A covalent organic framework-based multifunctional therapeutic platform for enhanced photodynamic therapy *via* catalytic cascade reactions

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ABSTRACT Utilizing the unique tumor microenvironment (TME) to conduct chemical reactions for cancer treatment becomes a hot topic recently. Nevertheless, single chemical reaction in TME is often restricted by scanty reaction substrates and slow reaction rate. Meanwhile, the toxic substances produced by the reactions are usually not enough to kill cancer cells. Herein, using covalent organic frameworks (COFs) as the template, Au nanoparticles (Au NPs) were subsequently grown on the surface of the COF, then a thin layer of manganese dioxide (MnO₂) was coated over the material, and finally hyaluronic acid (HA) was introduced to improve the biocompatibility. The resultant product, named COF-Au-MnO₂, was involved in several processes to form cascade reactions in the TME. Specifically, under hypoxic conditions, COF-Au-MnO₂ could react with intratumoral H₂O₂ to produce O₂ to enhance the type II photodynamic therapy (PDT), and Au NPs could decompose glucose to promote starving-like therapy. Besides, starving-like therapy can also produce H₂O₂ to increase O₂ production. Simultaneously, MnO₂ can consume glutathione (GSH) to enhance the antitumor efficacy, and the released Mn²⁺ could be used for T₁-weighted magnetic resonance imaging (MRI). Both *in vitro* and *in vivo* experiments had proven excellent cancer cell killing effect and antitumor efficacy of COF-Au-MnO₂ *via* such a cycle-like process.

Keywords: covalent organic framework, cascade reaction, tumor microenvironment, enhanced photodynamic therapy

INTRODUCTION

Tumor microenvironment (TME) [1,2], including hypoxia, overproduced H₂O₂, mild acidity and elevated

glutathione (GSH) content, severely reduced the effectiveness of several reactive oxygen species (ROS)-related cancer treatment modalities, such as chemodynamic therapy (CDT), sonodynamic therapy (SDT) and photodynamic therapy (PDT), etc. [3]. Hence, how to alleviate the TME or use the TME to kill cancer cells has become a hot topic recently [4–6].

Fortunately, researchers have achieved the goal by using the toxic substances in the TME to kill cancer cells [7]. For example, ROS, which mainly include hydroxyl radical ($\cdot\text{OH}$), singlet oxygen ($^1\text{O}_2$) and superoxide radical ($\cdot\text{O}_2^-$), were used to kill cancer cells [8]. However, the ROS-related cancer treatment modalities are highly dependent on the oxygen level in the TME [9]. Therefore, in order to enhance the antitumor efficacy, simultaneously alleviating the hypoxia condition, reducing the GSH content and increasing the H₂O₂ concentration are quite important [8]. It is well known that large amounts of hydrogen peroxide (H₂O₂) were produced in the tumor with the help of superoxide dismutase (SOD), which is one of the important features of solid tumors. The overexpressed H₂O₂ could be used for SDT or PDT by providing endogenous ROS [1]. Nevertheless, the amount of H₂O₂ inside the tumor is about 50×10^{-6} – 100×10^{-6} mol L⁻¹, which is not enough to produce endogenous oxygen to improve the efficiency of PDT or SDT [10]. Recently, it has been reported that some metal nanoparticles possess enzyme-mimic catalytic properties [11–13]. For example, Au nanoparticles (NPs) are quite similar to glucose oxidase (GOx), which could be used in oxidizing glucose to produce H₂O₂ in the presence of oxygen [14]. Manganese dioxide (MnO₂) can react with

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H_2O_2 to produce oxygen under the slightly acidic conditions of the tumor [15–19], and the released Mn^{2+} could be used as a contrast agent for T_1 -weighted magnetic resonance imaging (MRI) [20–22].

Covalent organic frameworks (COFs) are a kind of porous crystalline materials connected by covalent bonds [23]. Due to the advantages like adjustable pore size, excellent thermal stability and large porosity, COFs have been applied in many research fields like catalysis, gas storage and separation, etc. [24]. However, the application of COFs in biomedical fields is still in its early stage [25–32]. Recently, we have found that COFs could be used as photosensitizers for photodynamic cancer therapy [30]. Hence, it can be anticipated that by introducing artificial enzymes, such as metal nanoparticles and metal oxide, enough oxygen will be generated through cascade reactions and the photodynamic effect could be greatly enhanced *via* a synergistic effect. In this study, a COF-Au- MnO_2 -based therapeutic agent was designed for the augmented PDT and starving-like therapy. Specifically, the COF based on 1,3,5-tris(4-aminophenyl)benzene (TAPB) and 2,5-dimethoxyterephthalaldehyde (DMTP) was prepared at room temperature *via* a simple solution-based method [26]. Due to the presence of abundant amino groups in the COF, the *in-situ* formed Au NPs were easily attached on the surface of the highly uniform COF nanospheres, and subsequently, a thin layer of MnO_2 was deposited, which was formed by the reaction between potassium permanganate and amino groups.

