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Metal-Organic Framework Derived Nanozymes in Biomedicine

Dongdong Wang,[†] Deblin Jana,[†] Yanli Zhao^{*,†,‡}

[†]Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, 21 Nanyang Link, Singapore 637371, Singapore.

[‡]School of Materials Science and Engineering, Nanyang Technological University, 50 Nanyang Avenue, Singapore 639798, Singapore
Email: zhaoyanli@ntu.edu.sg

CONSPECTUS: Nanozymes that integrate the advantages of both nanomaterials and natural enzymes have accumulated enormous research interest over the past decades because of the opportunity it provides to appreciate and further cultivate artificial enzymes with comparable property. By mimicking the coordination environments of the catalytic sites in natural enzymes, nanozymes with confined nanostructures can serve as substitutes for many catalytic processes with comparable activity and robust stability even in harsh conditions. Since the pioneered report about peroxidase-mimicking ferromagnetic nanoparticles in 2007, the nanozymes are specialized for nanomaterials with intrinsic enzyme-mimicking property. With the rapid development in nanoscience and nanotechnology, nanomaterials with superior advantages such as large-scale production, desired activity, and robust stability can bridge the natural enzymes with nanozymes.

Metal-organic frameworks (MOFs) and their derivatives hold a great promise to serve as direct surrogates of conventional enzymes for enzymatic reactions. According to the chemical nature, MOF-based nanozymes can be divided into three main categories: pristine MOFs, enzyme-encapsulated MOF composites, and MOF-based derivatives. Due to the versatility of metallic nodes and bridging linkers together with the feasibility of post-synthetic engineering and modification, MOFs and their derivatives are envisioned as one of the most appropriate surrogates for this purpose. Using MOFs as precursors or sacrificial templates, multiple MOF-based derivatives including carbon-based nanomaterials (e.g., heteroatom-doped carbon or carbon with M-N-C moiety), metal oxide/carbon nanoparticles, and metal/carbon nanomaterials can be rationally synthesized through one-step direct carbonization/oxidation or indirect post-treatments of MOFs (e.g., bridging linker-exchange and metallic node-doping). Compared with the existing nanozymes, MOF-based derivatives open up a new avenue for constructing mesoporous nanozymes. In this way, the intrinsic mesoporous property of MOFs can still be maintained, while the stability and activity can be largely improved. In this Account, we highlight some important research advances in MOF-based derivatives (including M-N-C moiety (M = single metal atom), metal oxide/carbon, metal/carbon, and MOF derivatives obtained through post-synthetic linker exchange and metal doping strategies) with enzyme-mimicking activity. We also portray that, through integrating physicochemical properties of mesoporous nanomaterials and enzymatic activities of natural enzymes, MOF-derived nanozymes can provide multifunctional platforms in biomedical community such as anti-bacteria, biosensor, imaging, cancer therapy, and environmental protection. Finally, we propose future design principles and possible research approaches for deeper understanding of mechanisms, thus pointing out future research directions to offer more opportunities for conventional enzyme-engineering industry.

Key References

Wang, D.; Wu, H.; Lim, W. Q.; Phua, S. Z. F.; Xu, P.; Chen, Q.; Guo, Z.; Zhao, Y. A Mesoporous Nanoenzyme Derived from Metal-Organic Frameworks with Endogenous Oxygen Generation to Alleviate Tumor Hypoxia for Significantly Enhanced Photodynamic Therapy. *Adv. Mater.* **2019**, *31*, 1901893.¹ *A MOF-derived mesoporous metal oxide nanozyme with catalase-mimicking activity and tumor hypoxia-alleviating property for enhanced photodynamic therapy of tumor.*

Wang, D.; Wu, H.; Phua, S. Z. F.; Yang, G.; Lim, W. Q.; Gu, L.; Qian, C.; Wang, H.; Guo, Z.; Chen, H.; Zhao, Y. Self-Assembled Single-Atom Nanozyme for Enhanced Photodynamic Therapy Treatment of Tumor. *Nat. Commun.* **2020**, *11*, 357.² *A MOF-derived self-assembled single-atom nanozyme achieved through a metal node doping strategy to generate oxygen inside tumor tissues for enhanced photodynamic therapy under the guidance of magnetic resonance imaging.*

1. Introduction

Enzymes, composed of vast majority proteins and a few RNA molecules, are highly desirable catalysts that dominate the basic metabolisms and sustain life activities of living systems on earth.³ Due to the high catalytic activities and precise substrate specificity, enzyme thus has been the focus of intense research within industrial, medical, and biological fields.⁴ Especially, the enzymes remain the targeted frontier for therapeutic intervention

within pharmaceutical industry.⁵⁻⁷ Although with great potential, the nominal operational stability, expensive production costs, poor reusability, and diminished performance in organic media are the main limitations of natural enzymes when applying for practical applications.⁸ Since the pioneer report about peroxidase (POD)-mimicking ferromagnetic nanoparticles in 2007, the nanozymes are specialized for nanomaterials with intrinsic enzyme-mimicking properties.⁹ Inspired by viable opportunities, the past two decades have witnessed the rapid progress and great achievements in the field of nanozymes. Metal-organic frameworks (MOFs), as a relatively new type of porous solid materials, have accumulated enormous research interests in catalysis area on account of their well-defined coordination network, mesoporous structure, and tunable porosity.¹⁰ The diversity of metallic nodes, linking struts, and a wide array of coordination interactions in all possible directions make MOFs direct surrogates of natural enzymes, where the well-defined tailorable cavities and channels can offer a hydrophobic coordination environment similar to that of natural enzymes.

