Metal–organic framework-based nanocatalytic medicine for chemodynamic therapy

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Chemodynamic therapy (CDT) is an emerging and promising strategy based on the Fenton or Fenton-like reaction in tumors [1–3]. The tumor microenvironment (TME) has the characteristics of low acidity and over-expression of H_2O_2 [4,5], thus providing favorable conditions for initiating the Fenton or Fenton-like reaction. In CDT, intratumoral H_2O_2 is decomposed into highly toxic hydroxyl radicals ($\cdot\text{OH}$) through the Fenton or Fenton-like reaction catalyzed by a metal-based nanocatalyst, which will cause irreversible damage to DNA, lipids, and proteins [6,7]. TME-based CDT can inhibit tumor growth and reduce the side effects on normal tissues. Recently, many nanocatalytic medicines containing metal elements, such as iron oxide nanoparticles, bimetallic alloys, MnO_2 , and metal–organic frameworks (MOFs), have been developed for improving the CDT efficiency [6].

MOFs are a type of hybrid porous materials composed of metal ions (clusters) with organic linkers through coordination bonds. Owing to their unique physicochemical properties, such as tunable structure, high porosity, and easy functionalization, MOFs have been extensively used for gas storage/separation [8], sensing [9], catalysis [10], and biomedicine [11]. In particular, the development of nanoscale MOFs increases their potential application in biomedicine, including bioimaging, antimicrobial action, antitumor activity, biosensing, and biocatalysis. Note that, in the past few years, the research of MOFs in CDT has rapidly developed (Fig. 1). This is primarily attributed to the intrinsic structural characteristics. For example, the coordination bonds between the metal ions (clusters) and the organic linkers can be easily broken in the acidic

TME, which releases additional metal ions and provides additional catalysts for CDT [12]. Furthermore, the well-defined pores and excessive porosity enable nanoscale MOFs to act as a carrier for various cargos ranging from diagnostic agents to therapeutic agents. Herein, we highlight the application of MOFs in CDT (Table 1) and hopefully this can promote the development of MOF-based nanocatalytic medicine for CDT.

Fe^{2+} is a classical Fenton reaction catalyst for the disproportionation of H_2O_2 to $\cdot\text{OH}$. CDT efficacy based on the ferrous catalyst is determined by the safe delivery and controllable release of Fe^{2+} into the tumor. Owing to its excellent acid responsive ability, multiple Fe^{2+} -based MOFs have been developed for CDT. One of the simple and classical designs is from the work reported by Ranji-Burachloo *et al.* [13]. They developed a folic acid (FA)-modified Fe^{2+} -based MOF (rMOF-FA) by reducing NH_2 -

Figure 1 The mechanism for application of MOFs in chemodynamic therapy.

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Table 1 Examples of MOFs-based nanocatalytic medicines

Nanocatalytic medicines/MOFs	MOFs' major components	Fenton or Fenton-like catalyst	Ref.
rMOF/NH ₂ -MIL-88B(Fe)	Fe ³⁺ and 2-aminoterephthalic acid	Fe ²⁺	[13]
MD@Lip/MOF-Fe ²⁺	Fe ²⁺ and 2-aminoterephthalic acid	Fe ²⁺	[14]
Co-Fc@GOx/Co-Fc nMOF	Co ²⁺ and 1,1'-ferrocenedicarboxylic acid	Fe ²⁺	[15]
Zr-Fc MOF	Zr ⁴⁺ and 1,1'-ferrocenedicarboxylic acid	Fe ²⁺	[16]
Hf-BPY-Fe/Hf-nMOFs	Hf ⁴⁺ and 2,2'-bipyridine-5,5'-dicarboxylic acid	Fe ²⁺	[17]
MGH nanoamplifiers/MIL-100	Fe ³⁺ and 1,3,5-benzenetricarboxylic acid	Fe ³⁺	[18]
AMP NRs/MIL-101	Fe ³⁺ and 1,3,5-benzenetricarboxylic acid	Fe ³⁺	[19]
DMH NPs/MIL-100	Fe ³⁺ and 1,3,5-benzenetricarboxylic acid	Fe ³⁺	[20]
Cu-TBP nMOF	Cu ²⁺ and tetrakis(4-carboxyphenyl)porphyrin	Cu ²⁺	[21]
PCN-224(Cu)-GOD@MnO ₂ /PCN-224	Cu ²⁺ and tetrakis(4-carboxyphenyl)porphyrin	Cu ⁺	[22]
CaO ₂ @DOX@ZIF-67/ZIF-67	Co ²⁺ and 2-methylimidazole	Co ²⁺	[23]

