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Iron-based nanozymes induced ferroptosis for tumor therapy

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Abstract: Iron-based nanozymes are an emerging class of nanomaterials demonstrating significant potential in tumor therapy by inducing ferroptosis—a regulated form of cell death marked by iron-mediated lipid peroxidation (LPO). These nanozymes exhibit unique enzymatic activities, including peroxidase, oxidase, and glutathione oxidase-like functions, enabling them to generate reactive oxygen species (ROS) and disrupt tumor microenvironment homeostasis. Leveraging from Fenton chemistry, iron-based nanozymes amplify oxidative stress within tumor cells, overcoming therapeutic challenges such as drug resistance and non-specific toxicity. Despite significant advancements, the precise mechanisms by which iron-based nanozymes influence ferroptosis and their therapeutic efficacy remain underexplored. This review systematically categorizes these iron-based nanozymes, including iron oxides, single-atom enzymes, and metal-organic frameworks. We further elucidate their mechanisms in enhancing ferroptosis, focusing on their structural attributes, ROS generation pathways, and their enzymatic activities. Additionally, we summarized their biochemical applications alongside challenges in biosafety, nanozyme specificity, and advanced design and analysis approaches essential for maximizing their therapeutic efficacy.

1. Introduction

Malignant tumors, commonly referred to as cancer, pose a significant health threat worldwide. According to data from the Global Cancer Observatory, cancer was responsible for 22.8% of global deaths from noncommunicable diseases in 2022.1 Traditional cancer treatments—such as surgery,² radiation therapy,³ chemotherapy,⁴ immunotherapy,⁵ and targeted therapy⁶—are often associated with drawbacks. These include an increased risk of metastasis,² toxicity to resistance,4 tissues.³ normal multidrug immunosuppression,⁵ and dependence on tumor heterogeneity.⁶ Consequently, therapeutic strategies that induce selective cell death have garnered increasing attention recently.

Cell death is a vital biological process for mammalian development, homeostasis, and disease progression. ⁷ Traditionally, cell death is classified into

three main types: apoptosis (type I), autophagy (type II), and necrosis (type III).⁸ Recent research has refined this classification into two categories: accidental cell death (ACD) and regulated cell death (RCD). ACD occurs in response to uncontrolled chemical, physical, or mechanical stimuli, whereas pharmacological or genetic interventions can modulate RCD. RCD is subdivided into several major types, including necroptosis, pyroptosis, and ferroptosis.⁹ However, studies have shown that DNA damage-induced apoptosis often proves ineffective due to specific genetic mutations (such as p53 mutations), contributing to drug resistance in certain chemotherapy treatments.¹⁰ Given its critical role in tumor suppression and its potential to overcome drug resistance, ferroptosis has garnered significant research interest as a therapeutic strategy for cancer treatment.^{11, 12}

Ferroptosis, an iron-dependent form of programmed cell death, was first proposed by Brent Stockwell and Scott J. Dixon in 2012.¹³ This process is characterized by the accumulation of lipid peroxidation (LPO) induced by reactive oxygen species (ROS). A classical mechanism for ROS generation, Fenton chemistry, involves a redox reaction between Fe²⁺ and Fe³⁺, producing hydroxyl radicals (·OH).¹⁴ LPO, ROS, and ferroptosis are closely interconnected in tumor therapy.

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Peroxidized lipids, which are key to ferroptosis, compromise the integrity of the cell membrane, ultimately leading to tumor cell death.¹⁵ ROS, which are oxygen-derived radical species with unpaired electrons and high oxidative activity, are produced during redox reactions. As the primary inducers of LPO, ROS can oxidize polyunsaturated fatty acids, resulting in LPO accumulation and facilitating ferroptosis. Additionally, promote regulate the genome to ROS can ferroptosis.^{16,17} Ferroptosis can be initiated through various pathways, including the suppression of Glutathione Peroxidase 4 (GPx4), inhibition of the FSP1-CoQ10-NAD(P)H pathway, and disruption of mitochondrial voltage-dependent anion channels.^{8,14,18} Among these, GPx4 plays a crucial role in eliminating ROS and LPO at the tumor site by utilizing endogenous glutathione (GSH), thereby maintaining redox homeostasis within the tumor microenvironment (TME)^{19,20} and inhibiting ferroptosis. Therefore, increasing ROS levels while depleting GSH to trigger tumor ferroptosis presents a promising therapeutic strategy.

ROS-mediated nanozyme therapy has recently gained significant attention in cancer treatment due to its ability to regulate oxidation reactions, ROS, and GSH simultaneously within the TME.^{21,22, 23} Nanozymes are nanomaterials that mimic the biocatalytic functions of natural enzymes. Since 2007, when Gao et al. first described the peroxidase-like activity of Fe₃O₄ nanoparticles,²⁴ the potential of nanomaterials as a catalyst to biological processes has been extensively studied. Notably, studies have shown that certain natural enzymes, such as ACLS4 and LPCAT3, regulate the intake of polyunsaturated fatty acids into cell membranes, thereby inducing LPO²⁵ and facilitating specific biological activities.²⁶ Nonetheless, natural enzymes, which are primarily based on biological materials, have several limitations. These include susceptibility to denaturation under harsh conditions, challenges in recycling, and high synthesis costs.²⁷⁻²⁹ In contrast, nanozymes are favored by researchers due to their diverse enzymatic activities, excellent surface plasmon resonance (SPR) properties, photothermal

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conversion capability, and abundant Viewantibody conjugation sites.³⁰ Its ability to modulate key metabolic pathways—such as iron metabolism, lipid metabolism, energy metabolism, and amino acid metabolism allows nanozymes to enhance ferroptosis more efficiently than natural or artificial enzymes.³¹⁻³³

Given the abundance of earth resources, low costs, and superior enzymatic performance of nanozymes, Febased nanozymes have been widely selected to mimic natural enzymes for cancer therapy.^{34, 35, 36} These include iron oxides,^{37, 38} iron-based single-atom enzymes (SAzymes),^{39,} 40 iron-based metal-organic and frameworks (MOFs),^{41, 42} among others. It is well recognized that the ferric and ferrous sites within Febased nanozymes confer peroxidase-like (POD) activity by mimicking the active sites of the heme group in horseradish peroxidase (HRP). ^{24, 34} Moreover, the excess iron in these nanozymes is able to enhance ROS production via the Fenton reaction whilst depleting GSH to reduce GPx4 expression, thereby promoting LPO and advancing ferroptosis.^{43,44, 45} Consequently, Fe-based nanozymes are emerging as promising candidates for tumor therapy. Researchers typically design iron-based nanozymes to enhance ROS generation and modulate the TME, emphasizing the importance of understanding the underlying mechanisms from the perspectives of cellular metabolism, immunology, and organelle damage induced by ferroptosis.⁴⁶⁻⁴⁸ Hence, there are few systematic reviews that comprehensively explore the mechanisms of ferroptosis induced by iron-based nanozymes from the perspective of redox substances in the TME.49-51

To address this gap, this review first categorizes designed iron-based nanozymes, various newly single-atom including iron oxides, iron-based and iron-based MOFs, along with nanozymes, illustrations of their active sites. Subsequently, by focusing on the redox substrates involved in the ferroptosis mechanism—such as iron, LPO, and GSH—, we summarize the role of ROS in cancer therapy and that of Fe-based nanozymes in the ferroptosis process via Fenton chemistry. This review also highlights the multiple enzymatic-like activities of Fe-based

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nanozymes, including peroxidase-like activity (POD), oxidase-like activity (OXD), glutathione oxidase-like activity (GSHOx), catalase-like activity (CAT), superoxide dismutase-like activity (SOD), and glucose oxidase-like activity (GOx). Moreover, we examine the corresponding ROS generation mechanisms of these nanozymes, emphasizing their latest biochemical applications. Finally, the challenges and prospects of advancing iron-based nanozymes for tumor therapy through ferroptosis will be discussed.