According to the chemical nature, MOF-based nanozymes can be divided into three main categories: pristine MOFs, MOF-based composites, and MOF-based derivatives. However, for pristine MOFs and MOF-based composites (e.g., MOF/Fe₃O₄, MOF/Au, and MOF/enzyme composites), the unexpected degradation under physiological conditions and the restrained solubility in certain solutions seriously limit their real-life applications.¹¹ To address this issue, by using MOFs as precursors or sacrificial templates,

Figure 1. Classification of MOF-derived nanozymes (NEs) toward some representative biological applications.

multiple MOF-based derivatives including carbon nanomaterials (typical with M-N-C moiety, M = single metal atom), metal oxide/carbon, and metal/carbon nanomaterials could be rationally synthesized through one-step direct carbonization/oxidation or indirect post-synthesis. Compared with the existing mesoporous materials, MOF-based derivatives open up an avenue for constructing mesoporous nanozymes.¹² In this case, intrinsic mesoporous property of MOFs can still be maintained, while the stability and activity of the resulted nanozymes would be largely improved. Moreover, the mesoporous structure and multiple channels can enable a full contact with substrates and benefit the mass transport and diffusion of products when applied in nanomedicine.

In this Account, we review the current research status and future prospects of MOF-based derivatives with enzymatic activities and their biomedical applications. While there are some reviews discussing pristine MOFs and MOF/enzyme composites for enzyme-mimicking applications in the past four years,^{11,13} those pristine MOFs and MOF-based composites would not be included in this Account. In this Account, instead, we highlight MOF-based derivatives (M-N-C moiety, metal oxide/carbon, metal/carbon, and MOF-based derivatives through linker exchange and metal doping strategies) and their applications in nanomedicine (**Figure 1**). Due to the direct carbonization, oxidation, and post-treatments through metal node doping and organic linker exchange, the obtained derivatives may display a specific enzymatic activity and even multi-enzymatic activities. The detailed perspectives and suggestions are also presented for further development of MOF-based derivatives for enzyme-mimicking applications. While for biomedicine applications, there is still a lot of room to realize the bench-to-bedside translation, since the catalytic mechanisms and systemic biocompatibility of these nanozymes should be deeply comprehended.

2. Nanozyme and nanotechnology

Upon rapid development of nanotechnology, nanomaterials with superior advantages such as large-scale production, comparable catalytic activity, and high stability have shown a great promise in catalysis, medicine, biology, and other fields.¹⁴⁻¹⁶ Integrating the advantages of both nanomaterials and natural enzymes, nanozymes have attracted widespread attention in nanomedicine

in recent years. Due to the fact that the enzyme-based catalytic process is similar to that in chemistry and materials science, researchers can imitate the enzyme activities, while endowing nanomaterials with high stability and recycling ability even under high temperature and pressure with the assistance of nanotechnology.¹⁷ Recent studies are mainly focused on designing and synthesizing nanomaterials with inherent enzymatic activities such as catalase (CAT), oxidase (OD), POD, superoxide dismutase (SOD), glutathione peroxidase (GPx), glucose oxidase (GOx), and haloperoxidase (HPO).¹⁸ Benefiting from the advantages of materials synthesis, various nanomaterials with controlled morphology, size, and structure together with the post surface modification of biocompatible coating endow them with enzymatic activities and potential applications in environmental protection and biomedical fields such as anti-bacteria, biosensor, and cancer therapeutics.¹⁹

The rapid advancements in nanotechnology have raised a number of methods toward fabricating novel nanozymes. Moreover, with the development of computer science, possible enzyme-mimicking mechanism can be revealed through theoretical calculations. Especially for metalloenzymes, the well-defined structure makes it easy to comprehend the active catalytic centers. However, for enzyme-mimicking nanoparticles, the description of active sites may become more controversial. A typical example is noble metal nanoparticles. The active atoms may locate at the apices, edges, corners, and steps, where each of the positions may have different catalytic properties. As we know, catalytic activity and substrate selectivity are the two cornerstones of natural enzyme. Although some reported nanozymes exhibited comparable catalytic activities as natural ones, the intrinsic catalytic activities of most nanozymes are largely compromised due to issues such as low-exposed active sites, intrinsically deficient multilevel structure, and aggregation. For instance, for many metal oxide nanoparticle-based nanozymes such as Fe_3O_4 , CeO_2 , and V_2O_5 , only the superficial atoms contribute to the enzyme-mimicking activities, while a large popularity of inner atoms is either inert or may trigger undesired side reactions. Due to the versatility of metallic nodes and bridging linkers together with the feasibility of post-synthetic engineering and modification, MOFs and their derivatives are envisioned as one of the most appropriate surrogates for this purpose.

