Biomaterials 100 (2016) 76–90

Contents lists available at ScienceDirect

Biomaterials

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

Near infrared light responsive hybrid nanoparticles for synergistic therapy

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ARTICLE INFO

Article history:
Received 14 February 2016
Received in revised form
3 May 2016
Accepted 17 May 2016
Available online 21 May 2016

Keywords:
NIR-responsive
Photosolvolysis
Hybrid nanoparticles
Au nanorods
Synergistic therapy

ABSTRACT

A near infrared (NIR) light responsive chromophore 7-(diethylamino)-4-(hydroxymethyl)-*2H*-chromen-2-one (DEACM) was synthesized and incorporated to β-cyclodextrins with cRGD functionalized poly(-ethylene glycol), the amphiphiles were coordinated with Au nanorods or nanoparticles to load anticancer drug doxorubicin (DOX) for fabricating hybrid nanoparticles. The π-π stacking interaction between DEACM and DOX was formed in the hybrid nanoparticles, which contributed to the high drug loading content. The Au nanorods or nanoparticles enhanced the photosolvolysis of DEACM under the irradiation of NIR with 808 nm wavelength and triggered the accelerated drug release from the nanoparticles. The drug loaded hybrid nanoparticles with NIR irradiation exhibited efficient inhibition effect on the proliferation of 4T1 breast cancer cells in vitro. The in vivo anticancer activity study on breast cancer bearing mice revealed that the hybrid nanoparticles containing Au nanorods exhibited excellent anticancer activity under the irradiation of 808 nm wavelength NIR with 800 mW.

1. Introduction

Nanoparticles for anticancer drug delivery have been attracted great interest for cancer chemotherapy due to the enhanced permeation and retardant (EPR) effect of blood vessels in tumors [1,2]. The microenvironment of tumors is different from normal tissues [3–5], which inspired all kinds of stimuli-sensitive nanoparticles for chemotherapy. Taking the advantages of stimuli of weak acidity, high concentrated matrix metalloproteinases (MMPs), glutathione (GSH) and reactive oxygen species (ROS) in tumors, the pH, enzyme, redox, and ROS responsive nano drug delivery systems were extensively studied [6–10]. These intrinsic stimuli sensitive nanoparticles triggered drug release passively with contact modes to exhibit optimistic and effective treatment of cancers. Other exogenous stimuli such as light, temperature, magnetic field exerted active and remote control of drug release via noncontact mode [6,11–13].

Laser has been used in cancer therapy via activating the photosensitizers to produce single oxygen and kill cancer cells, which was called photodynamic therapy (PDT) [14–16]. The penetration of laser in tissues is weak due to its short wavelength, thus, the PDT is limited to epidermal diseases. The wavelength of near infrared (NIR) light is in the range from 700 nm to 1000 nm, the long wavelength of NIR light penetrated deeperin human tissues and resulted in less detrimental to healthy cells with the reduced absorption and scattering of NIR in water and biological substances [17,18]. Gold nanoparticles and nanorods have been reported to absorb near infrared light to transfer heat efficiently for photothermal therapy of cancers [19,20]. However, the surface coating of gold nanoparticles and nanorods to improve their biocompatibility would weaken the therapeutic efficacy [21,22].

Polymers with photochromic groups, which was induced by light to change the architectures, have been exploited as light-sensitive polymers [23]. The wavelength of light to trigger the reversible photoisomerization or irreversible photocleavage of light sensitive polymers was located in the region of UV or visible light [24,25]. Recently, the chromophore of a coumarin derivative was explored to design photocontrollable BCP micelles [26,27]. Although the irradiation of NIR light could cleave the chemical bond in the coumarin derivative, the light responsive BCP micelles were mainly activated by UV and visible light to avoid inefficient

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http://dx.doi.org/10.1016/j.biomaterials.2016.05.023
0142-9612/

two-photon absorption to weaken the cleavage efficiency [28].

Rational design of stimuli-sensitive nanocarriers is important to fabricate nanomedicines with promising chemotherapeutic efficiency. Polymeric micelles with π-π conjugated moieties including coumarin derivatives as hydrophobic segments have been proved to enhance drug loading content via the formation of π-π stacking interaction between anticancer drugs and micelles [29]. These π-π conjugated moieties modified polymeric micelles exhibited significant anticancer activity both in vitro and in vivo. Other than the interactions between drugs and carriers, the cage of cyclodextrin (CD) is also an effective strategy to load anticancer drugs efficiently, the diverse functionalizations of CDs have been reported in anticancer drug delivery [30].

In this paper, a NIR light sensitive hybrid nanoparticles for cancer chemotherapy was fabricated as shown in Fig. 1. A coumarin derivative chromophore moiety named 7-(diethylamino)-4-(hydroxymethyl)-*2H*-chromen-2-one (DEACM) was immobilized on β-CDs, the bond in DEACM was cleavable under the irradiation of NIR with the wavelength of 808 nm. Gold nanorods were cooperated with β-CDs to promote the NIR adsorption. Poly(ethylene glycol) (PEG) functionalized with cycle RGD peptide (cRGD) was linked to β-CDs for active targeting and long circulation. Anticancer drug doxorubicin (DOX) was loaded in the self-assembly β-CDs amphiphiles based hydrid nanoparticles. The NIR light irradiation activated the gold nanorods and it accelerated the photosolvolysis of DEACM to trigger the rapid release of DOX. Both in vitro and in vivo anticancer activities of the drug loaded hybrid nanoparticles with NIR sensitivity were investigated.

