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Aptamer-modified CuS nanocrystals/graphene oxide composites for controlled release of glucosamine and chemo-photothermal therapy of tumor cells

Ziqing Xu [a,b,1], Shicheng Wu [c,1], Guicheng Huang [a,*], Hongwei Ding [b], Rijun Gui [d,*], Baohua Zhu [b]

[a] Nanjing University of Chinese Medicine, Nanjing 210023, PR China
[b] The Second Traditional Chinese Medicine Hospital of Jiangsu Province, Nanjing 210017, PR China
[c] Traditional Chinese Medicine Hospital of Kunshan, Kunshan 215300, PR China
[d] College of Chemistry and Chemical Engineering, Qingdao University, Qingdao 266071, PR China

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ABSTRACT

In this paper, citrate-stabilized CuS nanocrystals were modified by NH_2-terminated aptamer of carcinoembryonic antigen to fabricate aptamer-CuS complex *via* carbodiimide-activated coupling. Then, the complex was conjugated with graphene oxide (GO) to form aptamer-CuS/GO conjugates *via* π-π stacking interactions. Finally, glucosamine (Glu) was loaded into aptamer-CuS/GO conjugates to prepare aptamer-CuS/GO/Glu composites. The composites enabled CEA-targeted and pH-sensitive Glu release. Under near-infrared light irradiation at 980 nm, the composites had photothermal-accelerated release of Glu and chemo-photothermal synergistic therapy *in vitro*. Due to combined advantages from tumor biomarker-targeted, pH-sensitive, photothermal-accelerated drug release, as well as chemo- photothermal therapy, the composites could be developed towards multifunctional drug-delivery systems for highly efficient treatment against tumor cells.

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1. Introduction

As an amino monosaccharide, glucosamine (Glu) has been widely used as alternative treatment for rheumatoid arthritis and osteoarthritis [1]. As established, Glu is extensively taken as a dietary supplement to relieve discomfort of osteoarthritis-related joint pain and is used as a prescription drug to achieve cartilage protective effects in knee osteoarthritis [2]. Significantly, Glu was first reported as an inhibitor of tumor growth by Quastel and Cantero [3]. Afterward, many researches on Glu-dominated tumor therapy *in vitro* and *in vivo* have been reported in succession [1–8]. Anticancer actions of Glu are mainly relative to uracil and adenine nucleotide contents, structural and functional disruption in cellular membrane, inhibition of protein, RNA and DNA synthesis [2]. Glu in a certain concentration could kill tumor cells without influence on normal cells [9], and therefore it is meaningful to develop Glu-carrying systems for drug delivery and tumor therapy.

In previous reports, Glu-carrying polymeric nanoparticles and microgels were prepared and used for drug release studies [10,11]. To improve the efficiency of tumor therapy, it is significant to introduce the characteristics of tumor biomarker-targeted delivery and synergistic therapy in Glu-carrying systems. Herein, a novel Glu-carrying system (in Scheme 1) was facilely prepared *via* non-covalent intercalation and π-π stacking. The system consisted of CuS nanocrystals (NCs), aptamer of carcinoembryonic antigen (CEA) and graphene oxide (GO). After loading of Glu, versatile composites of aptamer-CuS/GO/Glu were achieved. Due to the excellent photothermal effect of CuS NCs under near-infrared (NIR) light irradiation, tumor biomarker CEA-targeting and the larger adsorption of GO to Glu, the composites exhibited a great potential in tumor treatment, especially serving as a versatile Glu-carrying system for CEA-targeted, pH-sensitive, photothermal-accelerated Glu release, and chemo-photothermal synergistic therapy. So far, there is no report referring to simultaneous tumor-targeted Glu release and chemo-photothermal synergistic therapy in Glu-carrying systems.

2. Material and methods

Citrate-stabilized CuS NCs were prepared based on the reported methods (Part S1) [12,13]. GO was prepared from purified natural graphite powder based on a modified Hummer's method [14]. CuS

* Corresponding authors.
E-mail addresses: 635775299@qq.com (G. Huang), gui8078@126.com (R. Gui).
[1] Two authors have the equivalent contribution to this work.