3. MOF-derived M-N-C nanozymes

Since the pioneer work of MOF-derived mesoporous carbon nanostructure through thermal transformation of MOF precursors reported in 2008, various MOF derivatives have been produced using MOFs as the starting materials.²⁰ Due to the diversity of MOFs, the carbonization under different gaseous environment such as nitrogen, argon, and hydrogen through a precise control over the temperature has been a promising strategy to obtain carbon-based materials with various metal formulations such as alloy/carbon, pure carbon, and carbon doped with heterogeneous atoms. Usually, pure carbon with sp^2 -bonded carbon has no catalytic activity due to its integrated structure without the polarization.²¹ However, some carbon materials with intrinsic defects or edge oxidation could change the localized electronic structure of carbon, endowing the doped carbon with abundant active sites for catalytic reactions. Thus, a great progress has been achieved in carbon-based nanozymes such as fullerene, carbon dots, carbon nanotubes, graphene oxide, and carbon nitride.²² For example, Gao *et al.* reported N-doped carbon nanospheres (N-PCNs) derived from one-step pyrolysis of a F127 soft template containing melamine and formalin/phenol as N and C sources.²³ The as-prepared N-PCNs possess four enzyme-mimicking (OD,

Figure 2. (a) Schematic illustration for the synthesis of PMCS from ZIF-8 through one-step carbonization. (b,c) HAADF-STEM images of the PMCS nanozyme in sub-angstrom resolution, Zn single atoms are marked with red circles. (d) EXAFS spectra of Zn K-edge for PMCS nanozyme and other control samples. (e) ESR spectra for the generated •OH. (f) DFT calculation on the proposed reaction mechanism of PMCS. Zn, N, C, O, and H atoms are represented with pale blue, blue, gray, red, and white balls, respectively. (g) Photographs of *P. aeruginosa*-infected wound treated with (I) NaAc buffer, (II) NaAc buffer plus H₂O₂, (III) PMCS, and (IV) PMCS plus H₂O₂ during the treatment. Modified and adapted with permission from ref 28. Copyright 2019 Wiley-VCH.

POD, CAT, and SOD) activities with intracellular reactive oxygen species (ROS) generation for cancer therapy.

In nature, many enzymes exhibit catalytic activity through central coordinated metal sites as the cofactors. In cytochrome P450, a most-studied natural POD for its monooxygenation enzymatic activity, Fe(III) metal ion occupies the central position of porphyrin core and coordinates to four N terminals of porphyrin and another N of a cysteine residue.²⁴ By mimicking those metalloenzymes, a great catalytic activity can be achieved. MOFs may be another choice for constructing heterogeneous atom doped carbon materials, especially, single-atom nanomaterials with a universal M-N-C moiety. Compared with metal nanoparticles, unsaturated coordination environment and unique electronic structure of the M-N-C moieties enable them to be ideal catalysts for a variety of reactions. For instance, Chen and co-workers reported a series of metal (Mg, Ca, and Al) cofactor-centered nitrogen-doped graphene through direct carbonization of MOFs. Density function theory (DFT) calculations revealed that two nitrogen coordinated Mg cofactor showed an upward shift for p-band center and behaved extremely high oxygen reduction activity with a half-wave potential of 910 mV in alkaline media.²⁵

Recently, single-atom catalysts represent as the frontier research of catalysis field.^{26,27} The isolated dispersion of active catalytic sites endows the maximum atom utilization of metal atoms. Moreover, the well-defined coordination environment and electronic structure make understanding the catalytic mechanisms

easier. Using zeolitic imidazolate framework-8 (ZIF-8) MOF as a precursor, Liu *et al.* reported the Zn-N₄ single-atom nanozymes through one-step carbonization under N₂ atmosphere at 800 °C (Figure 2a).²⁸ As the annealing temperature is lower than the boiling point of Zn metal (908 °C), Zn species is preserved. The as-prepared MOF derivative with a Zn-centered porphyrin-like structure (named as PMCS) not only serves as a photosensitizer, but also exhibits POD-mimicking activity. The resultant PMCS nanozyme still maintained original morphology. Atomically dispersed single-atom Zn sites could be visualized through high-angle annular dark-field scanning transmission electron microscopy (HAADF-STEM) with bright isolated dots (Figure 2b,c). Extended X-ray absorption fine structure (EXAFS) characterization revealed the four-nitrogen coordinated single Zn atom microstructure (Figure 2d). Electron spin resonance (ESR) spectra certified the generation of •OH of PMCS in the presence of H₂O₂ (Figure 2e). Those isolated zinc atoms can serve as POD-mimicking catalytic active sites. DFT calculations were also performed to study the enzyme-mimicking mechanism (Figure 2f). In comparison with the heterolysis of H₂O₂* to O* having an energy barrier at -0.41 eV, the homolysis of H₂O₂* to 2OH* is much lower (-0.70 eV). The demonstrated Zn-N₄ single-atom active sites can effectively catalyze H₂O₂ decomposition for the generation of •OH free radicals. Furthermore, *in vivo* bactericidal efficiency was determined with a wound model infected using *P. aeruginosa* on mice. Mice treated with PMCS nanozyme at a low

Figure 3. (a) Synthesis procedure of MCOPP nanozyme and post-loading of Ce6 photosensitizer. (b) Schematic illustration of mesoporous MCOPP nanozyme for enhanced PDT of cancer. (c) ESR spectra of $^1\text{O}_2$ trapped by TEMP after different treatments under near infrared irradiation. (d) T_2 -weighted magnetic resonance imaging of murine breast tumor-bearing mouse after administration of MCOPP nanozyme. Tumor is marked with white dashed line. Modified and adapted with permission from ref 1. Copyright 2019 Wiley-VCH.

