A tumor microenvironment-activated metal-organic framework–based nanoplatform for amplified oxidative stress–induced enhanced chemotherapy

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Engineering a highly tumor microenvironment-responsive nanoplatform toward effective chemotherapy has always been a challenge in targeted cancer treatment. Metal-organic frameworks are a promising delivery system to reformulate previously approved drugs for enhanced chemotherapy, such as disulfiram (DSF). Herein, a tumor microenvironment-activated metal-organic framework–based nanoplatform DSF@MOF-199@FA has been fabricated to realize amplified oxidative stress–induced enhanced chemotherapy. Our results unveil that the copper ions and DSF released by DSF@MOF-199@FA in an acidic environment can be converted into toxic bis(N,N-diethyl dithiocarbamate) copper and then induce cell apoptosis. Simultaneously, we determined that the apoptosis outcome is further promoted by amplified oxidative stress through effective generation of reactive oxygen species and GSH elimination. In conclusion, this work provides a promising platform for effective anticancer treatment.

Chemotherapy still leads to the most prevalent modalities among a variety of anticancer treatments in recent years, although all kinds of treatment methods have developed (1–4). Currently, commonly used chemotherapy drugs include doxorubicin (5), cisplatin (6), paclitaxel (7), tirapazamine (8), platinum(IV) (9), camptothecin (10) and so on. In addition, as an old drug approved by the U.S. Food and Drug Administration (FDA), disulfiram (DSF) has been used for treating alcohol dependence for over 6 decades. Recent research illustrated that it can turn into toxic bis(N,N-diethyl dithiocarbamate) copper (II) (CuET) after chelated with Cu(II) to induce heat shock response and cancer cell death (11–14). However, the serious side effect, high system toxicity, and unsatisfactory therapeutic efficacy limited its application (15). Considering the high cost from the research of the pharmacokinetics and safety profiles of new drugs, searching for new anticancer drug formulations based on DSF is an attractive strategy to combat the aforementioned issue.

Metal-organic frameworks (MOFs), consisting of metal nodes and organic ligand, have been widely used in various advanced fields, such as gas sorption and separation, catalysis, food safety, drug delivery, and cancer therapy (16–21). In particular, MOFs recommended themselves as very promising hosts for old drugs loading to develop new anticancer drug formulations due to their high porosity (22–24). Of note, their metal nodes offer ample possibilities for fabricating tumor microenvironment (TME)–responsive platforms. For example, some Cu-based MOFs endow their particular merits toward TME-responsive therapy by releasing Cu(II) ions in acid TME. The resultant Cu(II) could trigger GSH depletion (25, 26) and Cu(I)-mediated •OH generation via self-cyclic valence alternation (27, 28), giving rise to amplified oxidative stress and further improve the chemotherapeutic effect (29, 30). In this sense, Cu(II)-based MOFs hold great advantages in promoting the CuET-mediated chemotherapy by the amplified intracellular oxidative stress.

Bearing the aforementioned considerations in mind, we employed the acid-responsive MOF-199 as the main material to fabricate an intelligent delivery system (DSF@MOF-199@FA) to promote the chemotherapy effect. As illustrated in Figure 1, the folic acid (FA) was wrapped on the surface of DSF@MOF-199 to endow it (DSF@MOF-199@FA) with cancer cell–specific targeting ability (31). In addition, the TME-responsive system could release Cu(II) ions and DSF. Thereinto, DSF could convert into CuET (Figs. S1 and S2) in situ to induce cell apoptosis. Besides, the released Cu(II) ions could be used to amplify intracellular oxidative stress by consuming intracellular GSH and generating •OH (generated from the Fenton-like reaction) via self-cyclic valence alternation. Finally, this DSF@MOF-199@FA mediated amplified oxidative stress strategy provides a new paradigm to amplify the CuET chemotherapeutic effect.

