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Programmed near-infrared light-responsive drug delivery system for combined magnetic tumor-targeting magnetic resonance imaging and chemo-phototherapy

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ABSTRACT

In this study, an intelligent drug delivery system was developed by capping doxorubicin (DOX)-loaded hollow mesoporous CuS nanoparticles (HMCuS NPs) with superparamagnetic iron oxide nanoparticles (IONPs). Under near infrared (NIR) light irradiation, the versatile HMCuS NPs could exploit the merits of both photothermal therapy (PTT) and photodynamic therapy (PDT) simultaneously. Herein, the multifunctional IONPs as gatekeeper with the enhanced capping efficiency were supposed to realize "zero premature release" and minimize the adverse side effects during the drug delivery *in vivo*. More importantly, the hybrid metal nanoplatform (HMCuS/DOX@IONP-PEG) allowed several emerging exceptional characteristics. Our studies have substantiated the hybrid nanoparticles possessed an enhanced PTT effect due to coupled plasmonic resonances with an elevated heat-generating capacity. Notably, an effective removal of IONP-caps occurred after NIR-induced photo-hyperthermia via weakening of the coordination interactions between HMCuS-NH_2 and IONPs, which suggested the feasibility of sophisticated controlled on-demand drug release upon exposing to NIR stimulus with spatial/temporal resolution. Benefiting from the favorable magnetic tumor targeting efficacy, the *in vitro* and *in vivo* experiments indicated a remarkable anti-tumor therapeutic efficacy under NIR irradiation, resulting from the synergistic combination of chemo-phototherapy. In addition, T_2-weighted magnetic resonance imaging (MRI) contrast performance of IONPs provided the identification of cancerous lesions. Based on these findings, the well-designed drug delivery system via integration of programmed functions will provide knowledge for advancing multimodality theranostic strategy.

Statement of Significance

As we all know, a series of shortcomings of conventional chemotherapy such as limited stability, rapid clearing and non-specific tumor targeting ability remain a significant challenge to achieve successful clinical therapeutic efficiency in cancer treatments. Fortunately, developing drug delivery system under the assistance of multifunctional nanocarries might be a great idea. For the first time, we proposed an intelligent drug delivery system by capping DOX-loaded hollow mesoporous CuS nanoparticles (HMCuS NPs) with multifunctional IONPs to integrate programmed functions including enhanced PTT effect, sophisticated controlled drug release, magnetic targeting property and MR imaging. The results showed HMCuS/DOX@IONP-PEG could significantly enhance anti-tumor therapeutic efficacy due to the synergistic combination of chemo-phototherapy. By this delicate design, we believe such smart and extreme versatile all-in-one drug delivery platform could arouse broad interests in the fields of biomaterials, nanotechnology, and drug delivery system.

1. Introduction

Notwithstanding its pharmacological effect for cancer therapy, conventional chemotherapy has been compromised by a series of

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shortcomings such as limited stability, rapid clearing and non-specific tumor targeting ability, which brought out serious side effects [1,2]. In order to address this, developing drug delivery system under the assistance of nanocarries is an increasingly recognized alternative method for cancer treatment [3,4]. Moreover, allowing for the complexity and variability of cancers, it is indispensable to require synergistic combination of several therapeutic approaches in a coordinated way. From this viewpoint, realizing multifunctional nanoparticles with distinct mechanisms is particularly anticipated to optimize cancer therapy.

Recently, copper sulfide nanoparticles (CuS NPs) have received tremendous attention for their unique characteristics of NIR localized surface plasmon resonances (LSPR). Unlike other NIR resonant materials, which usually kill cancer cells relying on one single principle such as heat or reactive oxygen species (ROS) generation, the versatile CuS NPs could exploit the merits of both photothermal therapy (PTT) and photodynamic therapy (PDT) simultaneously [5,6]. Among numerous CuS nanomaterials reported so far [7,8], hollow mesoporous CuS NPs (HMCuS NPs) were considered as an intelligent drug-delivery vehicle preferable to solid nanoparticles due to their uniform pore structure and high surface area for drug encapsulation [9–11]. Based on these advantages, a promising paradigm combining chemotherapy with phototherapy (including PTT and PDT) based on HMCuS NPs was spontaneously obtained for synergistic cancer therapy. Nevertheless, with regard to mesoporous materials without gatekeeper modification, the undesirable premature drug leakage in circulation should be taken into account prior to their biomedical application [12,13]. Thus, it might be a great copping strategy to cap the HMCuS NPs with a multifunctional smart gatekeeper, which would remedy the drug leakage defect to prevent any complications.