H_2O_2 concentration (100 μM) showed promoted wound healing efficiency within treated 6 days without showing obvious systematic biotoxicity (Figure 2g). Li *et al.* also reported single-atom Fe- N_4 nanozyme anchored within N-doped porous carbon (Fe-SAs/NC) through one-step carbonation of ZIF-8 MOF with encapsulated iron phthalocyanine under nitrogen atmosphere at 900 $^\circ\text{C}$.²⁹ The Fe-SAs/NC catalyst with bifunctional Fe- N_4 active moieties showed excellent CAT-mimicking and SOD-mimicking activities for eliminating intracellular H_2O_2 and O_2 to protect cells against oxidative stress. Moreover, Shi *et al.* reported an Fe-based single-atom nanocatalyst through high temperature carbonization of MOFs followed by PEGylation.³⁰ The single-atom Fe nanocatalyst showed excellent Fenton reaction activity toward H_2O_2 -overexpressed tumor for $\cdot\text{OH}$ generation, presenting efficient tumor elimination ability.

4. MOF-derived metal oxide and metal oxide/carbon nanozymes

Distinct from nanozymes with a certain M-N-C moiety, metal oxide nanoparticles have more widespread applications for their variable oxidation state of metal, low cost synthesis, and high ambient stability. In 2007, Yan *et al.* reported enzyme-mimicking activity of Fe_3O_4 nanoparticles with three different sizes that catalyze 3,3',5,5'-tetramethylbenzidine (TMB) to oxidized TMB (oxTMB) in the presence of H_2O_2 .⁹ Since then, various of metal oxide nanozymes have been synthesized. In a study reported by Tremel and co-workers in 2012,³¹ they found that vanadium pentoxide nanowires exhibited functionality akin to naturally occurring vanadium HPO. During the catalytic process, the generated singlet oxygen species would induce oxidative damage

on marine microorganisms, thus protecting the marine tools against biofouling in the ocean. The enzymatic activities are still limited due to the inefficiently exposed active sites, which are restricted to the surface atoms of nanoparticles. Limited structural features, random distribution of active sites and aggregation often hinder the practical use of conventional metal oxides. To solve these problems, one possible strategy is to increase the surface area. For example, Mugesh *et al.* reported that Mn_3O_4 nanoparticles with flower-like morphology can potentially exhibit the activities of three antioxidant enzymes namely SOD, CAT, and GPx.³² Furthermore, mechanistic studies demonstrated that the remarkable enzyme-mimicking activity is originated from not only the mixed oxidation states of Mn ($\text{Mn}^{3+}/\text{Mn}^{2+}$), but also the high surface area and large pore size. Very recently, Ling and co-workers reported MoO_{3-x} nanourchins with a high surface area, which also performed high therapeutic activity *via* multi-enzyme cascade reactions.³³

Photodynamic therapy (PDT) that utilizes photosensitizers and oxygen to generate cytotoxic singlet oxygen ($^1\text{O}_2$) under the irradiation of near-infrared light has a long history in pre-clinical research and clinical disease treatments.³⁴⁻³⁷ MOFs with periodic metal nodes are good candidates for constructing mesoporous MOF-based derivatives. Through rational composite design of MOF precursors followed by different annealing conditions (such as temperature, time, and atmospheres), various materials were prepared, including metal oxide/carbon, metal/carbon, carbides, chalcogenides, phosphides, and nitrides.³⁸ For example, through direct low-temperature annealing, fluorescent carbon dots could be produced with MOFs as source materials, showing excellent fluorescent property for bioimaging and biosensing.³⁹ Due to the

Figure 4. (a) Synthesis procedure of n-CeO₂ NSs with enhanced OD-like activity. (b) Scheme of n-CeO₂ NSs used as a multifunctional platform for synergistic cancer therapy. Modified and adapted with permission from ref 40. Copyright 2018 American Chemical Society.

intrinsic large surface area and regular pore size distribution of MOF precursors, during the one-step oxidation/carbonization process, the intrinsic properties can be preserved to the greatest extent, thus endowing the generated materials with high surface area and numerous active catalytic sites. Recently, we reported a mesoporous nanozyme derived from MOFs, which shows intrinsic CAT-mimicking catalytic activity toward intracellular H₂O₂ for endogenous O₂ generation.¹ As shown in **Figure 3a**, one step annealing of silica-coated Mn₃[Co(CN)₆]₂ MOFs in air resulted in monodisperse MnCoO nanoparticles. Loading of Ce6 and further surface modification led to the formation of final nanozyme (MCOPP-Ce6). On account of the intrinsic mesoporous feature of MOFs, three-dimensional mesoporous nanostructure

was well maintained during the one-step annealing process, presenting an enhanced photodynamic therapeutic efficacy (**Figure 3b**). The nanozyme showed excellent CAT-mimicking activity in the presence of H₂O₂ and a robust O₂ generation. The sustainable supply of O₂ is beneficial to the enhanced ¹O₂ generation from MCOPP-Ce6 under laser irradiation as shown by an enhanced signal in the ESR spectra (**Figure 3c**). Possessing a relatively high *r*₂ relaxivity of 56.4 mM⁻¹ s⁻¹, the MCOPP-Ce6 nanozyme showed time-dependent intratumor accumulation as evidenced by magnetic resonance imaging (**Figure 3d**).

