore, with a series of advantages such as good biocompatibility, excellent photothermal conversion, and easy modification with a variety of biological molecules, HGNs have broad application prospects in biomedical field. In this paper, we review the recent progress of HGNs in the fields of biomedical imaging, drug delivery, diagnostics, and photothermal therapy for disease treatments.

2. Synthesis, Surface Modification, and Bioconjugation of HGNs

2.1. Synthesis of HGNs. A variety of approaches have been developed for the synthesis of HGNs, mainly including sacrificial galvanic replacement of cobalt nanoparticles [10, 11], templated galvanic replacement reaction of silver for gold [12, 13], and electrochemistry [14]. In addition, there is

another method which uses nonmetallic structures as core and gold as shell to prepare hollow gold nanospheres. Among these, template substitution has been widely used because it could adjust the SPR peak position through controlling the size of templates and the amount of chloroauric acid.

2.1.1. Sacrificial Galvanic Replacement of Cobalt Nanoparticles. Sacrificial galvanic replacement of cobalt nanoparticles is a popular method to synthetize HGNs currently. The fundamental is introduced as follows. Cobalt nanoparticles (CoPNs) with uniform size distribution are synthesized through reducing $CoCl_2$ by $NaBH_4$ in anaerobic environment. After $NaBH_4$ is consumed totally, gold nanoparticles are deposited on the surface of CoPNs through replacement reaction between $HAuCl_4$ and CoPNs. After $HAuCl_4$ is consumed completely, unoxidized CoPNs are oxidized to Co^{2+} by oxygen dissolved in the solution. Sequentially, HGNs are obtained. The reaction equation is shown as follows [15]:

$$3Co + 2AuCl_4^- = 2Au + 3Co^{2+} + 8Cl^- \quad (1)$$

Liang et al. [15] first reported the use of sacrificial galvanic replacement of cobalt nanoparticles to synthesize uniform HGNs. They obtained HGNs in different size by adjusting the stoichiometric ratio of $HAuCl_4$ and reducing agent $NaBH_4$ and coated silica (SiO_2) on the surface of HGNs, finally characterized HGNs with transmission electron microscope (TEM), high resolution transmission electron microscopy (HRTEM), scanning electron microscopy (SEM), X-ray diffraction (XRD), electron diffraction, energy-dispersive X-ray analysis, and UV-visible absorption spectroscopy. The results showed that HGNs obtained by this method have uniform particle size, good dispersion, and adjustable SPR peak location. Subsequently, Schwartzberg et al. [16] also used sacrificial galvanic replacement of cobalt nanoparticles to synthesize HGNs and systematically studied the effects of various reactants to the formation of HGNs. The study showed that particle size and thickness of the shell of HGNs could be adjusted by changing the size of the cobalt template and the amount of $HAuCl_4$. The SPR peak position of HGNs would be adjusted from 550 nm to 820 nm with the various ratio of HGNs particle size and shell thickness. Cobalt template size can be adjusted by changing the concentration of reducing agent $NaBH_4$ and protective agent such as sodium citrate. The thickness of the HGNs shell can be adjusted through controlling the amount of $HAuCl_4$ solution. HGNs with good morphology can be prepared through this method, which has been adopted by many researchers. Preciado-Flores et al. [17] made experimental improvements afterwards and they introduced polyvinylpyrrolidone (PVP) as a stabilizer to prepare HGNs with good dispersion and SPR peak in near-infrared region (~800 nm).

2.1.2. Templated Galvanic Replacement Reaction of Silver for Gold. Templated galvanic replacement reaction of silver for gold is another important method of synthetizing HGNs. The principle is that, first, silver nanoparticles (Ag NPs) are synthesized, and then gold particles deposit on the surface of silver template through replacement reaction between $HAuCl_4$ and Ag NPs and gradually form gold shell. Many types of gold nanoparticles can be synthesized through this method; the morphology and size of gold nanoparticles are determined by the silver templates. Reaction equation is shown as follows [13]:

$$3Ag_{(s)} + AuCl_4^-{}_{(aq)} \longrightarrow Au_{(s)} + 3Ag^+{}_{(aq)} + 4Cl^-{}_{(aq)} \quad (2)$$

