Confined structure regulations of molybdenum oxides for efficient tumor photothermal therapy

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ABSTRACT Molybdenum oxide nanoparticles (NPs) with tunable plasmonic resonance in the near-infrared region display superior semiconducting features and photothermal properties, which are highly related to the crystalline and defective structures such as oxygen deficiencies. However, fundamental understanding on the structure-function relationship between crystalline/defective structures and photothermal properties is still unclear. To address this, herein, we have developed an “*in-situ* confined oxidation-reduction” strategy to regulate the defect features of molybdenum oxide NPs in the dual-mesoporous silica nanoreactor. Especially, the effects of crystalline structure/oxygen defects of molybdenum oxides on the photothermal performances were investigated by facilely tuning the amount of molybdenum resource and the reduction temperature. As a photothermal nanoagent, the optimal defective molybdenum oxide NPs encapsulated in PEGylated porous silica nanoreactor (designated as MoO_{3-x}@PPSNs) exhibit excellent biological stability and strong localized surface plasmon resonance effect in near-infrared absorption range with the highest photothermal conversion efficiency up to 78.7% under 808 nm laser irradiation. More importantly, the remarkable photothermal effects of MoO_{3-x}@PPSNs were comprehensively demonstrated both *in vitro* and *in vivo*. Consequently, we envision that the plasmonic MoO_{3-x} NPs in a biocompatible porous silica nanoreactor could be used as an efficient photothermal therapy agent for photothermal ablation of tumors.

Keywords: confinement effect, porous silica nanoreactor, molybdenum oxide, oxygen deficiency, photothermal therapy

INTRODUCTION

Compared with the traditional tumor treatments such as chemotherapy and radiotherapy, photothermal therapy (PTT) shows great application prospects because of its high effectiveness, minimal invasion, low toxicity and side effects [1–3]. Developing biocompatible, efficient, stable, and targeted photothermal conversion materials is of great importance. Up to date, carbon-based [4,5], noble metal [6], semiconductor [7,8], and organic compounds [9] have been widely designed as photothermal materials for converting near-infrared laser energy into heat energy, through local hyperthermia to kill tumor cells. Among these photothermal agents, semiconductor materials involving non-stoichiometric or doped transition metal oxides [10,11] and sulf-based compounds with copper defects [12] have gained exponentially growing interest in PTT due to their excellent localized surface plasmon resonance (LSPR) optical activities. Actually, LSPR is not limited to nanostructures but can also be achieved with appreciable free carrier concentration by varying the stoichiometric ratio, deficiency or doped ions [13–15].

To address the abovementioned issue, defective MoO_{3-x} nanomaterials have been attracting much attention because of their favorable features of easy synthesis, low cost, low toxicity, and good photothermal properties [16,17]. Exploring rational strategies for the preparation of MoO_{3-x} with high electron density and fluidity is critical to regulate LSPR and further improve the photothermal performance [18]. For example, Li *et al.* [19] described a surface-ligand protected reduction strategy to

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synthesize one-dimensional (1D) MoO_{3-x} nanobelts with widely tunable plasmonic absorption from ultraviolet (UV) to visible and near-infrared (NIR) region. Ding *et al.* [10] prepared oxygen-deficient molybdenum oxide quantum dots (MoO_{3-x} QDs) under hydrothermal conditions by varying the amount of chitosan, which possesses a broad and strong photo-absorption band largely matching the solar spectra. Guo *et al.* [20] synthesized amorphous MoO_{3-x} nanosheets by introducing Mo atoms into the interlayers of MoO_3 nanosheets *via* a hydrothermal method, and achieved a remarkably improved photothermal conversion efficiency of 61.79%. Although these reported molybdenum oxide nanobelts, nanocrystals or nanosheets exhibit great potentials in NIR-mediated PTT, the underlying relationship between molybdenum-based crystalline structures/oxygen deficiencies and photothermal properties is still unclear, due to the difficulty in manipulating the crystal transformation and defect density effectively.

In this work, a facile “*in-situ* confined oxidation-reduction” strategy has been proposed to prepare the molybdenum oxide nanoparticles (NPs) with tunable crystalline structure and oxygen vacancy in the biocompatible dual-mesoporous silica nanoreactor. The confinement method mainly involves the high-temperature oxidation of ammonium molybdate ($(\text{NH}_4)_6\text{Mo}_7\text{O}_{24}$) to MoO_3 phase in air and subsequent reduction transformation from MoO_3 to MoO_{3-x} phase at nanoscale with high defect density. In addition, the effects of the amount of ammonium molybdate and reduction temperature on the phase structure and LSPR properties of molybdenum oxides were investigated. With the PEGylation on the surface of silica porous nanoreactor, the resulting MoO_{3-x} -encapsulating PEGylated porous silica NPs (designated as MoO_{3-x} @PPSNs) showed good dispersibility and maximal absorbance at 808 nm in NIR region, thus resulting in the improvement of photothermal effects both *in vitro* and *in vivo*.