Beyond annealing temperature, the annealing methods/steps and conditions also have an important influence on the composition of MOF derivatives. For this regard, numerous MOF-derived metal oxide/carbon composites with desired structures and functionalities were fabricated through direct pyrolysis under an inert atmosphere or an inert-to-oxygen two-step annealing strategy.³⁸ For instance, Qu and co-workers reported that well-ordered crystalline cerium-based MOFs were thermally transformed into small-size CeO₂ nanoparticles encapsulated in porous carbonaceous frameworks (named as n-CeO₂ NSs) through one-pot facile calcination under N₂ atmosphere (**Figure 4a**).⁴⁰ Attributed to the excellent OD-mimicking induced oxidative damage and adenosine triphosphate deprivation induced energy depletion, synergistic cancer therapy efficiency was achieved with negligible side effects both *in vitro* and *in vivo* (**Figure 4b**). Moreover, the introduction of secondary metal species into the single-component metallic counterpart can also be an effective method to tune the catalytic property of heterogeneous catalysts. Through rational incorporation, the host-guest electronic properties can be changed to generate new geometrically catalytic active sites for achieving higher synergetic catalytic activity. For example, Huang and co-workers reported a universal strategy to fabricate a series of Co-based bimetallic hollow nanocages (C-CoM-HNC, M represents Ni, Mn, Cu, and Zn) through ion-assisted solvothermal reaction followed by low-temperature pyrolysis under Ar atmosphere with MOFs as precursors (**Figure 5**).⁴¹ DFT calculations revealed that the introduction of Cu can tailor the surface adsorption energy and *d*-band density of state of C-CoCu-HNC nanostructure. Their results showed that the obtained C-CoCu-HNC could act as an OD-mimicking nanozyme and a peroxydisulfate activator for highly efficient organic

Figure 5. Schematic illustration for a general synthesis approach of C-CoM-HNC through ion-assisted solvothermal reaction and subsequent low-temperature calcination. Modified and adapted with permission from ref 41. Copyright 2020 American Chemical Society.

Figure 6. (a) Synthesis of Co,N-HPC nanozyme through one-step pyrolysis of ZIF-67 for GSH detection. (b) TEM image of the Co,N-HPC nanozyme. Inset is the enlarged image with isolated Co nanoparticles in yellow circles (scale bar is 20 nm). (c) Photographs of three catalytic systems with different organic substrates. (d) UV-vis spectra of Co,N-HPC at various GSH concentrations. (e) Selectivity of Co,N-HPC toward GSH over other interferences. Modified and adapted with permission from ref 46. Copyright 2018 Elsevier.

pollutant elimination. Moreover, MOF-derived metal oxide and metal oxide/carbon nanozymes for anti-bacteria are also discussed (see the Supporting Information for details).

5. MOF-derived metal nanoparticle/carbon nanozymes

On account of facile synthesis procedure and post surface modification, metal nanoparticles have been widely studied in many fields such as catalysis, sensors, detection, imaging and so on. Many metal nanoparticles also exhibit intrinsic enzyme-mimicking catalytic activities. In 2004, Rossi and co-workers reported the GOx-mimicking catalytic activity of unmodified gold nanoparticles and studied the catalytic mechanism.⁴² They proposed the Eley-Rideal mechanism that glucose first adsorbed onto the surface of gold nanoparticles and then the oxygen around would approach and subsequently react with glucose to generate glucose acid and hydrogen peroxide. In addition, the surface modification has influences on the catalytic abilities and activities of nanozymes. For instance, Lin and co-workers reported that unmodified gold nanoparticles showed higher catalytic activity than both citrate-capped and amino-modified ones toward oxidation of TMB and 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS).⁴³ In another case, citrate-modified Au nanoparticles presented GOx-mimicking activity, while cysteine-modified Au nanoparticles exhibited POD-mimicking activity.⁴⁴ However, unpredictable heterogeneous distribution and undesired aggregation seriously compromise their catalytic activity and stability for practical enzyme-mimicking applications. The advancement of nanotechnology opens new opportunities for constructing supported hybrid catalysts via embedding metal nanoparticles into mesoporous matrix for high catalytic activity and long-term stability.

When metal species in the above-mentioned M-N-C nanozymes grow up from single-atom scale to nanoparticle scale, another category of MOF-based derivative is generated, which is the metal/carbon or metallic composite/carbon hybrid. Due to the natural advantage of plentiful metal nodes, MOFs can be easily transformed to metallic nanoparticles embedded into carbon matrix, offering promising candidates for catalytic reactions.⁴⁵ During the calcination process, the organic linkers of MOFs are

converted into porous carbon, generating metallic nanocomposites. The resulting mesoporous carbon not only acts as supporting matrix for anchoring metal nanoparticles, but also prevents the aggregation of isolated metal nanoparticles, thus increasing the surface area and enhancing the catalytic or enzymatic activities. For instance, Wang *et al.* reported copper nanoparticles encapsulated into mesoporous carbon via a one-pot thermolysis method of Cu-based MOFs. The resultant Cu/C composites not only possess the advantage for easy preparation, but also showed high affinity to H_2O_2 , presenting an enhanced POD-mimicking activity as compared with commercial horseradish peroxidase (HRP). This high activity was arisen from the isolated Cu nanoparticles encapsulated in mesoporous carbon matrix.

