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Mussel-inspired PLGA/polydopamine core-shell nanoparticle for light induced cancer thermochemotherapy

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ABSTRACT

Most photothermal converting systems are not biodegradable, which bring the uneasiness when they are administered into human body due to the uncertainty of their fate. Hereby, we developed a mussel-inspired PLGA/polydopamine core-shell nanoparticle for cancer photothermal and chemotherapy. With the help of an anti-EGFR antibody, the nanoparticle could effectively enter head and neck cancer cells and convert near-infrared light to heat to trigger drug release from PLGA core for chemotherapy as well as ablate tumors by the elevated temperature. Due to the unique nanoparticle concentration dependent peak working-temperature nature, an overheating or overburn situation can be easily prevented. Since the nanoparticle was retained in the tumor tissue and subsequently released its payload inside the cancer cells, no any doxorubicin-associated side effects were detected. Thus, the developed mussel-inspired PLGA/polydopamine core-shell nanoparticle could be a safe and effective tool for the treatment of head and neck cancer.

Statement of Significance

The described EGFR targeted PLGA/polydopamine core-shell nanoparticle (PLGA/PD NP) is novel in the following aspects:

Statement of Significance: Different from most photothermal converting nanomaterials, PLGA/PD NP is biodegradable, which eliminates the long-term safety concerns thwarting the clinical application of photothermal therapy.

Statement of Significance: Different from most photothermal nanomaterials, upon NIR irradiation, PLGA/PD NP quickly heats its surrounding environment to a NP concentration dependent peak working temperature and uniquely keeps that temperature constant through the duration of light irradiation. Due to this unique property an overheating or overburn situation for the adjacent healthy tissue can be easily avoided.

Statement of Significance: The PLGA/PD NP releases its payload through detaching PD shell under NIR laser irradiation.

Statement of Significance: The EGFR-targeted doxorubicin-loaded PLGA/PD NP effectively eradicate head and neck tumor *in vivo* through the synergism of photothermal therapy and chemotherapy while not introducing doxorubicin associated cardiotoxicity.

1. Introduction

Photothermal therapy (PTT) has been extensively explored for cancer treatment by coupling localized near-infrared (NIR) irradiation and locally accumulated photothermal converting agents (PTCAs) [1]. By far, most developed PTCAs are made of metal based nanostructures, such as gold nanorod, gold nanoshell, gold nanocage, CuSx nanocrystal [2–4]. Due to the localized surface plasmon resonance (LSPR) phenomenon, these nanoparticles generate heat upon light irradiation. By adjusting their size, shape, and geometry, the LSPR peaks of these nanostructures can be tuned to a tissue transparent window (650–900 nm), where light can penetrate deeply [5]. Because of that, upon NIR irradiation, PTCAs generate heat that can be applied for photothermal therapy for cancer and other

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diseases [5–12]. Due to the slow or non-degradable nature of these metal based PTCAs, they are retained in many organs after finishing their mission. It was found that, for hollow gold nanospheres, about 70% and 95% of them can be retained in the liver and spleen, respectively, 3 months postinjection as compared with their corresponding amounts 1 day postinjection [13]. On the contrary, only around 5% and 7% of CuS nanoparticles were retained in the liver and spleen, respectively, 3 months postinjection as compared with their corresponding amounts 1 day postinjection. Furthermore, Guo et al. revealed that there is an irreversible change in the proteomic profile of the liver in mice administered with hollow gold nanospheres, while the change in the proteomic profile of the liver in mice receiving CuS nanoparticles treatment is reversible. Thus, the long-term safety concerns have thwarted the clinical PTT application of gold nanoparticle based PTCAs [14,15].

Poly(lactic-co-glycolic acid) (PLGA) is a US Food and Drug Administration (FDA) approved biodegradable material, which has been extensively explored as drug carriers for cancer targeted therapy. Since PLGA is not responsive to pH and redox potential, the release of the payload from PLGA based carriers is mainly controlled by the degradation rate of the polymer, depending on its molecular weight and copolymer ratio [16,17]. To endow light triggerable release capacities to these carriers, PLGA nanoparticles have been coated or embedded with various metal-based PTCAs [18,19]. However, the inherited non-degradable nature of those PTCAs remains a challenge for their clinical translation.

Epidermal growth factor receptor (EGFR) is overexpressed in many cancer cells including non-small cell lung cancer, colorectal cancer, and head and neck cancer [20]. Cetuximab, a chimeric (mouse/human) monoclonal antibody for EGFR, has been approved by FDA as an EGFR inhibitor for the treatment of colorectal cancer and head and neck cancer [20–22]. Meanwhile, due to its specificity for EGFR overexpressing cancer cells, cetuximab has been explored as a targeting ligand to guide nanocarriers to selectively kill lung cancer cells, glioblastoma cells, and pancreatic cancer cells [23–25].