EXPERIMENTAL SECTION

Materials

Ammonium molybdate tetrahydrate ($(\text{NH}_4)_6\text{Mo}_7\text{O}_{24} \cdot 4\text{H}_2\text{O}$), tetrahydrofuran (THF) and ammonium hydroxide aqueous solution (28%) were purchased from Aladdin (Shanghai, China). Ethyl silicate (TEOS) was purchased from Lingfeng Chemical Reagent Co., Ltd. (Shanghai, China). Methoxy-polyethylene glycol-silane (mPEG-Silane, $M_w = 5000$) was acquired from Tansh-Tech. RPMI-1640, phosphate-buffered saline (PBS), cal-

cein acetoxymethyl ester (calcein AM), propidium iodide (PI), dilactate (DAPI) and Cell Counting Kit-8 (CCK-8) were all obtained from KeyGEN BioTECH (Nanjing, China). All reagents used were of AR grade and ultrapure water produced from a Milli-Q system was used in all experiments.

Characterization

The morphology was characterized by transmission electron microscopy (TEM) operated at 200 kV (JEM-2100). The light absorption properties were measured by UV-vis spectra (UV-3600, SHIMADZU). Dynamic light scattering (DLS) and zeta potential were conducted on Malvern Zetasizer Nanoseries. The nitrogen (N_2) adsorption-desorption isothermal curve and the corresponding pore-size distribution were analyzed by a Micromeritics Tristar II system. The photothermal effect was detected by an excitation source of 808 nm. The Fourier transform infrared (FT-IR) spectra were recorded by Thermo Scientific Nicolet iS5. Thermo gravimetric (TG) curve was obtained by TGA5550. X-ray photoelectron spectroscopy (XPS) was carried out on Thermo ESCALAB 250XI.

Synthesis of MoO_{3-x} @PPSNs

The porous silica NPs (PSNs) were prepared according to our previously reported work [21], and used as reactors for MoO_{3-x} loading. Typically, 50 mg of PSNs and 50 mg of $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24} \cdot 4\text{H}_2\text{O}$ were dispersed in 650 μL of water and sonicated for 10 min. After stirring for 1 h, the resulting suspension was then dried naturally at 60°C. The yellow products then underwent an “oxidation-reduction” process for obtaining MoO_{3-x} @PSNs: specifically, calcinated in air at 550°C for 5 h and then put in a tube furnace which was heated to 550°C at a rate of 3°C min^{-1} under Ar-diluted H_2 gas flow for 5 h. In order to obtain MoO_{3-x} @PPSNs, 10 mg of MoO_{3-x} @PSNs and 100 mg of mPEG-silane were dispersed in 10 mL of water and then stirred at 60°C for 48 h. MoO_{3-x} @PPSNs were obtained by centrifugation and washed with water three times.

Photothermal performance measurement

To study the photothermal performance of MoO_{3-x} @PPSNs, an aqueous solution (1 mL) containing MoO_{3-x} @PPSNs was irradiated using an NIR laser (808 nm) for 5 min. The temperatures of the solution were recorded every 10 s using an infrared thermal camera.

The photothermal conversion efficiency (η) was calculated using Roper’s method. η was calculated according to Equation (1):

$$\eta = \frac{hS(T_{\text{Max}} - T_{\text{Surr}}) - Q_{\text{Dis}}}{I(1 - 10^{-A_{808}})}, \quad (1)$$

where h is the heat transfer coefficient, S is the superficial area of the container, T_{Max} is the maximum temperature reached (53.1°C), T_{Surr} is the ambient temperature (26.4°C), Q_{Dis} is the heat dissipated from the laser absorbed by the quartz cuvette sample cell (0.0168), I is the laser power density (1 W cm⁻²), and A_{808} is the UV absorbance value of MoO_{3-x}@PPSNs at 808 nm (0.458).

hS is calculated by Equation (2):

$$hS = \frac{m_D C_D}{\tau_s}, \quad (2)$$

where τ_s can be obtained from Equations (3) and (4):

$$\theta = \frac{T - T_{\text{Surr}}}{T_{\text{Max}} - T_{\text{Surr}}}, \quad (3)$$

$$t = -\tau_s \ln \theta, \quad (4)$$

where τ_s is the sample system time constant (211.5 s) as measured from the cooling curve. In addition, m_D is the mass (1.0 g), and C_D (4.2 J g⁻¹) is the heat capacity of water. Accordingly, the photothermal η of MoO_{3-x}@PPSNs was calculated to be 78.7%.

Photostability of MoO_{3-x}@PPSNs

The MoO_{3-x}@PPSNs solution (300 µg mL⁻¹) was irradiated with an 808-nm NIR laser for 5 min (1.0 W cm⁻², laser on). Subsequently, the NIR laser was turned off for 10 min, and the solution was naturally cooled to room temperature (laser off). The laser on/off cycles were repeated five times, and the temperature change was monitored with an infrared camera.

Cytotoxicity of MoO_{3-x}@PPSNs under NIR irradiation

SMMC-7721 cells were seeded in the 96-well plate and cultured for 24 h before use. Fresh culture medium containing different concentrations of MoO_{3-x}@PPSNs (50, 100, 200, 250, 300 µg mL⁻¹) was then added to replace the old medium for an additional 4 h. After treatment, cells were exposed to an NIR laser for 5 min and the cell viabilities were measured using a CCK-8 kit.

Confocal laser scanning microscopy (CLSM)

SMMC-7721 cells were treated with fresh culture medium containing 200 µg mL⁻¹ MoO_{3-x}@PPSNs for 4 h and were then irradiated with an 808-nm NIR laser for 5 min. After incubation for 20 h, the cells were stained with calcein-AM and PI for 45 min and observed under CLSM.