After that, in order to improve the biocompatibility, hyaluronic acid (HA) was coated on the surface through electrostatic adsorption [33–38]. Finally, the *in vitro* cancer cell killing effect and *in vivo* antitumor efficacy were evaluated (Scheme 1).

EXPERIMENTAL SECTION

Materials

DMTP ($\text{C}_{10}\text{H}_{10}\text{O}_4$, AR, 97%, Jilin Chinese Academy of Sciences-Yanshen Technology Co., Ltd.), TAPB ($\text{C}_{24}\text{H}_{21}\text{N}_3$, AR, 98%, Alpha), acetic acid (CH_3COOH , AR, 99.5%, Beijing Chemical Works), acetonitrile (CH_3CN , 99.8%, Vetec), ethanol (AR, Beijing Chemical Works), hydrogen tetrachloroaurate (III) hydrate ($\text{HAuCl}_4 \cdot 4\text{H}_2\text{O}$, 99.9%, Strem Chemicals), sodium borohydride (NaBH_4 , AR, 98%, Aldrich), trichloroacetic acid ($\text{C}_2\text{HCl}_3\text{O}_2$, 99.9%, Aladdin), HA (97%, Macklin), hydroxylamine solution (NH_2OH , 50%, Aladdin), potassium permanganate (KMnO_4), glutathione (reduced) ($\text{C}_{10}\text{H}_{17}\text{N}_3\text{O}_6\text{S}$, 98%, Aladdin), and glucose ($\text{C}_6\text{H}_{12}\text{O}_6$, 80%, Macklin) were used as received.

Synthesis of COF

DMTP (3 mg, 0.018 mmol) and TAPB (3 mg, 0.0084 mmol) were dissolved in 3 mL of acetonitrile separately, and then the two solutions were mixed. Subsequently, 0.15 mL of acetic acid was added and the mixture was stirred at room temperature for 12 h. The precipitate

Scheme 1 Schematic illustration of the synthetic process of COF-Au- MnO_2 -HA and the therapeutic mechanism.

was collected by centrifugation and washed with ethanol for three times.

Synthesis of COF-Au

COF (3 mg) was mixed with HAuCl_4 (0.6 mL, 1.5 mg mL^{-1}) and stirred for 4 h. A NaBH_4 (2 mg mL^{-1} , 0.6 mL) solution was added into the above solution. After being stirred for 1 h, the precipitate was collected by centrifugation and washed with deionized water.

Synthesis of COF-Au-MnO₂

COF-Au (3 mg) was mixed with KMnO_4 (0.6 mL, 10 mg mL^{-1}) and stirred for 6 h. The precipitate was collected by centrifugation and washed with deionized water.

Modification of the as-synthesized products with HA

COF-Au-MnO₂ (10 mg) was mixed with HA (5 mg) in 5 mL of deionized water. After being stirred for 12 h, the precipitates were collected by centrifugation and washed with anhydrous ethanol several times. All the experiments were carried out at room temperature.

In vivo cascades reaction-based antitumor therapy

Female Balb/c mice were purchased from the Center of Experimental Animals, Jilin University. All animal studies were conducted in accordance with the guidelines of the National Regulation of China for Care and Use of Laboratory Animals. The 4T1 tumor models were successfully established by subcutaneous injection of 4×10^6 cells suspended in 100 μL of phosphate buffered saline (PBS) into the left axilla of each mouse. The mice were treated when the tumor volumes reached 80–100 mm^3 . The tumor-bearing mice were randomly divided into eight groups ($n=6$, each group), and treated with (1) PBS, (2) PBS under 650 nm laser irradiation, (3) COF-HA, (4) COF-Au-HA, (5) COF-Au-MnO₂-HA, (6) COF-HA under 650 nm laser irradiation, (7) COF-Au-HA under 650 nm laser irradiation, and (8) COF-Au-MnO₂-HA under 650 nm laser irradiation. Nanomaterials were injected by *in situ* injection, and each injection dose was 100 μL at a concentration of 1 mg mL^{-1} . For group (2), (6), (7) and (8), the tumors were exposed to a 650 nm laser (0.5 W cm^{-2}) for 10 min after 12 h post-injection. The body weight and tumor volume of each mouse were monitored every two days, and after 14 days treatment, the tumors were dissected and weighed to evaluate the therapeutic efficacy. In a typical calculation, the tumor volume was calculated by $V = \text{length} \times \text{width}^2/2$. The relative tumor volume was calculated as V/V_0 , where V_0