Figure 1. Schematic illustration of ferroptosis enhanced by iron-based nanozyme.

2. Classification of iron-based nanozymes

The intrinsic biocatalytic activity of nanomaterials, specifically peroxidase-like activity, was first studied in 2007 when Gao et al. discovered the inherent peroxidase-like activity of Fe₃O₄ nanoparticles.²⁴ Since then, nanomaterials with biocatalytic activity have been referred to as nanozymes. It has been proven that iron is the most abundant and essential trace element in the human body.^{24,52, 53} Iron has the ability to both accept and donate electrons, and is strongly associated with oxygen-related electron transfer processes and the metabolism of vital substances, hence it has significant biological importance. Subsequently, iron has been extensively investigated construct various to nanozymes, including iron oxides, iron-based SAzymes, iron-based MOF materials, etc. These iron-based nanozymes are designed to exhibit multiple enzymatic activities and enhance the generation of ROS, thereby boosting ferroptosis for tumor therapy. $^{\rm DOI:\ 10.1039/D5NR00880H}$

Due to their relatively legible structures, the enzymatic activities of iron-based nanozymes can be optimized by regulating their size, crystalline structure, morphology, coordination environment, electronic structure, etc.⁵⁴ As a typical example, compared to natural enzymes, Fe SAzymes with similar Fe-Nx active sites have been proved to possess a simplified synthesis and purification method and a wider operation range.⁵⁵ However, limited by their randomly dispersed active sites, the SAzymes' specific enzymatic activity would be affected. Herein, the approaches for regulating their properties and related enzymatic activities of Fe-based nanozymes are systematically reviewed in this section.

2.1. Iron oxide

Monometallic iron oxides, such as hematite and magnetite, iron hydroxides, and iron oxide hydroxides, are materials with great application potential in tumor therapy.^{56, 57} The comparatively simple composition and crystal structure facilitates the preparation and analysis of the structure and function of these nanozymes. The physicochemical properties of nanozymes, including size, morphology, and facets, can greatly influence the dynamics of the Fenton reaction by altering the reaction metabolism and pathways.⁵⁸ Therefore, it is crucial to modulate these properties within nanozymes in order to optimise their enzymatic activity. Yin et al. designed an a-Fe₂O₃ nanosheet with a predominant (311) facet to activity.59 POD-like The schematic enhance demonstration of the catalytic mechanism is shown in Figure 2a. They examined the adsorption energy of H_2O_2 on different facets, and the corresponding H₂O₂ activation energy barriers. Among the facets, the (311) facet showed the highest adsorption energy and the lowest activation energy barrier. This indicates a strong tendency for hydrogen peroxide adsorption and provides the most favorable pathway to convert H₂O₂ into hydroxy radicals (·OH), thus facilitating the initiation of POD-like activity. The ability to generate hydroxy radicals from H₂O₂ depicts its promising ability in pollutant depletion and LPO and GSH consumption, thus

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demonstrating its intrinsic ferroptosis-initiating potential.

Dong et al. prepared Fe₃O₄ nanoparticles to analyze the catalytic mechanism of POD-like activity of the nanoparticles. ⁶⁰ They discovered that the persistent catalytic activity of magnetite nanoparticles is achieved through the following processes. Primarily, a Fenton-like reaction occurs on the surface of the nanozyme, producing \cdot OH by the decomposition of H_2O_2 , while external Fe²⁺ is oxidized to Fe³⁺. Concurrently, internal Fe²⁺ transfers electrons to the outer surface Fe³⁺ via the Fe²⁺-O- Fe³⁺ chain, reducing surface Fe³⁺ and resulting in the migration of inner lattice Fe³⁺ to the surface. Once inner Fe²⁺ is depleted, the magnetite nanoparticles would transform into γ -Fe₂O₃. As shown in Figure 2b, the lattice of Fe₃O₄ nanozymes undergoes structural changes during the catalytic process. Their research elucidates the underlying principles of Fe₃O₄ nanozyme inactivation and identifies the ion migration process as the rate-limiting step of the POD-like activity. This theory could serve as a foundation for the future design of Fe₃O₄ nanozymes.

Bimetallic oxides refer to a type of complex oxides containing two different metal elements. Compared to single iron oxide, an iron oxide that is composited with other metal oxides shows better enzymatic activity due to improvements in oxygen defects or valence state modulation.⁶¹ Therefore, designing complex bimetallic oxides is a promising pathway toward enhancing tumor therapy. Yin et al. prepared a MnFe₂O₄- based nanozyme coated with MOF to enhance the production efficiency of ¹O₂ under photodynamic conditions.⁶² The MOF coating not only improves the photosensitive ability of the nanozyme but also facilitates the diffusion of H_2O_2 . The cascade enzymatic activity relies on the electron transfer ability of a multi-valence state metal oxide center, e.g. the conversion between Fe^{2+} and Fe^{3+} in Fenton-like reactions and oxidation of GSH to GSSG. In vivo tumor suppression results suggested that the antitumor ability of the experiment group with laser radiation exhibited the best result relative to the nonirradiated control group.

The presence of oxygen defects on bimetallic iron oxides can also contribute to the enzymatic activity of the nanozyme. For example, FeWO_x with surface oxygen defects demonstrates substantially higher catalytic activity than the original FeWO₄ without oxygen defects.⁶³ This enhancement stems from the increased exposure of iron ions on the surface of the nanozyme with oxygen vacancy sites, which formed during the synthetic processes through W⁶⁺ reduction. The authors declared that the intrinsic POD-like activity of this nanozyme enables it to be applied to cancer sensing by photoacoustic imaging. Herein, the FeWO_x bimetallic oxide nanozyme shows potential in tumor treatment from its inherent POD-like activity.

Efficient cellular delivery of inorganic iron oxide nanozymes remains challenging for enhancing in vivo tumor therapy. Surface modification of nanozymes can not only affect the cell affinity of nanozymes, but also improve the enzymatic activity of nanozymes.⁶⁴ For example, Chen et al. designed a FeOOH-based nanozyme modified with glutamine (Gln) and cellular uptake enhancer V9302 to test the effect of modification on cell intaking for enhanced pancreatic cancer treatment. The modified nanozyme demonstrated desirable ferroptosis-induced tumor suppression, compared to primitive FeOOH material without Gln coating.65

2.2. Iron-based single-atom enzymes

Iron-based SAzyme is a kind of artificial enzyme that constructs a single-atom iron onto metal oxides, metal sulfides, and carbon-nitrogen-based supplementary frameworks.⁶⁶ With a similar Fe-Nx coordination structure to the natural enzyme, Fe SAzyme shows a strong Fenton response, thus generating plentiful ROS and exhibiting good therapeutic activity.⁵² Compare to iron oxide nanozymes, Fe SAzymes can accomplish enzymatic activities with a significantly lower metal content. Besides, it is easier to regulate the active sites of single-atom metals in SAzymes by introducing multiple substances into the supplementary framework. For example, Ji et al. introduced poly-(cyclotriphospazene-co-4,4'diaminodiphenylether) (PZM) during synthesis to both

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coordinate with the metal center and regulate the coordination structure.⁶⁷ As shown in Figure 2c, the high-angle annular dark-field scanning transmission electron microscopy (HAADF-STEM) result and energydispersive X-ray spectroscopy (EDS) mapping demonstrate the uniform P atom distribution in the FeN₃P nanozyme. Compared to the porphyrin-like FeN_4C_4 structure on the traditional $Fe-N_4$ coordinated SAN, the FeN₃PC₄ structure shows reduced electron transfer from Fe to N due to the electron donation effect of the phosphorous atom. This advancement has led to progress in the POD-like activity compared to Fe₃O₄ (111) and Fe- N_4 coordinated nanozyme.

