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Tumor-targeted and multi-stimuli responsive drug delivery system for near-infrared light induced chemo-phototherapy and photoacoustic tomography

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ABSTRACT

In this work, a tumor-targeted and multi-stimuli responsive drug delivery system has been developed for combining photoacoustic tomography imaging with chemo-phototherapy. We utilized a kind of near infrared (NIR) resonant material-hollow mesoporous copper sulfide nanoparticles (HMCuS NPs) to encapsulate doxorubicin (DOX). After that, the outer surface of HMCuS NPs was capped with multifunctional hyaluronic acid (HA) simultaneously as smart gatekeeper as well as tumor targeting moiety. Herein, HMCuS-HA could serve as a powerful contrast agent for photoacoustic tomography (PAT) to guide chemo-phototherapy by providing the identification of cancerous lesions. *In vitro* and *in vivo* studies, the nanoplatform (DOX/HMCuS-HA) pinpointed MCF-7 cells via CD44 receptor-mediated endocytosis pathway. Subsequently, intracellular enzyme-responsive controlled drug release would take place in lysosome after the HA degradation by hyaluronidase. Under near infrared (NIR) light irradiation, HMCuS NPs could not only effectively convert NIR light into heat for photothermal therapy, but also generate high levels of reactive oxygen species (ROS) for photodynamic therapy. In addition, NIR light and low pH environment could facilitate intracellular tunable drug release with spatial/temporal resolution, and thus synergistic combination of chemo-phototherapy should be simultaneously driven by an 808 nm laser irradiation, which brought out an outstanding therapeutic effect. *In vivo* optical imaging demonstrated that HMCuS-HA significantly enhanced targeting and accumulation capacity in tumor site. Furthermore, tumor-bearing mice treated with DOX/HMCuS-HA under NIR irradiation (808 nm, 2 W/cm^2, 0.5 min) *in vivo* displayed the highest inhibition ratio of about 88.9%. Taken together, our present study of the tumor-targeted and multi-stimuli responsive drug delivery system provides new insights into multimodality theranostic applications in cancer treatment.

Statement of Significance

Until now, chemotherapy is still the major therapeutic approach applied in oncology. Despite their pharmacologically efficacy in cancer treatments, most chemotherapeutic agents without tumor-specific targeting ability have brought out serious toxicities to normal tissues. This study provides a promising near infrared (NIR) resonant material-hollow mesoporous copper sulfide nanoparticles (HMCuS NPs) with capping of multifunctional hyaluronic acid (HA) simultaneously as smart gatekeeper as well as tumor targeting moiety to address the above problem. After the nanoplatform (DOX/HMCuS-HA) pinpointed breast cancer cells via CD44 receptor-mediated endocytosis pathway, intracellular multi-stimuli responsive controlled drug release would take place with remarkable spatial/temporal resolution. Then photoacoustic tomography (PAT) and synergistic combination of chemo-phototherapy would be simultaneously driven by the same NIR irradiation in a coordinated way, which brought out an outstanding theranostic effect. This work can arouse broad interests among researchers in the fields of nanomedicine, nanotechnology, and drug delivery system.

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1. Introduction

To date, chemotherapy is still the major therapeutic approach applied in oncology. Despite their pharmacologically efficacy in cancer treatments, most chemotherapeutic agents without tumor-specific targeting ability have brought out serious toxicities to normal tissues [1,2]. One way to overcome this limitation has been achieved through developing tumor-targeted drug delivery systems (DDSs) with the help of nanomaterials [3–5]. In addition, on account of the multi-level complexities and variability of cancers, synergistic combination of chemotherapy and other therapeutic approaches with multi-mechanisms would be a promising strategy for optimizing cancer treatment [6–9]. Thus, to develop multifunctional nanocarriers combined two or more functions, such as diagnostics and therapy, should be of great significance.

Copper sulfide nanoparticles (CuS NPs), a rising star in near infrared (NIR) resonant materials, have drawn widespread attention in biomedical applications especially in cancer theranostics. With special physical properties, like surface plasmon resonance (SPR), CuS could not only be selected as a kind of photosensitizer for photothermal therapy (PTT) but also could generate cytotoxic reactive oxygen species (ROS) for photodynamic therapy (PDT) under NIR irradiation [10–12]. What's more important, CuS NPs could serve as a promising contrast agent for photoacoustic tomography (PAT) under NIR irradiation to guide phototherapy (including PTT and PDT) by providing the identification of cancerous lesions [13–15]. Thus, it is undoubtedly logical to obtain one single platform of CuS NPs with combined diagnostic and therapy functions simultaneously induced by the same NIR irradiation in a coordinated way. Of several CuS nanoparticles reported to date [16–19], hollow mesoporous CuS NPs (HMCuS NPs) with hollow interior, numerous mesoporous pores and large surface volume are emerged as one of the drug delivery vehicles superior to solid nanoparticles for drug encapsulation [20,21]. Inspired by the great efficiency of chemotherapeutic agents, a striking platform for synergistic combination of chemo-phototherapy offered by HMCuS NPs is considered a promising candidate for cancer treatment. However, for most naked mesoporous materials, lacking effective target capacity and the premature drug release should be settled urgently before their applications for drug delivery [22–24]. Therefore, it is highly desired to combine the tumor-targeting and controlled on-demand drug release strategy simultaneously through capping the HMCuS NPs with multifunctional smart gatekeeper.