The FDA-approved superparamagnetic iron oxide nanoparticles (IONPs), which featured inherent compatibility and high magnetization values, have been taken advantages in biomedical fields related to drug delivery, diagnostics and hyperthermia therapy [14–16]. Herein, IONPs with ultrafine particle sizes could act as a gatekeeper through capping onto HMCuS NPs to realize "zero premature release". In the meanwhile, the hybrid nanoplatform makes it possible to obtain some emerging exceptional characteristics. According to our interparticle coupling effects on the surface plasmon resonances of metallic complex structures could generate highly enhanced local electromagnetic field and further enhance the NIR absorption as reported in literatures such as Au-Fe_3O_4, Au-CuS and r-GO-Au [17–20]. Encouragingly, our results substantiated that the hybrid HMCuS@IONP nanoparticles with enhanced SPR effect could generate elevated photothermal transduction efficiency by lower power laser irradiation in a short time. In addition, a quantity of IONP-caps could be remotely removed from the surface of HMCuS by NIR-induced photo-hyperthermia, probably resulting from the weakening of the coordination interactions between HMCuS-NH_2 and IONPs [21]. Thus, it was more than critical that the NIR stimulus would make progress on controlled on-demand drug release with spatial/temporal resolution. Furthermore, the acknowledged intrinsic magnetic properties of IONPs would endow the nanoplatform with magnetic targeted therapeutic effect and T_2-weighted MR imaging contrast performance [22,23]. As a matter of course, the integration of IONPs on the HMCuS NPs surface certainly would offer great advantages in cancer treatment and diagnosis.

Herein, we proposed a programmed NIR-responsive drug delivery system for combined magnetic tumor targeting MR imaging and chemo-phototherapy. As illustrated in Scheme 1, HMCuS NPs was utilized to encapsulate the chemotherapeutical drug doxorubicin (DOX), and then capped with multifunctional IONPs to integrate programmed functions including enhanced PTT effect, sophisticated controlled drug release, magnetic targeting property and MR imaging, which indicated a smart and extreme versatile all-in-one drug delivery platform. In addition, hydrophilic PEG modification allowed the nanoparticles for biocompatibility and prolonged circulation characteristics [24,25]. The photothermal effect under NIR irradiation was evaluated by using a thermal camera. Next, the tunable drug release upon exposing to NIR stimulus was explored on MCF-7 cells. Based on the noticeable magnetic tumor targeting effect, it was envisioned that the synergistic combined chemo-phototherapy would significantly improve antitumor therapeutic efficacy with minimal side effects. Besides, the MR imaging was also tested *in vivo*. By this delicate design, such a versatile hybrid nanoplatform of HMCuS/DOX@IONP-PEG with multi-functional characteristics will show great promising potential in multimodality theranostic applications in cancer treatment.

2. Experimental section

2.1. Materials

Doxorubicin hydrochloride (DOX HCl) was purchased from Aladdin Reagent Database Inc. (Shanghai, China). PEG_{2000}-COOH, 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC HCl) and 1-Hydroxy-2,5-pyrrolidinedione (NHS) were obtained from Sigma-Aldrich (Boston, MA, USA). All other chemicals acquired from the suppliers were at analytical grade. All animal experiments were carried out in accordance with institutional guidelines and approved by the local ethical committee.

2.2. Synthesis of HMCuS/DOX@IONP-PEG

Synthesis of HMCuS NPs. Briefly, $CuCl_2$ (8.5 mg), poly-(vinylpyrrolidone) (PVP-K30, 240 mg) and hydrazine anhydrous solution (6.4 μL) were added to 50 mL deionized water under magnetic stirring at room temperature to form Cu_2O nanoparitcles. Subsequently, Na_2S (64 mg) was quickly added into the above solution. The mixture was maintained at 60 °C under strong stirring for 2 h. Then the resulting products (HMCuS NPs) were purified by washing three times with water. To obtain amination derivative of HMCuS, HMCuS NPs (1 mg/mL) was mixed with 2-aminoethanethiol (2 mg/mL) in PBS buffer under strong stirring for 24 h. As an end, the mixture was concentrated to obtain HMCuS-NH_2.

DOX loading. 1 mL of DOX in PBS (1 mg/mL) were added into 3 mL of HMCuS-NH_2 in PBS (1 mg/mL). After stirring for 24 h, the retrieved HMCuS/DOX was collected by centrifugation at 15,000 r/min for 5 min. The redundant DOX collected from supernatants was quantified by UV–vis spectroscopy measurements. DOX loading capacity (LC) was calculated in the following formula:

$$LC = \frac{M_{DOX-prep} - M_{DOX-supernatant}}{M_{DOX-prep}} \times 100\%$$

Synthesis of IONPs and IONPs capping onto HMCuS/DOX. The individual aqueous IONPs were synthesized by chemical co-precipitation method [26]. $FeCl_2$ (0.86 g) and $FeCl_3$ (2.35 g) were added into 40 mL of deionized water and then the mixture was heated at 60 °C under N_2 atmosphere. Subsequently, aqueous ammonia (5 mL) was slowly dropped into the above solution. After reaction for 30 min, citric acid (0.5 g/mL, 2 mL) was added. The as-prepared mixture was then maintained at 95 °C for 80 min and cooled to room temperature under continuous stirring. The resulting IONPs were collected with an external magnet. Finally, the resulting product (HMCuS/DOX@IONP) was obtained by mixing IONPs and HMCuS/DOX (1:5) under stirring via noncovalent interaction.