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A photosensitive liposome with NIR light triggered doxorubicin release as a combined photodynamic-chemo therapy system

Qingpo Li[1], Wei Li[1], Haixiao Di, Lihua Luo, Chunqi Zhu, Jie Yang, Xiaoyi Yin, Hang Yin, Jianqing Gao, Yongzhong Du, Jian You*

College of Pharmaceutical Sciences, Zhejiang University, 866 Yuhangtang Road, Hangzhou, Zhejiang 310058, PR China

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ABSTRACT

The targeted drug delivery with the help of nanocarriers and the controlled drug release at the lesion sites are the most effective ways to enhance therapeutic efficacy and reduce side effects. Here, we built a light sensitive liposome (Her2-I&D-LSL) which was formed by a special phospholipid (PLsPC) and a hydrophobically modified photosensitizer (ICG-ODA). DOX was employed as the therapeutic drug, encapsulating in the internal phase of the liposome whose surface was modified by Her2 antibodies for recognizing tumor cells with high Her2 receptor expression. Mediated by NIR light, Her2-I&D-LSL was proved to generate sufficient ROS to realize PDT, which then triggered the release of DOX for combined chemotherapy. The ROS generation and DOX release were verified to be strictly controlled by NIR light and the proportion of ICG-ODA. Thanks to the mediation of Her2 receptor, the specific DOX release and the combination of PDT-chemotherapy triggered by NIR light, Her2-I&D-LSL showed a significant accumulation in MCF7 and SKOV3 tumors, thus leading to the strongest tumor growth inhibition effect compared to PDT alone (I-LSL) or chemotherapy alone (D-LSL). Her2-I&D-LSL also possessed a great biocompatibility due to the targeted treatment, holding promise for future cancer therapy in clinic.

1. Introduction

Chemotherapy, as a principal cancer treatment approach in clinic, exhibits serious systematic toxicity resulted from the non-specific drug distribution in human body [1–3]. As a result, countless research efforts have been devoted to promote the specific cancer therapy by designing various drug delivery systems and diminishing the side effects for the past few decades [4–6]. Delivering the drug molecules to the tumor sites by organic or inorganic nanocarriers, such as polymeric micelles [7,8], liposomes [9] and a variety of metallic nanoparticles [10,11] has been proved practicable by many researchers. Unfortunately, there is still a long way to go since human cancers have been found to be extremely complicated with multiple gene mutations, leading to the exacerbation, metastasis and drug resistance [12,13]. Therefore, it is difficult to use a single treatment strategy for successful cancer therapy. Photodynaimc therapy (PDT), which relies on O_2 and light activation, was able to produce cytotoxic reactive oxygen species (ROS) for destructing the biomembrane of tumor cells and the microvessels of tumor tissues [14–17]. Normal tissues without light irradiation could be free from damage. Therefore, PDT has attracted more and more attention since its lowest systematic toxicity and treatment costs compared with the traditional surgery, chemotherapy and radiotherapy.

Although the drug carriers were capable of greatly improving the accumulation of drugs at the lesion sites, there will be no therapeutic effect if the drug could not be released from the carriers. Thus, the high stability of the drug delivery system (with no drug leakage during the circulation system) and the quick drug release at the tumor sites become a contradiction. To deal with this problem, series of tumor microenvironment responsive drug delivery nanocarriers were developed such as the pH and glutathione responsive materials, etc. [18–20]. Therapeutic drugs were delivered to the desired location where they could be released once the carriers were destroyed by specific substance. Additionally, there is also a strategy to trigger the drug release from external forces, such as the intervention of extra magnetic field, light, heat or ultrasonic [21–24], which undoubtedly provides a feasible way to increase the drug concentration at target sites. Among all these intervention technologies, near infrared (NIR) light (700–1000 nm) has a greater tissue penetration property compared with UV or visible light, which is an ideal choice for mediating the cancer treatment in deep tissues.

In this work, we have developed a NIR light controlled drug release nanosystem which exhibits the combination of PDT and chemotherapy.

