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Original Article

A tantalum oxide-based core/shell nanoparticle for triple-modality image-guided chemo-thermal synergetic therapy of esophageal carcinoma

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ABSTRACT

Early detection and therapy of esophageal cancer is very important for improving the prognosis and survival rate of the patient. A theranostic agent that combines multimodal imaging with cancer therapy may be used for augmenting the visualization and treatment of the cancer. Herein, we report the synthesis of a hollow tantalum oxide (TaO_x) nanoparticle that was successfully engineered by encapsulation of polypyrrole (PPy) and doxorubicin (DOX) in the core and conjugation with a near infrared fluorescence dye (NIRDye800) on the shell of the hollow TaO_x nanoparticles. The as-prepared core/shell nanoparticles showed multimodal imaging features including computed tomography (CT) (for the preliminary location of the tumor), photoacoustic (for the anatomical localization of the tumor), and fluorescence imaging (for real-time monitoring of the tumor margin) and pH- and thermal-sensitive drug release. Because the early esophageal carcinoma is a type of superficial cancer, a subcutaneous model in the thigh was used for the *in vivo* study. The core/shell nanoparticles shows high imaging contrast between the tumor and the adjacent tissues and controllable photothermal therapy (PTT) and chemotherapy. Our results indicated that the obtained core/shell nanoparticles had significant potential in the triple-modality imaging guided precisely chemo-thermal synergetic therapy of esophageal cancer. In addition, after aerosol administration, our nanoparticles also exhibited comparable therapeutic efficacy with the intravenous administration, which is more suitable for clinical therapy of esophageal carcinoma.

Introduction

In 2013, there were an estimated 442,000 new cases and 440,000 deaths worldwide from esophageal cancer, which was the sixth most common cancer in incidence and ranked fourth for the cause of death in China [1]. Diagnosis usually occurs when the cancer is in an advanced stage, resulting in an overall 5-year survival rate of <15% [2]. Early detection and intervention could lead to an improvement in the patient prognosis and survival rate [2,3]. Combining multimodal imaging technologies with topical and controllable cancer therapy represents a potentially powerful means to facilitate cancer diagnosis and therapy and to avoid side effects on normal tissues [4–6]. Multifunctional imaging nanoprobes may provide enhanced differentiation between tumor and adjacent normal or benign tissues [7–10]. Locally controlled cancer therapy can improve the therapeutic efficiency and reduce cytotoxicity on the normal tissue [11–13]. Therefore, there is significant interest in developing a theranostic agent that can augment visualization and treatment of the cancer.

As an ideal agent, it should provide both pre-treatment and in treatment imaging, allowing the discovery of the location of the tumors before and during the treatment to minimize the damage

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of the adjacent healthy tissues and improve diagnostic accuracy and therapeutic effectiveness [14]. This agent should also allow for both high imaging depth and spatial resolution for tumor visualization and highly sensitive and specific delineation of tumor margins. Among all diagnostic imaging techniques, computed tomography (CT) imaging has high spatial resolution to illustrate the biological structures of the body, which could be used to detect the preliminary location of the tumor however it has low sensitivity in soft-tissues and therefore can only be used to detect the preliminary location of the tumor [15]. Photoacoustic imaging with high imaging depth and spatial resolution at the microscopic level can be used for precise anatomical localization of the tumor [16–18], and due to the ultrahigh sensitivity of fluorescence imaging, this technique could be used to monitor the tumor margin in real time during the process of treatment to confirm that the tumor has been completely eradicated and to avoid recurrence and prevent damage of adjacent healthy tissues, however, its penetration depth was limited. Thus it could only be used for superficial cancer or intraoperative tumor imaging [19]. Thus, we think the combination of the three imaging modalities could realize the early detection of the tumor and precisely therapy of the cancer. Various multimodal imaging agents have been developed over the past decade [20–23], and several multifunctional nanoparticles combining fluorescence imaging with CT or photoacoustic imaging have shown significant advantages for tumor diagnosis and for monitoring the therapeutic effect [24–27]. However, the majority of CT and photoacoustic agents could result in fluorescence quenching [28–30]. To solve this problems, the construction of these nanoparticles needs to address multiple concerns such as difficult fabrication and the control of the space between the fluorescence agents and the CT or photoacoustic agents. Tantalum oxide (TaO_x) nanoparticles with a strong X-ray attenuation, represent as an ideal candidates for the assembly of multifunctional imaging agents with which to combine CT and fluorescence imaging and avoid the problem mentioned above [31–33].

