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Morphology control of self-deliverable nanodrug with enhanced anticancer efficiency

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ABSTRACT

The morphology of nanomedicines has a large influence on the anticancer efficiency of therapeutic agents in biological systems. In this study, camptothecin (CPT)-based nanodrugs with helical and spherical shapes were simply built without the need of any additional carriers. Self-deliverable spherical nanodrug represented a therapeutic advantage over the helical one, which was uncovered from the in vitro toxicity assay. Confocal imaging study indicated that the better outcome of spherical nanodrug was ascribed to the faster cellular uptake. With the aid of sonication treatment, helical nanodrugs with different lengths (HD-1, HD-2, HD-3, HD-4) were created. In comparing with the longest HD-1, the drug release kinetics indicated that the shortest HD-4 exhibited a 20% elevation in cumulative drug release at the first 10 h. The internalized drug amount of HD-4 was three-fold higher than that of HD-1 after the cultivation with 4T1 cells for 2 h. These results demonstrated that the anticancer efficacy of helical nanodrugs was inversely proportional to their lengths. The strategy demonstrated here presents great promise for the preparation of nanodrugs with suitable morphology for cancer therapy.

1. Introduction

Self-assembled spherical nanocarriers, represented by the micellar nanoparticle, have been widely used to escort the anticancer drugs to desirable lesion sites [1,2], with the purpose of achieving a better therapeutic effect via improving the solubility, pharmacokinetics and biosafety of hydrophobic therapeutic agents. In particular, drugs loaded in nanocarriers could be passively accumulated at tumor tissues due to the enhanced permeability and retention (EPR) effect [3]. To improve the drug loading capacity and ensure the identical drug content, polyprodrugs that are polymerized by therapeutic agents have also been proposed to optimize the therapeutic outcomes [4–6]. Recent studies have demonstrated that the morphology of nanocarriers could affect the anticancer efficiency of drugs in biological systems [7–10]. For example, the size of nanocarriers has been reported to play a vital role in dominating the penetrating efficiency as well as blood circulation half-life [11,12]. Smaller nanomedicines show better tumor penetration, and larger counterparts are favorable for long blood circulation. Similar to the size, the shape of nanomedicines is another critical parameter for their biological function. Therefore, various self-assembled nanocarriers such as nanofiber [13], nanotube [14], and nanorod [15] have been proposed to deliver anticancer drugs. Liu's group designed polyprodrug amphiphiles that could self-assemble into four nanostructures including spheres, smooth disks, large compound vesicles, and staggered lamellae through adjusting cosolvent type, composition, and water addition rate [16]. It was found that the lamellar nanostructure displayed the fastest cellular uptake rate and extended blood circulatory half-life. Using polystyrene nanoparticles with different sizes and shapes as the therapeutic platforms, Mitragotri demonstrated that rod-shaped nanomedicines outperformed the spherical counterparts, exhibiting higher cellular uptake and transport across intestinal cells [17]. Despite some discovery about the influence of shapes on their achievements in carrier-aided drug delivery, the overall therapeutic effects were to some extent not comparable because of batch-to-batch inconsistencies in the drug-loading capacities and degradation rates for those different shaped carriers. Furthermore, potential systemic toxicity and undesirable side effect from nanocarriers are far from satisfactory.

Self-deliverable pure nanodrug systems, constructed by therapeutic agents without any additional carriers, have emerged as a promising strategy for cancer therapy. In sharply contrast to conventional carrier-aided formulations, self-deliverable nanodrugs hold distinctive characteristics such as high drug loading efficiency, improved solubility and bioavailability, avoidable carrier-related

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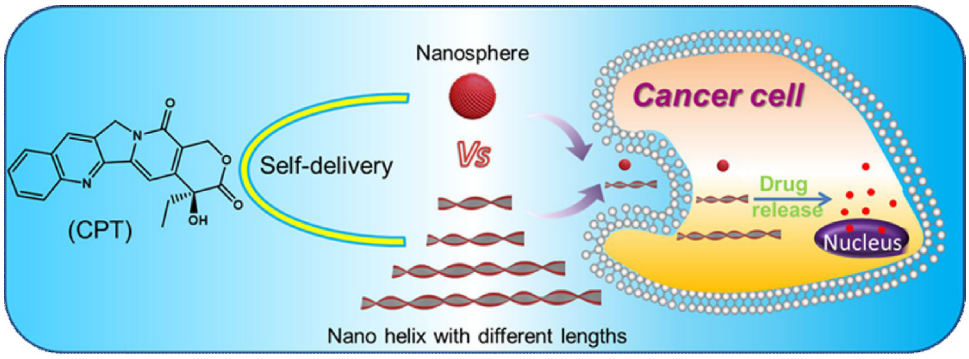