Sulfur is also an ideal element for the enhancement of iron-based enzymatic activity. Ironsulfur (Fe-S) structures in natural enzymes, essential for redox reactions in cell metabolism, have inspired the development of Fe-S-containing nanozymes to enhance multiple enzymatic-like activities, with dehydrogenases, hydrogenases, and certain monooxygenases being explored by researchers.⁶⁸ Choi et al. synthesized Fe-N₄ single-atom nanozymes with different ligand coordination: oxygen, sulfur without functional group, and sulfur with reduced and oxidized functional groups.⁶⁹ The synthetic method of the nanozyme is labelled in Figure 2d. They revealed that adding reduced and oxidized sulfur ligands to Fe-N₄ SAzymes induced a second-shell coordination modification, thereby optimizing the electronic and geometric structures. Density functional theory (DFT) calculations revealed that this reduced the energy barrier of the intermediate steps for the Fenton-like reaction, thereby enhancing the POD-like activity. They also examined the cytotoxicity of the SAzymes based on different cancer lines, given that the hydrogen peroxide cell concentration in cancer cells is significantly higher than that in normal cells. The in vitro and in vivo tumor cell cytotoxicity analysis results showed that, while ZIF-NC showed little cytotoxicity across all concentrations, the sulfur-modified nanozymes exhibited strong antitumor ability in both in vivo and in vitro analysis.

Furthermore, by introducing heteroatoms into iron-based SAzymes, the electronic structure of the

metal active site center in SAzymes canvibertuned, thereby improving their affinity to substrates.⁴⁰ For example, Zeng et al. introduced Mn single atoms into the iron-based nanozyme, fabricating a dual-atomic Fe-Mn enzyme that successfully tunes the iron atom's Dband center.⁷¹ According to the DFT calculations, compared to that of the Fe₁-NC_e single-atom catalyst, the D-band center of the Fe₁-Mn₁-NC_e dual atom nanozyme is closer to the Fermi level. Regarding the change in POD-like activity, Fe₁-Mn₁-NC_e shows a stronger affinity between the iron single atom and H₂O₂, resulting in enhanced enzymatic activity compared to Fe₁-NC_e single atom nanozyme.

The selectivity of multiple enzymatic activities in nanozymes is crucial for applications in tumor therapy. Zhang et al. discovered that by tuning the distance between neighboring iron single atoms in an iron singleatom nanozyme, the selectivity of CAT-like activity over POD-like activity would improve significantly.⁷² The authors argue that the adjacent activation centers of Fe₂-SAzyme reduce the free energy for the ratedetermining step by facilitating the end-bridge adsorption of H_2O_2 on the nanozyme. In contrast, the end-on adsorption mechanism of traditional Fe-SAzyme exhibits a higher free energy for the rate-determining step. A similar observation has been proposed for neighboring M₂-SAzymes (Pt, Ir). Their work offers insight into enhancing the enzymatic selectivity of nanozymes via the active site modification.

2.3. Iron-based MOFs

Metal-organic frameworks (MOF), composed of metal nodes and organic ligands, are characterized by their designing-functional adaptive structure, intelligent release capability, large specific area contributed by their porous structure, stimuli-response ability and drug-delivery ability compared to activated carbon material and organic carriers.⁷³⁻⁷⁶ Like single-atom nanozymes, iron-based MOFs also possess single iron atoms that act as the catalytic center for enhanced catalytic activity, however, MOF materials possesses more biotic proficiency, which demonstrates its better potential in clinical applications.⁷⁴ Due to its adjustable pore size, high selectivity and large surface area, iron-

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based MOFs can carry metal ions and drug molecules to targeted sites, thereby enhancing antitumor ability. Chen et al. designed an iron-based MOF by coordinating Fe³⁺ with a porphyrin-like ligand, assembled with doxorubicin (DOX) and modified with polydopamine (PDA), to produce PCN-DOX@PDA.⁷⁷ Figure 2e presents a schematic illustration of the mode of action for PCN-DOX@PDA. They analyzed the photothermal effect of the material along with the release of DOX under different pH values and photothermal conditions. The results show that the decomposition of PDA occurs either at pH = 5.4 or with NIR light treatment, suggesting that the synthesized material can intelligently release antitumor drugs. Additionally, the fluorescence results from confocal laser scanning microscopy (CLSM) revealed that the PCN@PDA material can generate ROS when exposed to LED.

Loading MOF materials with multiple enzymes could be an effective way to design cascade nanozyme for cancer therapy.⁷⁸ For example, Fang et al. designed a Co-ferrocene MOF loaded with glucose oxidase (GOx) (Co-Fc@GOx) to analyze cascade enzymatic activity with potential applications in tumor treatment.⁷⁹ The synthesized material exhibits a desired Fenton effect in the absence of GOx, while its cascade enzymatic activity is determined by TMB colorimetric reaction in aqueous glucose solution. Furthermore, the bioexperiment results confirm its enhanced *in vivo* antitumor efficacy.

MOF materials can also be modified to enhance the reduction of metal nodes, thereby increasing the efficiency of chemodynamic therapy (CDT), Photodynamic therapy, sonodynamic therapy (SDT) and magnetodynamic therapy (MDT).74,80,81 By introducing a radioactive isotope (125I) into an iron-based MOF, Wang et al. proposed a novel synergistic MOF material for enhanced POD-like activity.⁸² As shown in Figure 2f, they suggested that ¹²⁵I can generate hydrated electrons in aqueous environment, which can then facilitate the reaction from Fe³⁺ to Fe²⁺. The continuous supply of Fe²⁺, through the conversion of Fe³⁺, significantly enhances the tumor treatment efficiency of ¹²⁵I-MIL-88B (Fe) compared to both ¹²⁵I-doped SiO₂ and MIL-88B (Fe). This

Iron-based MOFs, capable of carrying monomeric compounds, can enhance CDT and be combined with immunotherapy to induce ferroptosis more effectively.⁸³ Li et al. designed a MIL-101 (Fe) based MOF material loaded with dihydroartemisinin (DHA), which reprograms tumor-associated macrophages (TAMs) into an anti-tumor M1 phenotype via ferroptosis, thereby improving tumor therapy.⁸⁴ The integration of DHA with MOF not only increases the hydrophilicity and targeting accuracy of DHA in vivo, but also promotes the generation of LPO, ROS, and iron ions through MIL-101 degradation in acidic environments (pH=5.2). Their work provides valuable insights into applying Fe MOF-based nanozyme in immunotherapy through ferroptosis induction.

Photodynamic therapy (PDT) has been recognized as an effective way of enhancing ROS generation and ferroptosis induction.⁸⁵ However, its tumor treatment efficiency is often restrained by the oxygen deficiency in TME. To address this limitation, MOF materials can be modified to uplift photocatalytic generation of dioxygen molecules in vivo, thereby enhancing the induction of ferroptosis through membrane lipid peroxidation. Following this theory, Xu et al. designed а multifunctional nanocomplex for effective tumor PDT.86 By modifying an iron-based MOF (MIL-53) with cMBP peptide, ferroptosis inducer sorafenib tosylate (ST), and photosensitizer Chlorin e6 (Ce6), the synthesized MIL-53@cMBP@ST/Ce6 (MMSC) nanozyme exhibits desired multiple enzymatic activity, including the oxidation of GSH together with POD-like and CAT-like activity. The enhancement of ferroptosis inducement under PDT was confirmed using a ferroptosis inhibitor, and cell viability analysis of MMSC treatment demonstrated a significant difference in treatment outcomes when exposed to varying laser intensities. Their research offers an innovative strategy for increasing O₂ generation to enhance ferroptosis.