Zhang et al. [18] successfully prepared HGNs using Ag NPs as template. They prepared Ag NPs by reducing silver nitrate with ethylene glycol in the presence of PVP firstly and then prepared HGNs through replacement reaction between $HAuCl_4$ and Ag NPs using Ag NPs as template. Prevo et al. [12] synthesized HGNs via the templated galvanic replacement reaction of silver for gold. The sizes of HGNs synthesized by this method range from 20 to 50 nm in diameter and the SPR absorbance of HGNs can be tuned to 800 nm.

2.1.3. Electrochemistry. Electrochemistry is another important method of synthesizing HGNs. You et al. [19] electrodeposited silver ions on indium tin oxide (ITO) glass surface directly through cyclic voltammetry to prepare Ag NPs without any surfactant or organic ligand and then gained HGNs by replacement reaction between $HAuCl_4$ and Ag NPs (using Ag NPs as template). HGNs surface obtained by this method can be modified with a variety of biological molecules, and the SPR peak position can be adjusted to the near-infrared region (~800 nm), which has very important applications in the field of biosensing.

2.1.4. Other Methods. Another method of preparation HGNs is using nonmetallic structure as core and gold as shell. Liu et al. [20] synthesized hollow C-60 nanometer shell, firstly. Then using the hollow C-60 nanometer shell as template, gold particles were deposited on the surface of C-60 by electrochemical reduction. Finally HGNs were deposited. Graf and van Blaaderen [21] synthesized SiO_2 nanoparticles by Stöber method firstly and adsorbed gold particles on the surface to form gold shell and finally obtained hollow gold nanospheres by dissolving SiO_2 core with hydrofluoric acid. Zhong et al. [22] used the cross-linked product of glucose oxidase (GOD) and glutaraldehyde as template and then used ascorbic acid to reduce $HAuCl_4$ and adsorbed gold particles on the template surface and finally prepared gold nanospheres with hollow structure.

2.2. Surface Modification and Bioconjugation of HGNS. In order to enhance the biocompatibility or achieve particular function of HGNs, it is necessary to modify the surface. HGNs have good surface chemical property, which can bind a lot of small organic molecules or biological macromolecules together in covalent or noncovalent manner.

In order to reduce electrostatic and hydrophobic interactions between nanoparticles and avoid being cleared by human reticuloendothelial system (RES), biocompatible stabilizers are often modified on the surface of nanoparticles. Polyethylene glycol (PEG) is a commonly used stabilizer, which can effectively prevent the nanoparticles being cleared

by the RES, and thus the nanoparticles have longer cycle time in the body [23]. In addition to PEG [19], there are many materials for surface modification of HGNs, such as silicon dioxide [15], PVP [17], dextran [24], sodium citrate [25], and the likes.

Drugs or nanoparticles generally have two approaches going into the tumor site: passive targeting and active targeting. Passive targeting aggregates drugs or nanoparticles at the tumor site through enhanced permeability and retention effect (EPR effect) of solid tumor tissue. However, this targeting approach is not effective for all tumors, because the degree of tumor angiogenesis and polarity will be different due to different tumor types and states. In addition, passive targeting is also easy to induce multidrug-resistant, which is not conducive to the treatment of tumors [9]. Active targeting makes up the deficiency of passive targeting. In active targeting, nanoparticles and the targeted molecules are bound in some ways. Directional marker to tumor is achieved through the bond between targeted molecules and tumor-specific cell surface receptor and ultimately attains treatment purposes. Active targeting can enrich nanoparticles or drugs at the tumor site initiatively which could significantly improve the accuracy of treatment and effectively reduce the digestion of drugs in body. Therefore, active targeting has significant advantages in treatment of tumors.

