CARBON 82 (2015) 479–488

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/carbon

Near-infrared absorbing mesoporous carbon nanoparticle as an intelligent drug carrier for dual-triggered synergistic cancer therapy

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ARTICLE INFO

Article history:
Received 22 August 2014
Accepted 29 October 2014
Available online 6 November 2014

ABSTRACT

Herein a novel multifunctional nanoplatform based on surface engineered mesoporous carbon nanoparticle (MCN) is developed for effective dual-triggered synergistic cancer therapy. MCNs employed in the study not only function as near-infrared absorbing agents but also as nanocarriers with a high drug loading efficiency. The surface modification of MCN with biomacromolecules (hyaluronic acid) through disulfide unit makes the system be sensitive to both intracellular hyaluronidase-1 and GSH to release the carried drug. The hyaluronic acid on MCN simultaneously confers the system biocompatibility and a cancer cell targeting ability. By combining these capabilities, the multifunctional nanoplatform shows an effective therapeutic efficiency toward the target cells.

1. Introduction

In the last three decades, cancer has become the leading cause of human death worldwide and its social and economic burden requires a spectrum of therapeutic methodologies [1,2]. Current approaches include surgery, radiotherapy, chemotherapy, photodynamic therapy, and photothermal therapy (PTT) [3–8]. Only rarely, however, can a single therapeutic treatment be sufficient to overcome cancer. Combination therapy has thus been considered as a promising strategy to improve therapeutic efficiency as well as minimize side effects [9–15]. An important advance in synergistic cancer therapy is achieved with the combination of PTT and chemotherapy, termed thermo-chemotherapy [16–22]. As a minimally invasive treatment, PTT involves use of optical absorbing agents to generate hyperthermia for "cooking" cancer under NIR light irradiation [9,16]. Further, under these conditions, the sensitivity of chemotherapy can be increased since cells exposed to higher temperature are more susceptible to certain chemotherapy drugs [17–22]. To date, many efforts have been undertaken to develop novel nanosystems possessing both the chemo- and photothermal therapeutic functions [16,17,19,21–30]. Due to the unique structure, biocompatibility, and relatively low cost, carbon materials including carbon nanotubes, graphene and graphene oxide have attracted particular attention [30–38]. These materials have been demonstrated to serve as efficient photosensitizers with high absorption in the near-infrared (NIR) region for photothermal therapy in vitro and in vivo [31,33–35]. Moreover, they could act as promising nanocarriers for delivery of drugs, functional proteins, or gene medicines into various types of cells [30,39–43]. For example, Yang et al. recently

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http://dx.doi.org/10.1016/j.carbon.2014.10.091
0008-6223/

reported the construction of surface engineered graphene with high drug loading efficiency for synergistic chemo-photothermal therapy [42]. Despite their promise, most of the carriers may bestow a drug-release profile that is not in favor of achieving optimal drug availability inside cancer cells [44]. That is, a premature and burst release for the loaded drugs within several hours after intravenous administration may be observed, resulting in unsatisfied local therapeutic efficacy. Therefore, it is highly desirable to develop a smart thermo-chemotherapy platform that is sensitive to the heterogeneous intracellular signals and capable of selectively releasing the drug to improve the overall therapeutic efficacy.