SDT applies ultrasound (US) irradiation to develop sonosensitizer-mediated technology that is based on

PDT.⁸¹ Iron-based MOF nanozymes serves as important sonosensitizers that can be activated by US irradiation to generate ROS, thereby enhancing ferroptosis. Cao et al constructed an Fe-MOF carrying Mn₂O₃ (FTM@AM) for enhanced treatment of Triple Negative Breast Cancer (TNBC) by SDT.⁸⁷ The evaluation of •OH generation by Fenton reaction under US irradiation has been proved to increase 33.8% compared to control group with no US irradiation applied. The in vivo antitumor ability analysis of FTM@AM with US and buffer solution shows that the tumor growth inhibition rate decreased by 93.6% compared to the control group. The results indicate that MOF-involved SDT leverages iron-based nanozymes to amplify ultrasound-triggered ROS generation through enhanced Fenton reactivity and ferroptosis synergy, achieving superior antitumor efficacy with targeted therapeutic precision.

MDT is a crucial measure for in vivo tumor detection and tumor therapy. Introducing iron MOFbased nanozymes in tumors could significantly enhance magnetic resonance imaging (MRI) signals due to their accumulation in tumor sites.⁸⁸ Yuan et al. explored the enhanced POD-like activity of magnetic nanozymes under a magnetic field.⁷⁴ They assembled a porphyrinbased Zr-MOF (PCN) on zinc ferrite (ZF) nanoparticles to produce a MOF-based magnetic nanozyme (PZFH) and reviewed the change in POD-like activity in response to varying magnetic field intensities. Their findings revealed that with increasing magnetic field intensity, the POD-like enzymatic kinetics uplifted significantly. Herein, the connection between magnetically responsive nanozymes and tumor detection and therapy is established, inspiring future research on MDT-based treatments.



Figure 2. a) Illustration of the mechanism of POD-like activity of α -Fe₂O₃ with (311) facet.⁵⁹ Reproduced from ref.59 with permission from Elsevier, Copyright 2024 b) TEM, HRTEM and SAED images of Fe₃O₄ nanoparticles before and after catalysis.⁶⁰ Reproduced from ref.60 with permission from Springer Nature, Copyright 2022 c) TEM, HAADF-STEM and EDS mapping image of FeN₃P nanozyme⁶⁷ Reproduced from ref.67 with permission from Springer Nature, Copyright 2021 d) Schematic view of the synthesis of the FS-FeN₄S₁-os SAzyme.⁶⁹ Reproduced from ref.69 with permission from Wiley-VCH, Copyright 2024 e) Schematic view of tumor therapy using PCN-DOX@PDA⁷⁷ Reproduced from ref.77 with permission from American Chemical Society, Copyright 2024 f) ¹²⁵I enhanced Fenton reaction.⁸² Reproduced from ref.82 with permission from Wiley-VCH, Copyright 2024.

3. Mechanism of Fe-based nanozymes enhanced ferroptosis

Nowadays, recent studies have demonstrated that ferroptosis acts as a tumor suppressor by eliminating damaged or nutrient-deprived cells. It plays a crucial role in key tumor suppressor pathways, with its sensitivity being influenced by the activities of p53 and KEAP1/NRF2.^{7, 89-91} Among them, as one of the most extensively studied tumor suppressor genes, p53 positively regulates the ferroptosis pathway by transcriptionally repressing the expression of the

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cystine/glutamate antiporter. Intracellular iron can be exported via the iron transporter protein (FPN), which is the only known iron exporter in mammals that controls iron efflux.⁹²⁻⁹⁴ Increased iron uptake or reduced iron export can make cancer cells more sensitive to oxidative damage and ferroptosis.⁹⁵

At the molecular level, lipid peroxides are further decomposed into reactive substances that can deplete nucleic acids and proteins, leading to cell death by ferroptosis. Lipid peroxidation mediated by ironcontaining enzymes, such as arachidonic acid lipoxygenases (ALOXs), has been shown to be a primary mechanism. The small scaffold protein Raf1 kinase inhibitory protein (RKIP1) actively regulates ferroptosis by binding to lipoxygenase ALOX15 and interfering with the production of phosphatidylinositol.^{96, 97}

Reduced glutathione (GSH) is synthesized in two steps from glutamate, cysteine, and glycine in the cytosol, catalyzed by the enzymes glutamate-cysteine ligase (GCL) and glutathione synthetase (GSS).⁹⁸ It is the primary antioxidant in mammalian cells. Ferroptosis is deeply related with the GSH depletion, either by blocking the uptake of cystine from the extracellular environment or inhibiting GSH biosynthesis. For instance, erastin inhibits system Xc- (one of the transporters which exerts the exchange of cystine and glutamate across plasma membrane) and buthionine sulfoximine (BSO) can inhibit γ-glutamylcysteine synthetase.⁹⁴

Additionally, in the cancer immunotherapy, ferroptosis is implicated in T cells and interferon-gamma (IFN γ)-mediated tumor suppression. Enhancing dietary intake of polyunsaturated fatty acids (PUFAs) or iron can increase the susceptibility of tumor cells to the proferroptotic effects of CD8+-T cell-dependent immune therapy.^{99, 100}

Fe-based nanozymes can serve as ideal mediators, effectively linking oxidation reactions with ROS, thereby enhancing the efficiency of ferroptosis. During the ferroptosis process of tumor cells, key physiological changes include an increase in iron ions and ROS levels, excessive accumulation of LPO, and the inactivation or suppression of GPx4, as GSH is eliminated.^{18,101} The oxidative stress pathway is widely recognized as a fundamental causal component of ferroptosis and plays a crucial role in the interplay among these three substances.⁸⁰ In this section, the specific mechanisms within ferroptosis mediated by iron-based nanozymes will be discussed, focusing particularly on the redox substrates involving iron, LPO and GSH.

3.1. Iron species transformation via Fenton chemistry

Fenton/Fenton-like reactions were first put forward by Henry J. Fenton in the 1890s,¹⁰² as can be seen in Fig. 3a. The reactions mainly refer to the cycle of Fe³⁺ to Fe²⁺ ions alongside the accompanied generation of ROS during the process. It was previously thought that iron-based nanomaterials induced apoptosis by releasing Fe²⁺ ions from exposed nanoparticles into the surrounding solution. This process was believed to increase intracellular iron levels through endocytosis, ultimately leading to the production of hydroxyl radicals (·OH) via the Fenton reaction. With a deep investigation into the intraparticle electron transport process, Yi et al found out that the presence of internal low-valence iron (Fe⁰ and Fe²⁺) in Wüstite (FeO) nanoparticles is able to facilitate the transformation of Fe³⁺ into Fe²⁺ ions, thereby elevating the overall catalytic activity and increasing the intracellular ROS level in mouse mammary carcinoma cells.¹⁰³ Consequently, the redox cycle between the different iron species plays a critical role in the Fenton reaction, as shown in Fig. 3b. To boost the transformation of Fe³⁺ into Fe²⁺ during ferroptosis, Zhang et. al put forward an X-ray-activated Fe²⁺ supply platform which comprised of a CaWO₄ core and surfacedecorated Fe₃O₄, to enhance tumor ferroptosis.¹⁰⁴ Upon X-ray irradiation, the ultraviolet light emitted by the CaWO₄ catalyzed the reduction of Fe³⁺ to Fe²⁺, hence initiating a Fenton reaction cascade that produces highly toxic ·OH. Moreover, to enhance the cycling of Fe²⁺ and Fe³⁺, Shi and his group recently designed an allicinmodified FeO_{1-x}OH nanozyme with varied iron valence states (Fe²⁺ and Fe³⁺).¹⁰⁵ The high levels of reduced GSH in TME promote the reduction of Fe³⁺ to Fe²⁺, accelerating the Fenton reaction and thereby amplifying ferroptosis-based therapeutic effects. In summary,

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optimizing the Fe³⁺ and Fe²⁺ transformation pathway can overcome the rate-limiting steps in Fenton chemistry. By introducing external energy sources and leveraging GSH inside the tumor, researchers can design iron-based nanozymes with enhanced ferroptosis efficiency.