Recently, Huang and co-workers synthesized Co,N co-doped mesoporous carbon hybrids with superior OD-mimicking activities for glutathione (GSH) detection (Figure 6a).⁴⁶ The Co,N co-doped carbon nanomaterials (Co,N-HPC) were synthesized through one-pot pyrolysis of ZIF-67 under nitrogen atmosphere. Benefiting from the self-template synthesis and a N-rich organic linker, the resultant product consists of isolated Co nanoparticles embedded into N-rich hierarchically porous carbon (Figure 6b). Co,N-HPC showed OD-mimicking activity toward TMB, *o*-phenylenediamine (OPD), and ABTS without the existence of H_2O_2 , especially with the fastest oxidation kinetics for TMB (Figure 6c). The addition of GSH can quench the color of the system, making the nanozyme a potential sensor to detect GSH through colorimetric assay. The nanozyme exhibited a linear decrease of the absorption peak with a detection range from 0.05 μ M to 30 μ M (Figure 6d). Moreover, the remarkable selectivity of this nanozyme toward thiol-containing molecules enabled its application for GSH detection in biological systems (Figure 6e). Through a precise control over the temperature and time of pyrolysis, Yoon and co-workers reported Cu@C-500 nanozyme with Cu nanoparticles embedded into porous carbon using Cu-based MOF (HKUST-1) as the precursor.⁴⁷ When combined with natural GOx, the generated Cu@C-500 showed high POD-mimicking catalytic activity for glucose biosensing.

Figure 7. (a) Schematic illustration for the synthesis of PZIF67-AT nanozyme for *in vivo* chemodynamic therapy. (b,c) TEM images of pristine ZIF-67 MOF and PZIF67-AT nanozyme. (d) Dark-field STEM image of PZIF67-AT nanozyme and element mappings of Co, C, N, and O signals. (e) Average weight of the tumor dissection after treatment. Asterisks indicate significant differences (*** $p < 0.001$). (f) Tumor volume changes of different groups during the treatment. Modified and adapted with permission from ref 51. Copyright 2020 American Chemical Society.

6. MOF-based linker exchange strategy

Compare to nanozymes derived from pyrolysis strategy from pristine MOFs, many MOFs possess intrinsic enzyme-mimicking activities themselves because of their Lewis acid and base active sites. The extremely ordered tailorable pores and channels can easily provide the central active metal nodes a hydrophobic confined environment that is similar to natural enzymes. There are numerous choices for metal nodes and organic linkers in constructing MOFs. Until now, various MOFs with intrinsic POD-mimicking catalytic activity have been fabricated, including Fe-based MIL-MOFs (MIL = Material Institute of Lavoisier), Zr-based UiO-MOFs (UiO = University of Oslo), Cu-based HKUST-MOFs (HKUST = Hong Kong University of Science and Technology), Ni-based MOFs, and Prussian blue-based MOFs.¹¹

In addition to pristine MOFs, post-synthetic modification (PSM) offers numerous opportunities for tailoring the catalytic properties of MOFs, since their fundamental structural characteristics and design principles provide a significant control over the framework architecture and pore chemistry.⁴⁸ Some of the popular MOFs such as UiO-66 have been successfully subjected to post-synthetic linker exchange strategy, generating various of MOF-based derivatives with desired catalytic activities. An interesting example is that Zr-based UiO-66 exhibits a limited catalytic activity toward the hydrolysis of dimethyl 4-nitrophenyl phosphate.⁴⁹ UiO-66-NH₂ showed an overall 20-fold enhancement for phosphate-ester hydrolysis compared to parent UiO-66 MOF after the exchange of the organic linker with amino groups that mimic the function of aspartate and histidine residues.

Another especially robust category of MOFs is the ZIF family. Karagiari *et al.* successfully achieved linker exchange in the robust ZIF-8 system, leading to a replacement of its parent 2-methylimidazolate (2-mim) linker with unsubstituted imidazolate (85% exchange) in *n*BuOH.⁵⁰ The resultant ZIF-8 based derivative possesses a truly zeolitic topology and exhibits Brønsted base catalytic activity that cannot be achieved by the parent ZIF-8 MOF. Very recently, Qu and co-workers adopted a post-synthetic

linker exchange method to fabricate amorphous MOF derivative with SOD-mimicking activity (Figure 7a).⁵¹ The authors firstly synthesized ZIF-67 MOF through the coordination between cobalt ion and 2-mim organic linker (Figure 7b). After which, a small-molecule inhibitor 3-amino-1,2,4-triazole (3-AT) was loaded through the coordination with Co²⁺ by taking the place of the 2-mim position, resulting in amorphous nanoparticles (Figure 7c). The homogeneous distribution of Co, C, N, and O elements through element mapping suggested the successful synthesis of PZIF67-AT nanoparticles (Figure 7d). The generated PZIF67-AT nanoparticles exhibited SOD-mimicking catalytic activity that could efficiently convert intracellular $O_2^{\bullet -}$ to H_2O_2 , promoting the generation of H_2O_2 . In this way, PZIF67-AT could disturb the metabolism of intracellular H_2O_2 and result in the accumulation of H_2O_2 . The over-generated H_2O_2 was subsequently decomposed into $\cdot OH$ free radicals to facilitate the Fenton reaction-based chemodynamic therapy. Murine hepatoma tumor-bearing mice treated with PZIF67-AT nanozyme showed significant suppression of the tumor growth as compared to other control groups (Figure 7e,f).