Herein, we report the synthesis of small-scale core/shell nanoparticles, performed according to the strategy shown in Scheme 1. These nanoparticles were successfully engineered by encapsulation of polypyrrole (PPy) and doxorubicin (DOX) in the core and conjugated with a near infrared fluorescence dye (NIRDye800) on the shell of the hollow TaOx nanospheres (PPy&DOX@TaOx-NIRDye800-PEG nanoparticles). The core/shell nanoparticles simultaneously possess CT/photoacoustic/fluorescence imaging features and chemo-thermal synergetic therapeutic effect. Interestingly, the release of the DOX can be modulated in response to external stimuli (including pH and near infrared (NIR) laser irradiation). The synergistic effect of the nanoparticles indicated that they have good biocompatibility and could realize precise image-guided and controllable chemo-thermal therapy of esophageal cancer.

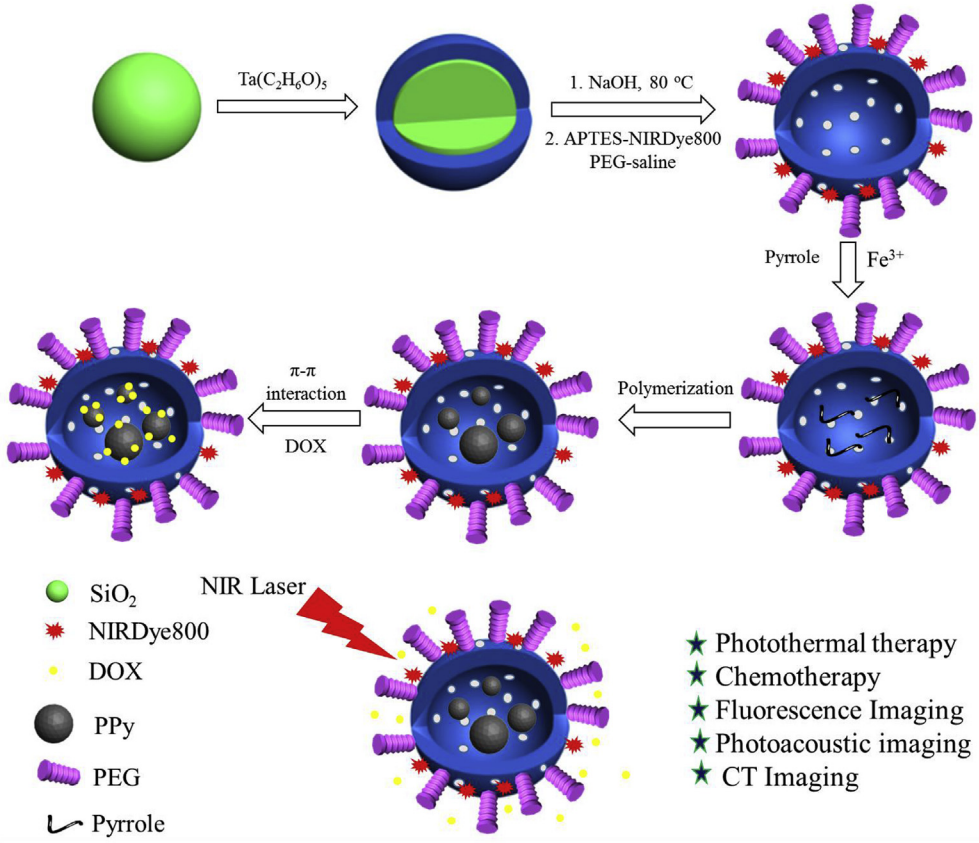
Materials and methods

The details of the materials and methods are available in the Supporting Information.

Results and discussion

Preparation and characterization of PPy&DOX@TaO_x-NIRDye800-PEG nanoparticles

The overall synthesis of the PPy&DOX@TaO_x-NIRDye800-PEG nanoparticles is shown in Scheme 1. The SiO_2 nanoparticles with an average size of approximately 50 nm were synthesized using a Stöber method with a slight modification [34]. Subsequently, a



Scheme 1. The synthesis of PPy@DOX@TaO_x-NIRDye800-PEG nanoparticles for multimodal imaging and photo-chemo therapy of cancer.