Moreover, despite the extensively used H_2O_2 , other peroxides including artesunate (ART) have been proven as the optional link between Fe^{2+}/Fe^{3+} and ROS. Chen et al. utilized ART as a non-Fenton-type substrate to generate free radicals by ferrous ions intratumor.¹⁰⁶ The mechanism involves the decomposition of ART's endoperoxide bridges, which is catalyzed by ferrous ions (Fe²⁺) and accompanied by the production of superoxide anions. This targeted release further enhanced the chemo-dynamic therapy (CDT) effect within tumor.

3.2. Lipid peroxidation (LPO) via Fenton chemistry

As the key biomarker for assessing susceptibility of ferroptosis, lipid peroxidation (LPO) refers to a complex process of lipid metabolism, which involves enzymatic reaction and a nonenzymatic Fenton reaction pathway.^{107,108,7} During the iron-based nanozymesmediated Fenton process in tumor cells, accumulated ROS react with polyunsaturated fatty acids (PUFAs) side chains in phospholipids, membrane receptors, and macromolecules to oxidize biological membranes.¹⁰⁹ This lipid peroxidation reaction results in the formation of LPO, such as malondialdehyde (MDA) and 4hydroxynonenal (HNE). Ultimately, the fluidity and permeability of the cell membrane are altered, leading to changes in cell structure and inducing tumor cell death.110, 111

Zhu et al. synthesized a metal-phenolic nanocatalyst containing ferric ions (Fe³⁺) and mitoxantrone (MT, a kind of chemotherapeutic drug) in a self-assembled reaction.¹¹² Upon internalization by tumor cells, the fabricated nanoplatform can release MT to promote irreversible ferroptosis by increasing ROS-sensitive PUFAs and inducing lethal LPO. To further reveal the mechanism of LPO, Li and his group prepared a diatomic iron nanozyme, as illustrated schematically in Fig. 3e.¹¹³

The Fe-O-Fe motif effectively aligns the energy levels of the Fe₂ minority β -spin d orbitals with the π^{+} orbitals of the pentadiene moiety in vesicle membranes. This alignment significantly lowers the activation barrier for the reaction (Fig. 3e). Therefore, designing Fe-based nanozymes that incorporate LPO-sensitive drugs can enhance LPO efficiency during the tumor therapy. Additionally, by regulating the structure and coordination environment of the iron center, the activation energy between the catalysts and lipid membranes can be lowered, optimising therapeutic outcomes.

Iron-based nanozymes selectively target lipid peroxidation processes in tumor cells by leveraging their unique catalytic properties and interactions with cellular components. Zhou et al. designed a kind of DNA nanozyme to enhance targeting delivery and induce ferroptosis within tumor by incorporating hemin, an iron-containing porphyrin cofactor, into its structure.¹¹⁴ The DNA nanozyme was constructed using rolling circle amplification and contains repeated AS1411 Gquadruplex (G4) units. These G4 units serve as active ligands for targeted tumor delivery due to their high affinity for nucleolin, which is overexpressed on the surface of tumor cells¹¹⁵, thus facilitating the LPO accumulation and GSH depletion during the treatment. Another approach involves the use of lipoxygenase (LOX) and phospholipase A2 (PLA2) to enhance lipid peroxidation (LPO) and ferroptosis in tumor cells. Zhang et al. developed a FeCo/Fe-Co dual-metal atom nanozyme co-loaded with LOX and PLA2.¹¹⁶ The upregulation of arachidonic acid (AA) expression through PLA2 catalysis can synergize with CD8+ T cellderived IFN-y to induce ACSL4-mediated immunogenic tumor ferroptosis. This process involves the incorporation of AA into membrane phospholipids, which then undergo peroxidation with the participation of LOX. In summary, iron-based nanozymes can be strategically designed by incorporating LPO-related enzymes or by being loaded onto highly biocompatible carriers to induce LPO, thereby achieving selective and effective cancer treatment.

3.3. Glutathione (GSH) oxidation via Fenton

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Glutathione (GSH), a key low molecular thiol, plays a crucial role as a cofactor in detoxifying reactive LPO and reducing ROS in conjunction with GPx4, which contributes to a diminished ferroptosis effect.¹¹⁷ Therefore, to depress the GPx4 pathway¹¹⁸ and enhance ferroptosis, it is essential to deplete the GSH levels within the TME.^{119, 120} Interestingly, iron-based nanozymes can oxide GSH into oxidized glutathione (GSSG) via Fenton chemistry, while replenishing Fe²⁺ ions which possess higher Fenton reaction activity (equation 1).¹⁰²

Fe^{3+} + GSH \rightarrow Fe^{2+} + GSSG (glutathione disulfide) (1)



Figure 3. Mechanism of Fe-based nanozymes enhanced ferroptosis. (a) The Fenton/Fenton-like reaction mechanisms. (b) Schematic diagram of enhancing surface Fenton reaction via intraparticle electron transport.¹⁰³ Reproduced from ref.103 with permission from Wiley-VCH, Copyright 2023 (c) and (d) Gibbs free energy profile for key intermediate and transition states in the LPO cycle. Energy unit: eV. ¹¹³ (e) Schematic illustration of lipid destruction upon treatment with Fe₂ dual atom catalysts.¹¹³ Reproduced from ref.113 with permission from Springer Nature, Copyright 2023 (f) Mechanism of DFMC nanoplatform with dual-glutathione consumption characteristics and POD-like enzyme activity. ¹²¹ Reproduced from ref.121 with

2022. DOI: 10.1039/D5NR00880H Yan and her group prepared pyrite peroxidase

nanozymes that exhibit a self-cascade mechanism to generate abundant ·OH while also depleting GSH. This effectively induces both apoptosis and ferroptosis in tumor cells.⁴⁵ By employing high resolution mass spectrometry, it was revealed that the GSSG was generated from GSH during the catalytic process. Moreover, by mimicking the physiological environment of TME, pyrite nanozymes were able to maintain the selectivity of oxidizing GSH without interference from other compounds. Besides, Wu et al.¹²¹ utilized Fe₃O₄ nanoparticles and CB-839 (a glutaminase inhibitor) to achieve a dual GSH depletion strategy for antitumor therapy. As shown in Fig. 3f, the Fe₃O₄ NPs facilitate the scavenging of GSH. Furthermore, CB-839 inhibits the synthesis of endogenous GSH by blocking glutamine metabolism and reducing tumor cell drug resistance. Therefore, to enhance ferroptosis efficiency by targeting the GSH oxidation process, we could design Fe-based nanozymes with enhanced Fe³⁺ level via valence regulation, implement surface modification to improve GSH affinity, and incorporate compounds (such as GSH inhibitors) or synergistic metallic elements to augment effectiveness.

4. Iron-based Enzyme-like activity

The enzymatic activity of nanozymes mainly involves the generation of ROS, which includes free radical species such as hydroxy radicals (·OH), singlet oxygen (${}^{1}O_{2}$), and superoxide ($\cdot O_{2}^{-}$), as well as nonradical molecules like hydrogen peroxide (H₂O₂), hypochlorous acid (HClO), and lipid peroxides (ROOH). Owing to their unpaired electrons with high oxidative activity, ROS can interact with biological macromolecules such as DNA, proteins, and lipids, resulting in oxidative chain reactions that are closely related to oxidative stress damage, cellular aging, programmed cell death, and disease development.^{122, 123} The enzyme-like activities involved in iron-based nanozymes possess include POD-, OXD-, GSHOx-, CAT-, SOD- and GOx-like activity. Herein, the relationship between various enzyme-like activities of iron-based

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nanozymes and ROS are summarized, thereby promoting biocatalytic reaction of substrates.

