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Construction of ICG encapsulated $W_{18}O_{49}$@MSN as a fluorescence carrier for real-time tracked photothermal therapy

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ABSTRACT

Photothermal therapy (PTT) has drawn tremendous attention because of its high therapeutic efficiency in targeting cells while minimizing the damage to normal tissues and organs. Tungsten oxide ($W_{18}O_{49}$, WO) plays a pivotal role in PTT development and its use in PTT systems has been extensively studied. However, it is difficult to control morphology of WO through conventional hydrothermal method. Which make its related researches have been limited up to now. In this study, we describe the construction and effects on tumor of a novel nanoplatform based on WO and indocyanine green (ICG) loaded in mesoporous silica nanoparticles (MSN) for dual-modal PTT and near-infrared imaging. (WO + ICG)@MSN could efficiently control WO shape without the need of surface modification due to its water-soluble of MSN. (WO + ICG)@MSN produced a PTT synergistic effect under irradiation of a single 808 nm near-infrared (NIR) laser. Notably, an enhanced lethal effect of the 808 nm laser triggering dual-modal therapy on B16 tumor cells was observed. The *in vivo* animal experiments showed that (WO + ICG)@MSN induced an effective solid tumor reduction under 808 nm NIR light irradiation, revealing the potential of these nanocomposites as a NIR-mediated dual-modal therapeutic platform for cancer treatment.

1. Introduction

Phototherapy (PTT) has drawn tremendous attention due to its high therapeutic efficiency in targeting tumor cells while minimizing collateral damage to normal tissues and organs [1–3]. Compared with other commonly-used treatments including chemotherapy [4] and radiotherapy [5–7] PTT shows less side effects. In PTT, near-infrared (NIR) light is converted into localized heat energy through nanomaterials, inducing cellular hyperthermia based cancer cell apoptosis or necrosis. NIR region (700–1100 nm) is a so-called transparency window where light has its maximum depth of tissue penetration [8]. In the PTT treatment protocol, various nanomaterials with localized hyperthermal effects under NIR light irradiation, such as grapheme oxide [9], gold nanostructures [10], and copper sulfide, have been extensively used for cancer therapy. Alternatively, tungsten oxide nanocrystals, a type of transition metal oxides, appeared to be an excellent potential photothermal agent for PTT [11]. Due to its strong localized surface plasmon resonances, nanostructured tungsten oxide can absorb NIR light with high efficiency to generate heat. Recent studies showed that transition-metal oxide nanoparticles such as tungsten oxide ($W_{18}O_{49}$,WO) can convert the absorbed light energy to produce heat [12]. They exhibit great properties of NIR light absorption due to the unique characteristics of their outer-valence electrons, thus appearing as ideal PTT agents for *in vitro* and *in vivo* cancer therapy [13,14]. The traditional method of preparing WO is through hydrothermal reaction of raw materials. However, compared with other PTT nanoparticles, it is difficult to control WO nanoparticles size and obtain a fusiform shape by direct hydrothermal method. Therefore, it is of utmost importance to find a preparation that enables the control of WO nanoparticles morphology. In this study, WO was loaded into mesoporous silica nanoparticles (MSN) in order to take advantage of the PTT properties of WO. Monodispersed spherical nanoparticles with a uniform size were prepared by template method. The advantage of this method is that the ready template of mesoporous silica nanoparticles can commendably control the particles size [15,16]. Hence, this method of preparing spherical WO nanoparticles can be used for animal experiments more effectively. Nevertheless, WO coated mesoporous silica nanoparticles cannot be used for imaging *in vivo* because of their lack of fluorescent properties [17]. Thus, the applications of PTT based on WO coated mesoporous silica nanoparticles are seriously limiting the use of PTT *in vivo* due to the lack of optical performance [18].

Interestingly, indocyanine green (ICG), a water soluble anionic tricarbocyanine dye, is the only FDA approved NIR agent, which strongly

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absorbs light around 808 nm with minimal scattering and fluorescence interference by biomolecules at this wavelength [19,20]. ICG has been widely used for cardiac output clinical determination, liver function and blood flow, as well as in ophthalmic angiography [21]. Moreover, ICG can simultaneously achieve PTT effect under single wavelength NIR laser [22]. However, ICG has also several intrinsic drawbacks, such as instability in aqueous solution, rapid body clearance, susceptible to self-bleaching and lack of targeting. These disadvantages significantly influence its imaging effect and PTT efficiency. To increase cell uptake efficiency, functional nano carriers may be a good choice. In our design, ICG was co-loaded with WO in MSN, which was used as nanocarrier for PTT visual image *in vivo*. The nanoparticles we constructed could limit the degradation of their own content after *in vivo* administration, enhance the imaging effect by delivering higher concentrations of ICG and protect the content from the effects of the cellular environment, such as, for example, lysosomes with their acidic PH environment and a certain number of enzymes able to decompose several substances [23] Moreover, the as-prepared (WO + ICG)@MSN achieved superior antitumor effect with a lower dose compared with WO or ICG alone, thus avoiding the side effects typical of therapeutic agents high doses.

In this work, ICG and WO co-loaded mesoporous silica nanoparticles ((ICG + WO)@MSN) have been developed for ICG imaging-guided PTT. As shown in Fig.1, The (ICG + WO)@MSN nanoparticles consisted of three parts: 1) $W_{18}O_{49}$ with substantial absorption in the NIR wavelength region and effective photothermal response, were selected for PTT; 2) ICG, which could be excited by NIR light, was chosen to track the nanoparticles *in vivo*; 3) The mesoporous silica nanosphere worked as a three dimension hard template for loading and protecting WO and ICG effectively from aggregation and diffusion *in vivo*. This new PTT approach could represent a novel technique to precisely kill cancer cells by ICG imaging-guided PTT *in vivo* [24,25].