Flow cytometry apoptosis analysis

SMMC-7721 cells were cultured with fresh medium

containing 200 µg mL⁻¹ MoO_{3-x}@PPSNs for 4 h and were then irradiated with an 808-nm NIR laser for 5 min. After incubation for 20 h, the cells were collected, washed, and stained with Annexin V-fluorescein isothiocyanate isomer (FITC) and PI and analyzed using flow cytometry.

Hemolysis assay

To study hemolysis, red blood cells (RBCs) were collected from Kunming mice, then washed five times and diluted into 0.9% NaCl. The diluted RBC suspension (20 µL) was then incubated with the MoO_{3-x}@PPSNs dispersions of different concentrations (0–2 mg mL⁻¹, 230 µL) for 3 h at room temperature. Afterwards, the supernatant was collected by centrifugation at 10,000 r min⁻¹, and measured for UV-vis absorbance at 577 nm by a microplate reader. The deionized water and 0.9% NaCl were used as the positive and negative control groups, respectively. The percentage of hemolysis was calculated by using the following equation:

$$\text{Hemolysis}(\%) = \frac{(A_{\text{sample}} - A_{\text{negative control}})}{(A_{\text{positive control}} - A_{\text{negative control}})} \times 100\%.$$

In vivo PTT

All animal procedures were performed in accordance with the Guidelines for Care and Use of Laboratory Animals of East China University of Science and Technology and the experiments were approved by the Animal Ethics Committee of East China University of Science and Technology. Flank xenograft SMMC-7721 tumors were prepared by subcutaneous injection of 1.5 × 10⁶ cells into the right flanks of BALB/c female mice (purchased from Shanghai Slake Experimental Animal Co., Ltd. 4–6 weeks, 18–20 g). The experiment was conducted when the tumor volume reached about 100 mm³. Nude mice bearing SMMC-7721 xenograft tumors were intravenously injected with MoO_{3-x}@PPSNs (2.5 mg mL⁻¹) and randomly divided into three groups: (I) NIR only, 1 W cm⁻², (II) MoO_{3-x}@PPSNs, (III) MoO_{3-x}@PPSNs + NIR, 1 W cm⁻². All laser irradiation was conducted for 5 min post 4 h intravenously injection. All mice were anesthetized by pentobarbital sodium before NIR irradiation, the IR thermal images and the temperature variation of mice were recorded by an infrared camera. The measurement of tumor volume was conducted by vernier calipers every two days for 21 days after treatment. The tumor volume was calculated by using the following equation: tumor volume = 0.5 × (tumor length) × (tumor width)². Relative tumor volume was quantified as V/V_0 , where V_0 was the initial tumor volume. The tumors and

organs of mice were collected for Hematoxylin and Eosin (H&E) staining, and terminal-deoxynucleotidyl transferase-mediated nick-end labeling (TUNEL) staining of tumors were conducted to reveal the detailed anticancer mechanism.

Statistical analysis

Statistical significance was determined by a two-tailed Student's *t*-test for two-group comparison. A *p* value of <0.05 was considered statistically significant ($p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$). Results are expressed as the mean $\pm$ standard deviation (SD).

RESULTS AND DISCUSSION

Preparation and characterization of MoO_{3-x}@PPSNs

As shown in Fig. 1a, PSNs with dual-mesoporous structure were firstly synthesized according to our previous report [21,22]. TEM images show a well-defined core-shell structure consisting of larger mesopores (> 10 nm) in the core and smaller mesopores (~ 2 nm) in the shell (Fig. S1). N₂ sorption isotherm results show that there is a dual pore size distribution at 1.6 and 15 nm, respectively, according to the Barrett-Joyner-Halenda (BJH) pore size distribution curves (Fig. S2a, b). Noticeably, due to the underestimation of BJH method for the small mesopores below 5 nm [23,24], the actual smaller pore size of PSNs is about 2.5 nm calculated by density functional theory (DFT) pore size distribution (Fig. S2c). In addition, the Brunauer-Emmett-Teller (BET) specific surface area and pore volume of PSNs have been calculated to be 691 m² g⁻¹ and 0.93 cm³ g⁻¹, respectively (Table S1). Then, PSNs was mixed with ammonium molybdate solution *via* a "solvent-evaporation induced capillary" method as described previously [25], and then oxidized in air at 550°C, resulting in the formation of molybdenum oxides@PSNs. To obtain defective molybdenum oxide, the resultant molybdenum oxides@PSNs experienced an *in-situ* reduction process at varied temperature in a reductive atmosphere. Finally, mPEG-silane molecules were grafted on the surface of silica nanospheres through a silane chemical reaction to improve the biocompatibility, resulting in the final defective MoO_{3-x}@PPSNs.

