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Design of high performance nanozymes: a single-atom strategy

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Nanozymes, nanomaterials with enzyme-like characteristics, are emerging as novel artificial enzymes (Gao et al., 2007; Manea et al., 2004; Yan, 2018). They are superior to natural enzymes in many ways, such as higher stability, lower cost in preparation, and better robustness toward harsh environments (Wei and Wang, 2013). Various nanomaterials (e.g., metal, metal oxide, carbon, and metal organic framework) have been developed to mimic natural enzymes (e.g., oxidase, peroxidase, catalase, superoxide dismutase, hydrolase, etc.). Despite the fact that great advances have been made in the last decade, the activity and selectivity of reported nanozymes are far from perfection when compared with their natural counterparts. Moreover, the development of nanozymes mainly relies on trial-and-error strategies and limited efforts have been made to provide molecular insights for understanding the mechanisms. This in turn significantly hampers the search for highly active and selective nanozymes. To meet the challenges, rational design of high performance nanozymes is a major step forward in this vital and emerging field (Wang et al., 2019; Wu et al., 2019).

Recently, single-atom catalysts (SACs) with isolated metal atoms dispersed on solid support have emerged as a new frontier in the field of catalysis because of their well-defined electronic and geometric structure, maximum atom efficiency as well as high activity and selectivity (Chen et al., 2018; Li et al., 2018; Peng et al., 2018; Wang et al., 2018a;

Wang et al., 2018b). SACs are heterogeneous catalysts with homogeneously dispersed active sites, bridging the homogeneous catalysis and heterogeneous catalysis. SACs offer opportunities to identify catalytic active sites, to reveal structure-activity relationship, and to control the electronic and geometric properties of active sites. Therefore, SACs have been intensively explored in electrocatalysis, photocatalysis, and organic conversions.

Interestingly, carbon-based SACs (M-N-C, M=Fe, Co, Mn, Zn, etc.) possess similar M-N_x sites within natural metalloenzymes, especially with respect to electronic, geometric, and chemical structures. It has been proposed that SACs can be used as bioinspired single-atom nanozymes (SAzymes) to mimic natural enzymes (Figure 1) (Wu et al., 2019). Very recently, three pieces of pioneering work have adopted carbon-based SACs as biocatalytic nanozymes and opened up a new avenue to design high performance nanozymes using the single-atom strategy (Ma et al., 2019; Xu et al., 2019; Zhao et al., 2019).

Mao's research team reported the first example of SAzymes with atomically dispersed Fe-N₄ catalytic sites anchored on nitrogen-doped porous carbon materials (Fe-SAs/NC) (Ma et al., 2019). Fe-SAs/NC SAzyme was prepared by high-temperature pyrolysis of iron phthalocyanine (FePc) loaded zeolitic imidazolate framework (ZIF-8). The isolated Fe atoms were revealed by aberration-corrected high-angle annular dark-field scanning transmission electron microscopy (HAADF-STEM). The Fe-N₄ catalytic sites were

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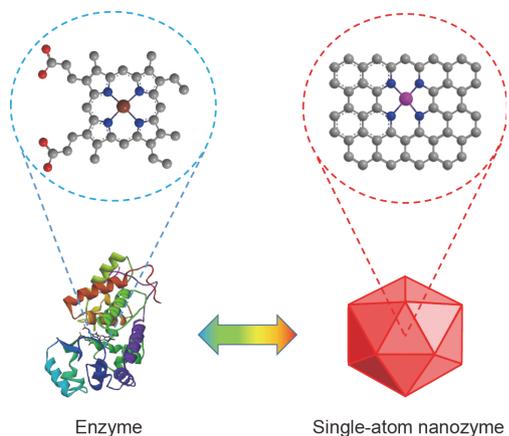


Figure 1 Single-atom nanozymes can be designed to mimic natural enzymes.

further confirmed by X-ray absorption spectroscopy (XAS). The developed Fe-SAs/NC SAzyme exhibited both superoxide dismutase (SOD)-like and catalase-like activities, which catalyzed the decomposition of $\cdot\text{O}_2^-$ into H_2O_2 and O_2 as well as H_2O_2 into H_2O and O_2 . The SOD-like activity of Fe-SAs/NC SAzyme was greatly improved after the incorporation of single atoms of Fe. The catalase-like Fe-SAs/NC SAzyme showed a high turnover frequency (TOF) of 1809.34 min^{-1} per active site. Inspired by its excellent ROS scavenging ability, antioxidant Fe-SAs/NC SAzyme was further explored to scavenge intracellular ROS and to protect live cells from oxidative stress. After cellular uptake into cytosol, Fe-SAs/NC SAzyme efficiently scavenged β -lactopachone induced ROS, relieved oxidative stress, and increased cell viability.