MIL-88B(Fe). After internalization by tumor cells, the as-prepared rMOF-FA was decomposed and Fe²⁺ was released into the lysosome. Then, the released Fe²⁺ could induce the intracellular Fenton reaction to produce a high concentration of ·OH to destroy tumor cells. However, the pH value of the lysosome was ~5.0, which cannot satisfy the requirements of an effective Fenton reaction (pH = 3.0–4.0). Moreover, the limited concentration of H₂O₂ in the tumor tissue significantly limits the CDT efficacy. To cope with these challenges, Sun *et al.* [14] constructed a liposomal formulation composed of dichloroacetic acid (DCA) and MOF-Fe²⁺ (MD@Lip). As an acetic acid derivative, DCA does not only enhance the intratumor acidity but also promotes glucose oxidation to produce H₂O₂ in mitochondria. The *in vitro* and *in vivo* experiments demonstrated that the CDT efficacy was significantly improved by the synergistic effect of DCA and MOF-Fe²⁺. In addition to DCA, glucose oxidase (GOx) is often used to increase the contents of H⁺ and H₂O₂ by catalyzing glucose oxidation in the presence of O₂. Accordingly, Fang *et al.* [15] fabricated a cascade enzymatic/Fenton catalytic reaction by incorporating GOx into a Co-ferrocene MOF. GOx was then activated by intracellular glucose to generate gluconic acid and H₂O₂, which effectively increased ·OH production through Fe²⁺-mediated Fenton reaction. However, the limited concentration of O₂ in the tumor tissue impaired the catalytic activity of GOx and hindered CDT efficacy. Considering the influence of temperature for an effective Fenton reaction, they fabricated a Zr-ferrocene MOF nanosheet using a Zr-O cluster and 1,1'-ferrocenedicarboxylic acid, which possessed excellent photothermal conversion efficiency [16]. Given the elevated temperature induced by photothermal therapy (PTT), Zr-ferro-

cene MOF exhibited excellent CDT effects against the tumor owing to the increased ·OH yield. The as-prepared Zr-ferrocene MOF is an “all-in-one” synergistic therapy for CDT and PTT that does not require any other auxiliary agents. In addition to directly delivering Fe²⁺, certain studies demonstrated that Fe³⁺ can be reduced into Fe²⁺ and catalyze the Fenton reaction to conduct CDT. For example, Gong *et al.* [17] synthesized a Hf-based MOF modified with Fe³⁺ (Hf-BPY-Fe), which promoted the conversion of Fe³⁺ to Fe²⁺ by enriched electrons after X-ray irradiation and ultimately promoted the Fenton reaction to produce ·OH. As shown in Fig. 2, this study provides a new strategy to simultaneously use the metal ion and organic linker in MOFs for realizing the synergistic therapy of CDT and radiotherapy.