was the tumor volume before the treatment. Finally, the major organs, such as liver, spleen, heart, lung, and kidney, were removed and fixed in 4% paraformaldehyde solution for histological examination in order to further investigate the biocompatibility of COF-Au-MnO₂-HA.

RESULTS AND DISCUSSION

Details for characterization of the materials are provided in the Supplementary information. Fig. 1a–c and Fig. S1 show the transmission electron microscopy (TEM) and scanning electron microscopy (SEM) images of COF, COF-Au and COF-Au-MnO₂, respectively. As shown in Fig. 1a and Fig. S1a, spherical COF NPs with a uniform size of 200 nm were successfully synthesized by the room temperature solution-based method. Au NPs with sizes around 3 nm were prepared by reducing chloroauric acid with NaBH_4 and decorated on the surface of COF (Fig. 1b). Finally, the resultant COF and Au were encapsulated by a layer of MnO₂ (Fig. 1c) [17]. The elemental mapping and energy-dispersive X-ray spectroscopy (EDS) results indicated the presence of Au and MnO₂ (Fig. 1d–i and Fig. S2) [10,39]. According to the inductively coupled plasma (ICP) result, the contents of Au and MnO₂ were about 4.5% and 26.1%, respectively. The X-ray diffraction (XRD) patterns demonstrated that COF and Au were obtained (Fig. S3). It should be noted that the spherical morphology of COF was still maintained after being coated with Au, MnO₂ and HA; however, the hydrodynamic size of the resultant product was steadily increased, and the corresponding zeta potentials were changed (Figs S4, S5 and Table S1) [34]. Meanwhile, excellent stability was found for COF-Au-MnO₂-HA after being immersed in H₂O, PBS and Dulbecco's modified Eagle medium (DMEM) for 5 days (Fig. S6). The X-ray photoelectron spectroscopy (XPS) results are shown in Fig. 1j and k. The two peaks located at 87.77 and 84.03 eV were assigned to Au 4f_{5/2} and 4f_{7/2} (Fig. 1j) [40], and those at 653.63 and 641.87 eV were attributed to Mn (IV) 2p_{1/2} and Mn (IV) 2p_{3/2}, respectively (Fig. 1k) [41]. All these results confirmed the formation of COF-Au-MnO₂.

Under slightly acidic conditions, MnO₂ will react with H₂O₂ to produce O₂ [17]. To mimic the TME, the dissolved oxygen was measured at pH 6.45 by using a dissolved oxygen meter. By injecting COF-Au-MnO₂ into the H₂O₂ solution with a concentration of $100 \times 10^{-6} \text{ mol L}^{-1}$, the concentration of dissolved O₂ increased rapidly, which suggested that COF-Au-MnO₂ could decompose H₂O₂ to produce O₂ through the reaction between H₂O₂ and MnO₂ in the presence of H⁺ [42]. It should be noted that the concentration of dissolved O₂

Figure 1 Characterization of COF-Au-MnO₂. TEM images of (a) COF, (b) COF-Au, and (c) COF-Au-MnO₂ nanoparticles. (d–i) The elemental mapping results of COF-Au-MnO₂. High-resolution XPS spectra of (j) Au 4f, and (k) Mn 2p.

increased much more by further introducing glucose (Fig. 2a). Such a phenomenon also indicated that the oxidation reaction of glucose can promote the generation of oxygen. Meanwhile, the dissolved oxygen content did not increase when GSH was added. Additionally, the GOx-like activity of Au NPs was investigated. Au NPs were capable of catalyzing the oxidation of glucose and producing gluconic acid (GA) and hydrogen peroxide in the presence of O₂ [43]. As the concentration of the COF-Au NPs increased, the amount of H₂O₂ produced in the glucose solution also increased (Fig. 2b). The GA was then detected by using a GA-specific colorimetric assay in this study. Specifically, COF-Au NPs were incubated with glucose for different times, and then the supernatant was obtained by centrifugation. After addition of Fe³⁺ and hydroxylamine (NH₂OH) into the supernatant, hydroxamate-Fe³⁺ was formed for GA in the solution and the intensity of the typical absorbance peak increased over time (Fig. S7) [12].