The morphology, pore structure and chemical composition of MoO_{3-x}@PPSNs were characterized by a variety of analytic methods. After the oxidation, dark dots were observed inside the pore channels of silica nanospheres (Fig. S3), suggesting the formation of molybdenum oxide NPs. Besides, N₂ sorption isotherms show that the BET surface area and pore volume of PSNs significantly de-

creased to 178 m² g⁻¹ and 0.5 cm³ g⁻¹ after the introduction of molybdenum oxide NPs (Table S1), respectively. Meanwhile, the smaller mesopores of 2.5 nm is absent and the larger mesopores of initial 15 nm become smaller to around 11 nm as can be seen in the DFT pore size distribution curve, indicating that the formed molybdenum oxide NPs are located both in the smaller mesopores and partially in the larger mesopores of PSNs (Fig. S4). After the reduction process, a spherical core-shell morphology of MoO_{3-x}@PSNs with an average particle size of ~300 nm remained (Fig. 1b, c). While the color of MoO_{3-x}@PSNs in water becomes dark-blue (Fig. S5), which indicates the transformation of Mo valence state from high to low [26]. Scanning TEM-energy dispersive X-ray spectroscopy (STEM-EDS) element mappings of MoO_{3-x}@PSNs reveal that the Si, O, and Mo elements are uniformly distributed in the whole structure (Fig. 1d). In addition, MoO_{3-x}@PSNs show a similar pore structure to molybdenum oxides@PSNs (Fig. 1e and Fig. S6), revealing that the reduction process has no significant effect on the pore structures and pore parameters of PSNs. After PEG introduction, the slight increase in the diameter and zeta potential change from -32 (± 1.7) to -7 (± 0.25) mV of MoO_{3-x}@PSNs reveal the successful PEG modification (Fig. S7). The functionalization with PEG was further confirmed by the emergence of a characteristic peak at 2920 cm⁻¹ in the FT-IR measurement which is attributed to the asymmetric and symmetric stretching vibrations of CH₂ units in PEG chain (Fig. S8) [27,28]. Benefiting from the hydrophilicity and shielding effect of PEG, MoO_{3-x}@PPSNs show good diameter stability in water, PBS, and culture medium (RPMI-1640), demonstrating the good stability in biological media (Fig. 1f). To further confirm the hydrophilic property, the water contact angle measurement of MoO_{3-x}@PPSNs was performed. As shown in Fig. S9, MoO_{3-x}@PPSNs possess a low contact angle of 23.59° $\pm$ 0.25°, suggesting its highly hydrophilic feature [29].

Phase structure and oxygen vacancy in MoO_{3-x}@PSNs

As reported previously [30], the biological properties of molybdenum oxide NPs are highly dependent on their phase structures. In the present work, to investigate the crystal structure of molybdenum oxides in the pores of MoO_{3-x}@PSNs, X-ray powder diffraction (XRD) was employed. As shown in Fig. 2a, the diffraction peaks of the oxidized molybdenum oxides@PSNs match well with those of MoO₃ (JCPDS no.35-0609), confirming the successful phase transformation from molybdenum salts to MoO₃ phase in the porous channels of PSNs. In con-

Figure 1 (a) Schematic illustration for the synthesis of $\text{MoO}_{3-x}\text{@PPSNs}$. (b, c) TEM images of $\text{MoO}_{3-x}\text{@PSNs}$ at different magnifications. (d) Element mapping for $\text{MoO}_{3-x}\text{@PSNs}$. (e) N_2 adsorption-desorption isotherm and the corresponding BJH pore size distribution of $\text{MoO}_{3-x}\text{@PSNs}$. (f) Diameter stability of $\text{MoO}_{3-x}\text{@PPSNs}$ dispersed in H_2O , PBS and RPMI-1640.

trast, XRD pattern of $\text{MoO}_{3-x}\text{@PSNs}$ shows four characteristic peaks at around 26° , 37° , 53.4° and 40.5° , which can be indexed to MoO_3 (JCPDS no.32-0671) and Mo (JCPDS no.42-1120) phases, respectively. In order to further verify the valence state of Mo species in the PSNs, XPS analysis was used. As shown in Fig. 2b, c, only Mo^{VI} exists in the sample of $\text{MoO}_3\text{@PSNs}$, which is consistent with the XRD results. Mo^{IV} , Mo^{V} and Mo^{VI} can be detected in $\text{MoO}_{3-x}\text{@PSNs}$ after the reduction, and the percentages of Mo^{IV} , Mo^{V} and Mo^{VI} have been calculated respectively to be 28.4%, 40.5% and 33.1%, indicating the generation of oxygen vacancies. As reported previously, the increase of oxygen vacancies on the surface of molybdenum oxides can be verified by the weakened or disappeared signal in the Raman spectrum [31]. The

Raman spectra in Fig. 2d evidence that the Mo=O , $\text{Mo}_3\text{-O}$, and Mo-O_2 peaks originating from MoO_3 phases have almost disappeared in $\text{MoO}_{3-x}\text{@PSNs}$, confirming the presence of a certain amount of the oxygen vacancies [32,33]. Moreover, the characteristic peaks located at 569 and 887 cm^{-1} in the FT-IR spectrum of $\text{MoO}_3\text{@PSNs}$ imply the formation of MoO_3 [34]. These two characteristic peaks disappeared in $\text{MoO}_{3-x}\text{@PSNs}$ after the reduction, and only one characteristic peak of Mo=O remained, demonstrating the successful transformation from MoO_3 to defective molybdenum oxides (Fig. S8) [35–37]. Fig. 2e shows the TGA curves of $\text{MoO}_3\text{@PSNs}$ and $\text{MoO}_{3-x}\text{@PSNs}$ in air. In detail, $\text{MoO}_3\text{@PSNs}$ show two main mass loss steps at 59 and 774°C , which can be assigned to the volatilization of physisorbed water and