Scheme 1. Scheme of self-deliverable nanodrugs with different morphologies for the optimal cancer therapy.

toxicity, and simple preparing procedure [18,19]. Furthermore, the undesirable immune reactions caused by the interaction between carriers and specific cell surface receptors can also be excluded [19,20]. Depending on the bottom-up strategy [21], various self-deliverable nanodrugs with different morphologies have been developed [22–24]. These nanodrugs displayed dramatically enhanced anticancer activities comparing with their corresponding free drugs. With the absence of carriers, notably, self-deliverable nanodrugs provide a feasible route to directly investigate the morphology-anticancer efficiency relationship. For instance, 10-hydroxycamptothecin (HCPT)-based nanorods exhibited better anticancer efficiency than spherical counterparts [25,26], and the therapeutic efficacy of nanorods gradually decreased with increasing the aspect ratio (AR) [27]. The findings provided some principles in the design of self-deliverable systems for cancer therapy. However, those studies only focused on the influence of single parameter (shape or AR) on the anticancer efficiency. Is it possible to construct a self-deliverable nanodrug with controllable shape and length and further investigate their combined influence on the therapeutic effects?

In our previous work, we found that camptothecin (CPT) could aggregate into pure nanodrug, which effectively protected the CPT-based drug from hydrolytic lactone opening and thereby ensured the bioactivity [28]. Based on these findings, we continue to investigate the influence of nanodrug morphology (shape and AR) on the anticancer efficiency. Self-deliverable CPT nanodrugs with helical shape and spherical shape were constructed in the present study. To our knowledge, helical nanodrugs have rarely been reported and their anticancer activities are relatively vacant. The in vitro anticancer efficiencies of helical and spherical nanodrugs were investigated (Scheme 1). To probe the influence of length on the therapeutic effect, helical nanodrugs with different lengths were further developed with the help of sonication treatment. The discrepancies in their cellular internalization and in vitro anticancer efficiency of these helical nanodrugs with different lengths were also uncovered. The results would assist in the future design of nanodrugs with suitable shape and size for the optimal efficacy of cancer therapy.

2. Materials and methods

2.1. Materials

Camptothecin (CPT) was provided by Tianjin Heowes Biochem LLC. Dimethylsulfoxide (DMSO) were obtained from Sinopharm Chemical Reagent Co., Ltd. and used as received. Dulbecco's phosphate buffered saline (PBS), Dulbecco's modified Eagle's Medium (DMEM), fetal bovine serum (FBS), and 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetra-zoliumbromide (MTT) were purchased from Invitrogen Corp.

2.2. Preparation of CPT nanodrugs with different shapes and lengths

The helical nanodrug was fabricated according to our previously published protocol [28]. In detail, 3×10^{-2} M CPT/DMSO solution was prepared and further dropped into aqueous solution under rapid hand shaking, making the final concentration of CPT to 1.5×10^{-5} M. The obtained helical nanodrugs were then divided into four groups and subjected to sonication treatment with different time courses (0, 2, 5, and 20 min) at 25 °C with the power of 180 w for the formation of nanodrugs with different lengths. These nanodrugs were marked with HD-1, HD-2, HD-3 and HD-4, respectively. To fabricate the spherical CPT nanodrug, the original helical nanodrug was subjected to a high pressure homogenizer (EmusiFlex-C5, made in Canada by AVESTIN) with the pressure of 10000 psi for ten minutes.

2.3. Morphology observation

The morphology of nanodrugs was investigated on a scanning electron microscope (SEM, Zeiss SIGMA FESEM). SEM samples were prepared by dropping 1 μL of nanodrug-containing aqueous solution onto a glass substrate. After slowly dried in air, the samples were further coated with gold for the observation.

2.4. Particle size measurement

The hydrodynamic size of self-deliverable spherical nanodrug was measured with Nano-ZS ZEN3600 (Malvern Instruments) at 25 °C. To investigate the stability of the nanodrug, the size change of nanodrugs was monitored by measuring the average size of nanosphere at different time intervals.

2.5. Drug release

The control release of CPT from nanodrugs with different morphologies was investigated. 2 mL of 1.5×10^{-5} M nanodrug solution were added into a dialysis tube (MWCO 3500) and dialyzed against 30 mL of PBS at 37 °C under shaking in a water bath for the drug release. Before recording the released drug concentration, all the buffer solutions outside the dialysis tubes were replaced by fresh buffer solution to move the unloaded drugs. Then, at each predetermined time, 1 mL of drug-containing PBS solution was withdrawn to each container, and 1 mL of fresh PBS was further added to offset the solution volume loss. The amount of released CPT from these nanodrugs was determined by fluorescence measurement at wavelength of 440 nm with the excitation wavelength at 365 nm.