**Results and discussion**

DSF@MOF-199@FA was fabricated by loading DSF into the pores of defective MOF-199 through simply physical absorption and then wrapped with FA. As identified by Figure 2A, the power X-ray diffraction pattern of MOF-199

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showed the same characteristic peaks as the simulated one, illustrating the MOF-199 was successful synthesized. The crystal structure and crystallinity of DSF@MOF-199, MOF-199@FA, and DSF@MOF-199@FA remained well compared with MOF-199. Compared with MOF-199, the obvious diffraction peaks at $2\theta = 9.25^\circ$, 9.95$^\circ$ in DSF@MOF-199 and DSF@MOF-199@FA. Besides, in terms of DSF@MOF-199 and DSF@MOF-199@FA, the emerged small diffraction peaks ($2\theta = 9.25^\circ$, 9.95$^\circ$) could be attributed to the DSF loading given the interaction between DSF molecules and Cu ions of MOFs, which was revealed by power X-ray diffraction and X-ray photoelectron spectroscopy measurements (Figs. S3 and S4). The scanning electron microscopy image in Figure 2B and transmission electron microscopy image in Fig. S5 of

Figure 1. Scheme illustration showing the preparation of DSF@MOF-199@FA, highlighting the amplified oxidative stress enhanced CuET-mediated chemotherapy. DSF, disulfiram; FA, folic acid; MOF, metal-organic framework.

Figure 2. Characterization of DSF@MOF-199@FA. A, PXRD patterns of simulated MOF-199, MOF-199@FA, and DSF@MOF-199@FA. B, scanning electron microscopy image of DSF@MOF-199@FA. C, elemental mapping images of the ultrathin slice of DSF@MOF-199@FA in TEM. D, TGA curves of MOF-199 and DSF@MOF-199. E, UV-vis absorbance spectra of folic acid, DSF, MOF-199, DSF@MOF-199@FA, F, zeta potentials of MOF-199, DSF@MOF-199, MOF-199@FA, and DSF@MOF-199@FA. DSF, disulfiram; FA, folic acid; MOF, metal-organic framework; PXRD, power X-ray diffraction.
DSF@MOF-199@FA displayed the unchanged octahedron morphology, suggesting the absence of structure and morphology variation of MOF-199 after loading with DSF and coating with FA.

Besides, the DSF@MOF-199@FA was sliced into ultrathin slices and the elemental mapping images were collected, in which Cu was attributed to MOF-199, S was assigned to DSF, and N contributed to DSF and FA (Fig. 2C), which demonstrated that DSF was loaded into the pores of MOF-199. As shown in Figure 2D, the weight loss between 200 °C and 300 °C was attributed to the DSF decompose (32), which further demonstrated that DSF was efficiently loaded into MOF-199. The loading efficiency of DSF was calculated to be 4.9% in the DSF@MOF-199@FA by inductively coupled plasma atomic emission spectrometry measurement. The UV-visible absorption spectrum of DSF@MOF-199@FA displayed significant change after subsequent DSF loading and FA coating, a new absorption band appeared (230–350 nm) due to the DSF and FA absorption (Fig. 2E). Particularly, the absorption band around 260 to 320 nm showed a difference between DSF@MOF-199 and DSF@MOF-199@FA, which was attributed to the FA coating. Besides, the new peak around 1608 cm⁻¹ in FTIR spectrum increased after modified by FA was contributed to the -NH stretching vibrations of -NH₂ in FA (Fig. S6). In addition, as displayed in Figure 2F, the zeta potential experiment indicated a change in the surface charge from a positive potential for MOF-199 (+8.04 mV) to a negative potential for MOF-199@FA (−4.05 mV) and DSF@MOF-199 (−4.92 mV) after FA modification and DSF loading, respectively. The potential was further reduced to −11.5 mV (DSF@MOF-199@FA) after loading with DSF and modifying with FA simultaneously. All the aforementioned results demonstrate the successful fabrication of DSF@MOF-199@FA.

Motivated by the successful fabrication of DSF@MOF-199@FA, the ROS generation, GSH depleting, and CuET formation performance were studied thoroughly by the in vitro experiments. Firstly, the acidity-responsive degradation performance of MOF-199 was evaluated by scanning electron microscopy observation. As shown in Figs. S7 and S8, the MOF-199 was physiologically stable after incubating with PBS in neutral condition (pH = 7.4) for 24 h, while degraded quickly in the acidic PBS solution (pH = 6.5), suggesting that the MOF-199 could degrade and release the copper ions and DSF for anticancer treatment in the acid environment. Furthermore, the polydispersity index of DSF@MOF-199@FA maintained stable in serum over 7 days, which confirmed its good stability in the blood circulation (Fig. S9). Then, terephthalic acid, which can react with •OH radicals to form 2-hydroxyterephthalic acid was used to evaluate the •OH (origin from the Fenton-like reaction) generation capability of DSF@MOF-199@FA. With the prolonged incubation time, a fluorescence enhancement around 450 ± 20 nm appeared, indicating that DSF@MOF-199@FA is capable of generating ROS.