Figure 2 (a) Wide-angle XRD patterns of MoO₃@PSNs and MoO_{3-x}@PSNs. Mo 3d XPS spectra of (b) MoO₃@PSNs and (c) MoO_{3-x}@PSNs. (d) Raman spectra of MoO₃@PSNs and MoO_{3-x}@PSNs. (e) TGA curves of MoO₃@PSNs and MoO_{3-x}@PSNs. (f) EPR spectra of MoO₃@PSNs and MoO_{3-x}@PSNs.

sublimation of molybdenum oxides, respectively. In contrast, a gradual weight increase at 337.5°C was found in the TGA curve of MoO_{3-x}@PSNs, which can be attributed to the oxidation of deficient MoO_{3-x} back to MoO₃. These differences further proved the existence of oxygen defects in MoO_{3-x}@PSNs [38,39]. Electron paramagnetic resonance (EPR) was adopted to further reveal the coordination state of Mo atoms in non-stoichiometric molybdenum oxide. As shown in Fig. 2f, MoO_{3-x}@PSNs exhibits a strong EPR signal at 1.92, proving that the Mo species of MoO_{3-x}@PSNs is unsaturated [40,41]. Moreover, the presence of signal at $g = 2.00$ for electrons directly indicates that MoO_{3-x}@PSNs possess a certain number of surface oxygen vacancies [20]. In contrast, no EPR signals are observed in MoO₃@PSNs since the electrons are all in pairs. The total loading amount of Mo in MoO_{3-x}@PPSNs has been calculated to be 7.32% by inductively coupled plasma optical emission spectrometry (ICP-AES) (Table S2).

Photothermal properties measurement

To explore the photothermal effect, the UV-vis-NIR spectra of MoO_{3-x}@PPSNs at different particle concentrations were recorded. As displayed in Fig. 3a, the absorbance peak of MoO_{3-x}@PPSNs solution gradually

intensified with the increase of sample concentration. Moreover, the MoO_{3-x}@PPSNs exhibit a distinct absorption peak at 808 nm, which can be attributed to the strong LSPR effect by the free carriers in the MoO_{3-x}@PSNs semiconductor nanostructure [42–45]. Subsequently, the temperature increments of MoO_{3-x}@PPSNs at different concentrations and laser power densities were monitored under 808-nm laser irradiation, as shown in Fig. 3b and c. The temperature of MoO_{3-x}@PPSNs at the concentration of 300 $\mu\text{g mL}^{-1}$ increases by 26.7 and 50.8°C in 5 min respectively at 1 and 2 W cm^{-2} of laser irradiation (Fig. 3c), indicating that the photothermal performance of MoO_{3-x}@PPSNs is both concentration- and power-dependent. According to the temperature curve and time linear fitting constants, the photothermal conversion efficiency of MoO_{3-x}@PPSNs was calculated to be 78.7% (Fig. 3d), which is higher than that of the reported Mo-based photothermal materials (Table S3). In addition, no photothermal performance degradation of MoO_{3-x}@PPSNs was detected in five successive heating/cooling cycles, which confirms the excellent photothermal stability of MoO_{3-x}@PPSNs (Fig. 3e).

As reported previously, the phase structure and valence state of molybdenum oxides were considered as two main

Figure 3 (a) UV-vis-NIR absorption spectra of $\text{MoO}_{3-x}\text{@PPSNs}$. (b) The photothermal heating curves of $\text{MoO}_{3-x}\text{@PPSNs}$ of different concentrations (808 nm, 1 W cm^{-2}). (c) Photothermal heating curves of $\text{MoO}_{3-x}\text{@PPSNs}$ (300 µg mL^{-1}) at varied power densities. (d) Temperature changes of $\text{MoO}_{3-x}\text{@PPSNs}$ (300 µg mL^{-1}) upon irradiation for 5 min followed by laser shutting-off, and the linear time data obtained from the cooling stage. (e) Photothermal stability curves of $\text{MoO}_{3-x}\text{@PPSNs}$ during five cycles. (f) UV-vis-NIR spectra of $\text{MoO}_{3-x}\text{@PPSNs}$ containing different amounts of Mo resource ($[\text{Mo}] = 17 \text{ µg mL}^{-1}$). (g) UV-vis-NIR spectra of $\text{MoO}_{3-x}\text{@PPSNs}$ obtained at varied reduction temperatures ($[\text{Mo}] = 17 \text{ µg mL}^{-1}$). (h) The infrared thermal images of (I) $\text{MoO}_{3-x}\text{@PPSNs}$ (10 mg), (II) $\text{MoO}_{3-x}\text{@PPSNs}$ (30 mg), (III) $\text{MoO}_{3-x}\text{@PPSNs}$ -350, (IV) $\text{MoO}_{3-x}\text{@PPSNs}$ -450, (V) $\text{MoO}_{3-x}\text{@PPSNs}$, (VI) $\text{MoO}_{3-x}\text{@PPSNs}$ -650, and (i) the corresponding heating curves of various samples at the same Mo concentration of 17 µg mL^{-1} (1 W cm^{-2}).

