Enhancing Resonance Imaging Sensitivity and Upconversion Emission of Gd-based Nanoscale Coordination Polymers by Combination With Au Nanoparticles

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Research Article

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Abstract

Nanoscale coordination polymers (NCPs) are attracting increasing research interest due to their highly tailorable structure, feasible functionality and promising application in various fields, especially in biomedical applications, they are excellent contrast agents for bioimaging, biosensing and clinical diagnosis. Currently, to overcome the low relaxation rate and unitary information of magnetic resonance imaging, the design of multifunction contrast agent is critical and challenging. Herein, a new Au nanoparticles/Gd-based coordination polymer (Au@GdCP) composite nanoparticles have been fabricated by a facile hydrothermal methodology. The Au@GdCP exhibit excellent magnetic resonance, bright upconversion luminescence (UC) and good biocompatibility. More importantly, with the introduction of Au nanoparticles, the magnetization and longitudinal relaxation rate (r_1) of the nanocomposite is enhanced significantly, with 131.6-fold from 5.19 emu/g to 683.52 emu/g and 11.5 fold from $0.248 \text{ mM}^{-1}\text{S}^{-1}$ to $2.853 \text{ mM}^{-1}\text{S}^{-1}$ enhancement, respectively, as well as better UC property over GdCPs. This work may offer a new way to develop multifunctional NCPs with enhanced performance in image-guided diagnosis and therapy.

Introduction

Magnetic resonance imaging (MRI) is a kind of non-radioactive imaging technology [1, 2]. It is an extremely important clinical diagnosis model for diseased tissues, including solid tumours, tissues, organs, and blood vessels. MRI has several advantages over other diagnosis models because it does not require ionizing radiation, can provide high spatial resolution and high-contrast three-dimensional images [3–5]. It functions as a contrast imaging by changing the longitudinal and transverse relaxation times of the body's water environment [6]. At present, there are many nanocarriers that can be used for MRI, such as noble metal nanoparticles, silica, and rare earth nanomaterials [7].

In particular, Gd^{3+} has a large magnetic moment due to its seven unpaired electrons, its compounds are widely used as magnetic contrast agents for clinical diagnosis [8]. For example, Gd-DTPA is one of the most used MRI agents. However, it is limited by the low relaxation rate and nephrotoxicity [9]. To address these problems, various efforts that focus on enhancing the relaxation rate of contrast agents and reducing their toxicity have been developed [10]. Among the techniques used, surface modification is an effective method to enhance MRI signals. For example, carbon quantum dots with good optical properties are used to modify Gd-based materials to improve relaxation rates [11]. Contrast agent materials coated with SiO_2 have been reported to improve the relaxivity information [12]. Other strategies have also emerged. For example, a radionuclide-Cu-64 labelled doxorubicin (DOX)-loaded polydopamine (PDA) gadolinium-metallofullerene core-satellite nano-theragnostic agent is developed for multimodal imaging-guided combination cancer therapy [13]. It was found that the compound showed good biocompatibility, strong near infrared (NIR) light absorption, and high relaxation rate. Hai et al. designed a Gd-based probe through γ -glutamyltrypsinase cleavage and intracellular condensation reaction to enhance the T_2 -weighted MR contrast [14]. Another strategy for enhancing MRI signals is to control the internal structure

of the nanomaterials, such as the formation of core-shell structures and heterojunction structures. Adah Almutairi et al. reported a modulation of the interfacial layer thickness to enhance the MRI signal [15]. Recently, Ye et al. exploited an MRI material through liposome surface modified (cRGD@MLP-Gd) exhibiting T_1 and T_2 weighted contrast enhancement in vivo [16]. Compared to the single modal imaging, multimodal imaging probe is significant not only for the great improved detection sensitivity, but also for decreasing the toxicity risk and other side effect [15]. Thereby providing accurate diagnosis and precise therapy.

The most developed nanostructured multimodal imaging probe is the combination of MRI and optical imaging [17], which can overcome the limitations of each modal to generate more comprehensive imaging information with high spatial resolution, infinite tissue penetration and high sensitivity. Gd-based nanomaterials have been proved to be an ideal candidate for multifunctional materials, which combine with upconversion luminesces and MRI [18]. Lanthanide-doped CP upconversion nanoparticles demonstrate an anti-Stokes behavioural process, which converts continuous low energy (such as NIR light or IR light) into high energy light (visible light) by continuous multiphoton absorption or energy transfer processes [19, 20], providing a broad range of applications, from electrochemistry to biomedicine [21, 22]. One of the major attractions for biomedical application of lanthanide-doped upconversion nanoparticles (UCNPs) is that the anti-Stokes process can eliminate background autofluorescence and light scattering effects of the biological material [23]. The other conspicuous attraction is the irradiation light can achieve high tissue penetration depth and have low toxicity to the tissue [24]. Nevertheless, the overall upconversion efficiency is relatively low, and their practical application for biomedical are still limited [25]. As a result, it is desirable to develop simple and versatile synthetic routes for UCNPs with enhanced performance.