Figure 3. GSH consumption and Fenton-like reactions of DSF@MOF-199@FA. A, illustration of ROS generation, GSH depleting, and CuET formation process within DSF@MOF-199@FA. B, determination of the formation of •OH treated with DSF@MOF-199@FA by terephthalic acid as the fluorescent probe. Reaction conditions: DSF@MOF-199@FA (50 μg ml⁻¹), TA (0.05 mM), pH = 6.5. C, GSH depleting ability of DSF@MOF-199@FA at different concentration with thiolite green as the detection agent for GSH. D, UV-vis spectrum of degradation product of MOF-199@FA and DSF@MOF-199@FA. DSF, disulfiram; FA, folic acid; MOF, metal-organic framework; ROS, reactive oxygen species.
•OH in the acidic TME efficiently (Figs. 3B and S10) while the DSF@MOF-199@FA or H2O2 alone do not generate any •OH. The Fenton-like effect of DSF@MOF-199@FA was proved to be derived from free Cu^2+ ions by the control experiments of CuET and Cu^{2+} (Fig. S11). Moreover, thiolite green was selected as the detection agent for GSH. As shown in Fig. S12, the solution showed the faint green fluorescence at 520 nm in the presence of H2O2 and DSF@MOF-199@FA, which proved that DSF@MOF-199@FA displayed excellent GSH consumption capacity (Fig. S12). Besides, the fluorescence was gradually faded (Fig. 3C) with the concentration of DSF@MOF-199@FA increased. In addition, compared with MOF-199@FA, the UV-visible spectrum of degradation product originating from DSF@MOF-199@FA presented a characteristic peak around 450 nm (the peak of CuET), suggesting that the DSF@MOF-199@FA could release copper ions and DSF in the acidic environment and then form CuET complex in situ for chemotherapy (Fig. 3D). With the extension of incubation time, the absorption at 450 ± 20 nm increased gradually with the extension of incubation time in the acidic environment, which proved the formation of CuET (Figs. S13 and S14). Given DSF@MOF-199@FA could generate •OH and consume GSH via self-cyclic valence alternation, it is implied that DSF@MOF-199@FA can promote the CuET-mediated chemotherapeutic effect by amplifying the intracellular oxidative stress.

Encouraged by the aforementioned experiments, we decided to investigate the •OH generation performance of DSF@MOF-199@FA in cancer cells via confocal laser scanning microscopy imaging, in which the 4T1 cells were stained with hydroxyphenyl fluorescein. As illustrated in Figure 4A, compared with the blank group, the green fluorescence of hydroxyphenyl fluorescein increased significantly for DSF@MOF-199@FA with/without H2O2 groups. Besides, the fluorescence almost disappeared upon •OH scavenger (ascorbic acid, AA) added, indicating the •OH generation ability of DSF@MOF-199@FA within 4T1 cells. Meanwhile, the enhanced fluorescence intensity of DSF@MOF-199@FA (Fig. 4B) with the addition of H2O2 demonstrating that the additional H2O2 is able to facilitate the Fenton-like reaction and further improve •OH generation.

Apart from reactive oxygen species, GSH also plays an important role in amplifying oxidative stress. Therefore, thiolite green was utilized to assess the GSH level in the 4T1 cells after different treatments. Obviously, in contrast to the blank group, a decreased GSH concentration could be observed upon DSF@MOF-199@FA treated. As displayed in Figure 4C, compared with the DSF@MOF-199@FA group, the concentration of GSH increased with AA addition, which probably attributed to the inhibition of GSH consumption by AA. Moreover, GSH level could even be reduced further when H2O2 added. It demonstrated that DSF@MOF-199@FA can effectively consume the intracellular GSH due to the released Cu(II) that was reduced to Cu(I) by GSH through redox reaction. The aforementioned results further confirmed that DSF@MOF-199@FA can be used to amplify oxidative stress by producing •OH and consuming GSH for enhanced chemotherapy.