2. Materials and methods

2.1.1. Materials

All the reagents were purchased ready-to-use. ICG (United States Pharmacopeia –USP- Reference Standard) was purchased from Sigma-Aldrich (USA); Tungsten chloride (WCl_6, ≥99.0%), Tetraethylorthosilicate (TEOS, ≥99%), cetyltrimethylammonium bromide (CTAB, ≥99%), sodium chloride (NaCl, ≥99.0%), sodium hydroxide (NaOH, ≥98%) were purchased from Sigma-Aldrich (USA). Water was purified by a Millipore Ultrapure water system and had a resistivity of 18.2 MΩ·cm at room temperature.

2.1.2. MSNs synthesis

MSNs were synthesized by CTAB template method as previously described [26]. The final product was resuspended into 30 mL n-propyl alcohol and stored at room temperature before further use.

2.1.3. WO loaded mesoporous silica nanoparticles (WO@MSN) synthesis

WO@MSN was prepared according to the template method. Briefly, WCl_6 was dissolved in n-propyl alcohol (30 mL) to form a 2 mol/mL solution which was used as the starting material. 10 mL of the WCl_6 solution prepared as above and 10 mL MSN solution were mixed together

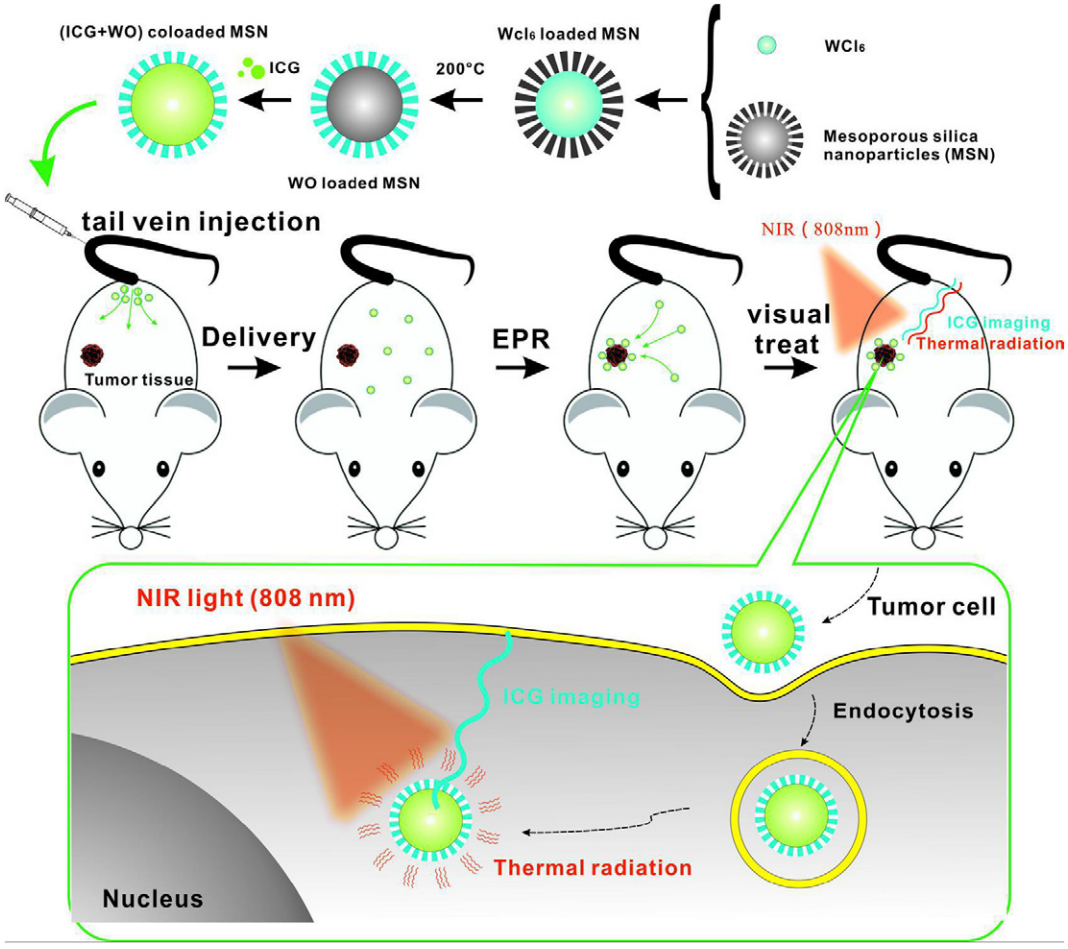

Fig. 1. The schematic diagram showed the synthesis and applications of (WO + ICG)@MSN for targeting the tumor region and ICG fluorescence imaging-guided visual photothermal therapy *in vivo*. In this schematic illustration, the ICG and WO assembled mSiO2 nanoparticles (ICG + WO)@MSN had been developed for ICG imaging-guided PTT. The (WO + ICG)@MSN delivery system consists of four parts: 1) The nanoparticles were injected into mice with tumors through tail vein; 2) The (WO + ICG)@MSN were delivered to the whole body through the circulation of the blood; 3) The (WO + ICG)@MSN gathered at tumor tissue according to EPR effect; 4) Tumor region was irradiated by 808 NIR laser to destory tumor cells.