Commonly used tumor targeted molecules include antibody molecules [26], polypeptide [27], aptamer [28], antagonist [29], and folic acid (FA) [30]. Liu et al. [31] applied HGNs conjugated with monoclonal antibody (anti-$TROP_2$) to photothermal therapy of cervical cancer (HeLa) cells. The monoclonal antibodies can specifically bind highly expressed trophoblast cell surface antigen 2 (TROP2) of HeLa cells. Studies have showed that under the laser irradiation of right intensity, comparing with tumor cells incubated with nontargeted probes, the growth of tumor cells incubated with HGNs that conjugated monoclonal antibodies was significantly inhibited. Tian et al. [27] compared the intake behaviors between HGNs probes with targeted RGD (arginine-glycine-aspartic acid) peptide IA-RGD-PEG-HGNs and probes without targeted molecules after the intravenous injection in mouse liver cancer model. The results showed that, 24 h after intravenous injection, intake of probes with RGD was much higher than that without RGD (0.20 versus 0.099% ID/g; $P < 0.001$), which showed advantages of active targeting compared with passive targeting.

3. Biomedical Applications of HGNs

HGNs are widely used in biosensing, biomedical imaging, photothermal cancer therapy, and delivery transportation of drugs or genes.

3.1. HGNs in Biological Sensing. Gold nanoparticles (Au NPs) have unique localized surface plasmon resonance (LSPR) characteristic. The LSPR peak position is closely linked with morphology, size, and surrounding medium of nanoparticles, especially the refractive index (RI) of matter close to the nanoparticle surface. Compared with solid gold nanospheres (SGNs), HGNs have a higher refractive index sensitivity [32, 33]. LSPR sensors based on changing the LSPR peak position of Au NPs have been widely used in biosensing [34, 35]. Liu et al. [36] modified HGNs to the surface of electrode using crosslinking agent 1, 6-thiol, and fixed DNA on the modified electrode to prepare novel electrochemical sensors for DNA. They studied hybridization between the probe and the target DNA by cyclic voltammetry and differential pulse voltammetry. The results showed that HGNs can significantly enhance the hybridizing ability of DNA. The DNA sensor had lower detection limit (1 pM), wide dynamic range (1 pM~ 10 nM), high stability, and reusability. Zhang et al. [37] fabricated an electrochemiluminescence (ECL) biosensor based on HGNs modified graphene (C60-rGO) and glucose oxidase (GOX), which could be used to detect knife legumin A (ConA). GOX could catalyze the oxidation of glucose and *in situ* react with a large number of hydrogen peroxides. HGNs would catalyze ECL reactions between luminol and hydrogen peroxide. The joint action of GOX and HGNs caused ECL luminol signal strength to be greatly enhanced. The biosensor had high sensitivity, which could detect ConA within 0.10~100 ng/mL and the detection limit was as low as 30 pg/mL (SNR = 3). These findings explained the important applications of HGNs in nanobiosensing aspect.

3.2. Biomedical Imaging of HGNs. The biomedical imaging applications of HGNs include transmission electron microscopy (TEM), computed tomography (CT), surface-enhanced Raman scattering (SERS) imaging, and photoacoustic imaging (PAI). Among these imaging modes, PAI has drawn much attention. Photoacoustic imaging is a noninvasive biomedical imaging method developed in recent years. Biological tissue generates heat under laser irradiation. The heat results in local temperature increases and thus leads to thermal expansion and pressure wave which means photoacoustic signals. Through the information of body optical absorption characteristics carried in photoacoustic signals, researchers can reconstruct the image of the body optical absorption distribution [38]. Combining the dual advantages of deep penetration in ultrasound imaging and high selectivity in optical imaging, tissue photoacoustic imaging with high contrast and high resolution can be obtained. The most important advantage of photoacoustic imaging is that photoacoustic signal phase and amplitude of sample can be measured directly without pretreatment. The operation is simple and could maintain the natural state of biological sample, which can be detected *in vivo*.