Hyaluronic acid (HA), one of the extracellular matrix substances, is a kind of macromolecule polysaccharide with an expanded random coil structure [25]. Moreover, it could be degraded into small sized fragments such as tetrasaccharides by intracellular lysosomal enzyme hyaluronidase (Hyal-1) which is over-expressed in tumor cells [14]. Attractively, the HA modification is expected to endow HMCuS with numerous merits. On the one hand, HA can be selected as tumor targeting moiety to bind its CD44 receptor that over-expressed on various cancer cells [26,27], thus a platform for tumor-targeted drug delivery could be obtained. On the other hand, it also could act as a gatekeeper by forming a dense layer around the hollow nanoparticles, which is responsible for minimizing premature drug release and intracellular enzyme responsive controlled drug release profile [28]. In addition, with hydrophilic character, HA capping would extraordinarily improve the stability and biocompatibility of the system. Based on these advantages, the versatile HA modification will bring up an admirable multifunctional drug delivery system.

In this work, we constructed a tumor-targeted and multi-stimuli responsive drug delivery system for near-infrared light induced chemo-phototherapy and photoacoustic tomography. As shown in Scheme 1, the chemotherapeutical drug doxorubicin (DOX) was loaded into HMCuS NPs. After that, HMCuS NPs were capped with multifunctional HA to further realize cell-specific targeting and controlled on-demand drug release. The tumor targeting efficiency of HA was evaluated *in vitro* and *in vivo*, respectively. Next, the tumor intracellular tunable drug release in response to multi-stimuli with spatial/temporal resolution was also tested. Considering the outstanding absorption character with NIR absorption of HMCuS NPs, we firmly believe that synergistic combination of chemo-phototherapy under NIR irradiation here would dramatically enhance anti-tumor efficacy and reduce toxic side effects. Additionally, photoacoustic tomography of tumor *in vivo* was further explored to identify cancerous lesions for guiding PTT and PDT. According to our design, the tumor-targeted and multi-stimuli responsive drug delivery system of DOX/HMCuS-HA will open exciting opportunities for theranostic biomedical applications.

2. Experimental section

2.1. Materials

Doxorubicin hydrochloride (DOX·HCl, purity >98%) was obtained from Dalian Meilun Biological Technology Co. Ltd. Sodium hyaluronic acid (HA, molecular weight 12 kDa–14 kDa) was purchased from Freda Biochem Co. Ltd. (Shandong, China). 2-aminoethanethiol, N-(3-dimethylamino propyl-N′-ethylcarbodii mide) hydrochloride (EDC·HCl) and N-Hydroxysuccinimide (NHS) were bought from Aladdin Industrial Corporation. Hyaluronidase from bovine vitreous humor was received from Shanghai Sangon Biological Engineering Technology & Services. All other chemical reagents and solvents gotten from the suppliers were used without further purification. All animal experiments were performed in compliance with the Institutional Animal Care and Use Committee.

2.2. Synthesis of DOX/HMCuS-HA

Synthesis of HMCuS NPs. Briefly, poly-(vinylpyrrolidone) (PVP-K30, 0.24 g) was added to 25 mL of deionized water and then $CuCl_2$ solution (100 μL, 0.5 mol/L) was added dropwise into the solution under stirring at room temperature. Subsequently, NaOH solution (25 mL, 0.02 mmol/L) and moderate hydrazine anhydrous solution were added to form Cu_2O nanospheres. Then a stoichiometric amount of Na_2S was added to the above mixture, and stirred at 60 °C for 2 h. At last, the resulting products (HMCuS NPs) were collected by centrifugation at 12,000 r/min for 10 min and purified by washing several times with deionized water, and then freeze-dried in vacuum overnight.

Amination derivative of HMCuS. The HMCuS NPs (50 mg) were suspended in 50 mL of phosphate buffered saline (PBS) buffer and sonicated to form a homogeneous suspension. Subsequently, 2-aminoethanethiol (100 mg) was added. After stirring at room temperature for 24 h, the sample was concentrated to obtain HMCuS-NH_2.

DOX loading. Free DOX (3 mg/mL) was mixed with HMCuS-NH_2 (1 mg/mL) in PBS buffer under strong stirring for 24 h. Subsequently, the retrieved DOX/HMCuS was collected by centrifugation at 12,000 r/min for 10 min and washed with PBS buffer several times to remove any residual free DOX. The amount of free DOX collected from supernatants was determined by high performance liquid chromatography (HPLC, 1100 Agilent, USA) setting a fluorescence detector (excitation/emission = 480 nm/582 nm) with the following conditions: an Kromasil-C18 column (150 m m × 4.6 mm, 5.0 mm); mobile phase, methanol: 0.01 M KH_2PO_4 buffer (55:45, V/V); column temperature, 30 °C; flow rate, 1.0 mL/min; and injection volume, 20 μL. The loading capacity (LC) of DOX was calculated by the following formula:

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