The type II PDT could kill cancer cells by using ¹O₂, which will damage the DNA of tumor cells directly [34]. As shown in Fig. S8, a broad absorption band centered at around 460 nm was observed for the as-synthesized COF, and no obvious change was found after the incorporation of Au and MnO₂. The ¹O₂ generation ability under 650 nm laser irradiation was investigated through a ty-

pical chemical probe, 1,3-diphenylisobenzofuran (DPBF) [33]. The decrease of the absorption intensity at around 410 nm indicated the degradation of DPBF, which also reflected the amount of ¹O₂ produced. Almost no change was found for the intensity of the characteristic peak of DPBF under 650 nm laser irradiation for 12 min, suggesting that no ROS was generated for DPBF under 650 nm laser irradiation (Fig. S9). As shown in Fig. 2c and d, after adding H₂O₂, the ability to produce ¹O₂ of COF-Au-MnO₂ has been greatly enhanced due to the increased O₂ generation [42]. The ¹O₂ generation capability of COF-Au-MnO₂ was also evaluated by the electron spin resonance (ESR) test with 2,2,6,6-tetramethylpiperidine (TEMP) as the ¹O₂ trapper. As shown in Fig. S10, the characteristic ¹O₂-induced signals upon 650 nm laser irradiation (0.5 W cm⁻², 10 min) were observed for COF-Au-MnO₂ solution, and the intensity increased in the presence of H₂O₂. Meanwhile, the temperature of COF-Au-MnO₂ aqueous solution did not increase obviously under 650 nm laser irradiation. Therefore, the photothermal effect of COF-Au-MnO₂ under 650 nm laser irradiation is negligible (Fig. S11). The photodynamic effect was further investigated under normoxic and hypoxic environments, respectively (Fig. 2e and f). The phenomenon was similar, and compared with COF, the photodynamic effect of COF-Au-MnO₂ was

Figure 2 (a) O₂ generation in pH 6.45 solution with different samples. (b) H₂O₂ production with different concentrations of COF-Au. UV-vis absorption curves of DPBF solution treated with (c) COF-Au-MnO₂+650 nm laser, and (d) COF-Au-MnO₂+H₂O₂+650 nm laser. PDT effects of the samples irradiated under (e) normoxic and (f) hypoxic environments, respectively.

greatly enhanced in the presence of H₂O₂, which should be attributed to the decomposition of H₂O₂ and generation of ¹O₂ by COF-Au-MnO₂. Therefore, COF-Au-MnO₂ can indeed relieve hypoxia in the presence of H₂O₂ and thus improve the photodynamic effect under laser irradiation. The ability for COF-Au-MnO₂ to deplete GSH was further confirmed with a UV spectrophotometer measurement (Fig. S12) [44].

The ROS generated in cells was tested by using 2,7-dichlorodi-hydrofluorescein diacetate (DCFH-DA) as an indicator [34,45]. As shown in Fig. 3a, under normoxic environment, the 4T1 cells incubated with COF-HA and COF-Au-MnO₂-HA both showed green fluorescence after irradiation by a 650 nm laser. However, under hypoxic environment (1% O₂, 5% CO₂, and 94% N₂) [42], only the cells incubated with COF-Au-MnO₂-HA could produce fluorescence under laser irradiation, which also indicated that COF-Au-MnO₂-HA could relieve hypoxia efficiently. Subsequently, the cellular uptake process was investigated. As shown in Fig. S13, the red emission for the rhodamine B (RhB)-conjugated COF-Au-MnO₂-HA became stronger as the culture time increased, suggesting the effective endocytosis of the materials [29].