7. MOF-based metal doping strategy

In addition to the post-synthetic linkers exchange, the engineering of metal nodes can also be used for constructing MOF derivatives with enzyme-mimicking activities.⁵² As most natural protein enzymes consist of metal cofactors as the catalytic active centers, a rational design of organic linkers and metal nodes can endow the pristine MOFs with enzyme-mimicking catalytic activities. Among the various strategies, PSM through metal node engineering offers numerous possibilities for a targeted approach to regulate the properties of MOF-based derivatives.⁵³ As a subset of the popular PSM methods for constructing functionalized MOF derivatives, two main metal node engineering strategies have been widely adopted, *i.e.*, either through the addition to coordinating groups or through counter-ion exchange in charged frameworks. The introduction of catalytic active sites via coordination can also generate high performance MOF-based nanozymes. For instance,

Figure 8. (a) Schematic illustration for the synthesis of OxgeMCC-r SAE consisting of active single-atom Ru site anchored in Mn₃[Co(CN)₆]₂-Ce6. (b) Enzymatic active center of OxgeMCC-r and its magnetic resonance imaging ability. (c) CAT-mimicking activity of OxgeMCC-r SAE for enhanced PDT of cancer. Modified and adapted with permission from ref 2. Copyright 2020 Nature Publishing Group.

Willner and co-workers reported UiO-based MOF nanoparticles composed of (1) Zr⁴⁺ bridged by 2,2'-bipyridine-5,5'-dicarboxylic acid ligand and (2) post-modified Cu²⁺ species as catalytic centers through coordination between bipyridine unit and Cu²⁺.⁵⁴ The resulting nanoparticles exhibited enhanced catalytic activity toward dopamine oxidation as compared with Cu²⁺ alone or mixture of Cu²⁺ and bipyridine. In a study reported by Hwang and co-workers, they demonstrated that the binding of aliphatic diamines to unsaturated Fe metal nodes in MIL-100(Fe) can significantly enhance the POD-mimicking catalytic activity of the functionalized MOFs, since the surface with enhanced negative potential could show higher affinity to charge-positive TMB.⁵⁵ In addition to transition metal nodes, noble ones can also be used to construct metal-organic structures with catalytic or enzyme-mimicking abilities.⁵⁶ For instance, Wang *et al.* successfully synthesized a series of coordinated single-atom (Co, Cu, and Au) metal sites with zirconium porphyrinic hollow MOF nanotubes as

the supporting matrix.⁵⁷ During the synthesis process, porphyrin molecule not only serves as the bridging linker, but also provides central coordination environment for anchoring and regulating the electronic properties of single metal atoms.

Another interesting approach is the post-synthetic exchange of metal nodes with catalytic active ones. Very recently, we proposed a new strategy to fabricate active single-atom catalytic centers through a one-pot doping and reducing strategy during the self-assembly process.² On account of the high affinity of Ru to ligands, Ru ion takes partially the position of Co ion (**Figure 8a**). After reducing by NaBH₄, the as-prepared self-assembled PDT nanoagent, OxgeMCC-r single-atom enzyme (SAE), consisting of single-atom ruthenium as active catalytic site doped into the skeleton of Mn₃[Co(CN)₆]₂ MOF encapsulated with a photosensitizer. The content of the single-atom Ru was calculated to be 2.23 wt%. These isolated Ru single atoms could serve as active catalytic sites for oxygen generation in the presence of

H₂O₂, making OxgeMCC-r a high-performance CAT-mimicking nanozyme. The OxgeMCC-r nanozyme can significantly ameliorate the hypoxic condition and down-regulate the expression of hypoxia-inducible factor 1 α (HIF-1 α) within hypoxic tumor cells, as confirmed by immuno-fluorescence imaging and subsequent Western blot analysis at a low nanozyme concentration. Due to the existence of high-spin Mn-N₆ ($S = 5/2$) species in the skeleton, the OxgeMCC-r nanozyme also exhibited excellent T₁-weighted magnetic resonance imaging ability for real-time *in vivo* tracking of the nanozyme and monitoring of the therapeutic efficacy (Figure 8b). The r_1 relaxivity of the OxgeMCC-r nanozyme was calculated to be 5.44 mM⁻¹ s⁻¹, which was higher than the clinically used Gd-based contrast agent (Magnevist, $r_1 = 4.56$ mM⁻¹ s⁻¹). The remarkable CAT-mimicking activity to relieve the tumor hypoxia makes the OxgeMCC-r nanozyme a promising anticancer nanoagent for enhanced PDT of tumor under the guide of magnetic resonance imaging modality (Figure 8c).