4.1. POD-like activity

Peroxidase (POD) enzymes can catalyze the oxidation of H_2O_2 or organic peroxides with H_2O_2 as an electron acceptor, producing high activity intermediate species. Most natural POD enzymes refer to heme proteins.¹²⁴ Since 2007, when Gao et al. discovered that iron-containing magnetite nanoparticles (Fe₃O₄ NPs) exhibit similar activity,²⁴ there has been a surge of research focusing on the POD-like enzymatic activity of nanomaterials. There are two primary strategies for enhancing the POD-like activity of iron-based nanozymes: regulating the valence state of iron active sites and modifying the coordination environment of the metal active centers.

Wan et al proposed a reaction pathway for the peroxidase-like activity for Fe_3O_4 nanoparticles.¹²⁵ According to the result by DFT calculation, as shown in Figure 4a and 4b, they argued that an $Fe^{IV}=O$ bond is present in the nanozyme structure because the Fe-O bond length was found to be 1.64 Å, which is an important intermediate for the generation of $\cdot OH$. The analysis of POD-like activity under different redox substrate treatment also indicated that when Fe_3O_4 NPs are treated with oxidative species, i.e. NalO₃, the POD-like activity is comparatively higher than those with and without NaBH₄ treatment.

Modifying the coordination environment of Fe SANs has proved to be a promising measure for enhancing the POD-like activity of nanozymes. Han et al. regulated the coordination structure of carbon-dot supported iron single-atom nanozymes using phenanthroline to produce ph-CDs-Fe SAzyme.¹²⁶ Based on DFT calculation, the authors claim that, compared to CDs-Fe SAzyme, ph-CDs-Fe SAzyme possesses a higher ratio of pyrrolic N in the coordination structure. Moreover, the slightly protruding structure of Fe atoms on the surface of the nanozyme strengthens the adsorption effect of H₂O₂. As shown in Figure 4c, the adsorption effect of H₂O₂ plays a crucial role in POD-like activity of ph-CDs-Fe. Moreover, the enzyme kinetics data shows a slight increase of H_2O_2 adsorption and an increase in V_{max} up to three times of ph-CDs-Fe SAzyme compared to CDs-Fe SAzyme.

For the selective enhancement of POD-like activity, Jiao et al. proposed a heteroatom-doping strategy on the carbon-nitrogen framework of FeNC single atom nanozyme.¹²⁷ They applied X-ray photoelectron spectroscopy (XPS) for testing the doping nature of boron in the nanozyme. The result of the enzymatic activity test shows that the POD-like activity of FeBNC is enhanced by 191.2%, while the CAT-like activity enhancement is only 11.9% compared to FeNC, indicating that the strategy of boron atom doping is effective for the selective enhancement of POD-like activity. They attributed the selective enhancement to the electronic structure rearrangement induced by heteroatom doping. They proposed that the introduction of B atoms could achieve an electron structure rearrangement of the center metal atom, thereby selectively enhancing the POD-like activity.

The quantitative analysis of POD-like activity for nanozymes involves three main factors: K_m , which evaluates the affinity of certain substrate to nanozymes; V_{max} , which describes the maximum velocity for enzymatic reactions, and k_{cat}/K_m , which is the specific constant of enzymatic kinetics. The specified kinetic data for several typical types of nanozymes as classified in this review is labelled below in **Table 2**.

Table 2. the comparison of POD-like activity kinetics ofselected nanozymes.

Nanozyme	Substrate	<i>K_m</i> (mM)	V _{max} (mM min ⁻¹)	k_{cat}/K_m (mM ⁻¹ Min ⁻¹)
Fe ₃ O ₄ NPs ¹²⁵	TMB	9.93	2.61×10-3	5.25×10 ²
	H ₂ O ₂	0.92	2.55×10-6	8.93×10 ⁻³
FeWO _x NSs ⁶³	TMB	0.03	7.35×10 ⁻³	NA
	H ₂ O ₂	3.26	0.261	NA
FeNC ¹²⁷	TMB	24.25	0.034	22.8
	H ₂ O ₂	1.48	0.0329	1.80×10 ²
FeBNC ¹²⁷	TMB	25.24	0.0109	3.04×10 ³
	H ₂ O ₂	2.22	0.0768	8.79×10 ²
ph-CDs-Fe ¹²⁶	TMB	5.55×10 ⁻²	1.11×10 ⁻²	2.47
	H ₂ O ₂	24	16.66	8.50
PZF unexposed to AMF ⁷⁴	H_2O_2	14.23	2.62×10 ⁻⁶	2.79×10 ⁻³
PZF exposed to AMF ⁷⁴	H_2O_2	13.98	1.29×10 ⁻⁵	1.40×10 ⁻²
D/P@ZUCO128	H ₂ O ₂	1.06×10 ⁻³	8.36×10 ⁻³	NA
HRP ²⁴ (Fe	TMB	0.434	6.00×10 ⁻³	5.53×10 ⁵
Species)	H ₂ O ₂	3.70	5.23×10-3	5.64×10 ⁴

4.2. OXD-like activity

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Oxidase-like (OXD) enzyme-mediated catalytic decomposition reactions generally refer to redox reactions involving oxygen molecules (O₂). These reactions can oxidize O₂ into ROS such as H₂O₂, ¹O₂, or \cdot O₂⁻. These ROS can further react with GSH or lipid species, thereby depleting GSH and generating LPO to promote ferroptosis. Notably, this family of enzyme activities also includes glutathione oxidase-like (GSHOx) and glucose oxidase-like (GOx) activities.¹²⁹

4.2.1. $\cdot O_2^-$ participated OXD-like activity.

The generation of superoxide anions $(\cdot O_2^{-})$ results in cytotoxic effects, as these reactive oxygen species can interact with and damage various biomolecules, including lipids, proteins, and nucleic acids.¹³⁰ Superoxide anion species can serve as precursors for generating H₂O₂, which produce hydroxy radicals either by Fenton reactions or decomposition reactions by POD-like nanozymes.

Huang et al. utilized the oxidase-like (OXD) enzymatic activity of tetranitro iron phthalocyanine (TNFe(II)Pc) to oxidatively treat phenol and chlorophenol-contaminated water.¹³¹ They were the first to propose a reaction process involving superoxide anions (O_2^-) , suggesting that the formation of O_2^- and the degradation of these phenolic substrates were results from the substrates continuously transferring single electrons to O_2 . Building on this work, Qin et al. explored the OXD-like activity of catalyzing dissolved oxygen into $\cdot O_2^-$ for the enhancement of ferroptosis.¹³² The electron spin resonance (ESR) spectra displayed in figure 4e reveal distinct characteristic peaks for ¹O₂ and $\cdot O_2^{-}$. Their findings indicate that the catalytic activity of TMB oxidation is enhanced under 100% dissolved oxygen level but inhibited in N₂ atmosphere. The antitumor ability shown in figure 4d is assessed regarding the cascade enzymatic activity. The results of the in vitro cell viability test demonstrate that, with the progression of near-infrared (NIR) irradiation, Fe/N-MCN exhibits superior tumor inhibition ability as a nanozyme. The in vivo assessment of antitumor ability of Fe-N/MCN of MCF-7 and 4T1 bearing mice shows that with NIR irradiation, Fe-N/MCN can not only inhibit the

growth of in situ breast tumor but can also supress the distal metastasis of the tumor to lung and liver.