factors that affect their photothermal properties [46,47]. In the present work, to understand the mechanism of enhanced photothermal effects, the effects of Mo resource dosage and reduction temperature on the photothermal properties of $\text{MoO}_{3-x}\text{@PPSNs}$ were explored. Firstly, $\text{MoO}_{3-x}\text{@PPSNs}$ were prepared by adjusting the amount of $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24}\cdot 4\text{H}_2\text{O}$ from 10 to 30 mg. As shown in Fig. S10, no apparent molybdenum oxide NPs were observed inside the pore channels of $\text{MoO}_{3-x}\text{@PPSNs}$ (10 and 30 mg), which can be explained by the insufficient filling of Mo resource. As the amount of $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24}\cdot 4\text{H}_2\text{O}$

increased to 50 mg, dark molybdenum oxide nanocrystals can be clearly seen in the large mesopores of $\text{MoO}_{3-x}\text{@PPSNs}$ (Fig. 1b, c). N_2 adsorption results show that the DFT pore size distribution curve of $\text{MoO}_{3-x}\text{@PPSNs}$ (10 mg) still exhibits two sets of mesopores located at 2.2 and 14.9 nm, respectively. In addition, the smaller mesopores of $\text{MoO}_{3-x}\text{@PPSNs}$ (30 mg) almost disappeared, while the larger mesopores were still present (Fig. S11), revealing that the Mo species is mainly located in the small mesopores when less $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24}\cdot 4\text{H}_2\text{O}$ was used. The particle size of

MoO_{3-x}@PPSNs determined by DLS has no significant difference with the change of the addition amount of Mo resource (Fig. S12). As shown in Fig. 3f, with the Mo source decreasing from 50 to 30 or 10 mg, the LSPR absorbance peak at 808 nm disappeared, thus leading to the moderate temperature increment under NIR irradiation (Fig. 3h, i). To gain a deep understanding on the poor PTT effect, XRD patterns of MoO_{3-x}@PPSNs (10 and 30 mg) were collected. As shown in Fig. S13, no well-defined diffraction peaks could be found, suggesting the formation of amorphous molybdenum oxides due to the confinement of small mesopores when less molybdenum resource was used. With the increase of molybdenum resource to 50 mg, a certain amount of molybdenum species entered the large mesopores and experienced the growth and reduction of molybdenum oxide nanocrystals, resulting in the enhanced photothermal effect caused by the lattice vacancies [48].

In addition to the amount of molybdenum resource, the influence of reductive temperature on the photothermal effect of MoO_{3-x}@PPSNs was also investigated. For this purpose, the samples reduced at 350, 450 and 650°C (designated as MoO_{3-x}@PPSNs-350, MoO_{3-x}@PPSNs-450, MoO_{3-x}@PPSNs-650) were synthesized, while other parameters were kept unchanged. TEM images show that all the three samples display a well-defined core-shell morphology and the MoO_{3-x} NPs are evenly dispersed in the mesoporous channels (Fig. S14). N₂ sorption isotherms show that these samples have similar pore structure and pore diameter with that of MoO_{3-x}@PPSNs (Fig. S15). DLS results show that the hydrodynamic sizes of these samples are ~300 nm (Fig. S16), indicating that the temperature changes have no significant influences on the whole particle sizes of MoO_{3-x}@PPSNs. As shown in Fig. 3g, when the reduction temperature was increased from 350 to 550°C, the absorbance intensity at 808 nm increased accordingly. As a result, the temperature increment of MoO_{3-x}@PPSNs-350, MoO_{3-x}@PPSNs-450, MoO_{3-x}@PPSNs, and MoO_{3-x}@PPSNs-650 are 2.8, 22.0, 25.3, and 17.8°C at the same Mo concentration of 17 ppm, respectively (Fig. 3h, i). The photothermal conversion efficiencies of MoO_{3-x}@PPSNs-450 and MoO_{3-x}@PPSNs-650 were calculated to be 46.3% and 78.11% (Fig. S17), which are slightly lower than that of MoO_{3-x}@PPSNs. To better understand the excellent photothermal properties, XRD and XPS were used to monitor the changes of phase structure and valence state of MoO_{3-x}@PPSNs with the reduction temperature varied. As shown in Fig. S18, XRD pattern of MoO_{3-x}@PPSNs-350 shows the MoO₃ phase due

to the insufficient reduction at such a low temperature. As the temperature increased to 450°C, the characteristic peaks of MoO₃ become relatively weakened, while the peaks assigned to MoO₂ phase can be found. When the temperature was elevated to 650°C, only the characteristic peaks of zero-valent Mo were detected, demonstrating that the reduction temperature has an important impact on the crystal transformation of MoO_{3-x}. As shown in Fig. S19 and Table S4, with the temperature increased from 350 to 550°C, the relative amount of Mo^{VI} decreased from 36.7% to 31.9%, while that of Mo^{IV} increased from 0.3% to 45.6%, which means the elevated concentration of oxygen vacancies in MoO_{3-x}@PPSNs in comparison to those of two control samples. In addition, the temperature of MoO₃@PPSNs solution increased only by 1.1°C in a 5-min irradiation, indicating the very poor photothermal effect of MoO₃@PPSNs (Fig. S20). Consequently, both the crystal structure of MoO₂ in the larger mesopores and oxygen vacancies in MoO_{3-x}@PPSNs together contribute the excellent photothermal effects of MoO_{3-x}@PPSNs prepared by using enough molybdenum resource (50 mg) and reduced at 550°C.

