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Poly(acrylic acid) conjugated hollow mesoporous carbon as a dual-stimuli triggered drug delivery system for chemo-photothermal synergistic therapy

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ABSTRACT

In this work, we described the development of the redox and pH dual stimuli-responsive drug delivery system and combination of the chemotherapy and photothermal therapy for cancer treatment. The poly(acrylic acid) (PAA) was conjugated on the outlets of hollow mesoporous carbon (HMC) *via* disulfide bonds. PAA was used as a capping to block drug within the mesopores of HMC for its lots of favorable advantages, such as good biocompatibility, appropriate molecular weight to block the mesopores of HMC, extension of the blood circulation, and the improvement of the dispersity of the nano-carriers in physiological environment. The DOX loaded DOX/HMC-SS-PAA had a high drug loading amount up to 51.9%. The *in vitro* drug release results illustrated that DOX/HMC-SS-PAA showed redox and pH dual-responsive drug release, and the release rate could be further improved by the near infrared (NIR) irradiation. Cell viability experiment indicated that DOX/HMC-SS-PAA had a synergistic therapeutic effect by combination of chemotherapy and photothermal therapy. This work suggested that HMC-SS-PAA exhibited dual-responsive drug release property and could be used as a NIR-adsorbing drug delivery system for chemo-photothermal synergistic therapy.

1. Introduction

The inability of traditional chemotherapy to distinguish tumor tissue from normal tissues limited the therapeutic efficiency and induced the systemic toxicity and side-effects. Recently, tremendous research works have been done to develop the targeted drug delivery systems to decrease side-effects *via* selective delivery of *anti*-cancer agents to tumor tissue [1,2]. However, targeted drug delivery systems still needed to be improved due to the premature drug leakage before reaching the tumor tissue [3].

Recently, the study of stimuli-responsive drug delivery systems became increasingly mature and gained more and more attention for its efficient drug encapsulation and precise drug release at the targeted site [4]. All manner of stimuli including pH, enzyme [5], temperature and clinical irradiation have been fully considered to design stimuli-responsive drug delivery systems. The designed systems can be delivered to targeted tumor tissues and make an on-demanding drug release to avoid premature leakage induced toxicity and side-effects. Besides, the stimuli-responsive delivery systems could improve therapeutic effect and minimize the adverse effects of toxic drugs.

Among these stimuli, redox as an internal stimulus has received a great deal of attention owing to the distinct difference in the concentration of glutathione (GSH) between extracellular fluids (*ca.* 10 μM) and intracellular fluids (1–10 mM) [6]. Moreover, the cytosolic concentration of GSH in most tumor cells is at least 3 times than that in normal cells [7]. Therefore, disulfide bonds are relatively stable in extracellular fluids and could be broken easily in intracellular fluids, making it widely used for the development of stimuli-responsive drug delivery. Recently, the dual stimuli-responsive systems have been investigated to further realize optimally controlled drug release by responding to two stimuli simultaneously [8–10]. Hence, we constructed a redox and pH dual stimuli-responsive systems to perform site-specific drug delivery.

Numerous materials were used as stimuli-responsive carriers to perform site-specific drug delivery. Among those organic and inorganic nanomaterials developed for drug delivery platform, mesoporous carbon nanoparticles with a high surface area and pore volume, good biocompatibility together with an easily functionalized surface were found to be as an ideal carrier for stimuli-responsive drug delivery. Recently, mesoporous carbon, a kind of NIR-light-absorbing agent, has been widely investigated for photothermal therapy owing to its unique physiochemical properties, such as high photothermal conversion capability and π-π stacking for drug loading [11–13]. Meanwhile, a higher temperature can make the tumor cells more sensitive to anticancer agents and the therapeutic effects of anticancer agents can be enhanced

