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Amphiphilic semiconducting polymer as multifunctional nanocarrier for fluorescence/photoacoustic imaging guided chemo-photothermal therapy

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ABSTRACT

Chemo-photothermal nanotheranostics has the advantage of synergistic therapeutic effect, providing opportunities for optimized cancer therapy. However, current chemo-photothermal nanotheranostic systems generally comprise more than three components, encountering the potential issues of unstable nanostructures and unexpected conflicts in optical and biophysical properties among different components. We herein synthesize an amphiphilic semiconducting polymer (PEG-PCB) and utilize it as a multifunctional nanocarrier to simplify chemo-photothermal nanotheranostics. PEG-PCB has a semiconducting backbone that not only serves as the diagnostic component for near-infrared (NIR) fluorescence and photoacoustic (PA) imaging, but also acts as the therapeutic agent for photothermal therapy. In addition, the hydrophobic backbone of PEG-PCB provides strong hydrophobic and π-π interactions with the aromatic anticancer drug such as doxorubicin for drug encapsulation and delivery. Such a trifunctionality of PEG-PCB eventually results in a greatly simplified nanotheranostic system with only two components but multimodal imaging and therapeutic capacities, permitting effective NIR fluorescence/PA imaging guided chemo-photothermal therapy of cancer in living mice. Our study thus provides a molecular engineering approach to integrate essential properties into one polymer for multimodal nanotheranostics.

1. Introduction

Development of nanotechnology in the past few decades has stimulated the emergence of nanotheranostics for simultaneous diagnosis and therapeutics of diseases [1]. Nanotheranostics has the ability to monitor disease status before and during treatment, providing optimized therapeutic window and personalized treatment strategy [2-4]. Recently, chemo-phototherapy has been regarded as a promising treatment for solid tumors [5-7]. In particular, chemo-photothermal nanotheranostics integrating anticancer drug with thermal ablation not only overcomes the multidrug resistance of conventional chemotherapy, but also brings in synergistic therapeutic effect to improve therapeutic outcome [8-10]. Such combined nanotheranostics thus has the potential advantages of reduced risk of cancer recurrence and minimized side effects relative to monotherapy [11].

Current chemo-photothermal nanotheranostic systems often use fluorescence for diagnosis mainly due to its low cost and high sensitivity for whole-body imaging [12,13]. However, fluorescence imaging often encounters the issue of shallow penetration depth as a result of tissue autofluorescence and light scattering [14,15]. Thus, photoacoustic (PA) imaging that breaks the optical diffusion limit has recently been integrated into chemo-photothermal nanotheranostics, which has the advantage of increased imaging depth theoretically up to 7 cm [16-21]. Till now, numerous theranostic nanoagents have been exploited for chemo-photothermal therapy, such as 2D nanomaterials, [22-25] gold nanostructures, [26,27] carbon-metal composites, [28] small-molecule dye loaded nanoparticles, [29] and so on [30]. However, because most chemo-photothermal nanotheranostic systems comprise more than three

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components (imaging agents, drug, photothermal agents and encapsulating polymers et al.), clinical translation of these nanotheranostics faces many challenges, which include complex and unstable nanostructure as well as unexpected conflicts in optical and biophysical properties among different components. As a result, rational design of nanotheranostics with minimal components and simple nanostructure is highly desired.

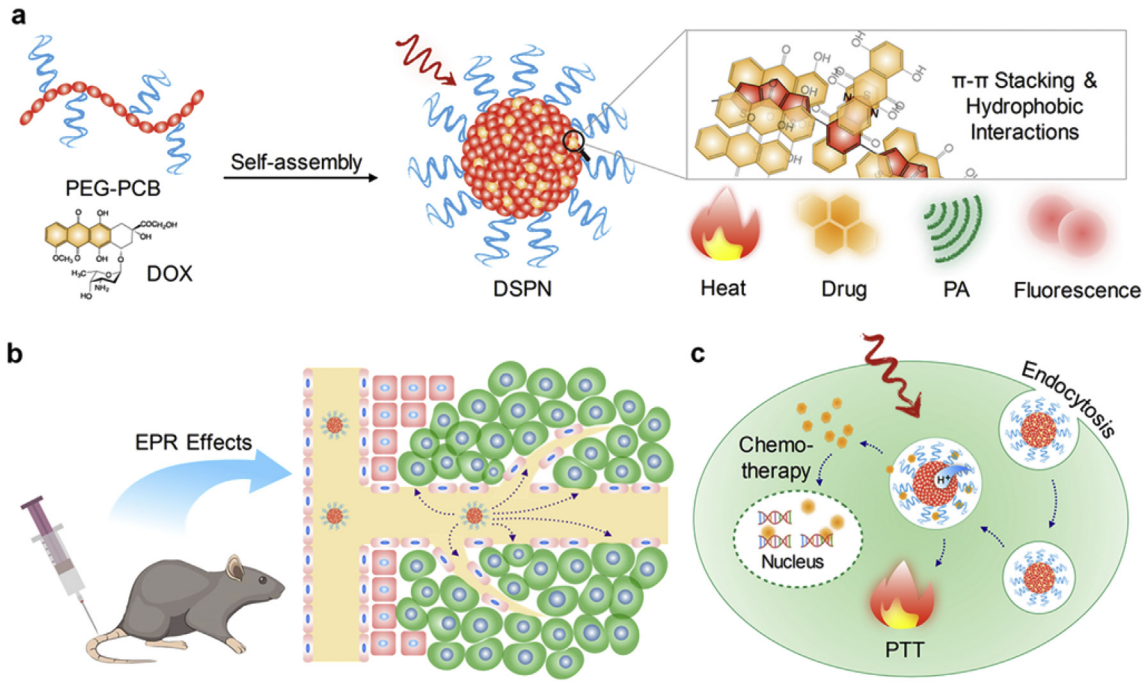
Semiconducting polymer nanoparticles (SPNs) have been recently transformed to organic theranostic nanoagents owning to their higher absorption and photothermal conversion efficiencies in near-infrared (NIR) region as compared with other inorganic nanoparticles such as carbon nanotubes and gold nanorods [31–37]. Because their optical and photothermal properties come from long π-electron delocalized backbones, SPNs generally possess better photostability than small-molecule dyes [38]. Recently, we have applied SPNs for fluorescence and PA imaging applications as well as photothermal therapy and control of neural activity [39–47]. Despite their promise in nanotheranostics, SPN-based chemo-photothermal systems are rarely developed, [48–50] which are complicated and composed of more than three components.

