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Enhanced up/down-conversion luminescence and heat: Simultaneously achieving in one single core-shell structure for multimodal imaging guided therapy

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ABSTRACT

Upon near-infrared (NIR) light irradiation, the Nd^{3+} doping derived down-conversion luminescence (DCL) in NIR region and thermal effect are extremely fascinating in bio-imaging and photothermal therapy (PTT) fields. However, the concentration quenching induced opposite changing trend of the two properties makes it difficult to get desired DCL and thermal effect together in one single particle. In this study, we firstly designed a unique $NaGdF_4$:0.3%Nd@$NaGdF_4$@$NaGdF_4$:10%Yb/1%Er@$NaGdF_4$:10%Yb @$NaNdF_4$:10%Yb multiple core-shell structure. Here the inert two layers ($NaGdF_4$ and $NaGdF_4$:10%Yb) can substantially eliminate the quenching effects, thus achieving markedly enhanced NIR-to-NIR DCL, NIR-to-Vis up-conversion luminescence (UCL), and thermal effect under a single 808 nm light excitation simultaneously. The UCL excites the attached photosensitive drug (Au_{25} nanoclusters) to generate singlet oxygen ($^1O_2$) for photodynamic therapy (PDT), while DCL with strong NIR emission serves as probe for sensitive deep-tissue imaging. The *in vitro* and *in vivo* experimental results demonstrate the excellent cancer inhibition efficacy of this platform due to a synergistic effect arising from the combined PTT and PDT. Furthermore, multimodal imaging including fluorescence imaging (FI), photothermal imaging (PTI), and photoacoustic imaging (PAI) has been obtained, which is used to monitor the drug delivery process, internal structure of tumor and photo-therapeutic process, thus achieving the target of imaging-guided cancer therapy.

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1. Introduction

In the past decade, lanthanide doped nanoparticles (LDNPs) have drawn considerable research attention deriving from their intrinsic up/down-conversion luminescence properties and promising application in bio-imaging and disease diagnosis [1–8]. Especially, the up-conversion nanoparticles (UCNPs), which can absorb photons in the near-infrared region and convert low-energy excitation to high-energy emission in shorter wavelength region (UV–Vis region), are considered to have deeper bio-penetration and better bio-compatibility by using NIR light excitation [9–17]. On the other hand, such energy conversion process can also be utilized to excite some functional photosensitive drugs (PSD) for PTT and PDT through the fluorescence resonance energy transfer (FRET), when LDNPs were used as drug carrier to overcome the phototoxicity of the original excitation light (always in UV–Vis region) [18–25]. In this case, the cancer therapy effect may combine with the imaging effects of the LDNPs to form the imaging-guided therapeutic platform, which is conducive to achieve the real-time monitoring in the therapeutic process under the NIR light irradiation [26–29]. However, the up-conversion emission intensity may be strongly weakened by FRET process between the drug and LDNPs, which makes it difficult to guarantee the effects of imaging and therapy simultaneously [30–36]. Furthermore, considering the relatively low quantum efficiency (<5%) of the up-conversion

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process, it is far-fetched to only rely on the up-conversion process to achieve desired imaging and therapy effects.

Recently, the Nd^{3+} sensitized up-conversion nanoparticles have received much interest in the fields of material science and biomaterials for their strong up-conversion emission under 808 nm light, which is proven to have deeper penetration depth and lower heat effect in bio-tissue than 980 nm light [6]. Furthermore, when excited by the 808 nm NIR light, a down-conversion emission phenomenon of the Nd^{3+} doped LDNPs can also be detected in the region of 850–900 nm [37–41], which can be utilized for bioimaging. On account of the fact that the excitation and emission light are both in the optical window, this 808 nm light excited imaging mode can be expected to be more sensitive and suitable for imaging in deep bio-tissue [42–50]. Besides, when coupled with the up-conversion luminescence sensitized by Nd^{3+} under the excitation of 808 nm light, the concurrent down-conversion imaging effect can release the up-conversion luminescence to fully excite the PSD without concerning about weakened luminescence intensity due to the FRET effect anymore [51–58]. However, to the best of our knowledge, no literature has reported the dual-mode luminescence process of the Nd^{3+} doped LDNPs under the excitation of 808 nm NIR light. Furthermore, the photothermal effect of the Nd^{3+} doped LDNPs has also been detected in previous reports [59,60], which make it possible to design and fabricate the Nd^{3+} doped LDNPs with both luminescence and photothermal effect under NIR light irradiation. However, the down-conversion luminescence and heat/photothermal effect of the Nd^{3+} doped LDNPs have opposite changing trend with the concentration of Nd^{3+}. More specifically, the highest down-conversion intensity can be obtained with an optimized Nd^{3+} concentration (at relatively low level) and gradually weaken with an increased Nd^{3+} concentration for the concentration quenching effect [41]. On the contrary, the photothermal effect induced by doped Nd^{3+} under NIR light prefers a higher Nd^{3+} concentration. Thus, to obtain better DCL imaging and therapy effect, it is highly desirable to design a kind of LDNPs with unique structure, which can achieve the co-enhancement of the DCL intensity and photothermal effect simultaneously.