To avoid side effects on normal cells, we modified DSF@MOF-199 with FA to enhance its cancer cell–specific

![Figure 4](image_url)
targeting capability. The cancer cell–specific targeting behavior of DSF@MOF-199@FA were evaluated by cell uptake experiments with FAR (folate receptor) abundant cells (HeLa: human cervical cancer cell) and FAR negative cells (HEK 293FT: human embryonic kidney cells). To characterize the process of the endocytosis of DSF@MOF-199@FA into cancer cells clearly, DSF@MOF-199@FA were labeled with FITC (DSF@MOF-199@FA-FITC) (Fig. S15). As illustrated in Figs. S16 and S17, DSF@MOF-199@FA-FITC preferentially accumulated in HeLa cells but not in HEK 293T cells, HeLa cells which incubated with DSF@MOF-199-FITC and the HeLa cells which were incubated with free FA in advance. Then, cell uptake experiments with 4T1 cells (mouse breast cancer cells, FAR abundant cells) also demonstrated that FA–modified can effectively target FAR-overexpressing cancer cells (Fig. S18). Moreover, the cytotoxicity was evaluated via standard (4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay using HEK 293T cells (human embryonic kidney cell), SW480 cells (human colorectal carcinoma cell), HeLa cells (human cervical cancer cell), and 4T1 cells (mouse breast cancer cell). As shown in Fig. S19, more than 90% of HEK 293T cells survived after being incubated with different concentration of DSF@MOF-199@FA (0–80 μg ml⁻¹) for 12 h, suggesting their low cytotoxicity to healthy cells and excellent biocompatibility. In contrast, cell viability of 4T1 cells decreased along with an increase in the concentration of DSF@MOF-199@FA (Fig. 5A), the treated HeLa cells and SW480 cells showed similar results (Fig. S20). The cell viability of 4T1 cells was further decreased after H₂O₂ addition because of the amplified oxidative stress triggered by H₂O₂. Notably, as shown in Fig. S21, H₂O₂ (100 μM) displayed ignorable cytotoxicity. These results reveal that DSF@MOF-199@FA can selectively induce cancer cells apoptosis and then avoid side effects effectively.

Strategically, we deployed a systematic protocol to evaluate toxicity of DSF after chelated with Cu(II) ions as well as amplified oxidative stress–induced chemotherapy effect, including standard (4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide and 3D multicellular tumor spheroid assays (Fig. 5). Evidently, in contrast to the ignorable cytotoxicity toward 4T1 cells and 3D multicellular tumor spheroids treated with DSF or MOF-199@FA, DSF@MOF-199@FA (with equal concentration of DSF) displayed obviously cytotoxicity elaborating the in situ generated CuET.
could serve as a chemotherapeutic agent. DSF@MOF-199@FA with H₂O₂ treatment group displayed much lower cell viability due to the generated OH originating from the Fenton-like reaction amplified by the intracellular oxidative stress. In addition, upon AA (reduced oxidative stress) added, the survival rates increased.

Inspired by the amplified oxidative stress and CuET-mediated chemotherapy of DSF@MOF-199@FA, the systematic performance of therapeutic effect was further evaluated by confocal laser scanning microscopy observation (Fig. 6A). Red propidium iodide signal could be observed in the DSF@MOF-199@FA group demonstrating its chemotherapy outcome against tumor cells. Upon AA (reduce oxidative stress) or H₂O₂ (amplify oxidative stress) added, weakened or enhanced propidium iodide signal could be collected, respectively, corroborating the amplified oxidative stress–induced enhanced chemotherapy performance. Moreover, the aforementioned results were further confirmed by flow cytometry (Fig. 6B). With the addition of H₂O₂, DSF@MOF-199@FA induced 99.43% apoptotic cells, which was obviously higher than that of with AA (82.18%) or without H₂O₂ (97.05%) treatment. All the aforementioned in vitro results showed that DSF@MOF-199@FA can be used to enhance CuET-mediated chemotherapy by the amplified oxidative stress.

Based on the surprising in vitro therapeutic effect of amplified oxidative stress–induced enhanced CuET-mediated chemotherapy, the in vivo biological behavior of DSF@MOF-199@FA, including circulation, biocompatibility, and anticancer ability were investigated on the 4T1 breast tumor–bearing female BALB/C nude mice. Initially, the pharmacokinetic behavior of DSF@MOF-199@FA in blood circulation was studied by intravenous injection, and the half-life was calculated to be 2.47 h within the bloodstream (Fig. 7B). Afterward, the female BALB/C mice bearing 4T1 tumor were randomly divided into five groups (n = 5) and intravenous injected with PBS, DSF only, MOF-199 only, DSF@MOF-199 only, and DSF@MOF-199@FA only,

