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NIR-triggered high-efficient photodynamic and chemo-cascade therapy using caspase-3 responsive functionalized upconversion nanoparticles

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ABSTRACT

Stimuli-responsive nanoparticles with multiple therapeutic/diagnostic functions are highly desirable for effective tumor treatment. Herein novel caspase-3 responsive functionalized upconversion nanoparticles (CFUNs) were fabricated with three-in-one functional integration: near-infrared (NIR) triggered photodynamic damage along with caspase-3 activation, subsequent caspase-3 responsive drug release, and cascade chemotherapeutic activation. CFUNs were formulated from the self-assembly of caspase-3 responsive doxorubicin (DOX) prodrug tethered with DEVD peptide (DEVD-DOX), upconversion nanoparticles (UCNP), a photosensitizer (pyropheophorbide-a methyl ester, MPPa), and tumor-targeting cRGD-PEG-DSPE to afford multifunctional CFUNs, MPPa/UCNP-DEVD-DOX/cRGD. Upon cellular uptake and NIR irradiation, the visible light emission of UCNP could excite MPPa to produce reactive oxygen species for photodynamic therapy (PDT) along with the activation of caspase-3, which further cleaved DEVD peptide to release DOX within tumor cells, thus accomplishing NIR-triggered PDT and cascade chemotherapy. CFUNs presented silent therapeutic potency and negligible cytotoxicity in the dark, whereas *in vitro* and *in vivo* experiments demonstrated the NIR-triggered cascade therapeutic activation and tumor inhibition due to consecutive PDT and chemotherapy. Current NIR-activated cascade tumor therapy with two distinct mechanisms is significantly favorable to overcome multidrug resistance and tumor heterogeneity for persistent tumor treatment.

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1. Introduction

Tumor is the primary lethal disease in the world today, up to 13 million tumor cases are newly diagnosed every year [1]. Photodynamic therapy (PDT) based on the formation of cytotoxic reactive oxygen species (ROS) from the reaction between photosensitizers and oxygen molecules upon light irradiation has been approved by FDA for the treatment of oncological, cardiovascular, dermatological, and ophthalmic diseases [2,3]. Compared with traditional tumor therapeutic modalities such as radiotherapy and chemotherapy, PDT has been increasingly applied in tumor treatment due to its minimal side effects, improved tumor specific killing, and relatively low cost [4–6]. However the short absorption wavelength of most currently available photosensitizers resulted in poor tumor penetration and limited the application of PDT [7–9]. Some endogenous chromophores such as melanin, oxyhemoglobin, deoxyhemoglobin as well as fat tissues have minimum absorbance in NIR window (700–1100 nm), which offers NIR much deeper penetration [10,11]. Lanthanide (Ln^{3+})-doped upconversion nanoparticles (UCNP) have attracted considerable attention due to its nonlinear anti-stokes process, which can absorb two or more photons and convert into a higher-energy photon, thus transforming NIR to visible light [12–15], and even UV light [16,17]. Integrated advantages of UCNP including sharp emission band width, long lifetime, low autofluorescence, high detection sensitivity make UCNP-based therapeutic nanoparticles extensively applied in biomedical imaging and tumor therapy [18–24]. Despite the widespread exploration of PDT or UCNP, single therapeutic modality of PDT or UCNP is still immature and inefficient to overcome tumor heterogeneity and multidrug resistance [25–27]. Recently, compared with monotherapy, combination therapy with different

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forms of medical treatment has been developed as a promising alternative strategy for tumor treatment in view of improved therapeutic efficiency [21,28–30].

On the other hand, controlled drug release at targeted sites with minimal premature leakage is favorable to achieve high therapeutic efficiency and less side effects in tumor therapy [31]. Many stimuli-responsive therapeutic systems based on the lesion-specific triggering features such as pH [32,33], GSH [34,35], light [36–41], ROS [42], and enzymes [43–45] have been frequently developed. Among these, external stimuli-activated apoptosis or programmed cell death has been demonstrated in tumor therapy, in which caspases, a family of cysteine proteases are known as critical endogenous components and key mediators to execute cell death in most forms of apoptosis [46–50]. Many therapeutic modalities including photodynamic process, radiotherapy or treatment with anticancer drugs would result in the activation of caspases [51–54]. Since caspase-3 is tightly associated with cell apoptosis, some smart caspase-3 responsive fluorogenic nanoparticles were developed to monitor the therapeutic process [55–58]. Thus we envisaged that the exploration of endogenously activated caspases to trigger other therapeutic process would be potential to kill surrounding residual tumor cells and even eliminate persistent tumors, whereas this kind of cascade combination therapy was rarely concerned [46–50].