The hypoxia probe [Ru(dpp)₃]Cl₂ (RDPP) was used in this study to measure the generated O₂ for COF-Au-

MnO₂-HA NPs, as the fluorescence of RDPP will be strongly quenched in the presence of O₂ [46]. As shown in Fig. 3b, red fluorescence could be observed for the control and COF-HA-treated groups. In contrast, the intensity of red emission for the COF-Au-MnO₂-HA group was obviously weakened, which indicated that MnO₂ in COF-Au-MnO₂-HA NPs could decompose endogenous H₂O₂ to produce O₂ and the hypoxic condition would be alleviated after the NPs were internalized by the 4T1 cells. It further demonstrated that the COF-Au-MnO₂ NPs could overcome tumor hypoxia efficiently. The degradation of glutathione at the cellular level was then measured. 4T1 cells were cultured with different concentrations of COF-Au-MnO₂-HA for about 24 h, then the GSH assay kit was used to detect the content of intracellular GSH (Fig. 3c). As the concentration of COF-Au-MnO₂-HA increased, the content of GSH was reduced dramatically, suggesting the efficient depletion of GSH by COF-Au-MnO₂-HA [44].

The biocompatibility of COF-HA and COF-Au-MnO₂-HA was evaluated through the standard methyl thiazolyl tetrazolium (MTT) assay [31]. As shown in Fig. 3d, the survival rate of L929 cells was still over 80% even at a high concentration of 200 μg mL⁻¹, revealing the good biocompatibility of COF-HA and COF-Au-MnO₂-HA. The

Figure 3 (a) The inverted fluorescence microscopy images of DCFH-DA in 4T1 cells under different conditions. (b) The inverted fluorescence microscopy images of RDPP in 4T1 cells under different conditions. (c) Intracellular GSH depletion with different concentrations of COF-Au-MnO₂-HA (0, 50, 100, 200 and 400 µg mL⁻¹). (d) *In vitro* cytotoxicity test for COF-HA and COF-Au-MnO₂-HA against L929 cells. The survival of 4T1 cells with COF-HA/laser and COF-Au-MnO₂-HA/laser in (e) normoxic and (f) hypoxic environments, ****p* < 0.001. Scale bar is 20 µm.

photodynamic effect *in vitro* under normoxic and hypoxic environments was further tested through MTT assay and cell apoptosis measurement. For the MTT test, under normoxic environment, both COF-HA and COF-Au-MnO₂-HA exhibited excellent photodynamic effect, and the mortality rate of 4T1 cells treated with 200 µg mL⁻¹ of COF-Au-MnO₂-HA was almost 80%, which was higher than that of the COF-HA-treated cells (50%, Fig. 3e). However, under hypoxic condition, no obvious cytotoxicity was found for the COF-HA-treated 4T1 cells under 650 nm laser irradiation, but the cell viability was decreased to about 50% for the COF-Au-MnO₂-HA-treated group at a concentration of 200 µg mL⁻¹ (Fig. 3f). Therefore, the photodynamic effect is largely limited by the oxygen content. Moreover, the cell apoptosis was investigated by flow cytometric analysis through the annexin V-fluorescein isothiocyanate

(FITC)/propidium iodide (PI) apoptosis detection kit under normoxic and hypoxic environments, respectively (Figs S14 and S15) [34]. Under normoxic environment, the cell apoptosis of COF-Au-MnO₂-HA+laser group was 24.0%, which was higher than that of the COF+laser group (17.9%), consistent with the MTT result. Nevertheless, under hypoxic environment, only the COF-Au-MnO₂-HA+laser group had an apoptotic rate of 15.2%, and no obvious damages were observed for the other groups. Therefore, it is further demonstrated that COF-Au-MnO₂-HA can enhance the photodynamic effect under hypoxic environment.

Mn²⁺ is an excellent T₁ MRI contrast agent owing to its unique molecular orbital, and in this study, Mn²⁺ could be released through the decomposition of MnO₂ by GSH inside the tumor [47–49]. As shown in Fig. 4a, due to the five unpaired 3d electrons of Mn²⁺, the longitudinal re-

Figure 4 (a) *In vitro* T_1 -weighted MRI of COF-Au-MnO₂ recorded using 1.2 T MRI scanner at different concentrations of Mn with or without excessive GSH treatment and the corresponding relaxation rate r_1 versus the concentration of Mn²⁺. (b) *In vivo* T_1 -weighted MRI of tumor-bearing mice before and after injection of COF-Au-MnO₂-HA. Tumor positions are marked by red circles.