4.2.2. ¹O₂ participated OXD-like activity.

Unlike superoxide anions, ${}^{1}O_{2}$ can react directly with lipids to cause lipid peroxidation, thereby damaging the cell membrane and producing LPO.¹³³ The generation of ${}^{1}O_{2}$ involves the participation of a photosensitizer, light irradiation and molecular oxygen, in which the molecular oxygen is converted to bioactive singlet oxygen via a light-induced transition involving energy transfer from the photosensitizer.¹³⁴

Feng et al. designed an iron single-atom nanozyme (FeSA-OLC) by calcinating Fe(phen)_x with an onion-like carbon support.¹³⁵ The catalytic product of OXD-like activity is characterized. ESR results show distinctive resonance peaks for both ${}^{1}O_{2}$ and ${}^{\cdot}O_{2}{}^{-}$ in the reaction system, demonstrating the details for the intermediate steps of the O₂ present catalysis of TMB oxidation. Their results also indicate that the generation of singlet oxygen (${}^{1}O_{2}$) and superoxide anion (${}^{\cdot}O_{2}{}^{-}$) is temperature dependent.



Figure 4. Schematic review of POD-like activity and OXD-like activity. (a) The optimized structure of Fe_3O_4 (111).¹²⁵ (b) The adsorption structure, E_{ads} and d_{O-Fe} of $H_2O_2^*$, H_2O^* , OH*, and O*.¹²⁵ Reproduced from ref.125 with permission from Wiley-VCH, Copyright 2022 (c) Schematic illustration of the catalytic mechanism of ph-CDs-Fe.¹²⁶ Reproduced from ref.126 with permission from Wiley-VCH, Copyright 2023 (d) Schematic illustration of cascade enzymatic activity of Fe/N-MCN in enhancing ferroptosis.¹³² (e) Electron spin resonance

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(ESR) spectra-measured ${}^{1}O_{2}$, O_{2}^{-} and $\cdot OH$ in different reaction conditions with/without the presence of O_{2} , $H_{2}O_{2}$ and NIR.¹³² Reproduced from ref.132 with permission from Elsevier, Copyright 2025.

The coordination structure of OXD-mimicking nanozyme can affect OXD-like activity. Liu et al. synthesized an axial O atom-modulated $Fe(III)N_4$ nanozyme. The reaction formulas of OXD-like catalytic activity are labelled below.

O-Fe (II)- N₄+ O₂≓O-Fe (III)- N₄+ ·O₂

O-Fe (II)- N₄+ H₂O₂→O-Fe (III)- N₄+·OH+2OH⁻

 $2 \cdot O_{2}^{-} + 2H_{2}O \rightarrow {}^{1}O_{2} + H_{2}O_{2} + 2OH^{-}$ (4)

Its catalytic reaction process was evaluated by DFT calculations.¹³⁶ It revealed that, by anchoring an axial oxygen atom on the FeN₄ active site, the symmetrical structure of the active site broke, causing the d-band center to approach the Fermi level. The tumor inhibition of the nanozyme was also evaluated. The *in vivo* tumor growth inhibition (TGI) rate of the material was measured to be 86.1%. Thanks to this remarkable TGI rate, the survival period of mice treated with O-Fe-N₄ extended up to 55 days.

4.2.3. GSHOx-like activity (GSH involved OXD-like activity).

Glutathione (GSH) is an intracellular peptide primarily involved in detoxification, free radical scavenging, antioxidation, and regulation of key cellular processes such as DNA synthesis and immune function.¹³⁷ In the presence of glutathione peroxidase, GSH reduces reactive oxygen species (ROS) that cause lipid peroxidation and cellular damage to prevent physiological oxidative stress damage in the mitochondria. However, to maintain homeostasis and balance ROS accumulation, tumor cells often counteract by increasing intracellular GSH levels (approximately four times that of normal cells). This elevated GSH content can lead to an efflux of View Pt based chemotherapeutic drugs from cells, leading to drug resistance. Additionally, it hinders the use of nanozyme platforms that introduce external ROS for mediated therapy.¹³⁷ Therefore, research on strategies to promote intracellular GSH depletion to modulate the tumor microenvironment (TME) has surged, aiming for more effective catalytic therapy.^{118, 138}

Fan et al. synthesized Fe-TCPP MOFs and explored their responsiveness to glutathione.¹³⁹ By analyzing the color change and the fluorescence signal intensity of (1) GSH-incorporated Fe-MOF-RP solution, they observed a GSH concentration-dependent reduction in $^{(2)}$ fluorescence intensity, accompanied by a notable color change as demonstrated in Figure 5a. This indicates that (3)a redox reaction between GSH and Fe³⁺ has taken place, leading to the oxidative consumption of GSH. They further evaluated the antitumor effect of Fe-TCPP MOF with laser on mice with melanoma with distal lung metastasis. The in vivo antitumor assessment shows good result induced by triggering strong immune response with GSH depletion in tumor sites.

Besides being oxidized with the involvement of oxygen (O_2) , GSH can also be oxidized with the presence of hydrogen peroxide or organic peroxides. Wu et al. characterized the ability to oxidize GSH of synthesized Fe_3S_4 nanozyme in the presence of H_2O_2 by DTNB (5,5'dithiobis (2-nitrobenzoic acid)) colorimetrv assessment.¹⁴⁰ The color change of DTNB is analyzed by measuring the absorption peak at 412 nm, which corresponds to the typical absorption peak of the reaction product between GSH and DTNB. The addition of Fe₃S₄ nanozyme resulted in a significant decrease of the absorption value, suggesting that the catalytic reaction between Fe₃S₄ nanozyme and GSH was effectively carried out. The antitumor effect assessment displayed in Figure 5b illustrates the superior antitumor ability of Fe_3S_4 nanozyme compared to the control group.

4.2.4. GOx-like activity (Glucose involved OXD-like activity)

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Glucose is an essential substance in tumor metabolism. Via aerobic glycolysis, glucose can be converted into the basis for cellular compounds, e.g. NADPH and ATP.¹⁴¹ Nanozymes with glucose oxidasemimicking activity (GOx) can effectively promote glucose consumption by decomposing glucose into gluconic acid and H_2O_2 .¹⁴² The depletion of glucose by GOX-mimicking nanozymes can also trigger hungerinduced apoptosis, and the produced H_2O_2 is also involved in other enzymatic reactions that trigger The ferroptosis-induced cell death. iron-based nanozyme modified with GOx-mimicking nanocatalysts can effectively enhance the nanozyme's cascade enzymatic activity to enhance the effects of tumor therapy.

One effective measure to achieve tandem enzymatic activity is to modify MOF materials with the natural GOx enzyme.¹⁴³ Liu et al. designed an ultrathin 2D Cu-TCPP (Fe) MOF with GOx adsorption to convert glucose into gluconic acid and H₂O₂, thereby promoting the production of highly toxic hydroxy radicals.¹³¹ Another newly-developed method for cascade enzymatic activity design involves attaching artificial GOx mimics, i.e. Au nanoparticles, to iron-based nanozymes. By attaching Au NPs to Fe₂O₃ nanoparticles, Zeng et al. produced Fe₂O₃/Au nanozyme with tandem enzymatic activity including GOx-like activity.144 The indigo-carmine method was employed to detect the presence of H₂O₂ produced from the oxidation of glucose. The tabulated result indicates that, similar to Au nanoparticles, Fe₂O₃/Au nanozyme exhibits GOx-like activity (6.4 U/mL). Additionally, the result of the cytometry test shown in Figure 5e demonstrates the nanozyme's excellent ability to trigger cell death.

