Biomaterials 124 (2017) 35–46

Contents lists available at ScienceDirect

Biomaterials

journal homepage: www.elsevier.com/locate/biomaterials

Shape-controlled fabrication of magnetite silver hybrid nanoparticles with high performance magnetic hyperthermia

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ARTICLE INFO

Article history:
Received 24 August 2016
Received in revised form
10 January 2017
Accepted 28 January 2017
Available online 31 January 2017

Keywords:
Magnetic nanoparticles
Silver
Nanocomposites
Shape control
Hyperthermia

ABSTRACT

Superparamagnetic Fe_3O_4 nanoparticles (NPs)-based hyperthermia is a promising non-invasive approach for cancer therapy. However, the heat transfer efficiency of Fe_3O_4 NPs is relative low, which hinders their practical clinical applications. Therefore, it is promising to improve the magnetic hyperthermia efficiency by exploring the higher performance magnetic NPs-based hybrid nanostructures. In the current study, it presents a straightforward *in situ* reduction method for the shape-controlled preparation of magnetite (Fe_3O_4) silver (Ag) hybrid NPs designed as magnetic hyperthermia heat mediators. The magnetite silver hybrid NPs with core-shell (Fe_3O_4@Ag) or heteromer (Fe_3O_4-Ag) structures exhibited a higher biocompatibility with SMMC-7721 cells and L02 cells than the individual Ag NPs. Importantly, in the magnetic hyperthermia, with the exposure to alternating current magnetic field, the Fe_3O_4@Ag and Fe_3O_4-Ag hybrid NPs indicated much better tumor suppression effect against SMMC-7721 cells than the individual Fe_3O_4 NPs *in vitro* and *in vivo*. These results demonstrate that the hybridisation of Fe_3O_4 and Ag NPs could greatly enhance the magnetic hyperthermia efficiency of Fe_3O_4 NPs. Therefore, the Fe_3O_4@Ag and Fe_3O_4-Ag hybrid NPs can be used to be as high performance magnetic hyperthermia mediators based on a simple and effective preparation approach.

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1. Introduction

Colloidal hybrid nanoparticles (NPs), which include multiple components in a single nanosized object, are attractive for biomedical applications because novel important properties and multiple or enhanced functions can be generated due to the synergy of the individual component in the hybrid NPs [1–4]. Among the multitude of investigations to date, superparamagnetic NPs-based hybrid NPs have been considered as an important family of multifunctional or enhanced functional nanocomposites [5]. These types of NPs have shown great application potential in various biomedical fields such as drug delivery, magnetic resonance imaging and hyperthermia treatment [6]. Especially, based on the fact that magnetic NPs such as iron oxide NPs can generate heat when an alternating current magnetic field (ACMF) is applied to them [7,8], the magnetic hyperthermia is increasingly becoming one of the novel noninvasive approaches for cancer therapy. Cancer cells, more sensitive to temperature (≥40 °C) than healthy cells [9,10], can be selectively killed [11] by the magnetically induced heating, which can damage the biological integrity of the cell membrane and cytoskeleton [12]. However, the clinical trials has demonstrated that a considerably high concentration of iron oxide NPs [13,14] is needed for the efficient cancer thermal treatment because of the relatively poor heat transfer efficiency of current Fe_3O_4 NPs [15], which hinders their practical applications. In this regard, the

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http://dx.doi.org/10.1016/j.biomaterials.2017.01.043
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development of high-performance hyperthermia mediators such as magnetic NPs attached therapeutic agents is of great importance to the practical applications of magnetic NPs-based hyperthermia [7,16,17].

Noble metallic silver (Ag) NPs have been recognized as a potential anti-cancer or antibacterial agent and extensively studied in the biomedical fields [18–20]. Recently, several recent studies have demonstrated that Ag NPs can enhance the efficiency of hyperthermia [13,21–24]. For example, Wang et al. [25] reported that Ag NPs improved the thermo-sensitivity of C6 cells. Liu et al. [13] studied the influence of a mixture of Fe_3O_4 and Ag NPs on magnetic hyperthermia, and found that the presence of Ag NPs enhanced the cancer cell death from magnetic heat both *in vitro* and *in vivo*. However, the heat generated by Fe_3O_4 NPs can only transmit very short distances and induce highly focused heating [15], and thus the separation of Fe_3O_4 and Ag NPs may limit the sensitivity of Ag NPs to Fe_3O_4 NPs-mediated hyperthermia.

It is promising to attain the lattice-mismatched heterojunctions by tailor-made chemical combining Fe_3O_4 and Ag NPs into a single unit; this would integrate the properties of the two NPs as well as enhance the functions between them at nanoscale level [26–29]. Various approaches have been reported for the preparation of Fe_3O_4-based magnetite silver hybrids with various morphologies, including centric or eccentric core@shells [30–32], phase-segregated core-satellites [33–35] and heteromer architectures [36,37]. However, the study on shape control of the magnetite silver hybrid NPs is still scarce [38–40].

In this study, we present a simple and effective *in situ* reduction strategy to prepare the magnetite silver hybrid NPs. It designed the pre-existing carboxyl-rich Fe_3O_4 NPs to carry inorganic Ag bonding junctions [2] in order to overcome the high interfacial energy barrier. Based on this design strategy, the shape of magnetite silver hybrid NPs can be tuned easily by adjusting the concentration of the intermediate product Fe_3O_4-COOAg NPs to produce core-shell Fe_3O_4@Ag or heteromer Fe_3O_4-Ag structures after *in situ* reduction. The cytotoxicity of the magnetite silver hybrid NPs is much lower than the individual Ag NPs. Compared to the individual Fe_3O_4 NPs, both Fe_3O_4@Ag and Fe_3O_4-Ag NPs exhibited greatly enhanced hyperthermia effects *in vitro* and *in vivo*. To the best of our knowledge, so far, this is the first case in which magnetite silver hybrid NPs were applied to *in vitro* and *in vivo* magnetic hyperthermia, thereby providing a novel and effective approach to improve the hyperthermia efficiency.