In recent years, nanoscale CPs have aroused extensive research interest in the fields of chemistry, physics, medicine, nanotechnology, and materials [26–29]. Particularly, in biomedical, they are excellent contrast agents for bioimaging benefiting from the highly tunable composition and structures, they are intrinsically biodegradable and easy to combine multiple modalities [30]. Furthermore, by combining with suitable materials, the properties of CPs can be improved, with enhanced functionality/stability, ease of preparation, and selectivity of operation [31]. It is expected that CP composites may find extensive applications in near future [32–35]. However, to date, few reports have appeared on the preparation and application of GdCP composites, and rare work studying GdCPs with enhanced MRI effects. Based on the localized surface plasmon resonance (LSPR) effect of Au nanoparticles (AuNPs) and the limitations of its low relaxation rate and potential biotoxicity of Gd-based nano-compounds [36].

In this work, we present the synthesis and characterization of a new MRI/upconversion luminescence multimodal contrast agent, the as-obtained GdCP nanospheres have good uniformity and monodispersity, the effect of Au NPs used for enhancing upconversion luminesces, relaxation information, and T_1 -weight MRI and biocompatibility of Au@GdCP has also been explored. Au@GdCP may offer great potential for future biomedical applications.

Results And Discussion

Synthesis of Au@GdCP nanocomposites

The preparation method of Au@GdCP composite nanoparticles contains the following processes. Firstly, AuNPs were synthesized by reduction of chloroauric acid (HAuCl_4 , 1 mL, 0.025 mol/L) under sodium citrate solution (3 mL, 0.035 mol/L) and hexadecyl trimethyl ammonium bromide (CTAB, 20 mL, 0.125 mol/L) was used as stabilizer, the gold nanoparticles (AuNPs) with an average diameter of about 20 nm was diluted with DI water to 5 mL. Afterwards, 0.2 mmol rare earth ions solution which contains $\text{Gd}(\text{NO}_3)_3$, $\text{Yb}(\text{NO}_3)_3$ and $\text{Er}(\text{NO}_3)_3$ (molar ratio of Gd: Yb: Er = 0.16: 0.03: 0.01) were add into allantoin solution (0.3 mmol) stirring for 15 min at room temperature. Subsequently, the above solution was mixed with together and transferred into a Teflon lined stainless-steel autoclave with capacity of 50 mL, heated at 160 °C for 15 h. As the autoclave was cooled to room temperature naturally. Finally, the product was isolated by centrifugation and washed with deionized water and absolute ethanol for three times, and dried in vacuum at 60 °C for 12 h. The products marked as Au@GdCP. Meanwhile, the GdCP prepared with same method without Au NP introduced.

Characterization

The morphologies and sizes of the samples were obtained through scanning electron microscope (SEM, HITACHI S-3400N, 30 kV) and transmission electron microscope (TEM, Hitachi JEM2100, 200 kV). XRD pattern were performed on a Rigaku X-ray diffractometer with Cu K α radiation ($\lambda = 154178 \text{ \AA}$) with the range of 5–90°, FT-IR data was obtained with Nicolet 6700 FT-IR spectrometer using KBr pellet between 4000 cm^{-1} and 500 cm^{-1} at room temperature. Photoluminescence (PL) emission spectra were recorded with an FLS 980 (Edinburgh Instruments, England). Elemental analysis was carried out on an EA3000 elemental analyzer. Magnetic properties were measured using a SQUID magnetometer equipment. The relaxation information was performed on a 0.5T NMI20-Analyst NMR system (Niumag Corporation, Shanghai, China).

Characterization of GdCP and Au@GdCP

The morphologies and sizes of the as-obtained GdCPs were initially characterized by scanning electron microscopic (SEM). As can be seen in Figure. 1(a), the products were discrete and spherical, with a mean diameter of $\sim 179 \text{ nm}$ and relative narrow size distribution, as determined by dynamic light scattering (DLS, insert of Figure. 1a). TEM images under different magnifications (Figure. 1b and c) further verify that GdCP is uniformly round and monodispersed. Interestingly, after combination with Au nanoparticles, A decrease in the particle size was obtained, with an average size of 150 nm (Figure. 1d) for Au@GdCP, which is helpful for the biomedical applications. The reduction in diameter probably due to the Au particles acting as the nuclei, leading to a decrease in the size of the final product, which is always observed in the growth of the crystal. The TEM image in Figure. 1e shows the internal structure of Au@GdCP. It can be clearly observed that each nanosphere encapsulating several Au nanoparticles.

