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Reactive oxygen species activated nanoparticles with tumor acidity internalization for precise anticancer therapy

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ABSTRACT

The fact that the sensitivities of different tumor cells and different individuals to the actions of drug delivery system varied greatly, restricted the anticarcinogen to a desired therapeutic concentration. How to determine the destiny of drug delivery system in space and time is the main challenge to realize the precise anticancer therapy. In this paper, we reported a preparation of degradable nanoparticles (designated Pros-PDC) loaded DOX and IR780 with three functional domains: the charge-conversional feature with long circulation time and enhanced internalization, light-triggered reactive oxygen species (ROS) generation and subsequently ROS responsive anticancer drug release with a spatially and temporally precise fashion. The spatiotemporal drug release from the ROS activated Pros-PDC nanoparticles could be controlled by when and how long to perform laser irradiation. In the present work, multifunctions of DOX and IR780 loaded Pros-PDC nanoparticles, as a flexible, easily controllable drug release platform, had been certificated *in vitro* and *in vivo*.

1. Introduction

Biodegradable polymeric nanoparticles as one kind of the most promising drug delivery systems in successful cancer chemotherapy possessed the advantage of accumulation at the tumor site *via* the enhanced permeability and retention (EPR) effect [1–6]. However, the EPR effect can only enhance the accumulation of nanoparticles in tumor tissues. The inherently short blood circulation time and poor cell uptake of nanoparticles were also limited the therapeutic effect. Moreover, the sensitivities of different tumor cells to the actions of drug delivery system varied greatly, and the sensitivities of different individuals with the same kind of tumor also varied significantly, which hampered the efficacy of cancer chemotherapy due to undesired therapeutic concentration at the targeting site [7–9]. The personal aspects have always been neglected in the current treatment of cancer [10,11]. How to determine the destiny of nanocarriers in spatial and temporal precision with individual comprehensive therapy is the main challenge in the drug delivery applications to realize the precise anticancer therapy.

Cellular uptake depends on the physicochemical properties of surface charge due to the interactions between nanoparticles and biological environment [12–15]. Nanoparticles with negative and neutral charged were adsorbed less on cell membranes and limited internalization extent comparing to positively charged nanoparticles [16–20]. However, the nanoparticles with positive charges showed strong interaction with bovine serum albumin protein which caused severe aggregation and clearance from blood circulation [18,21–23]. Therefore, pH-dependent charge conversion has been proved to be a very efficient strategy for the improved drug delivery [24–26].

The antitumor effect of most drug delivery nanoparticles was passive role without controllably spatial and temporal drug release. Despite great advances, the strategies have mainly focused on the responsive carriers and led to suboptimal therapeutic effect. Nanoparticles with response to physiological events are extensively studied, such as changes in extracellular pH [27–31]. However, in the vast majority of cases, we need the controllable drug release in different stages of cancer therapy and different individuals, not the sooner the better. Therefore the intrinsic limitation of nanoparticles with a spatially and temporally precise fashion of drug release were the main challenges in the drug delivery applications to overcome the fact that sensitivities of different tumor cells varied greatly to the actions of drug delivery system.

Only rarely, however, is a single therapy enough to overcome

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cancer. The requirement has inspired combination regimens that overcome the additive, synergistic, and complementary interactions between treatments [32–36]. Photodynamic therapy (PDT) has been intensively studied and employed as a promising treatment strategy for the treatment of various tumors based on activation of photosensitizer with specific light irradiation resulting energy transfer cascades that ultimately yield ROS [37–39]. Due to fact that light could be triggered from outside of the system and localized in space and time, light has attracted much attention [40]. Combination the properities of photosensitizer to produce ROS after light irradiation and the advantage of light itself, the ROS responsive nanoparticles activated by an external light stimulus maybe provide the advantages of a precise controllability release of encapsulated substances both spatially and temporally. The combined photodynamic treatment (just for generation ROS) with chemotherapy may be a choice to determine the destiny of nanocarriers in a spatially and temporally precise fashion with individual comprehensive therapy to realize the precise anticancer therapy.

In this paper, we prepared two functional copolymers to construct degradable nanoparticles (designated Pros-PDC). One copolymer was designed with ROS sensitive thioether chain and the other with acid-labile β-carboxylic amides pendants. As shown in Scheme 1, the anticancer drug and photosensitizer loaded Pros-PDC nanoparticles comprised of three functional domains: the acid-labile β-carboxylic amides providing the charge-conversional feature, light-triggered ROS generation and the subsequently ROS activated anticancer drug release with on-demand fashion. After intravenous injection, the DOX and IR780 loaded Pros-PDC nanoparticles (Pros-PDC/DOX + IR780) with charge-conversion is expected to simultaneously prolong blood circulation time and enhance the internalization. Then the timing and speed of drug release could be controlled by when and how long to perform laser irradiation because the light-triggered ROS could induce nanoparticles disassembly with a controllably spatially and temporally precise fashion. Therefore, the speed of drug release could be adjusted to the optimal content in the different treatment stage or the different individuals, anytime and anywhere.