Tumor cell ablation of MoO_{3-x}@PPSNs

Motivated by the excellent photothermal effects of MoO_{3-x}@PPSNs under NIR laser irradiation and good biocompatibility, we then explored the photothermal killing effect on tumor cells. Firstly, the cellular uptake of MoO_{3-x}@PPSNs was observed after the fluorescence labeling with FITC modification. As shown in Figs S21 and S22, the green fluorescence signal intensities in SMMC-7721 tumor cells gradually increase with the prolonged incubation time, indicating that MoO_{3-x}@PPSNs can enter cancer cells and exhibits a time-dependent manner. The cytotoxicity of MoO_{3-x}@PPSNs against normal NIH/3T3 cells and human hepatocellular carcinoma SMMC-7721 cells were examined by CCK-8 assay. Results show above 95% cell viability at varied concentrations from 50 to 300 µg mL⁻¹ (Fig. 4a), indicating the excellent biocompatibility of MoO_{3-x}@PPSNs. Fig. 4b shows the cytotoxicity of MoO_{3-x}@PPSNs to SMMC-7721 cells. In the absence of NIR laser irradiation, the cell viability remains at above 90% even at the concentration up to 300 µg mL⁻¹, while the toxicity of MoO_{3-x}@PPSNs to SMMC-7721 cells becomes much stronger after NIR laser irradiation and exhibits a laser power-dependent manner. Moreover, the killing effect of MoO_{3-x}@PPSNs (200 µg mL⁻¹) to SMMC-7721 cells at varied laser power densities was visualized by the calcein-AM and PI (Fig. 4c). The confocal images show that MoO_{3-x}@PPSNs

Figure 4 (a) Viabilities of 3T3/NIH cells treated with $\text{MoO}_{3-x}\text{@PPSNs}$ for 24 h. (b) Assay of the viability of SMMC-7721 cells after various treatments. (c) Live/dead cell staining of SMMC-7721 by confocal imaging after different treatments. (d) Flow cytometry analyses of the apoptosis rate of SMMC-7721 cells. (e) UV-vis-NIR absorption spectra of hemoglobin released from RBCs. (f) Hemolytic rates and the corresponding digital photos of $\text{MoO}_{3-x}\text{@PPSNs}$ ($^* p < 0.05$, $^{**} p < 0.01$, and $^{***} p < 0.001$).

or NIR alone does not induce the death of cells even at the laser power up to 2 W cm^{-2} . Also, almost no dead cells can be found when treated with $\text{MoO}_{3-x}\text{@PPSNs}$ plus 1 W cm^{-2} NIR irradiation. Interestingly, almost all the cells died by increasing the power density to 2 W cm^{-2} . Furthermore, the cell apoptosis of these treated SMMC-7721 cells was quantitatively analyzed by flow cytometer through the annexin V-FITC/PI double staining method (Fig. 4d). Especially, in the case of $\text{MoO}_{3-x}\text{@PPSNs}$ under 2 W cm^{-2} irradiation, the cell apoptosis rate of tumor cells is as high as 99.5%, demonstrating the effective PTT performance *in vitro*. The hemolytic assay was used to explore the interaction between $\text{MoO}_{3-x}\text{@PPSNs}$ and RBCs. No obvious hemolysis of RBCs was observed even at a high concentration of 1.84 mg mL^{-1} in 3 h of co-incubation (Fig. 4e, f), demonstrating its good blood biocompatibility for further PTT *in vivo*.

In vivo anti-tumor efficacy

To investigate the tumor inhibition effect of $\text{MoO}_{3-x}\text{@PPSNs}$ *in vivo*, an SMMC-7721 tumor-bearing mouse model was established by subcutaneously injecting the nanomaterials into female BALB/c mice (Fig. 5a). In 4-h post intravenous injection, the tumor sites were irradiated with an 808-nm laser (1 W cm^{-2}) for 5 min. During the whole therapy process, the temperature changes in tumor sites were recorded with a thermal imaging camera. As depicted in Fig. 5b, c, in 5 min of irradiation, the temperature of PBS plus NIR group increased by 8.3°C . In contrast, the temperature elevation of the $\text{MoO}_{3-x}\text{@PPSNs}$ plus NIR group was up to 22.8°C , which is high enough to trigger tumor cell necrosis [49]. To further study the anti-tumor effect, the tumor volumes of different groups were measured by a vernier caliper every two days. As shown in Fig. 5d, no significant differences on the tumor inhibition were observed between PBS plus NIR and $\text{MoO}_{3-x}\text{@PPSNs}$ group. In comparison, the $\text{MoO}_{3-x}\text{@PPSNs}$ plus NIR group displayed a remarkable anti-tumor effect with the tumor inhibition rate of 98%, which can be assigned to the thermal ablation of tumor tissues through the photo-thermal conversion effect of $\text{MoO}_{3-x}\text{@PPSNs}$ under NIR irradiation. The digital photos (Fig. S23) of mice treated with different groups (PBS and $\text{MoO}_{3-x}\text{@PPSNs}$) after laser irradiation showed that no evident damage was observed at the tumor site of the mouse treated with PBS plus NIR irradiation, while apparent eschar appeared at the tumor region of the mouse treated with $\text{MoO}_{3-x}\text{@PPSNs}$ plus NIR irradiation. This can be attributed to the high temperature-induced