HGNs are excellent photoacoustic contrast agents, because they can effectively enhance the specific absorption of organizations and have much higher photoacoustic efficiency than blood. Lu et al. [39] intravenously injected the PEG-modified HGNs (PEG-HGNs) in nude mice. Two h later, the photoacoustic image was displayed. Photoacoustic image obtained using PEG-HGNs as contrast agent had high contrast resolution, in which the diameter of vessels was as thin as 100 μm, and the contrast agent had no obvious toxicity to the liver, spleen, and kidneys of nude mice. The results showed that the PEG-HGNs was a very promising contrast agent in photoacoustic imaging and had high

resolution and sensitivity. Lee et al. [40] monitored the temperature of tumor site using optoacoustic imaging during the photothermal therapy. The results showed that tumor temperature was raised from 37°C to over 50°C when shining a laser on to the tumor injected with DOX@PEG-HGNs probes. It showed the promising applications of HGNs for photoacoustic imaging and monitoring the temperature of the tumor.

3.3. HGNs in Photothermal Therapy of Tumors. Cancer is a serious threat to the health of people around the world. Traditional cancer treatments (such as surgery, chemotherapy, and radiation therapy) have significant limitations. For example, surgery and radiation therapy cannot solve the problem of systemic metastasis of tumor cells; the chemotherapy needs to send drugs to all parts of the body through blood vessels, so the body cells, whether malignant cells, are damaged, which causes a lot of side effects. Photothermal therapy has become a new cancer therapy. The basic principle is that changing the environment of tumor cells by the method of laser irradiation results in the tumor tissue temperature being raised to the unbearable temperature (41~47°C) [41]. Then, different sensitivity of normal cells and tumor cells to temperature results in necrocytosis and achieves the purpose of treatment of cancer, finally. Photothermal therapy attracts extensive attention because the advantages of less damaging normal tissue and their immune system. Near-infrared light has a good tissue penetration in the human body because human tissues and body fluids have few absorption of light in the near-infrared region. Photothermal therapy using near-infrared light as the light source has been widely used in the treatment of tumors.

At present, scientists have developed a number of nanometer materials for photothermal therapy of cancer, such as carbon nanotubes [42], gold nanometer materials [43], and copper sulfide [44], which can convert light energy into heat under laser irradiation and finally kill cancer cells. Currently, the research on photothermal conversion materials focuses on the gold nanometer materials.

In the gold nanomaterials with different morphologies and structure, HGNs exhibit unparalleled advantages in photothermal therapy of tumor because of so many advantages such as spherical shape, small size, absorption peak which can be adjusted to the near-infrared region, easily modified with a variety of biological targeted molecules on the surface, and good biocompatibility. Conjugating biological targeted molecules (antibodies or ligands) on HGNs and binding with targeted molecules (antigens or receptors) on the surface of tumor cells result in HGNs concentrating in the tumor cells. Then near-infrared light is irradiated to tumor cells. HGNs absorb light and convert light energy into heat energy. It is a very attractive photothermal therapy model to kill tumor cells [45].

Lu et al. [46] prepared targeted biological probes of NDP-MSH-PEG-HGNs, which could actively enriched in melanoma cells of mouse, by coupling targeted molecules of α-melanocyte stimulating hormone analogue (NDP-MSH) with HGNs and modifying stabilizer of PEG. They compared the survival condition of cells being incubated with the targeted probes and nontargeted probes under the same laser irradiation conditions. The results showed that the targeted probes had maximum lethality to cells under near-infrared laser irradiation, while nontargeted probes, independent laser irradiation, or targeted probes had small lethality. Melancon et al. [47] conjugated antibody anti-EGF to the HGNs to prepare anti-EGFR-HGNs probes which could be positioned in the A431 cells of epidermal carcinoma cell line. The probes were applied to the photothermal therapy at cellular level. The results showed that the majority of A431 cells incubated with targeted probes were killed, while cells under laser irradiation alone or incubated with nonspecific targeted probe under laser irradiation almost had no damage. The results proved the targeted HGNs have excellent effect on photothermal therapy of tumor cells. Thus, the HGNs conjugated with targeted molecules have a very important practical value in the near-infrared photothermal therapy of tumor.