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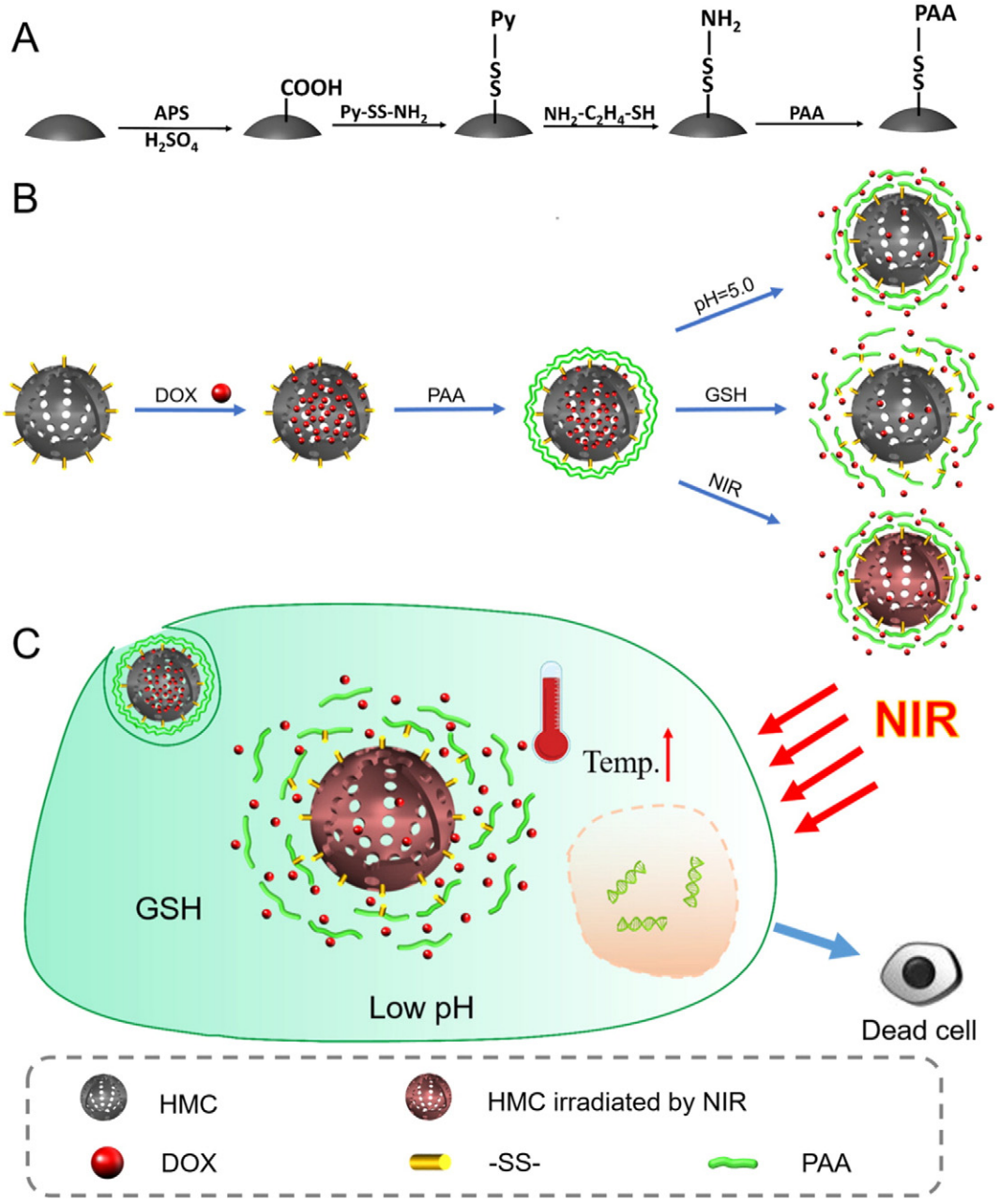
at the environment of high temperature, generating the synergistic therapeutic effects. Notably, hollow mesoporous carbon (HMC) with a hollow cavity and the mesoporous shell structure is superior to conventional mesoporous carbon because the hollow cavity could efficiently encapsulate more drugs with a higher loading capacity. However, to our knowledge, the combined application of HMC as a drug vehicle for stimuli-responsive drug delivery and photothermal therapy has been rarely reported.

It has been reported that mesoporous carbon as foreign invaders could be recognized by reticuloendothelial systems (RES) [14,15], which will cause the rapid clearance of HMC from the blood circulation. Thus, the polyanion polymer poly(acrylic acid) (PAA), used as a "gatekeeper", was grafted onto the entrance of HMC *via* the disulfide bonds due to its favorable features, such as the good biocompatibility, the ability to improve the dispersing stability and prolong the circulation time of HMC in physiological conditions. It is well known that, compared with normal tissues, the tumor and inflammatory tissues are more acidic, which could provide a potential stimulus to trigger drug release [16]. PAA chains possessed abundance of carboxyl groups which can effectively load and block drugs within the mesoporous channels of HMC by the electrostatic interactions. With the decrease of pH, the PAA was protonized, which would cause the dissociation of the electrostatic interaction and the release of the drug. Moreover, PAA was grafted onto the pore entrance of HMC *via* disulfide bonds that can be removed by the intracellular GSH, which would also lead to the drug release.

In this work, the HMC-SS-PAA was used as a drug carrier and NIR-absorbing nanomaterial to achieve a high drug loading, a redox/pH dual-triggered drug release and the photothermal therapy for tumor, in which the anionic polymer PAA was coated on the surface of HMC by the disulfide bonds as described in Scheme 1. The doxorubicin hydrochloride (DOX) was employed as a model drug to investigate the drug loading process and releasing property of DOX/HMC-SS-PAA under



Scheme 1. Schematic illustration of (A) synthetic process of HMC-SS-PAA, (B) drug loading and the dual-stimuli responsive and NIR-induced release property, and (C) synergistic therapeutic effect of DOX/HMC-SS-PAA by combination of chemotherapy and photothermal therapy.