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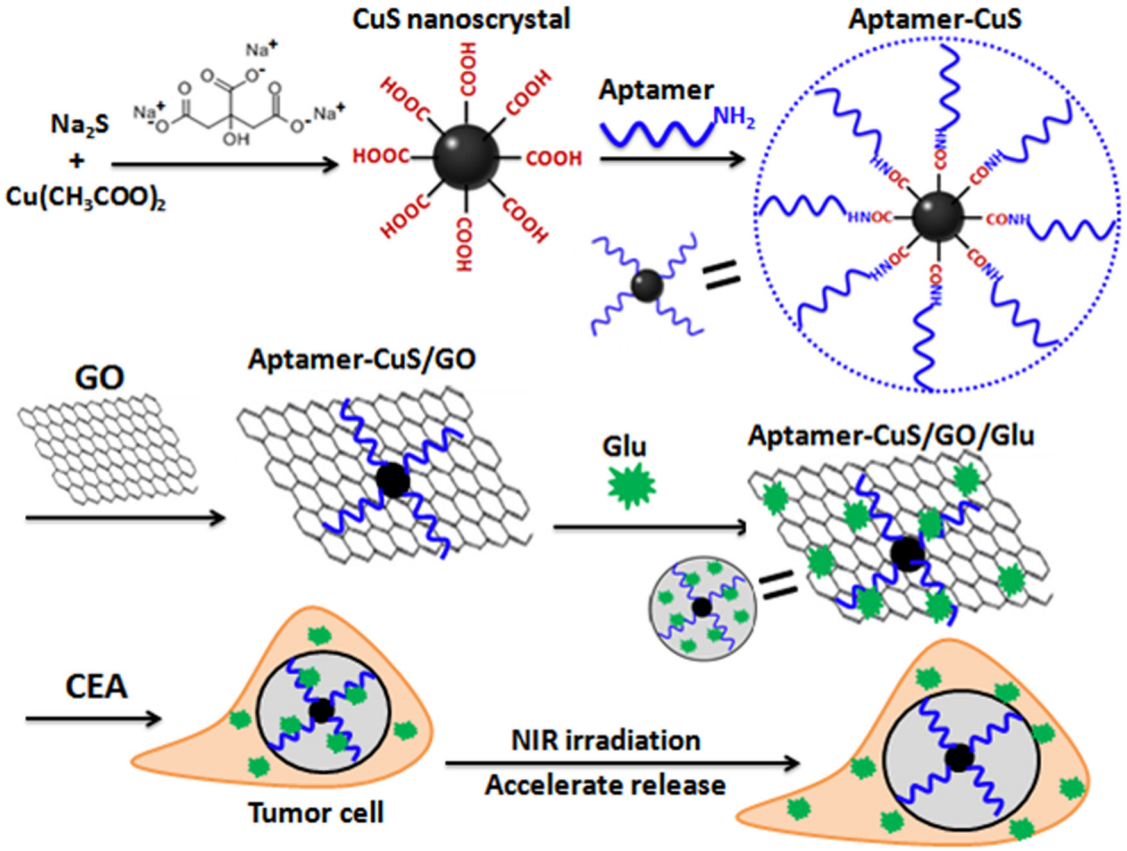

Scheme 1. Schematic illustration of the preparation and drug release of aptamer-CuS/GO/Glu composites.

NCs were combined with NH_2-terminated aptamer of CEA to form aptamer-CuS complex, followed by continuous conjugation with GO to form aptamer-CuS/GO conjugates. In aqueous suspension of the conjugates, Glu was added to form the composites of aptamer-CuS/GO/Glu (Part S2).

Transmission electron microscope (TEM) images were acquired with a JEOL JEM-1400 TEM, operating at 120 kV of acceleration voltage. UV–vis-NIR absorption spectra were recorded on a UV-2450 spectrophotometer. Raman spectra were measured by a Horiba spectrometer, equipped with a 10 × objective lens with 90 s of acquisition time. Zeta potential was measured by a dynamic light scattering apparatus. Cytotoxicity assays were conducted according to a standard MTT method (Part S3) [15]. A 980 nm laser (0.5 W) as a selected NIR light was utilized to irradiate samples to induce photothermal effect. In sample aqueous suspension, temperature was recorded by thermocouple and Glu concentration [Glu] was measured with high-performance liquid chromatography [16].

3. Results and discussion

In Fig. 1(a), TEM images of the as-prepared CuS NCs show nearly monodisperse particles with regular and spherical morphology. The average diameter is approximately ~8.5 nm. Characteristic flat and wrinkled sheets-like intrinsic shape of GO were observed in Fig. 1(b). After carbodiimide-activated coupling, citrate-stabilized CuS NCs were conjugated with NH_2-terminated CEA aptamer to form aptamer-CuS complex. Under π-π stacking interaction, aptamer-CuS complex was attached on GO to form aptamer-CuS/GO conjugates [17]. Compared with Fig. 1(a and b), Fig. 1(c) shows monodisperse distribution of spherical CuS NCs on GO, indicating formation of aptamer-CuS/GO conjugates. In Fig. 1(d), UV–vis spectra of GO have an optical absorption peaked at ~235 nm, originating from π-plasmon of carbon. The absorption peak maintains almost unchanged in UV–vis-NIR spectra of aptamer-CuS/GO conjugates. Notably, a weak transverse plasmon band at ~600 nm and a strong longitudinal surface plasmon band over 1000 nm are observable, attributed to the presence of CuS NCs [12]. Raman spectra were used to characterize carbon structure of GO before and after conjugation with aptamer-CuS complex. In Fig. 1(e), the D band of GO at ~1345 cm^{-1} is usually assigned to local defects or disorders, while the G band at ~1590 cm^{-1} is mainly due to sp^2 graphitized structure [18]. Compared to GO, Raman peak positions and intensities of aptamer-CuS/GO conjugates hardly any change, implying a negligible influence from aptamer-CuS complex on GO.

In Fig. 1(f), aptamer-CuS complex has an average Zeta potential of −7.6 mV, which is from negatively charged feature of CEA aptamer [19,20]. When attached on GO, average Zeta potential of aptamer-CuS/GO conjugates reached to −11.5 mV, attributed to substantial carboxyl and hydroxyl on GO [17,18]. Under electrostatic interaction, positively charged Glu was loaded to form aptamer-CuS/GO/Glu composites, together with a decreased average Zeta potential (−3.2 mV). Continuous exposure of aptamer-CuS/GO aqueous suspension to a NIR light irradiation (980 nm, 0.5 W) for 5 min induced a rapid temperature elevation from 20.0 to 47.3 °C (Fig. 1(g)). It is a unique feature of CuS NCs-carrying systems for controllable drug delivery and photothermal ablation therapy to tumors [21]. Using phosphate buffer solution (PBS) and HeLa cells-cultured medium as the control, negligible temperature increases (<5 °C) were detected under the same

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