8. Conclusion and outlook

In this Account, we have highlighted the recent research progress in the field of MOF-derived nanozymes and their applications in anti-bacteria, bio-sensing, ROS scavenger, bio-imaging, cancer therapy, and pollutants treatment. Compared with natural enzymes, nanozymes show advantages that are often unattainable through natural ones such as low-cost synthesis, high stability, good reusability, and comparable performance even under critical conditions. However, there are still some issues on the chemical and physiological stability of pristine MOFs with enzyme-mimicking activities under catalytic reaction conditions. Thus, rational transformation of pristine MOFs to MOF-based derivatives should be a feasible strategy for maintaining catalytic ability and enhancing catalytic activity at the same time.

Thus, through a rational design of the organic linkers and metal nodes, various 3d transition metal (*e.g.*, Fe, Co, Cu, and Mn) based MOF derivatives have been synthesized with desirable catalytic activities. Further expanding the metal species from 3d to 4d, 5d transition, and even rare earth elements may open new chapters for synthesizing other MOF-based nanozymes that mimic the coordination environments of metallic cofactors in some natural enzymes. In addition, the generated carbon matrix during annealing process could be used for tailoring the coordination number and environment within active catalytic centers through doping with other light elements such as N, O, P, and S for better imitation of the architecture and catalytic performance of natural enzymes. Currently, for MOF-derived heteroatom-doped nanozymes (*i.e.*, single-atom or single-site nanozymes), the synthesis strategy is mainly limited to the ZIF series as the starting materials. Thus, other MOFs and doping strategies should be discovered to precisely control the content, microstructure, and distribution of the heteroatoms.

Upon the rapid development within the past decade, nanozymes have been widely studied and shown many practical applications. Due to the complicated structures of nanomaterials, however, only the surface of nanomaterials contributes to the performance of the whole nanozymes in some cases. The mechanisms of the catalytic reactions still need to be deeply understood, especially for the relationship between catalytic performance and microstructure from whole materials to atoms and then to the electron structure. Although synchrotron radiation X-ray absorption spectroscopy is powerful, it just gives the information (*e.g.*, coordination numbers) of catalysts under unreacted conditions even with 20% error interval. Other advanced *in situ* characterization technologies such as *in situ* scanning tunneling microscope and femtosecond-laser

spectroscopy may be used for temporal and spatial observation of interactions between the catalytically active sites and substrates during the reaction processes. Moreover, DFT simulations can be rationally integrated to experimental measurements to give a fully comprehensive understanding of the mechanisms at the microscale, thus well guiding the design and synthesis of high-performance enzyme-mimicking nanomaterials.

Although some nanozymes for detection have been realized for practical applications, the applications of nanozymes for other domains such as public health (*e.g.*, anti-bacteria, anti-virus, and cancer therapy) and environmental protection (*e.g.*, water treatments and pollutant elimination) are still rare and in the experimental stage. Moreover, it still remains a formidable challenge to synthesize nanozymes with comparable catalytic activities as natural ones. Last but not least, for biological applications, the biocompatibility of nanozymes is a main issue to be well addressed before pre-clinical translation. Hopefully, natural enzymes will be replaced by nanozymes with higher activity, better biocompatibility, and bench-to-bedside translation capacity, thus offering breakthrough opportunities to conventional enzyme-engineering industry.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on ACS Publication website.

Additional discussions about MOF-derived metal oxide and metal oxide/carbon nanozymes for biosensing and anti-bacteria (PDF).

AUTHOR INFORMATION

Corresponding Author

Yanli Zhao - Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, 21 Nanyang Link, Singapore 637371 Singapore;

School of Materials Science and Engineering, Nanyang Technological University, 50 Nanyang Avenue, Singapore 639798, Singapore;

orcid.org/0000-0002-9231-8360; Email: zhaoyanli@ntu.edu.sg

Authors

Dongdong Wang - Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, 21 Nanyang Link, Singapore 637371 Singapore; orcid.org/0000-0002-6278-0706

Deblin Jana - Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, 21 Nanyang Link, Singapore 637371 Singapore

Notes

The authors declare no competing financial interests.

Biographies

Dongdong Wang received his BSc degree from Lanzhou University in 2013 and then obtained his PhD degree under the supervision of Prof. Qianwang Chen at University of Science and Technology of China in 2018. He is currently a research fellow in Prof. Yanli Zhao's group at Nanyang Technological University, Singapore. He mainly works on functional nanomaterials for nanomedicine.

Deblin Jana is a graduate student in Prof. Yanli Zhao's group at Nanyang Technological University, Singapore. He studies functional inorganic nanomaterials for nanomedicine.

Yanli Zhao is currently a Full Professor at Nanyang Technological University, Singapore. He received his BSc degree in 2000 and PhD degree in 2004 under the supervision of Prof. Yu Liu at Nankai University. He was a postdoctoral scholar with Prof. Sir Fraser Stoddart (University of California Los Angeles and subsequently Northwestern University) and Prof. Jeffrey Zink (University of California Los Angeles). His current research focuses on self-assembled nanomaterials for disease diagnostics and therapeutics, as well as porous nanomaterials for energy storage and catalysis.

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