2. Materials and methods

2.1. Materials

β-Cyclodextrin and monochloroacetic acid was purchased from Sinopharm Chemical Reagent. 1-ethyl-(3-dimethyllaminopropyl) carbodiie hydrochlide (EDC·HCl), *N*-hydroxysuccinimide (NHS), 1-hydroxy-benzotriazole monohydrate (HOBT), and cyclo(RGDfC-SH) were purchased from GL Biochem. Ltd. (Shanghai, China). Methoxy poly(ethylene glycol) (mPEG, Mw = 2000 g/mol), poly(ethylene glycol) (PEG, Mw = 2000 g/mol), and 3-maleimidopropionic acid (MAL) were purchased from Sigma-Aldrich Co. Ltd. *N*,*N*-diisopropylethylamine (DIEA), 7-Diethylamino-4-methylcoumarin, 2-aminoethanethiol, methyl benzenesulfonyl (TsCl), $HAuCl_4 \cdot 3H_2O$, cetyltrimethylammonium bromide (CTAB), ascorbic acid, $NaBH_4$, and triethylamine (TEA) were purchased from Asta Tech (Chengdu) Biopharm. Co. Ltd. Doxorubicin hydrochloride (DOX·HCl, Zhejiang Hisun Pharmaceutical, China) was deprotonated according to the method previously reported [31]. All the solvents were purchased from Chengdu Kelong Chemical Co. (China) and purified before used. Dulbecco's modified Eagle's medium (DMEM), 100× mycillin, fetal bovine serum (FBS) and cell counting kit-8 (CCK-8) were purchased from HyClone Inc. and used for cytotoxicity test.

2.2. Characterizations

The ^{1}H NMR spectra were performed on Bruker Avance II NMR spectrometer at 400 MHz using tetramethylsilane as the internal standard. The measurements of size and size distribution of the nanoparticles were carried out using a dynamic light scattering (DLS) spectrometer (Malvern ZetasizerNano ZS). Scanning electron microscope (SEM, S4800, Hitachi Ltd, Tokyo, Japan) and transmission electron microscopy (TEM, JEM-100CX-JEOL, Japan) were employed to observe the morphology of the nanoparticles. The lyophilized nanoparticles were redispersed in distilled water and dropped onto silicon pellet, the samples were dried overnight at room temperature for SEM. The TEM samples were prepared by dipping a copper grid with Formvar film into the freshly prepared nanoparticles solution. The copper grid was dried overnight at room temperature. UV–vis absorption (Specord 200 PLUS) and Fluorescence spectra (F-7000, Hitachi, Japan) were used to measure the drug loading content, releasing profile and π-π interaction between drug and carriers.

2.3. Synthesis of compound 1

Carboxymethyl β-cyclodextrin was prepared according to the method previously reported [32]. β-cyclodextrin (7.1 mmol) was

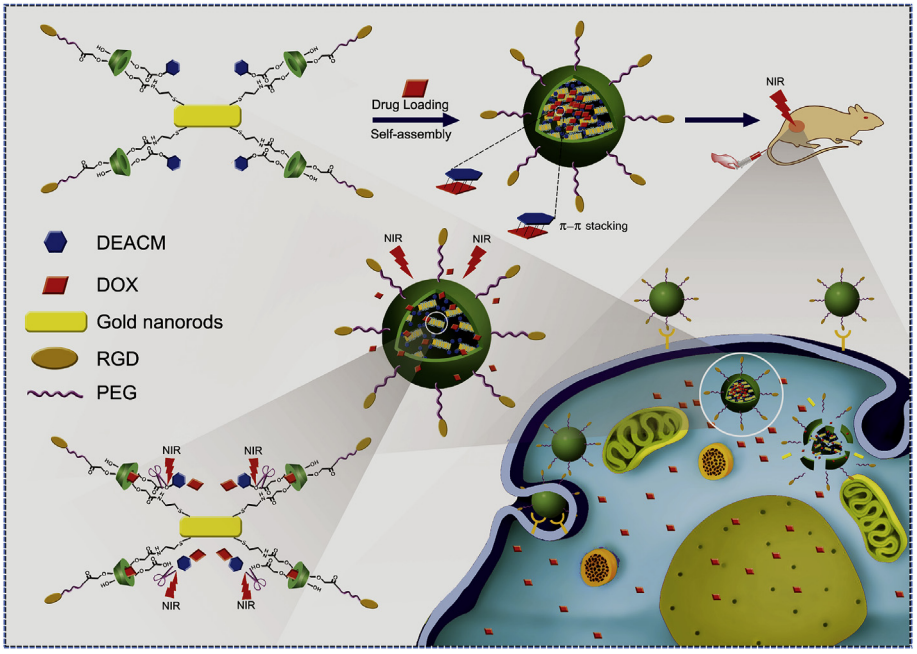

Fig. 1. The schematic illustration of NIR-responsive hybrid nanoparticles for cancer therapy.