Zhang *et al.* [18] fabricated a nanoamplifier by loading GOx into a Fe³⁺-based MOF (MIL-100) and coating it with hyaluronic acid (HA). The as-prepared nanoamplifier had an excellent theranostic effect against tumor owing to the synergistic amplification effect of GOx and MIL-100. Subsequently, they reported that MIL-100 can simultaneously serve as a carrier for 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) and a peroxidase-like nanozyme [19]. The fabricated ABTS@MIL-100/PVP (AMP) nanoreactors achieved the combined therapy of enhanced CDT (ECDT) and PTT using a “two-step rocket launching-like” process (Fig. 3). Recently, Xue *et al.* [20] constructed DMH nanoparticles composed of MIL-100, doxorubicin (DOX), and an HA coating. The HA coating enabled the DMH nanoparticles to target tumor cells. Then, the loaded DOX combined with the ·OH generated from the Fenton-like reaction significantly enhanced the antitumor efficiency.

In addition to Fe-containing catalysts, other metal ions,

Figure 2 Schematic of the synthesis of Hf-BPY-Fe and its anti-tumor mechanism. Reproduced with permission from ref. [17], Copyright 2020, American Chemical Society.

Figure 3 Schematic of the synthesis of AMP and its anti-tumor mechanism. BTC stands for benzenetricarboxylic acid; AM represents ABTS@MIL-100; PAI stands for photoacoustic imaging. Reproduced with permission from ref. [19], Copyright 2019, John Wiley & Sons Inc.

such as Cu^{2+} , Cu^+ , Co^{2+} and Mn^{2+} , can trigger a Fenton-like reaction to produce $\cdot\text{OH}$. Therefore, other metal-based MOFs can serve as a catalyst for initiating a CDT process. For example, Ni *et al.* [21] synthesized Cu^{2+} -based MOFs using 5,10,15,20-tetra-benzoatoporphyrin (TBP) as a ligand (Cu-TBP). The pH-sensitive Cu-TBP was then internalized in cells and decomposed to Cu^{2+} and TBP, which could be used for CDT and PDT, respectively. Moreover, the synergistic effect of Cu-TBP-mediated radical treatment and anti-PD-L1 immunotherapy effectively inhibited the growth of distant tumors in B16F10 tumor-bearing mice. Recently, Wang *et al.* [22] incorporated GOx into a Cu^{2+} -based MOF (PCN-224), which was then coated with MnO_2 to avoid GOx damaging normal cells. MnO_2 then reacted with the endogenous H_2O_2 to generate O_2 , which promoted the catalytic oxidation of glucose by GOx to produce abundant H_2O_2 for CDT. The released Cu^{2+} from PCN-224 consumed the intratumor glutathione (GSH) and was converted into Cu^+ . They demonstrated that Cu^+ synchronously induced the production of $\cdot\text{OH}$ and $^1\text{O}_2$ through a Fenton-like reaction and the Russell mechanism, respectively. These results reveal a potential new research direction for nanocatalytic therapy based on the Russell mechanism. Compared with the Cu-based MOF, a

Co-based zeolitic imidazolate framework (ZIF-67) has improved acidic responsiveness, which enables the faster release of Co^{2+} to induce a Fenton-like reaction. Thus, we developed a nanocatalytic medicine ($\text{CaO}_2\text{:DOX@ZIF-67}$) by encapsulating DOX and calcium peroxide (CaO_2) within ZIF-67 [23]. In the acidic TME, ZIF-67 was broken down to release Co^{2+} and DOX. Then, the exposed CaO_2 reacted with H_2O to generate both O_2 and H_2O_2 [24]. The generated H_2O_2 promoted a Co^{2+} -based Fenton-like reaction that generated $\cdot\text{OH}$; however, the generated O_2 relieved tumor hypoxia and enhanced the DOX efficacy (Fig. 4). This simple design can simultaneously enhance the efficacy of CDT and chemotherapy. Loading a Fenton or Fenton-like reaction catalyst into an MOF is another approach to initiate CDT. Considering high loading capacity and acid sensitivity, Ranji-Burachaloo *et al.* [25] used a Zn-based MOF (ZIF-8) as a carrier to simultaneously deliver GOx and natural hemoglobin to tumor tissue. The pH-sensitive ZIF-8 released GOx and hemoglobin into the tumor tissue under the acidic TME. GOx then consumed glucose to produce gluconic acid and H_2O_2 . Furthermore, the released hemoglobin provided Fe^{2+} to catalyze the Fenton reaction. Because of the increased acidity and H_2O_2 content in the tumor tissue, the CDT efficacy was considerably enhanced. Recently,

Figure 4 Schematic of the synthesis of $\text{CaO}_2\text{:DOX@ZIF-67}$ and its anti-tumor mechanism. Reproduced with permission from ref. [23], Copyright 2019, John Wiley & Sons Inc.