Magnification of the TEM image in Figure. 1f demonstrate that the Au@GdCP nanosphere has an outer layer with thickness of approximately 50 nm. In addition, the energy dispersive spectroscopy (EDS) mapping analysis of a single nanosphere are illustrated in Figure. 1g, the C, O, N, Gd, Yb, and Er elements coexist and are distributed homogeneously throughout the particle. However, the Au element is aggregated and located in the internal part of the Gd-based coordination polymers. All this evidence verifies that AuNPs have successful embedded within GdCP.

To assess the structure of the compounds, powder X-ray diffraction (XRD) patterns of GdCP spheres and Au@GdCP nanocomposites are presented in Figure. 2. No obvious diffraction peak is observed for GdCP, indicating that GdCP is amorphous and not crystalline. While the Au@GdCP exhibits four distinct peaks at $2\theta = 38.37^\circ, 44.56^\circ, 64.75^\circ, 77.72^\circ$, which can be assigned to the (111), (200), (220) and (311) planes of the standard data for hexagonal phase of Au (JCPDS 04-0784). The HRTEM image (Figure.1f) shows lattice fringe with the interplanar spacing of 0.252 nm, corresponding to the (200) planes of Au. The result was further proved the presence of AuNPs in the product and the formation of Au@GdCP.

Magnetic properties

The magnetic properties of GdCP and Au@GdCP nanocomposites were measured by SQUID magnetometer. Figure. 3 shows the magnetization of the magnetic field (M-H) curves of samples at 300 K. The magnetization of GdCP and Au@GdCP are 5.19 emu/g and 683.52 emu/g at 300 k, respectively. With the introduction of AuNPs, the magnetization was enhanced remarkably. No hysteresis loop was observed. The magnetization curve of the samples displayed typical paramagnetic properties. These results show that even after introduction of AuNPs, the particle keep well paramagnetic properties.

Luminescence properties of Au@GdCP

The upconversion emission spectrum of Au@GdCP under 980 nm laser excitation is shown in Figure. 4. Simultaneously, GdCP was used as the control under the same conditions. In this system, Yb^{3+} acts as a sensitizer and transfers the absorbed excitation energy to the activator ions of Er^{3+} . First, Yb^{3+} is excited from the state level ($^7\text{F}_{7/2}$) to the exciting level ($^5\text{F}_5/2$) under the continuous 980 nm laser excitation. Subsequently, Er^{3+} ions are excited to the intermediate state ($^4\text{I}_{11/2}$) and then transfer energy to the excited state ($^4\text{F}_{7/2}$), which resulting the energy transfer of Er^{3+} ions from $^4\text{F}_{7/2}$ levels to the levels of $^2\text{I}_{11/2}$, $^4\text{S}_{3/2}$, and $^4\text{H}_{9/2}$ with nonradioactive process, respectively [37–39]. The emission spectra exhibited three bands, attributed to green emission (525 nm and 545 nm) and red emission (655 nm). Compared with GdCP, an obvious enhanced emission intensity of 38.4% was obtained after Au ions modification, coupled with a slight blue shift for 4 nm, mainly attributed to the LSPR effect of the AuNPs [38]. LSPR strengthens the local crystal field, resulting in the enhancement of excitation field intensity [41]. Meanwhile, coupling between the broad LSPR peaks of AuNPs and the upconversion luminescence enhances the energy transfer effect, improving the decay rate of luminescent centres and the efficiency of the emission intensity [42, 43]. Therefore, AuNPs play a role in enhancing the fluorescent intensity in

