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pH-responsive metallo-supramolecular nanogel for synergistic chemo-photodynamic therapy

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ABSTRACT

Benefited from the high orientation of coordinated interaction, metallo-supramolecular materials have attracted enormous interest in many fields. Herein, a novel metallo-supramolecular nanogel (SNG)-based drug delivery system for synergistic chemo-photodynamic therapy is explored to enhance anticancer efficacy. It is fabricated by the metallo-supramolecular-coordinated interaction between tetraphenylporphyrin zinc (Zn-Por) and histidine. It can respond to tumor acid microenvironment to release the co-delivered anticancer drug and photosensitizer to kill the lesion cells. Zn-Por moieties in SNG keep the photosensitivity in the range of visible wavelength and possess the ability of generating active oxygen species for photodynamic therapy. The drug-loaded SNG provides a di-functional platform for chemotherapy and photodynamic therapy. Compared with the single chemotherapy of free doxorubicine (DOX) or photodynamic therapy of Zn-Por in SNG, DOX-loaded SNG with irradiation shows higher *in vitro* cytotoxicity and *in vivo* anticancer therapeutic activity, endowing the SNG with great potential in cancer treatments.

The statement of significance

A combination of multiple non-cross-resistant anticancer agents has been widely applied clinically. Applying multiple drugs with different molecular targets can raise the genetic barriers and delay the cancer adaption process. Multiple drugs targeting different cellular pathways can function synergistically, giving higher therapeutic efficacy and target selectivity. Overall, developing a combination therapeutic approach might even be the key to enhance anticancer efficacy and overcome chemo-resistance. Herein, a novel metallo-supramolecular nanogel (SNG) is fabricated by the metallo-supramolecular-coor dinated interaction between tetraphenylporphyrin zinc (Zn-Por) and histidine. The DOX-loaded SNG provides a di-functional platform for chemotherapy and photodynamic therapy because it can respond to tumor acid microenvironment to release the co-delivered anticancer drug and photosensitizer to kill the lesion cells.

1. Introduction

In the biological system, supramolecular chemistry plays an important role, such as hemoglobin carrying oxygen efficiently from lungs to the tissues of the body by the metallo-supramolecular interaction between iron-porphyrin and L-histidine. It is only in recent years that supramolecular chemistry has progressively drawn increasing attention and has been successively employed to construct the functional structure-defined materials for application in many fields. Compared with covalent interactions, supramolecular interactions [1], as a kind of non-covalent interaction, such as π–π conjugation [2], host–guest recognition [3,4], metallo-supramolecular interaction [5], halogen bonding [6], and hydrogen bonding [7], exhibit their unique convenience and flexibility. On account of the dynamic and reversible nature of non-covalent interactions, the materials based on supramolecular interactions have the ability to adapt to their environment and possess some intriguing properties, such as degradability, stimuli-response, and self-healing, making them special candidates of intelligent materials [8,9].

Considering various mentioned physical interactions, metal–ligand coordination is a preeminent approach for constructing many types of supramolecular materials due to the high degree

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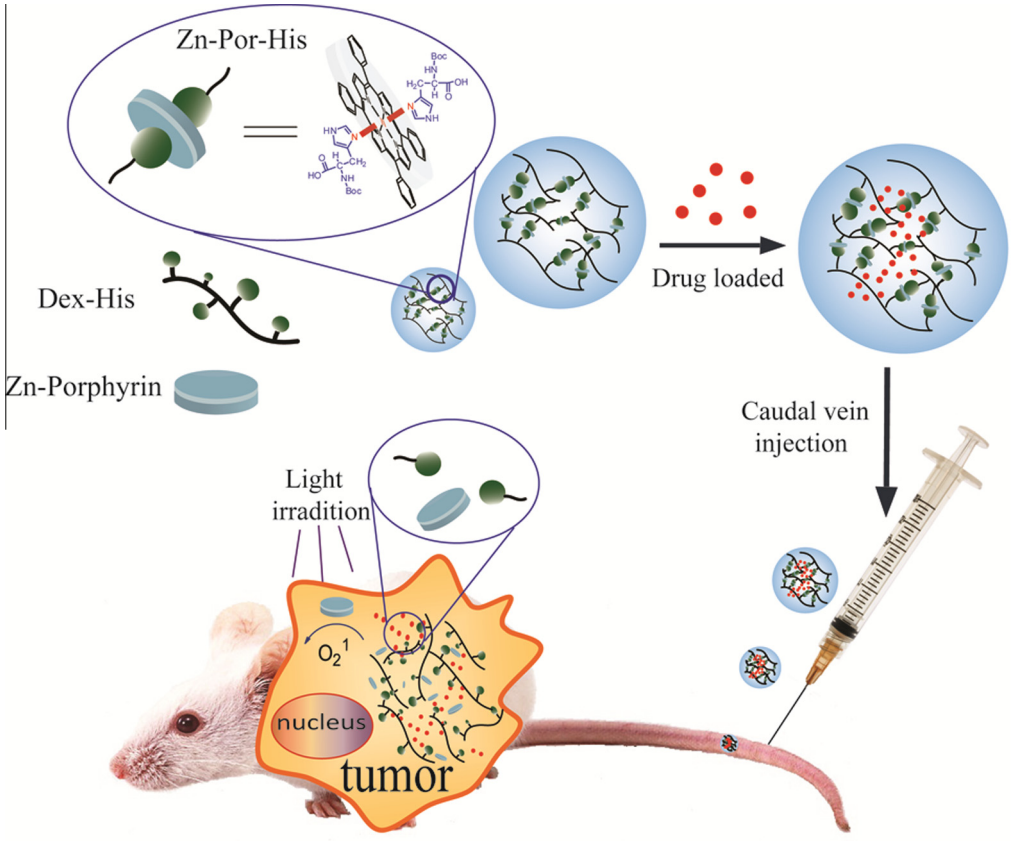