In this work, novel caspase-3 responsive functionalized upconversion nanoparticles (CFUNs), MPPa/UCNP-DEVD-DOX/cRGD, were fabricated from the self-assembly of caspases-3 cleavable DEVD-DOX prodrug, UCNP, and MPPa (Scheme 1a). DEVD-DOX endowed CFUNs with potential caspase-3 responsive cleavage and on-demand DOX release feature. Upon NIR irradiation, the emitted visible light from UCNP was employed to excite MPPa, affording reactive oxygen species (ROS), such as singlet oxygen ($^1O_2$), which caused oxidative damage to biological substrates and concurrent activation of caspase-3 to initiate the cell apoptotic process. Subsequently, the activated caspase-3 could specifically cleave the peptide sequence within DEVD-DOX and release activated DOX at tumor sites, thus arousing cascade chemotherapy to combat remaining tumor cells after previous PDT (Scheme 1b). Furthermore, the released DOX may potentially activate much more caspase-3, which would cleave more DEVD-DOX and further release much more DOX to achieve a positive feedback and an amplified therapeutic cycle. The proposed sequential and repetitive processes are expected to enhance and amplify the therapeutic efficiency by apoptotic activation to neighboring tumor tissues. The NIR-initiated two-step treatments including PDT and cascade chemotherapy with distinct tumor killing mechanisms based on tumor-targeting CFUNs are promising to overcome tumor heterogeneity and multidrug resistance in future precision tumor therapy.

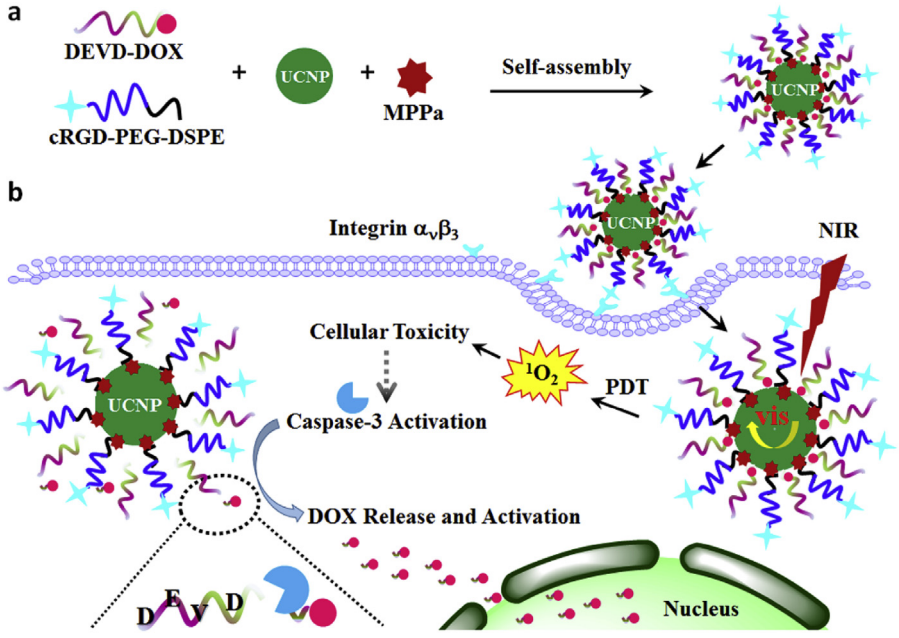
2. Experimental section

2.1. Materials and characterization

Ln $(NO_3)_3 \cdot 6H_2O$ (Ln = Yb, Y, Er), Doxorubicin hydrochloride (DOX) and 6-Maleimidohexanoic acid N-hydroxysuccinimide ester were purchased from Aladdin Industrial Inc.; MPPa (pyropheophorbide-a methyl ester) was purchased from J&K Scientific Ltd.; Carboxyl group-terminated DSPE-PEG-COOH (1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-N-[carboxy (polyethylene glycol)]) and DEVD peptide were purchased from GL Biochem (shanghai) Ltd. CCK-8 and fluorescein isothiocyanate (FITC), propidine iodide (PI) was purchased from Dojindo Laboratories (Kumamoto, Japan). Water used in this study was deionized with a Milli-QSP reagent water system (Millipore) to a specific resistivity of 18.4 MΩ cm.

2.2. Synthesis of UCNP

The $NaYF_4$:Yb^{3+}, Er^{3+} upconversion nanoparticles (UCNP) were synthesized by a hydrothermal route [59,60]. NaOH (0.6 g) was dissolved in 2 mL deionized water to form a clear solution, then added with 20 mL ethanol and 10 mL oleic acid, 0.8 mL $Y(NO_3)_3$ (0.5



Scheme 1. Schematic illustration of NIR-triggered high-efficient photodynamic and chemo-cascade therapy. (a) The aqueous self-assembly and fabrication of caspase-3 responsive functionalized upconversion nanoparticles tethered with anticancer doxorubicin (DOX) (CFUNs, MPPa/UCNP-DEVD-DOX/cRGD). (b) Proposed mechanism of NIR-triggered photodynamic therapy (PDT) and the concurrent activation of caspase-3, which further mediated the intracellular DOX release and drug activation for cascade chemotherapy based on CFUNs.

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