Relaxation information and T_1 -weighted MRI maps

Gd-based composites have good kinetic and thermodynamic stabilities. They can accelerate the T_1 relaxation of water protons, and improve the brightness of MRI signals. Approximately 40% of MRI scans employ Gd^{3+} chelates for contrast agent in clinical [44]. However, free Gd^{3+} ions are known to have serious toxic effect due to the replacement of Ca^{2+} ions in the body, further improvement is required. Thanks to the biocompatibility and tuneable morphology, AuNPs have been frequently used in clinical applications. In recent years, they have been exploited to create very promising tools for multimodal imaging and MRI-guided therapies [45]. To estimate the performance of GdCP and Au@GdCP as MRI contrast agent, the relaxation rate and T_1 -weighted MRI were investigated in vitro at the low field of 0.5T. As shown in Figure. 5(a, c), with the increase of Gd concentration, the longitudinal relaxation time and transverse relaxation time of GdCP showed a good linear relationship. Based on the slop, the longitudinal relativity (r_1) and transverse relativity (r_2) were calculated to be $0.248 \text{ mM}^{-1}\text{S}^{-1}$ and $1.292 \text{ mM}^{-1}\text{S}^{-1}$, respectively. In comparsion with GdCP, Au@GdCP exhibited increased values with $2.853 \text{ mM}^{-1}\text{S}^{-1}$, $13.797 \text{ mM}^{-1}\text{S}^{-1}$ for r_1 , r_2 , respectively. Calculated to be 11.5 fold and 10.8 fold enhancements. The appealing improvement of the Au@GdCP is mainly due to the confined tumbling of Gd^{3+} in a biomacromolecule, which result a longer rotational correlation time. Besides, compared with previous reported modified UCNPs materials (such as the UCNPs@mSiO₂-PEG nanocomposite with a r_1 of $0.6361 \text{ mM}^{-1}\text{S}^{-1}$), our results exhibited stronger signals. [46]. The excellent longitudinal and transverse relaxation information with relativel high r_2/r_1 ratio ($r_2/r_1 = 4.83 > 3$) of Au@GdCP is expected to achieve T_1 - T_2 dual mode MRI.

The T_1 -weighted MRI of Au@GdCP and GdCP nanocomposites were also obtained (Fig. 3b, d), in which T_1 -weighted MRI signals got brighter and brighter with the increasing concentration of Gd^{3+} . Compared with the T_1 -weight MRI signal of both nanocomposites, the contrast effect of Au@GdCP is much better than GdCP, demonstrating that the existence of AuNPs greatly enhances the MRI signal intensity and the contrast of the MRI signal.

It is well known that reducing the inversion rate of the contrast agent in the aqueous proton solution can reduce the average spin-nuclear spin and the dipole-dipole interaction between the contrast agent, and it can prolong the inversion time, which can improve the relaxation efficiency of the contrast agent [25]. With the introduction of AuNPs, the LSPR of the AuNPs may strengthen the external magnetic field, which results in intermolecular dipole-dipole interactions, increasing the contrast relaxation rate and the T_1 -weighted MRI signal [47–48]. Moreover, the strong light scattering of AuNPs translates the absorbed light to the plasmon wavelength, resulting in enhancement of T_1 -weighted MRI signals [49].

Biocompatibility of the Au@GdCPs

As is well known, good biocompatibility is an important prerequisite and crucial factor for biological applications. In this work, the in vitro biocompatibility of Au@GdCP was evaluated through the 3-(4,5-

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dimethylthiazol-2-yl)-2,5- diphenyltetrazolium bromide (MTT) assay with incubated HeLa cells. Meanwhile, GdCP was tested as a control under the same conditions. Figure. 6 shows that with the increasing concentration of Au@GdCP and GdCP, the relative cell viability of HeLa gradually decreased. When the concentration of Au@GdCP and GdCP reached 1.0 mg/mL, the relative cell viability is 80% and 82.2%, respectively. The MTT results indicate that Au@GdCP exhibit low toxicity and good biocompatibility.

Conclusions

In summary, Au@GdCP nanocomposites were fabricated through a facile hydrothermal method. With the increasing concentration of GdCP and Au@GdCP, the longitudinal relaxation time and lateral relaxation time exhibited an excellent linear relationship, and T_1 -weight MRI displayed brighter and brighter. When AuNPs were introduced into GdCP, based on the LSPR of AuNPs, the longitudinal relaxation rate of Au@GdCP was much higher than that of GdCP. Meanwhile, Au@GdCP displayed good upconversion luminesces and excellent biocompatibility. These properties demonstrated that Au@GdCPs can be effectively applied to MRI/ upconversion luminescence multimodal contrast agent and are promising for biomedical applications.

Declarations

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Compliance with ethical standards

Conflicts of interest. There are no conflicts to declare.

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Figures

Figure 1

SEM (a) and TEM (b, c) images of GdCP. SEM (d) and TEM (e, f) images of Au@GdCP nanoparticles and energy dispersive spectroscopy (EDS) mapping spectra of Au@GdCP (g).

Figure 2

X-ray diffraction (XRD) patterns of GdCP and the Au@GdCP nanocomposite.

Figure 3

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The magnetic properties of GdCP (a) and Au@GdCP(b).

Figure 4

Upconversion emission spectra for GdCP (a) and Au@GdCP (b).

Figure 5

Relaxation information and T1-weighted MRI maps with different concentrations of GdCP (a, b) and Au@GdCP (c, d).

Figure 6

Relative cell viability of HeLa incubated with various concentrations of GdCP and Au@GdCP at 37°C for an incubation time of 24 h.