* Corresponding author at: College of Pharmaceutical Sciences, Zhejiang University, 866 Yuhangtang Road, Hangzhou 310058, Zhejiang, China.
E-mail address: youjiandoc@zju.edu.cn (J. You).
[1] These authors contributed equally to this paper.

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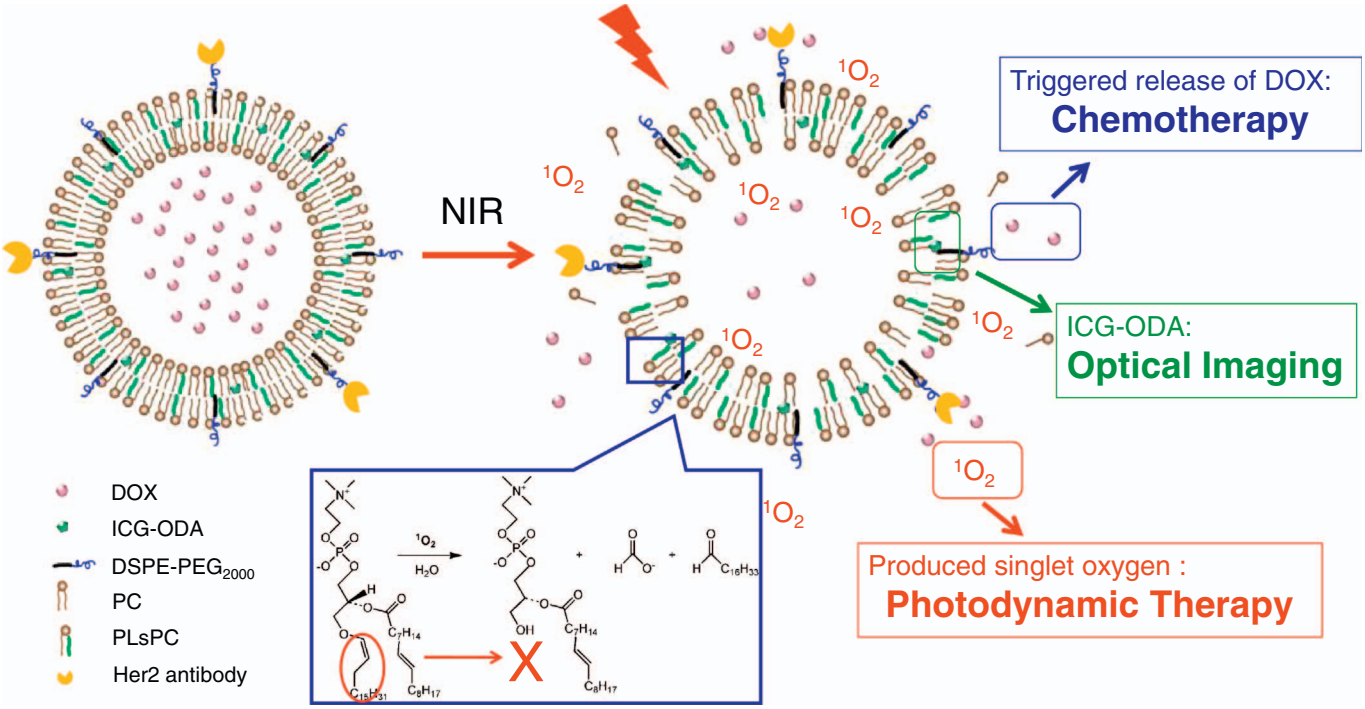

Scheme 1. The illustration of the NIR light mediated specific drug release and synchronous PDT and chemotherapy.

A special-structured phospholipid material (PLsPC) and a hydrophobically modified photosensitizer (ICG-ODA) were employed to form the most important factors of the light sensitive liposome (LSL). DOX, a chemotherapy drug, was then encapsulated in the liposome whose surface was further conjugated with Her2 antibodies (has specific affinity with human epidermal growth factor receptor-2) to endow it with an active targeting ability toward Her2 receptor positive-expressed tumors. The obtained nanosystem (Her2-I&D-LSL) showed a PDT effect under NIR light, and the produced ROS could destroy the structure of the liposome, thus triggering the release of DOX for chemotherapy (Scheme 1). Our study presented a novel tool of controlling drug release and a strategy of combined PDT and chemotherapy, which will provide efficient alternative for cancer therapy in future clinical application.