Accordingly, in the present work, a five-layer core-shell structured Nd^{3+} doped LDNPs has been designed and fabricated through a layer-by-layer metal-organic decomposition method. An energy-blocked method, which can prevent unwanted energy transfer process and concentration quenching under the 808 nm NIR light excitation, has been introduced into this LDNPs thus a remarkable co-enhancement of the DCL, UCL and photothermal effects can be achieved. Besides, by reasonably arranging the shell configuration, the as-prepared LDNPs can emit dual-mode luminescence (up/down-conversion) under the excitation of 808 nm NIR light. As an energy donor, the LDNPs can excite the conjugated PSD (Au_{25} nanoclusters) by the NIR-to-Vis up-conversion and FRET effect to produce $^1O_2$ and work together with the heat generated from Nd^{3+} upon 808 nm laser to lead to a synergistic therapeutic effect. Meanwhile, a sensitive deep-tissue fluorescence imaging can be also achieved from the strong NIR-to-NIR down-conversion emission, which is almost unaffected by the conjugated Au_{25}. Besides, the obvious signal enhancement by Gd^{3+} ions also indicates that the as-synthesized nanoparticles can also serve as the MRI imaging probe. All these imaging and cancer therapy effects have been thoroughly investigated *in vitro* and *in vivo*.

2. Experimental section

2.1. Reagents and materials

All the chemicals used in this paper were purchased from Sigma-Aldrich except PEG500–silane, which was purchased from Beijing Kaizheng Biotech Development Co., Ltd. Chemicals were used as received without further purification.

2.2. Synthesis

2.2.1. Synthesis of oleic-acid-stabilized β-$NaGdF_4$:0.3%Nd^{3+}

The β-$NaGdF_4$:0.3%Nd^{3+} nanoparticles were synthesized as follow: The solution containing 1 mmol of rare earth oleate (99.7% gadolinium oleate + 0.3% neodymium oleate, molar ratio), 0.5248 g NaF, 15 mL oaic acid (OA) and 15 mL octadecene (ODE) was added to the round-bottom flask and keep the temperature at 110 °C under a vacuum for 30 min. Then after, the temperature of the reaction system is improved to 310 °C and kept this condition for 1 h in N_2 atmosphere environment. The β-$NaGdF_4$:0.3%Nd^{3+} nanoparticles were obtained.

2.2.2. Synthesis of core-shell structured LDNPs

To fabricate β-$NaGdF_4$:0.3Nd^{3+}@β-$NaGdF_4$ sample, a template-directed crystal growth method has been adopted. Firstly, the β-$NaGdF_4$:0.3%Nd^{3+} cyclohexane solution was added to a four-neck round-bottom flask. 20 mL solution contain OA and ODE ($V_{OA}/V_{ODE} = 1/1$) were added to the flask, and keep the temperature of solvent at 120 °C under a vacuum with continuous magnetic stirring for 1 h. After that, the solution was heated to 310 °C. On the other hand, another solution containing 1.5 mL OA and 1.5 mL ODE, 1 mmol $Gd(CF_3COO)_3$, and 1 mmol CF_3COONa was introduced into above solvent. The solution was kept at the temperature of 310 °C and N_2 atmosphere for another 1.5 h. Then the solution was cooled to room temperature to make the β-$NaGdF_4$:0.3%Nd^{3+}@β-$NaGdF_4$ further crystallization. Further coating processes were similar as the above step and just change the rare earth reagents content. The sample prepared in each steps was named as follows: β-$NaGdF_4$:0.3%Nd^{3+}@β-$NaGdF_4$, LDNPs-2; β-$NaGdF_4$:0.3%Nd^{3+}@β-$NaGdF_4$@β-$NaGdF_4$:10%Yb^{3+}/1%Er^{3+}, LDNPs-3; β-$NaGdF_4$:0.3%Nd^{3+}@β-$NaGdF_4$@β-$NaGdF_4$:10%Yb^{3+}/1%Er^{3+}@β-aGdF_4:10%Yb^{3+}, LDNPs-4; β-$NaGdF_4$:0.3%Nd^{3+}@β-$NaGdF_4$@β-$NaGdF_4$:10%Yb^{3+}/1%Er^{3+}@β-$NaGdF_4$:10% Yb^{3+}@β-$NaNdF_4$:10%Yb^{3+}, LDNPs- 5.

2.2.3. Preparation of PEI-stabilized LDNPs-5

To obtain PEI-stabilized LDNPs, a ligand exchange method was carried out by using poly(ethylene imine) (PEI). Typically, add above LDNPs-5 chloroform solution into a solution with 20 mL H_2O and 1.5 g PEI slowly. The solution was vigorously stirred for 24 h. The final PEI-stabilized LDNPs-5 sample was obtained by centrifugation and washed with deionized water for two times.

2.2.4. Preparation of $Au_{25}(Capt)^-_{18}$

Typically, solution A containing 7.12 mL $HAuCl_4 \cdot 3H_2O$ (0.08 g/mL), 0.4 mmol TOAB and 10 mL methanol was vigorously stirred for 0.5 h. Then, solution B with 1.5 mmol captopril in 7 mL of methanol was added in the reaction A and stirred for another 30 min. After that, solution C with 2 mmol $NaBH_4$ and 5 mL H_2O at the temperature of 0 °C was added under vigorous stirring. After 8 h stirring, the reaction mixture was centrifuged. The precipitate received further purification with methanol and ethanol was obtained and dried in vacuum.

2.2.5. Preparation of $Au_{25}(Capt)^-_{18}$ conjugated LDNPs-5

The conjugation reaction was conducted in a 20 mL aqueous solution with 15 mg 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), 5 mg *N*-hydroxysuccinimide (NHS), 25 mg $Au_{25}(Capt)^-_{18}$ and 110 mg PEI-functional LDNPs-5. After overnight stirring, the precipitates were obtained by centrifugation and washed with deionized water for three times. The sample was named as LDNPs-5-Au_{25}.

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