damage of the tumor and skin tissues, which is consistent with the previous reports [50–52]. In addition, all animals survived during the whole treatment process (Fig. S24). The body weights of mice showed no significant change during the whole treatment process (Fig. 5e), demonstrating the negligible *in vivo* toxicity of $\text{MoO}_{3-x}\text{@PPSNs}$. After the treatments, the tumors were collected and weighed after dissection (Fig. 5f), the average tumor weight of the $\text{MoO}_{3-x}\text{@PPSNs}$ plus NIR group was extremely small, in contrast to those in the NIR and $\text{MoO}_{3-x}\text{@PPSNs}$ groups. Furthermore, H&E and TUNEL staining of tumor tissues reveal the serious damage in tumor tissues of $\text{MoO}_{3-x}\text{@PPSNs}$ plus NIR group (Fig. 5h). Specially, the blue-purple signal in H&E images represented the intact nuclei of rapidly growing cancer cells. As we expected, obvious irregular shapes, shrunken cell nuclei, and lighter cytoplasm staining were observed in the $\text{MoO}_{3-x}\text{@PPSNs}$ plus NIR group. Moreover, the increased green fluorescence of TUNEL staining results in $\text{MoO}_{3-x}\text{@PPSNs}$ plus NIR group also proved the highest apoptosis of tumor cells among the three groups.

Besides, compared with other control treatments, a higher cell apoptosis rate of 48.7% was obtained in the tumor slices of mice treated with $\text{MoO}_{3-x}\text{@PPSNs}$ plus NIR group (Fig. 5i). To further study the systemic toxicity of $\text{MoO}_{3-x}\text{@PPSNs}$, the main organs (heart, liver, spleen, lung, and kidney) were collected and analyzed by H&E staining. As shown in Fig. S25, no detectable pathological changes could be found in all these organs, indicating that $\text{MoO}_{3-x}\text{@PPSNs}$ have no significant toxicity in mice at the current injection doses. All the biochemical indicators in Table S5 remained normal after the injection for 12 days, indicating the negligible side effects of $\text{MoO}_{3-x}\text{@PPSNs}$ on the hematological system. In addition, no statistically significant differences on the liver and kidney functions could be found between the $\text{MoO}_{3-x}\text{@PPSNs}$ group and the control group (Fig. 5j, k), demonstrating the good biocompatibility of $\text{MoO}_{3-x}\text{@PPSNs}$. Thus, it can be concluded that the resultant $\text{MoO}_{3-x}\text{@PPSNs}$ can be applied as a high-quality photothermal agent for efficient and low-toxicity tumor therapy.

CONCLUSIONS

In summary, we have developed a facile “*in-situ* confined oxygen-reduction” strategy to regulate the phase structures and oxygen defects of molybdenum oxides confined in a biocompatible porous silica nanoreactor with dual-mesoporous structure ($\text{MoO}_{3-x}\text{@PPSNs}$). The resultant nanoagent features well-tuned photothermal effects de-

Figure 5 (a) Scheme of *in vivo* antitumor experiments. (b) Photothermal images and (c) the corresponding tumor temperature changes in 4 h of intravenous injection with $\text{MoO}_{3-x}\text{@PPSNs}$ (808 nm, 1 W cm^{-2}). (d) Tumor volumes and (e) body weights of mice after various treatments. (f) Digital image and (g) weights of tumors after dissection. (h) H&E (upper) and TUNEL (down) of tumors in different groups. (i) Apoptosis rate analyzed according to TUNEL diagram. Blood biochemistry assays of (j) kidney function markers (urea and creatinine (Crea)), and (k) liver function markers (alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP)) after treatment with $\text{MoO}_{3-x}\text{@PPSNs}$ at the 12th day ($p < 0.05$, $p < 0.01$, and $p < 0.001$).

pendent on the oxygen deficiencies/phase structures, which can be well-regulated by varying the amount of Mo resource and reduction temperature. As a result, the abundant oxygen deficiencies and MoO₂ phase structure in the pore channels endow MoO_{3-x}@PPSNs with intensified LSPR absorption in the NIR region and an extraordinarily high photothermal conversion efficiency of 78.7%, which ensures excellent PTT effects upon 808-nm NIR laser irradiation both *in vitro* and *in vivo*. This work provides a simple strategy for the design and development of high-quality photothermal agents with strong LSPR absorption for efficient and safe photothermal tumor treatment.

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Conflict of interest The authors declare that they have no conflict of interest.

Supplementary information Supporting data are available in the online version of the paper.

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氧化钼的限域调控及其肿瘤光热治疗研究

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摘要 氧化钼纳米材料在近红外区域具有可调节的等离子共振吸收, 并表现出优异的半导体特性和光热特性, 这与其晶体结构和表面氧缺陷息息相关. 然而, 氧化钼晶体结构/氧缺陷和光热性能之间的关系仍不清楚. 基于此, 我们发展了一种简便的“原位限域氧化-还原”策略来精准调控双介孔二氧化硅纳米反应器中氧化钼纳米颗粒的晶体结构及缺陷位点. 通过调节钼源的引入量和还原温度, 详细研究了氧化钼的晶体结构/氧缺陷对其光热性能的影响. 作为一种光热转换材料, 聚乙二醇(PEG)修饰且负载缺陷态氧化钼的多孔氧化硅纳米颗粒($\text{MoO}_{3-x}\text{@PPSNs}$)在近红外吸收范围内表现出良好的生物相容性和较强的局域表面等离子共振(LSPR)效应, 808 nm激光下的光热转换效率可达78.7%, 并在细胞及活体水平验证了其优异的光热性能. 因此, 我们认为这种生物相容性多孔二氧化硅纳米反应器中的等离子 MoO_{3-x} 纳米粒子可以作为一种有效的光热试剂用于肿瘤的光热消融.