In nature, mussels powerfully adhere to various surfaces mainly attributes to 3,4-dihydroxyphenyl-l-alanine (DOPA), which contains reactive catechol, and lysine [26]. Inspired by the unique of mussel, Messersmith et al. developed a surface modification technology with dopamine, which contains catecholamine functional groups [27]. In weak basic environment, dopamine can be self-polymerized to form a polydopamine (PD) layer on the surface of numerous materials. Furthermore, the newly formed PD layer can subsequently react with thiol or amine containing biomolecules to yield surface functionalized materials [27–29]. In addition, researchers found that PD nanoparticle has a strong absorbance in the NIR region and can generate heat upon NIR irradiation [30]. PD coated manganese oxide nanoparticles and Fe_3O_4 nanoparticle have been explored for the treatment of cancer by photothermal therapy [31,32]. Hereby, we developed a photothermal converting nanomaterial based on the core/shell structure of biodegradable PLGA and polydopamine (Fig. 1A). To be more effective in killing cancer cells, doxorubicin (DOX) was encapsulated into the cetuximab functionalized nanoparticle. We expect that NIR irradiation can induce photothermal effect, and subsequently trigger the release of the encapsulated DOX to exhibit both photothermal therapy and chemotherapy for head and neck cancer (Fig. 1B). In addition, different from CuS_x nanoparticles, the proposed system does not involve the copper homeostasis to control its systemic toxicity.

2. Materials and methods

2.1. Chemicals

Poly(lactic-co-glycolic acid) (PLGA, 50/50, 16 kDa) was purchased from Lakeshore Biomaterials, Inc. (Birmingham, AL, USA). Polyvinyl alcohol (PVA, Mw = 9000–10,000 Da), (3-(4,5-dimethyl thiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), Poly(ethylene glycol) methyl ether thiol (PEG-SH, Mn = 2000 Da), Propidium

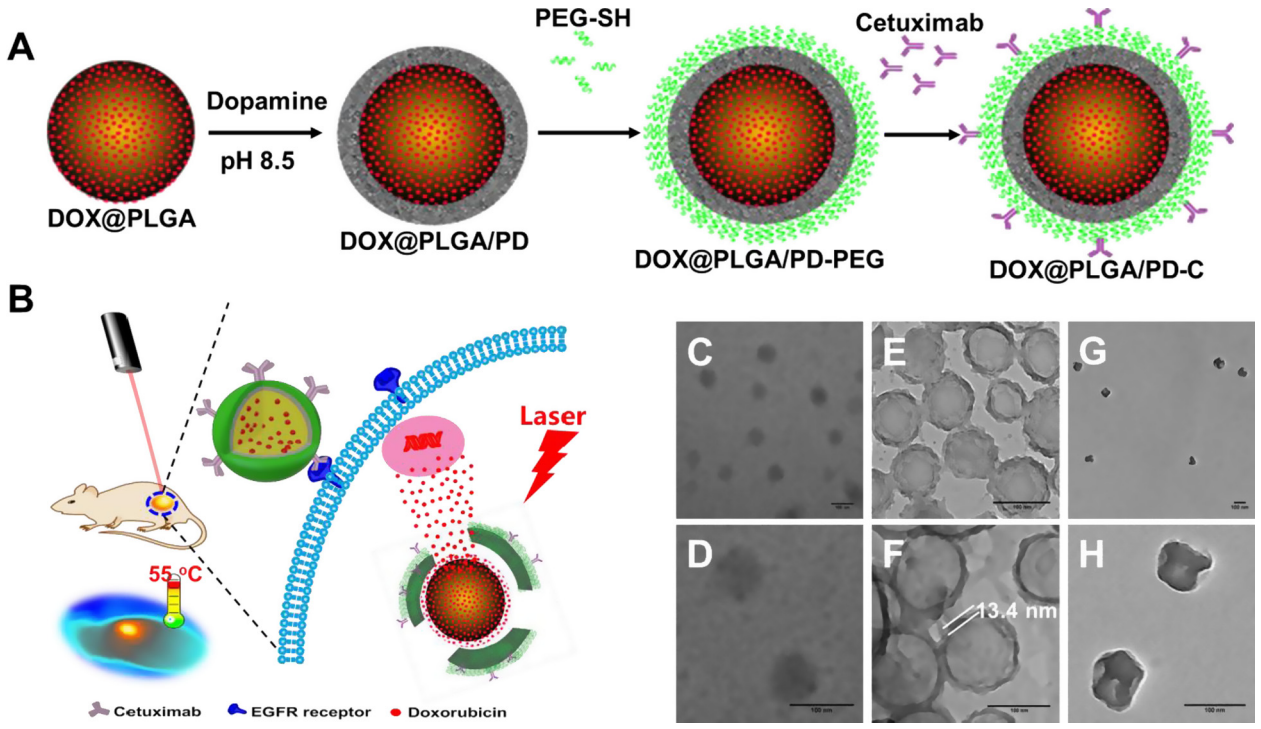

Fig. 1. Schematic illustration of the fabrication of epidermal growth factor receptor targeted mussel inspired nanoparticle (A), and its proposed action pathway (B). TEM images of DOX@PLGA (C-D), DOX@PLGA/PD (E, F), and DOX@PLGA/PD after NIR irradiation (G, H). Scale bars are 100 nm in (C–H).