In a more comprehensive study, Wu's group reported another carbon-based single Fe atom catalyst as a SAzyme (Zhao et al., 2019). The new Fe SAzyme was obtained by a high-temperature gas-migration strategy. Aberration-corrected HAADF-STEM and XAS revealed the heme-like Fe-N_4 active site, which was similar to that in heme-containing natural enzymes. Therefore, the Fe SAzyme exhibited multiple enzyme-like activities, including oxidase, peroxidase, and catalase. It was noteworthy that the peroxidase-like activity of Fe SAzyme was greater than the representative Fe_3O_4 nanozyme by a factor of 40. To unravel the origin of the superior peroxidase-like activity and to understand the mechanism behind, *Operando* X-ray absorption fine structure (XAFS) spectroscopy and density functional theory (DFT) calculations were carried out. The single-atom Fe active sites facilitated the activation of H_2O_2 substrate to generate Fe=O/O=Fe=O intermediate by the strong interaction of orbitals of Fe and O. The reaction energy profile with an overall change of -2.80 eV and a rate-determining step energy of 0.67 eV indicated the thermodynamically favorable reaction catalyzed by Fe SAzyme. This study clearly demonstrated the powerful single-atom strategy in designing

high performance nanozymes.

Besides Fe-based SAzymes, Zn-based SAzyme was also explored as high performance nanozyme using the single-atom strategy. Liu, Yan, Fan, and co-workers reported a ZIF-8 derived SAzyme with atomically dispersed Zn active sites on carbon as a highly efficient peroxidase mimic (Xu et al., 2019). The isolated Zn atoms with Zn-N_4 local structure were confirmed by aberration-corrected HAADF-STEM and XAS. Due to the unique electronic and geometric structure of Zn-N_4 active sites and the high loading of Zn (3.12 wt%), the developed Zn SAzyme exhibited superior peroxidase-like activity through the generation of $\cdot\text{OH}$ intermediate. The structure-activity relationship was systematically investigated by DFT calculations. The coordinatively unsaturated Zn centers favored the absorption of H_2O_2 substrate with an adsorption energy of -0.45 eV and the homolytic cleavage to generate $\cdot\text{OH}$ intermediate with a reaction energy of -0.70 eV . Therefore, excellent performance was achieved by the single Zn atom strategy. Encouraged by the high peroxidase-like activity of Zn SAzyme, it was further applied in bacteria-infected wound model for disinfection and significantly promoted wound healing.

Despite still in its infancy, the design of high performance nanozymes by the single-atom strategy represents a novel and promising avenue to the search for highly active and selective nanozymes. The developed SAzymes combine the merits of homogeneous catalysts and heterogeneous catalysts with uniform and tunable active sites, excellent catalytic performance, high stability and recyclability, and low cost. To boost the field of SAzymes, several challenges need to be addressed in the future: (1) The loading of metal atoms in the SAzymes are still low at the current stage. Higher loading of metal atoms is demanded to create more active sites and enhance the enzyme-mimicking efficiency. (2) So far, all the reported SAzymes are limited to carbon-based nanocatalysts. Other supporting solids (e.g., metal and metal oxide) can also be explored to host the single-atom active sites. (3) SAzymes have been reported to mimic oxidase, peroxidase, catalase, and SOD. Enzymes are known to catalyze broader types of reactions. More efforts need to be devoted to exploring new SAzymes to mimic other enzymes. (4) Most of the reported SAzymes can mimic at least two kinds of enzymes while natural enzymes are involved in specific reactions with high specificity. Future works are expected to solve the problem and design SAzymes with high specificity. (5) Nanozymes lie at the interface of nanotechnology and biology (Chen and Liang, 2018; Zhang et al., 2018). SAzymes should be exploited for broader biological applications (e.g., diagnosis and therapeutics) to fulfill their potential.

Compliance and ethics The author(s) declare that they have no conflict of interest.

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