2. Materials and methods

2.1. Materials

1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy (polyethylene-glycol)-2000] (DSPE-PEG_{2000}), soya bean lecithin (S100) were obtained from lipoid Co. (Ludwigshafen, Germany). 1-(1z-octadecenyl)-2-oleoyl-sn-glycero-3-phosphocholine, (PLsPC) was purchased from Avanti Polar Lipids, Inc. (Alabaster, AL, USA). DOX•HCl was supplied by Hisun Pharmaceutical Co., Ltd. (Zhejiang, China). Cholesterol (Chol), N,N-Disuccinimidyl carbonate (DSC), and octadecylamine (ODA) were acquired from Hushi Chemical Co., Ltd. (Shanghai, China). Indocyanine green (ICG) was supplied by TCI (Tokyo, Japan). 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT reagent), 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) and Hoechst 33,324 were purchased from Sigma-Aldrich Inc. (St Louis, MO, USA). 4-dimethylaminopyridine (DMAP) was obtained from Sinopharm Chemical Reagent Co.,Ltd. (Shanghai, China). Live/Dead viability/cytotoxicity kit was purchased from Invitrogen Corp. (Carlsbad, CA, USA). DCFH-DA was acquired from Beyotime Institute of Biotechnology (Jiangsu, China). The chemicals and solvents were of analytical grade and used as received.

2.2. Cell culture and animal models

MCF7 (human breast cancer), SKOV3 (human ovarian cancer), A549 (human lung cancer) and S180 (mouse osteosarcoma) cell lines were obtained from Institute of Biochemistry and Cell Biology (Shanghai, China). Cells were cultured in RPMI 1640 Medium (MCF7 and SKOV3) or Dulbecco's Modified Eagle Medium (A549 and S180) containing 10% fetal bovine serum (Life Technologies, Inc., Carlsbad, CA) in a humidified atmosphere containing 5% CO_2 at 37 °C.

All the animal studies were performed as the approval of Institutional Animal Care and Use Committee. To establish different tumor models, 8×10^6 MCF7, SKOV3 or A549 cells were subcutaneously injected at the armpits of male nude mice (4–6 weeks), 1×10^6 S180 cells were subcutaneously injected at the right abdomen of ICR mice and allowed to grow to solid tumors.

2.3. Synthesis of ICG-ODA

The synthesis procedure of ICG-ODA was showed in Fig. S1A. ICG (0.8 mg/mL, dissolved in DMF) were mixed with EDC, DMAP (1 mg/mL, dissolved in deionized water, ICG:EDC:DMAP = 1:3:3, mol/mol) and stirred for 1 h at 45 °C. Then, ODA (1 mg/mL, dissolved in DMF, ICG:ODA = 1:6, mol/mol) were added and stirred for another 24 h. The reaction solution was dialyzed with a dialysis bag (MWCO: 3.5 kDa) in deionized water for 48 h and collected after lyophilization. The chemical structure of the resulted ICG-ODA was identified by ^1H NMR and mass spectrometry (Bruker Amazon ETD, Germany).

2.4. Synthesis and characterization of light-sensitive liposomes (I&D-LSL)

ICG-ODA, S100, PLsPC, Chol and DSPE-PEG_{2000} were dissolved in chloroform at a specific ratio and then rotary-evaporated at 45 °C to form a lipid film. Subsequently, 250 mM ammonium sulfate solution was added for hydration. After probe supersonic (130 w, 8 min) and repeated extrusion through a polycarbonate membrane (Avanti, pore size: 100 nm) at 45 °C, homogeneous ICG encapsulated liposomes (I-LSL) were obtained. The solution was dialyzed with a dialysis bag