3.4. HGNs in Drug Delivery. Chemotherapy is an important method of treating cancer. Many anticancer drugs are difficult to give full play to efficacy in treatment because of poor stability, low solubility, being nontargeted, and easy removal by metabolism. However, loading cancer drugs on a suitable support cannot only extend residence time of drugs in the body, thereby improving the utilization of drugs, but also control the release of drugs. In addition, if the carrier is conjugated with targeted molecules, it can also greatly reduce the cytotoxicity of drugs to normal cells caused by no targeting. Ideal drug carriers should have characteristics of chemically stable, long half-life, nontoxic or low toxic, biodegradable, large drug loading capacity and others. Among the many nanometer materials, HGNs have been widely used as drug carriers because of cavity structure, large specific surface area, good biological safety and biocompatibility, and easy surface functional modification. You et al. [48] loaded the antitumor drug doxorubicin (DOX) with GNSs and HGNs (shell thickness of 4 nm) of same gold content and size of 40 nm. If DOX can only be loaded on the surface, drug load of HGNs will be twice that of GNSs, theoretically. However, the results showed that drug load on HGNs was 3.5 times that of GNSs. Thus, the drug was not only present in the outer surface of HGNs but also loaded in their cavity, which made drug loading capacity of HGNs greatly increased. Zhao et al. [49] coupled antitumor drug DOX and biological targeted molecule aptamer (Apt) to HGNs and studied the releasing process of DOX at low pH. The results showed that, at pH 5.0 or 6.0, DOX released 80% and 68% in 2 h, respectively, while, at pH 7.4, DOX released only 7.5% within 2 h. The normal human blood pH is 7.35~7.45, and pH of early and late endosomes in tumor cells is 6.0 and 5.0, respectively. Therefore, drug loading system of HGNs has a significant advantage in reducing the side effects of drugs.

In addition to transport drugs, HGNs can also be used to transport genes. Lu et al. [50] coupled small interfering RNA (siRNA) and biological targeted molecules folic acid (FA) to HGNs. HGNs delivered siRNA to tumor cells. Under

the near-infrared laser irradiation, siRNA separated from HGNs and bound the transcription factor NF-κB (the transcription factor plays a role in genetic expression of tumor cells), which made it not able to function properly and thereby inhibited tumor cell growth.

3.5. HGNs in Combined Photothermal Therapy and Chemotherapy. Near-infrared (NIR) laser induced photothermal therapy (PTT) is considered a good choice to treat tumor cells; however, it is difficult to eradicate tumor cells by PTT alone because of the nonuniform heat distribution. There have been quite a few studies that combine PTT with chemotherapy and the results are proved to be better than PTT or chemotherapy alone. You et al. [51] loaded antitumor drug DOX to PEG coated hollow gold nanospheres (DOX@PEG-HAuNS); they studied the antitumor activity of DOX@PEG-HAuNS combined with NIR laser *in vitro and in vivo*. They found that the nanoparticles displayed decreased systemic toxicity compared to free DOX or liposomal DOX and exhibited enhanced antitumor effect after the irradiation of laser. You et al. [52] also synthesized DOX-loaded hollow gold nanospheres that target EphB4 (T-DOX@HAuNS). They confirmed the release of DOX from DOX@HAuNS after being treated with NIR laser by dual radiotracer technique and proved the greater tumor growth inhibiting effect of T-DOX@HAuNS plus laser compared to HAuNS plus laser.

4. Conclusion

HGNs plays an important role in biosensing field, especially in LSPR sensors. Meanwhile, its applications in biomedical field have drawn much more attention. Diagnosis and treatment drugs of combining imaging and treatment in nanostructures have received an astonishing amount of attention in the field of cancer diagnosis and treatment. Compared with other types of gold nanostructure, HGNs have many advantages such as small size, hollow spherical structure, and strong absorption peak which can be adjusted to near-infrared region. In particular, its cavity structure can be used to load functional reagent (like anticancer drugs) and then achieve the combination of light therapy and chemotherapy, which has important applications in anticancer medicine. Besides, the conjugation of HGNs to biomolecular can target for the tumors and make it more effective to treat tumors. It can be predicted that multifunctional nanoparticles based on HGNs will play an increasingly important role in the integrated treatment of tumors.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors' Contribution

Qiong-Qiong Ren and Ling-Yu Bai equally contributed to this paper.

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