2. Materials and methods

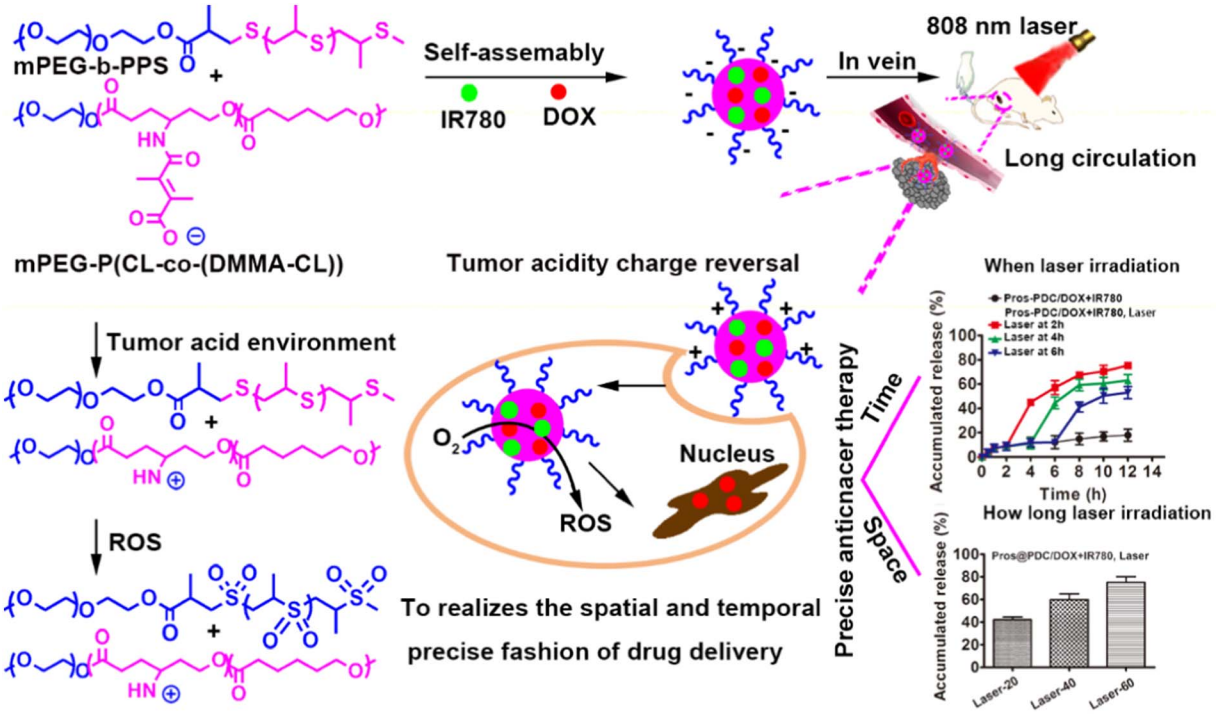
2.1. Materials

mPEG-P(CL-co-(DMMA-CL)) was synthesized in our lab as previous described [41]. Methoxy poly (ethylene glycol)-b-poly-(propylene sulfide) ($mPEG_{45}$-b-PPS_{60}) was prepared and detail information in supporting information. (mPEG, Mn = 2.0×10^3 g/mol), stannous octoate ($Sn(Oct)_2$), and ε-caprolactone (ε-CL) were purchased from GL Biochem (Shanghai) Ltd. $mPEG_{45}$-b-PCL_{35} were prepared in our lab as previous described [41]. Dichlorodihydrofluorescein diacetate (DCFH-DA), singlet oxygen sensor green (SOSG) and 1,1′-dioctadecyl-3,3,3′,3′-tetramethyl indotricarbocyanine iodide) (DIR) were used as received from Sigma-Aldrich (Milwaukee, USA). Methacryloyl chloride, 2,2-azobisisobutyronitrile (AIBN), thioacetic acid, sodium methylate, and propylene sulfide were purchased from GL Biochem (Shanghai) Ltd. Tetrahydrofuran (THF) and triethylamine were dried by refluxing over Na metal under an argon atmosphere and distilled immediately before use. Dichloromethane (DCM) was purified by vacuum distillation with CaH_2. 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was purchased from Sigma-Aldrich. Doxorubicin hydrochloride (DOX HCl) was purchased from Wuhan Hezhong Biochemical in manufacturing Co.,Ltd.

4T1 cells were purchased from American Type Culture Collection (ATCC; Manassas, VA). Cell culture medium and fetal bovine serum were from WisentInc (Multicell, WisentInc., St. Bruno, Quebec, Canada). 4T1 cells were maintained in Dulbecco's Modified Eagle's Medium (DMEM) with 10% fetal bovine serum and 1% antibiotic solution. All cells were cultured in a humidified atmosphere containing 5% CO_2 at 37 °C.

2.2. Preparation of nanoparticles

Nanoparticles were prepared by dialysis method. Typically, 10 mg mPEG-P(CL-*co*-(DMMA-CL)) polymers and 10 mg $mPEG_{45}$-b-PPS_{60} polymers were dissolved in DMF and added dropwise to double distilled water. After that, the solution was transferred to a dialysis bag



Scheme 1. Illustration of construction of Pros-PDC nanoparticles with long circulation time and enhanced internalization. The light-triggered ROS generation and subsequently ROS activated anticancer drug release of the DOX and IR780 co-loaded Pros-PDC nanoparticles with a spatially and temporally precise fashion.