4.3. CAT-like activity

Catalase (CAT) is widely present in all aerobic organisms and some anaerobic organisms. It is a hemecontaining enzyme that catalyzes the decomposition of less toxic hydrogen peroxide (H_2O_2) into oxygen (O_2) and water (H₂O).¹⁴⁵ By mimicking this activity, nanomaterialbased enzymes have broad application prospects in improving tumor hypoxia, antibacterial therapy, cardiovascular diseases, and biosensing, among other fields.^{146,147} Additionally, CAT-like activityew playsolina constant role in relieving the anaerobic environment within the tumor microenvironment to help enhance the cascade reaction efficiency.

Wang et al. synthesized a Fe-SA/N-BCNT SAzyme with mixed valence states of the Fe atom.¹⁴⁸ Its CAT-like activity was analyzed, revealing the results of the dissolved oxygen from the reaction of Fe-SA/N-BCNT in an excess H₂O₂ aqueous solution. While N-BCNT showed no oxygen evolution, the oxygen evolution index of Fe-SA/N-BCNT proved to be satisfying; with an increase of nanozyme concentration, the amount of oxygen produced increased synchronously. As shown in Figure 5c, the animal experiments on tumor suppression demonstrate the effective antitumor capability of the nanozyme, as characterized by tumor volume measurements. Additionally, the biosafety of the nanozyme was also evaluated.



Figure 5. (a) Fluorescence spectra of Fe-TCPP MOFs after the incubation with GSH.¹³⁹ Reproduced from ref.139 with permission from American Chemical Society, Copyright 2024 (b) Images of tumor at Fe₃S₄-injected mice (left) and photos of the dissected tumor from mice after the treatment.¹⁴⁰ Reproduced from ref.140 with permission from Elsevier, Copyright 2023 (c) Schematic

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on in vivo anti-tumor procedures; body weight, average tumor volumes, survival rate and tumor weights collected of different groups. G1: Control, G2; iRFA, G3: iRFA+TSN, G4: iRFA+Fe-SA/N-BCNT, G5: iRFA+TSN@Fe-SA/N-BCNT.¹⁴⁸ Reproduced from ref.148 with permission from Wiley-VCH, Copyright 2024 (d) In vivo bioluminescence imaging of 4T1-Luc tumor-bearing mice on the fifth and twentieth days.¹⁴⁹ Reproduced from ref.149 with permission from Elsevier, Copyright 2021 (e) The Annexin-FITC/PI apoptosis assay of Fe₂O₃/Au-PEG incubated with 4T1 cells.¹⁴⁴ Reproduced from ref.144 with permission from Elsevier, Copyright 2023.

4.4. SOD-like activity

Superoxide dismutase-like (SOD) enzymes are important antioxidants that catalyze the decomposition of superoxide radicals ($\cdot O_2^{-}$) in the microenvironment into oxygen (O_2) and the less toxic hydrogen peroxide (H_2O_2).¹⁵⁰ These enzymes serve as effective tools for removing reactive oxygen species (ROS), combating aging, and mitigating inflammation.¹⁵¹

The assessment of SOD-like activity is conducted inhibition by analysing the of pyrogallol autooxidation.¹⁵² Under alkaline conditions, pyrogallol undergoes autoxidation, resulting in a product that shows an absorption peak at 412 nm under UV-Vis analysis. Wang et al. characterized the SOD-like enzymatic activity of iron-phosphate based FePOs nanozyme using this method.¹⁴⁹ The UV-Vis result convey that in the absence of FePOs, the pyrogallol solution exhibits a strong absorption peak at wavelength 320 nm; however, this peak declines rapidly upon the addition of FePOs. The tumor inhibition ability of FePOs was evaluated using in vivo bioluminescence imaging of 4T1-Luc tumor-bearing mice on the 5th and 20th day of treatment. As shown in Figure 5d, tumors in mice treated with H₂O₂ and FePOs disappeared after 20 days, while for the other mice grew or remained constant.

Conclusion and Prospectives

Iron-based nanozymes have emerged as a potent tool for tumor therapy through their ability to induce

ferroptosis, a regulated form of cell death characterized by iron-mediated lipid peroxidation. This review has examined various categories of iron-based nanozymes, including iron oxides, single-atom nanozymes, and ironbased MOFs, with each offering unique advantages in modulating reactive oxygen species (ROS) and disrupting cellular homeostasis in tumors. Their enzymatic activities-mimicking peroxidase, oxidase, catalase, and superoxide dismutase-enable precise control over ROS production within the tumor microenvironment (TME), thereby enhancing ferroptosis and reducing off-target toxicity to surrounding healthy cells. By integrating these catalytic properties with tumor-selective targeting mechanisms, iron-based nanozymes offer a promising approach to addressing therapeutic challenges like drug resistance and the need for targeted treatment. However, there are still problems existing in the clinical application regarding tumor treatment of iron-based nanozyme.

Notably, the biosafety of iron-based nanozymes requires further investigation, particularly for widely studied but high-risk nanozymes such as iron oxide nanoparticles. It has been proved that bare Fe₃O₄ nanoparticles possess low stability in physiological environment and would generate harmful radicals in vivo.54 While previous research has also demonstrated solutions for increasing the stability and biocapability by coating with certain materials, including polymer materials¹⁵³ and Au shell¹⁵⁴. Furthermore, engineering pH-responsive coatings or enzyme-mimicking active sites (e.g., Fe-Nx centers) could enhance release enabling differentiation specificity, between pathological and healthy microenvironments. These chemical designs not only mitigate biosafety concerns but also relieve the translational potential risk of ironbased nanozymes.

Furthermore, the selectivity of enzymatic activity over redox substrates is a vital issue that should be combatted for enhanced ferroptosis efficiency. As demonstrated in the previous passage, for POD-like activity and CAT-like activity which both involve H_2O_2 as a reactant, the competitive reactions would limit the generation of ROS. Therefore, analyzing the competitive

effect between these activities by modulating the structure of nanozymes, including the atomic distance of active sites and atomic defects on the nanozyme surface, is a possible future research direction of nanozyme development and design.

As a novel developed measure for clinical tumor therapy, nanozymes have been proved to exhibit tumor cell eliminating ability on mouse tumor models. However, current research prospects are based mainly on tumor cell lines, e.g. Hela and 4T1, inoculated on mouse models, while the effect of triggering ferroptosis by nanozymes targeting specific tumor modelling, including lung cancer, colorectal cancer, hepatocellular carcinoma, gastric signet ring cell carcinoma, has unusually been reported. With the primary purpose of accelerating the clinical translation of nanozymes, the study based on specific tumor modelling of nanozymes should be applied in future nanozyme research.

In conclusion, further exploration based on novelly evolved analytical measures e.g. artificial intelligence (AI) and cryo-electronic microscopy (cryo-EM) is required to improve the catalytic mechanism of nanozymes. A thorough understanding of structureactivity relationship is essential to optimally design high performance nanozymes. Although theoretical measures including density functional theory (DFT) calculations and machine learning have been applied to predict the catalytic activity of nanozymes, the cost of these measures are still high, and there are challenges surrounding differences in actual versus experimental catalytic activity results predicted by DFT. Therefore, the accumulation of results from further research would greatly enlarge the 'database' of nanozyme, thereby providing a promising theoretical basis for the application in tumor therapy of nanozymes.

Author contributions

C.D. and Z.Y. contributed equally to this work, regarding the writing, editing and finalization of the manuscript. J.G. conceived this work. C.J.Z., H.C. and J.G. revised the manuscript. All authors read and approved the final manuscript.

Conflicts of interest

There are no conflicts of interest to declare. View Article Online DOI: 10.1039/D5NR00880H

Data availability

Data availability does not apply to this article as no new data were created or analyzed in this study.

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Data Availability Statement

No primary research results, software or code have been included, and no new data were generated or analyzed as part of this review.