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Near infrared radiated stimulus-responsive liposomes based on photothermal conversion as drug carriers for co-delivery of CJM126 and cisplatin

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ABSTRACT

Synergistic therapy has caused increasing interest in recent treatment of cancer owing to its preferable therapeutic efficiency to most single antineoplastic protocol. Herein, we design a co-delivery two drugs nanosystem based on biodegradable liposomes, loading cisplatin, Indocyanine green (ICG), and CJM126 coupled with cholesterol derivative (CJM-Chol) for the purpose of synergistic therapy. The obtained nanoparticles showed a uniform diameter of 103.8 nm and a favorable morphology. The investigation on near infrared radiated (NIR) responsive release showed that NIR mediated photothermal conversion induced a controllable drug release from liposomes. Furthermore, the designed liposomes (only 50 μg/mL) displayed an inspiring photothermal conversion efficiency and received a high temperature (65.6 °C, Tm = 42 °C) when exposed to an 808 nm near infrared laser (1.54 W, 5 min). Besides, it turned out that the delivery system could be efficiently endocytosed by tumor cells, which attributed to its admirable biocompatibility and the targeting role of folate. The prepared nanoparticles showed significantly excellent inhibitory effect (3.05% cell viability in 24 h) on MDA-MB-231 cells when added irradiation as compared with free cisplatin (28.41%) or treatment without NIR (11.24%) in our study. Our research highlights the present nanoparticles provide a promising strategy for targeted delivery and photothermal treatment.

1. Introduction

As one of the most outstanding categories of antineoplastic agents, platinum drugs have been widely used in clinical cancer therapy for their broad-spectrum property, strong inhibitory ability, and high activity [1]. Since approved by FDA in 1978, cisplatin has played a critical role in treating various cancers including colorectal, genitourinary, esophagus, and breast cancers [2]. However, the severe side effects, poor water solubility, and possible resistance of platinum drugs have hindered their more extensive applications in antitumor field [3]. To overcome the above drawbacks and decrease the uptake by healthy tissues, it is critical to select a feasible strategy to enhance the accumulation of drug molecules in tumor sites.

Nanoscaled carriers have attracted broad attention in the potential use as supporters for chemotherapeutic drugs in the past decades [4–8]. There are various advantages concentrated on nanocarriers, such as enhanced endocytosis, prolonged circulation, controlled release, and multiple functional potentials [9–15]. Considering the desirable characteristics of nanocarriers, it is reasonable to believe that they would play an increasingly important role in the cancer treatment in the future. Meanwhile, many groups have indicated that nanocarriers can evidently enhance the antitumor efficacy in transporting drugs to tumor tissues [16–22]. As a kind of multifunctional delivery systems initially proposed for drug formulation in medicine, polymer nanoparticles has been studied in clinical application progressively, since polymeric nanoparticles can release medicine in a controllable and sensitive way resulted from the change of pH value or temperature in tumor sites as well as its favorable biocompatibility [23–24]. In general, to improve the accumulation of nanocarriers in tumor sites, the nanoparticles are usually conjugated with tumor-specific recognitions of peptides, antibodies, or small molecules [25–27]. The folate receptor (FR), a glycosylphosphatidylinositol (GPI)-anchored membrane glycoprotein, has been demonstrated to be overexpressed on the surface of a variety of human tumor cells but minimally distributed in normal tissues [28–29]. The illustrated difference of FR expression between malignant and normal cells makes it an excellent candidate target for cancer therapy. As reported in published literatures, folate turned into a desirable choice for the active targeting owing to the high affinity to FR [30].

Photothermal therapy (PTT), a novel therapy relative to conventional methods based on converting near infrared irradiation into thermal energy effectively through specific agents, has caused great attention and extensive studies in recent years [31–34]. As the only photosensitizer approved by FDA to treat tumors, indocyanine green (ICG) has been

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successfully applied in numbers of formulations and demonstrated desired performance [35–37]. Based on the photothermal conversion, nanocarriers encapsulated ICG would degrade after been irradiated and release drug molecules rapidly. Therefore, to prepare controllable nanocarriers, an 808 nm near infrared laser that could penetrate deeply into biological tissues was introduced as a simulation in vitro.

In the published studies, the 2-(4-aminophenyl) benzothiazole molecule (CJM126) has been reported could restrain the bioactivities of a series of human breast cancer cell lines [38–40], and our previous study has further confirmed that a synergistic effect was achieved from CJM126 and cisplatin [41]. At present work, a bran-new conjugate was fabricated by coupling CJM126 with cholesterol to enhance the drug loading capacity of liposomes, and we hope to develop a recombinant strategy to achieve an improved synergistic therapeutic efficacy along with cisplatin based on a photothermal conversion responsive-release nanoplatform stimulated by near infrared light (Fig. 1). Besides, Folate was introduced as the navigation to selectively increase tumor cellular internalization through receptor-mediated endocytosis. Our research highlights the present nanoparticles provide a promising strategy for targeted delivery and stimulus-release based on photothermal conversion for cancer treatment.