As a rising star in material sciences, mesoporous carbon nanoparticle (MCN) with superior physical and chemical properties has triggered enormous research activities recently [45–53]. They are used extensively as electrode materials for batteries, fuel cells, and supercapacitors, as sorbents for separation processes and gas storage, and as supports for many important catalytic processes [54–60]. In particular, MCNs are highly promising for the biomedical applications because of their merits such as high specific surface area, large pore volume, tunable pore morphologies and well-defined surface properties [45–52,60–63]. Recent study reveals that MCN could also be used as NIR-resonant nanomaterials combining with the drug-loading for chemo-photothermal therapy [61]. Motivated by these salient features, MCNs are employed herein to construct thermo-chemotherapy platform that could respond to heterogeneous intracellular stimuli to release the carried drug to overcome the challenges mentioned above. Through rational design, we expect that such a system could not only achieve a high drug loading efficiency but also be cancer cell-specific, sensitive to intracellular stimuli to release drugs and capable of localized heating upon NIR exposure. To accomplish this, we have engineered the surface of MCN with hyaluronic acid (HA) to construct end-capped nanoparticles (Fig. 1). As one of the extracellular matrix components, HA is a negatively charged, naturally occurring polysaccharide with non-immunogenic, biocompatible, and biodegradable characters [64–70]. It has been recently reported that HA could be used as a drug carrier or targeting moiety due to the specific interaction with CD44, which is overexpressed on various cancer cells [65–68,70]. Thus the HA attached on the MCN could not only act as cap for trapping the drug molecules within the porous channels but also afford MCN colloidal stability, biocompatibility, cancer target ability and functional groups for fluorophore-labeling. To achieve a high therapeutic index, the HA gatekeepers are covalently connected onto the particle surface via disulfide unit. Since the HA could be specially degraded by intra-cellular enzyme hyaluronidase-1 (Hyal-1) after receptor mediated endocytosis, such a nanocarrier will be capable of fast drug release in tumor cells in response of two type of signals. Our results demonstrate that the combination of these capabilities in single nanoparticle entities significantly enhance the efficacy of thermo-chemotherapy, which promise future explorations of MCN-based platform for cancer therapies.

2. Experimental section

2.1. Materials

Nanopure water (18.2 MΩ; Millipore Co., USA) was used in all experiments and to prepare all buffers. Pluronic F127 (Mw = 12,600, PEO_{106} $PPO_{70}PEO_{106}$), (1-ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride) (EDC), and N-Hydroxysuccinimide (NHS) were obtained from Sigma–Aldrich. Phenol and formalin aqueous solution were purchased from Aladdin. Doxorubicin (DOX) was purchased from Sangon (Shanghai, China).

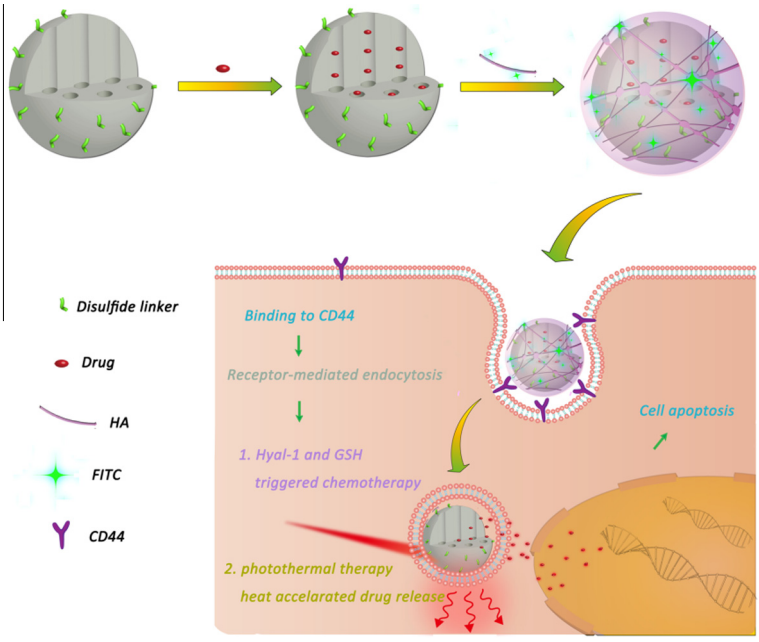

Fig. 1 – Schematic of the preparation process of DOX-MCN-HA and intra-cellular Hyal-1 and GSH-responsive chemotherapy and NIR triggered photothermal therapy. (A color version of this figure can be viewed online.)