Figure 6. In vitro therapy performance of DSF@MOF-199@FA. A, CLSM images of 4T1 cells stained with calcein AM/PI after different treatments (scale bar: 100 μm). B, 4T1 cells treated with DSF@MOF-199@FA apoptosis analyzed by flow cytometry after different treatment using annexin V-FITC and PI as indicators of apoptosis. CLSM, confocal laser scanning microscopy; DSF, disulfiram; FA, folic acid; MOF, metal-organic framework; PI, propidium iodide.
respectively. During the whole therapeutic period, the body weight changes of the five groups mice showed an upward tendency and no damage was observed in the major organs (heart, liver, spleen, lung, and kidney) (Figs. 7C and S22). The high therapeutic biosafety of DSF@MOF-199@FA was further validated through blood routine examination (Fig. S23). Remarkably, compared with the other groups, DSF@MOF-199@FA group exhibited a significantly suppressed effect on 4T1 tumor growth (Figs. 7D, S24 and S25). Furthermore, the TUNEL, Ki-67, and H&E stained tumor pathological sections showed that the DSF@MOF-199@FA can induce cell necrosis in the tumor section, indicating the new anticancer drug formulations based on DSF has the better anticancer efficiency (Figs. 7E and S26).

**Conclusion**

In summary, we have constructed a TME-active nanotheranostic platform, DSF@MOF-199@FA, for amplified oxidative stress–induced enhanced CuET-mediated chemotherapy. The results show that the released DSF and Cu(II) ions in acidic environment can form toxic CuET species in situ to induce chemotherapy outcome. Meanwhile, the therapeutic effect can be further enhanced by the copper ions mediated amplified oxidative stress through •OH generation (origin from Fenton-like reaction) and GSH consumption. This work not only represents a distinctive paradigm of a TME-activated nanosystem for amplified oxidative stress–induced enhanced CuET-mediated chemotherapy but also provides insight into repurposing FDA-approved drugs as versatile cancer therapeutics for effective cancer treatment.

**Experimental procedures**

**Synthesis of defective MOF-199**

Cu(NO$_3$)$_2$ aqueous solution (0.9 ml, 0.1 M), CTAB aqueous solution (9.6 ml, 0.1 M), and benzene-1,3,5-tricarboxylate triethylammonium salt aqueous solution (0.6 ml, 0.1 M) were added in the mixture of ethanol (15 ml) and deionized water (15 ml). Next, the aforementioned mixture was stirred vigorously at the room temperature (RT) for 10 min and then collected by centrifugation (5000 rpm, 1 min).

**Synthesis of DSF@MOF-199**

DSF (20 mg) was dispersed in the acetone (10 ml) first and then MOF-199 (20 mg) was added under continuous sonication. The aforementioned mixture was stirred at RT for 4 h. The light blue products were obtained by centrifugation, washing, and drying after the reaction finished.
Metal-organic framework for enhanced chemotherapy

**Synthesis of MOF-199@FA/DSF@MOF-199@FA**

FA (50 mg) was dispersed into N,N-dimethylformamide (DMF) (50 ml) under sonication. After that, MOF-199/DSF@MOF-199 (50 mg) was added into the aforementioned solutions and stirred at 30°C overnight without light interference. Thereafter, the products were washed with DMF three times to remove the excess FA and then washed with ethanol three times again; the light blue product was preserved in ethanol.

**Synthesis of DSF@MOF-199@FA-FITC**

FITC (2 mg) was dispersed into DMF (2 ml) and then DSF@MOF-199@FA (2 mg) was added into the aforementioned solutions and stirred overnight. Thereafter, the products were washed with DMF and ethanol three times, respectively. The light blue product was preserved in ethanol.

**Synthesis of CuET**

About 87 mg DSF and 50 mg CuCl2 were added to 100 ml deionized water and stirred at RT for 24 h. The solution was extracted with chloroform and dried to form a black solid.

**Data availability**

All data generated or analyzed during this study are included in this published article and its additional files.

**Supporting information**—This article contains supporting information.

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**Author contributions**—D. L. conceptualization; X. L., W. Z., W. D., Y. T., and D. L. methodology; B. L. and J. L. software; B. L., J. L., and Y. T. formal analysis; B. L., X. Y., J. L., X. L., W. Z., and W. D. investigation; X. Y. data curation; B. L. and X. Y. writing—original draft; D. L. writing—review & editing; D. L. supervision.

**Conflict of interest**—The authors declare that they have no conflicts of interest with the contents of this article.

**Abbreviations**—The abbreviations used are: AA, ascorbic acid; DMF, N,N-dimethylformamide; DSF, disulfiram; FA, folic acid; MOF, metal-organic framework; TME, tumor microenvironment.

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