2. Experiment section

2.1. Materials

Folate-poly (ethylene glycol)-distearoylphosphatidylcholine (FA-PEG_{2000}-DSPE) was purchased from Shanghai Ponsure Biotechnology Co., Ltd. (Shanghai, China). Indocyanine green (ICG) was purchased from Shanghai Meryer Chemical Technology Co., Ltd. (Shanghai, China). Cisplatin was purchased from Shandong Boyuan Pharmaceutical Co., Ltd. (Jinan, Shandong, China). Cholesterol and lecithin were purchased from Sinopharm Chemical Reagent Co., Ltd. (China). Dulbecco's Modified Eagle's Medium (DMEM) and RPMI-1640 medium were obtained from Gibco Laboratories (NY, USA). 3-(4, 5-Dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) assay was purchased from Sigma-Aldrich Chemical Company (St. Louis, MO). The human breast and gastric cancer cell lines were obtained from the Cell Bank of the Chinese Academy of Sciences (Shanghai, China). All other chemicals were of analytical grade and used without further purification.

2.2. Synthesis of CJM126-conjugated cholesterol (CJIM-Chol) derivative molecule

CJM-Chol molecule was synthesized by coupling the CJM-COOH molecule with cholesterol through the bridging effect of malonyl dichloride. CJM-COOH molecule was synthesized from CJM126 as our previous work reported. Briefly, CJM-COOH (0.5 g, 1.60 mmol) was activated by EDCl and Hobt at 0 °C for 3 h, and then certain mass of cholesterol (0.7 g, 1.81 mmol) was added to the mixture. About 16 h later, the pale yellow product was obtained after being filtered and washed by diethyl ether. To purify the color product, we use anhydrous ether to wash and subsequently dried in vacuum drying oven, Yield: 72.60%.

2.3. Preparation of cisplatin loaded CJM-Chol liposomes (CC-Pt@FA-NPs)

To obtain nanoparticles with uniform particle size and high loading capacity, CC-Pt@FA-NPs was formulated by a film hydration method reported in our previous work [42]. Briefly, lecithin (20.0 mg), FA-PEG_{2000}-DSPE (2.0 mg), and CJM-Chol (CC) (5.0 mg) were weighted into a 50 mL round flask and moderate dichloromethane (30 mL) was added to fully dissolve the mixture. A thin film was formed after excluding solvent by a rotary evaporator. The organic solvent was removed completely when the flask was placed in vacuum desiccator overnight. Then, deionized water (30 mL), containing cisplatin (4.0 mg) and indocyanine green (3.6 mg) was added to the flask and oscillated by ultrasonic for 8 min. To ensure a well dispersibility, the formed suspension was shaken for 8 min at 30 °C. The above result was then centrifuged at 3000 RCF for 10 min, filtered by a 0.22 mm filter, lyophilized, and further stored at −20 °C for future use.

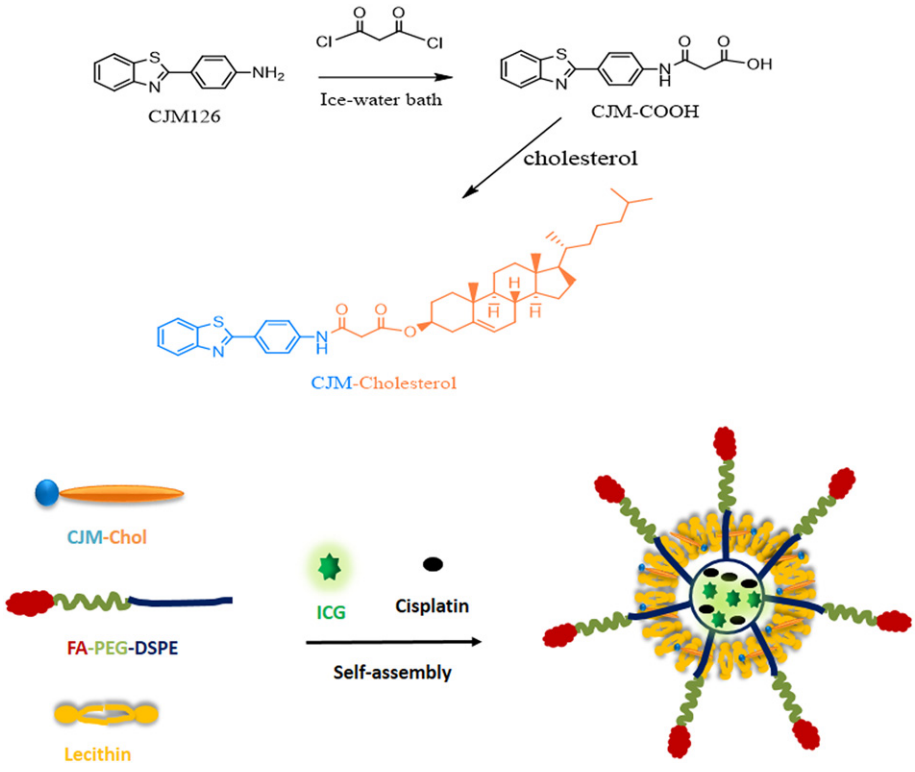

Fig. 1. Fabrication of CC-Pt@FA-Lipo liposomes by CJM-cholesterol synthesis and subsequent self-assembly with lecithin and FA-PEG_{2000}-DSPE.