Xie *et al.* [26] synthesized a double-layer ZIF-8 construction termed as O₂-Cu/ZIF-8@Ce6/ZIF-8@F127 (OCZCF) to co-deliver O₂, Cu²⁺, and chlorin e6 (Ce6). Cu²⁺ both doubled the O₂ loading capacity of ZIF-8 and catalyzed the Fenton-like reaction after being reduced by GSH. Therefore, OCZCF realized the enhanced synergetic PDT and CDT by relieving hypoxia and consuming GSH.

Recently, the application of MOFs as a CDT has attracted considerable attention. In this review, we summarize the recent developments in the application of MOFs in CDT. Most studies utilize the pH sensitivity of MOFs, which can provide usable metal ions for the Fenton or Fenton-like reaction. Moreover, the well-defined pores of MOFs can be used to deliver other therapeutic agents, which can enhance CDT or allow for the development of combined treatment strategies. Therefore, MOFs are a class of promising nanocatalytic medicine. Although the application of MOFs in CDT has yielded encouraging results, certain challenges remain. First, multiple studies demonstrate that MOFs have unfavorable properties such as poor water solubility and poor stability. Poor water solubility leads to severe aggregation and increases the toxic side effects; however, poor stability leads to premature decomposition during circulation. Thus, additional efforts should be made to prepare MOFs that are hydrophilic and stable. Secondly, certain studies reported that MOFs show minimal catalytic activity under physiological conditions; thus, auxiliary reagents become indispensable, which complicates the preparation of MOFs-based nanocatalytic medicine further. Therefore, developing a simple method for integrating multifunction into MOF-based nanocatalytic medicine is desirable. Thirdly, although MOFs can deliver more Fenton or Fenton-like catalysts to a tumor to enhance CDT efficacy, the retention of these heavy metal ions in the body may have potential toxic side effects. Furthermore, toxicity induced by organic linkers is another problem. Construction of MOF-based nanocatalytic medicine using endogenous or biosafe organic linkers and metal ions is a preferable method to meet this challenge. MOF-based nanocatalytic medicine is still in its infancy; thus, the development of new strategies to overcome these obstacles would expand the application prospects of MOF-based nanocatalytic medicine in CDT. We believe that MOFs have considerable potential in improving the CDT efficacy.

Received 9 July 2020; accepted 8 September 2020;
published online 13 October 2020

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Acknowledgements This work was supported by the National Natural Science Foundation of China (31971304 and 21601046), the Natural Science Key Foundation of Hebei Province (B2017201226), and the Doctoral Candidate Innovation Funding Project of Hebei Province (CXZZBS2020022).

Author contributions Gao S and Han Y wrote the paper with support from Zhang J. All authors contributed to the general discussion.

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

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金属-有机框架纳米催化药物在化学动力学中的应用

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摘要 化学动力学疗法是一种基于芬顿或类芬顿反应原理的肿瘤纳米催化治疗方式, 已成为一种极具发展潜力的肿瘤治疗策略. 金属-有机框架材料, 因具有比表面积大、孔隙度高、负载能力强、酸响应性能好等优点, 已被用于合成各种纳米催化药物. 本文总结了近年来基于金属-有机框架材料的纳米催化药物的设计、合成策略, 分析并展望了其用于肿瘤化学动力学治疗所面临的问题和未来的发展趋势.