Scheme 1. Schematic illustration of DOX loading and *in vivo* microenvironment-triggered release from DOX-loaded SNG and photodynamic therapy.

of orientation of the coordination bond [10]. In addition, a wide range of easily functionalized ligands can be chosen, and the interaction strength can be well tuned by choosing appropriate metal ions and/or ligands. Moreover, the introduction of metal complexes in the polymer structure endows electrochemical [11], photo-physical [12], catalytic [13], and magnetic [14] properties, potentially, allowing these copolymers as precursors to generate the inorganic or hybrid structures. The presence of metal centers in polymers also offers many unique opportunities to construct external stimuli-responsive materials [15]. However, as we know, the stimuli-responsive materials based on metallo-supramolecular interaction as "smart" drug delivery systems are seldom reported.

Metalloporphyrins, as a group of organic compounds with a conjugated macrocyclic structure, have attracted increasing attention because of their potential applications in catalytic, photo-physical, and biological fields. In particular, some metalloporphyrins, such as zinc-porphyrins, have been used as a kind of photosensitizer in clinical photodynamic therapy because of the effective generation of cytotoxic reactive oxygen species, such as singlet oxygen [16]. Several examples of dual effect combining the photodynamic action with a known therapeutic agent are reported [17–20]. Zhang and co-workers synthesized two kinds of zinc(II) phthalocyanine–erlotinib conjugates. *In vitro* photodynamic activities and selective affinity of these conjugates toward HepG2 cancer cells and A431 tumor tissues were evaluated [21]. Recently, our group had fabricated a kind of dual pH-responsive mesoporous silica nanoparticle (MSN)-based drug delivery system for synergistic chemo-photodynamic therapy, which could respond to the cancer extracellular and intercellular pH stimuli. This dual pH-sensitive MSN-based drug delivery system showed higher *in vitro* cytotoxicity than the single chemotherapy of free DOX or photodynamic therapy of Zn-Por [22].

Doxorubicin (DOX) has been widely used in chemotherapy to treat several types of cancers. However, severe heart toxicity limited its clinical efficiency and applications [23]. Moreover, it will be cleared fast from the blood system because of nonspecific protein adsorption and result in an immune response, or even severe systemic toxicity. To overcome this drawback, many nanoparticles with biocompatibility and biodegradability have been constructed for drug delivery systems [24,25]. Nanoparticles can deliver drugs to the cancer tissue under the help of the enhanced permeability and retention (EPR) effect, which is the property by which certain sizes of molecules (typically liposomes, nanoparticles, and macromolecular drugs) tend to accumulate in tumor tissue much more than they do in normal tissues [26]. Administering a single drug is unlikely to succeed in the treatment of cancer. A combination of multiple non-cross-resistant anticancer agents has been widely applied clinically [27]. Applying multiple drugs with different molecular targets can raise the genetic barriers and delay the cancer adaption process [28]. Multiple drugs targeting different cellular pathways can function synergistically, giving higher therapeutic efficacy and target selectivity. Overall, developing a combination therapeutic approach might even be the key to enhance anticancer efficacy and overcome chemoresistance.

In our previous work [29–31], we have made a detailed study on the pH-responsive metallo-supramolecular coordinated interaction between histidine and porphyrin. By this interaction, pH-responsive supramolecular nanogels can be fabricated to delivery the anticancer drug for single chemo-treatment. Based on the above mentioned work, herein, a much deeper research has been done to realize the combination of chemo-treatment and

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