Figure 5 (a) Body weight and (b) relative tumor volumes of mice treated with different methods, *** $p < 0.001$, ** $p < 0.01$. (c) Representative photographs of tumors for all groups on the last day of treatment. (d) H&E stained images of major organs and tumor slices of mice for COF-Au-MnO₂-HA/laser-treated group. (1) PBS, (2) PBS under 650 nm laser irradiation, (3) COF-HA, (4) COF-HA, (5) COF-Au-MnO₂-HA, (6) COF-HA under 650 nm laser irradiation, (7) COF-Au-HA under 650 nm laser irradiation, and (8) COF-Au-MnO₂-HA under 650 nm laser irradiation. Scale bar is 20 μ m.

laxivity (r_1) of GSH-treated group was $5.71 \text{ L mmol}^{-1} \text{ s}^{-1}$, which was much higher than that of the untreated group ($0.77 \text{ L mmol}^{-1} \text{ s}^{-1}$) [49]. For the *in vivo* T_1 -weighted MRI test, the relative intensity at the tumor site of the 4T1 tumor-bearing BALB/c mouse was significantly enhanced after *in-situ* injection of COF-Au-MnO₂-HA (Fig. 4b).

The *in vivo* experiments were finally performed to verify the antitumor efficacy of COF-Au-MnO₂ [3,29,34]. The 4T1 tumor-bearing BALB/c mice with an average tumor volume of 100 mm^3 were randomly divided into eight groups ($n = 6$, per group) and treated with different ways: (1) PBS, (2) PBS under 650 nm laser irradiation, (3) COF-HA, (4) COF-Au-HA, (5) COF-Au-MnO₂-HA, (6) COF-HA under 650 nm laser irradiation, (7) COF-Au-HA under 650 nm laser irradiation, and (8) COF-Au-MnO₂-HA under 650 nm laser irradiation. It was found from Fig. 5a that the weights of mice for the eight groups steadily increased during the treatment, suggesting the great *in vivo* biocompatibility of the materials [6,20,21]. As shown in Fig. 5b and c, the relative tumor volume of groups (1)–(5) increased rapidly; however, upon laser irradiation, the groups (6)–(8) all had a certain therapeutic effect, and the best antitumor efficacy was achieved for the group (8) due to the enhanced PDT by efficient relieving hypoxia. No significant damages to the major organs and obvious lesions to the tumors were observed for the hematoxylin and eosin (H&E) staining images (Fig. 5d) [9,31].

CONCLUSIONS

A multifunctional therapeutic platform based on COF-Au-MnO₂ was synthesized. The resultant COF-Au-MnO₂ could catalyze endogenous H₂O₂ to produce O₂ and consume GSH to enhance the O₂-dependent PDT, and the generated O₂ could also facilitate the decomposition of glucose by Au NPs. At the same time, the starving-like therapy can in turn promote the catalytic efficiency of MnO₂ and form cycle-like cascade reactions. The *in vitro* and *in vivo* experiments confirmed the excellent cancer cell killing effect and antitumor efficacy of COF-Au-MnO₂ on account of the combination of relieving intratumoral hypoxia, enhancement of PDT and starvation-like therapy. This study further demonstrated the excellent biomedical application of COF, especially by using TME to conduct the catalytic cascade reactions, and also provides an approach to construct COF-based therapeutic platform for cancer treatment.

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

Supplementary information Experimental details and supporting data are available in the online version of the paper.

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一种基于共价有机框架的多功能治疗平台通过催化级联反应增强光动力治疗

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摘要 近年来,利用肿瘤独特的微环境进行肿瘤治疗成为了热门研究话题,然而这种治疗方法经常受到诸多条件的限制,如较少的反应底物和较慢的反应速率,反应所产生的毒性物质也不足以杀死癌细胞等.本文以共价有机骨架(COFs)为模板,在表面生长金纳米颗粒,然后再包覆一层二氧化锰,最后用透明质酸修饰以提高材料的生物相容性.最终得到的产物可以在肿瘤微环境中形成级联反应:在缺氧条件下,二氧化锰可以分解肿瘤内部的过氧化氢产生氧气以增强II型光动力疗法;金纳米颗粒可以通过分解葡萄糖用于饥饿疗法,同时,饥饿疗法所产生的过氧化氢又可以促进氧气的生成.此外,肿瘤内部的谷胱甘肽可以将二氧化锰分解为二价锰离子,而二价锰离子可以用于T₁加权MR成像.最终体内和体外实验证明,该复合材料具有良好的癌细胞杀伤能力和抗肿瘤效果.