In this study, we report a simple dual-component nanotheranostic system based on SPNs for NIR fluorescence/PA imaging guided chemo-photothermal therapy (Scheme 1a). Such a nanotheranostic design takes advantage of an amphiphilic poly(ethylene glycol) (PEG) grafted poly(cyclopentadithiophene-*alt*-benzothiadiazole) (PEG-PCB), which is a highly integrated multifunctional component that self-assembles into homogenous nanoparticles in aqueous solution. As a result of π-conjugated backbone, PEG-PCB not only serves as the diagnostic component for NIR fluorescence and PA imaging, but also acts as the photothermal agent by efficiently converting photon energy into heat. In addition, the hydrophobic π-conjugated backbone of PEG-PCB provides strong hydrophobic and π-π interactions with the aromatic anticancer drug such as doxorubicin (DOX) for drug encapsulation and delivery. Such a unique trifunctional feature of PEG-PCB leads to the greatly simplified nanotheranostic system with only dual components but multimodal imaging and therapeutic capacities. In the following, we first describe the synthesis and characterization of PEG-PCB and drug-loaded PEG-PCB (DSPN), followed by *in vitro* studies of the cellular internalization and chemo-photothermal therapeutic efficacy. At last, the proof-of-concept application of theranostic DSPN in fluorescence/PA imaging guided chemo-photothermal therapy of tumor in living mice is demonstrated.

2. Results and discussion

The amphiphilic PEG-PCB was synthesized via a grafting-on approach (Fig. 1a). Monomers 1 and 2 were copolymerized via Suzuki polycondensation reaction to afford the polymer with bromide side groups (PCB-Br). The bromide groups were converted to azide, allowing for copper(I)-catalyzed azide-alkyne click reaction (CuAAC) to graft hydrophilic PEG chains onto highly hydrophobic polymer backbones. The resulted polymer (PEG-PCB) could be directly dissolved in water and self-assemble into nanoparticles. Drug-loaded nanoparticles (DSPNs) were prepared via nanoprecipitation of deprotonated DOX and PEG-PCB under controlled pH condition, followed by dialysis to remove excess free DOX. The solutions of nanoparticles kept translucent before and after drug loading (Fig. 1b), while the color of solutions changed from cyan to crimson owning to the incorporation of DOX. Dynamic light scattering (DLS) revealed the diameter increased from 40 nm for PEG-PCB to 100 nm for DSPN with the highest drug loading capacity (LC = 20.3%, $W_{DOX}/W_{PCB} = 5$, termed as $DSPN_5$) (Fig. 1c). Spherical morphology was observed for both PEG-PCB and $DSPN_5$ by transmission electron microscopy (TEM) (Fig. 1d). In addition, no precipitation or obvious change in diameter was observed for both PEG-PCB and $DSPN_5$ after storage in 1 × PBS (pH = 7.4) for two months, suggesting their excellent aqueous stability (Fig. S4, supporting information).

Optical properties of DSPN were studied and compared with PEG-PCB under physiological conditions. PEG-PCB had one absorption peak at 670 nm assigned to PCB (Fig. 2a), while DSPN showed an additional absorption peak at 500 nm attributed to DOX.



Scheme 1. (a) Schematic illustration of preparation of DSPN. (b) and (c) Synergistic effect of chemotherapy and PTT of cancer by DSPN.