2. Materials and methods

2.1. Preparation of magnetite silver hybrid NPs

2.1.1. Synthesis of monodisperse hydrophobic Fe_3O_4-OA NPs

The Fe_3O_4-OA NPs (OA: oleic acid) were prepared by the classical thermal decomposition method [41,42]. In a typical chemical preparation, iron chloride ($FeCl_3 \cdot 6H_2O$, 2.16 g) and sodium oleate (7.3 g) were dissolved in a mixture solvent consisting of ethanol (16 mL), pure water (12 mL) and hexane (28 mL). The mixture was stirred for 4 h at 70 °C. Then the upper organic layer containing the iron-oleate complex was washed three times with pure water in a separating funnel, and subsequently, hexane was evaporated off. The as-prepared iron-oleate complex was collected and dried overnight in a drying oven at 40 °C under vacuum. Then, the iron-oleate complex (3.4 g) and oleic acid (500 μL) were dissolved in the high boiling 1-octadecene solvent (20 mL). With the protection of nitrogen, the solution was programmed heated from the room temperature to 320 °C at 3.3 °C/min, and held isothermally for 30 min at 120 °C (open to air so as to remove trace water) and 320 °C, respectively. When the synthetic procedure was completed, the resulting mixture was cooled, and the Fe_3O_4-OA NPs were precipitated by ethanol (50 mL) and separated by centrifugation. The NPs were washed 3 times with 1:3 hexane and acetone, and collected by centrifugation, and finally dried under vacuum. The obtained Fe_3O_4-OA NPs were in a black solid form.

2.1.2. Synthesis of hydrophilic Fe_3O_4-PAA NPs

Fe_3O_4-PAA NPs (PAA: Poly(acrylic acid)) were prepared following a previously reported method [43]. In a typical process, under an inert nitrogen atmosphere, diethylene glycol (DGE, 35 mL) mixed with PAA (2 g) was heated to 120 °C with strongly stirring with the injection of the prepared Fe_3O_4-OA NPs toluene solution (100 mg/mL). Then the mixture was heated to 210 °C under reflux for 1 h. After the mixture was cooled down to room temperature, a brown-black magnetic powder was collected by the addition of dilute hydrochloric acid and magnetic separation. The precipitate of Fe_3O_4-PAA NPs was washed several times with pure water, and then well dispersed in pure water by ionizing the carboxyl groups with triethylamine to reserve. Fe_3O_4-PAA NPs were purified by ultrafiltration with an Ultra centrifugal filter unit (Millipore, 100,000 NMWL).

2.1.3. Synthesis of core-shell magnetite silver hybrid NPs (Fe_3O_4 @ Ag)

Aqueous solutions of Fe_3O_4-PAA NPs (1.5 mg/mL, 13.33 mL) and silver nitrate ($AgNO_3$, 40 mg/mL, 10 mL) were mixed and shaken vigorously on a micro-oscillator for 20 min. A massive precipitate of Fe_3O_4-COOAg NPs was produced and collected by magnetic separation. The precipitate was ultrasonically redissolved in an aqueous solution of sodium citrate (Na_3Cit, 10.6 mmoL/L, 16 mL). After 12 h stirring and membrane filtration (220 nm), a saturated solution of Fe_3O_4-COOAg NPs was obtained. Then the saturated solution of Fe_3O_4-COOAg NPs (5.55 mg Ag/mL, 15 mL) was stirred and added with aqueous solution of freshly prepared sodium borohydride ($NaBH_4$, 26 mmol/L, 100 μL) in every 10 s to a total volume of 1 mL, and stirring was continued for 30 min. The resulting mixture was purified by ultrafiltration to yield Fe_3O_4@Ag.

2.1.4. Synthesis of heteromer magnetite silver hybrid NPs (Fe_3O_4-Ag)

A saturated solution of Fe_3O_4-COOAg NPs (5.55 mg Ag/mL, 15 mL) was diluted with an aqueous solution of Na_3Cit (10.6 mmol/L) to prepare an unsaturated solution of Fe_3O_4-COOAg NPs (4.37 mg Ag/mL). Then an aqueous solution of freshly prepared $NaBH_4$ (26 mmol/L, 100 μL) was added in every 10 s to a total volume of 1 mL under stirring. The solution was stirred for 30 min, and purified by ultrafiltration to yield Fe_3O_4-Ag.

2.2. Experimental setup and measurements for magnetic hyperthermia

The magnetically induced heating efficiency of Fe_3O_4-PAA, Fe_3O_4@Ag and Fe_3O_4-Ag NPs was measured and recorded with a commercial system (illustrated in Fig. S1) with a moderate radio frequency (390 KHz) heating machine equipped with an inductive copper coil of 3 turns, an inner diameter of 31 mm, an outer diameter of 41 mm (Shuangping SPG-06-II, China); and a fiber optic temperature sensor (UMI8 universal multichannel, FISO Technologies Inc., Quebec, Canada) fitted with a pre-calibrated fiber optic temperature probe (FISO, model FOT-L-SD-C1-F1-M2-R1-ST). The prepared NPs at a concentration of 2 mg Fe/mL were placed inside the copper coil of the applied ACMF (390 KHz, 18 A). Specific absorption rate (SAR) was used to quantify the heating efficiency generated per unit gram of Fe per unit time [56], expressed as Equation (1):

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