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Nanozymes with biomimetically designed properties for cancer treatment

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Nanozymes, as a type of nanomaterials with enzymatic catalytic activity, have demonstrated tremendous potential in cancer treatment owing to their unique biomedical properties. However, the heterogeneity of tumors and the complex tumor microenvironment pose significant challenges to the *in vivo* catalytic efficacy of traditional nanozymes. Drawing inspiration from natural enzymes, scientists are now using biomimetic design to build nanozymes from the ground up. This approach aims to replicate the key characteristics of natural enzymes, including active structures, catalytic processes, and the ability to adapt to the tumor environment. This achieves selective optimization of nanozyme catalytic performance and therapeutic effects. This review takes a deep dive into the use of these biomimetically designed nanozymes in cancer treatment. It explores a range of biomimetic design strategies, from structural and process mimicry to advanced functional biomimicry. A significant focus is on tweaking the nanozyme structures to boost their catalytic performance, integrating them into complex enzyme networks similar to those in biological systems, and adjusting functions like altering tumor metabolism, reshaping the tumor environment, and enhancing drug delivery. The review also covers the applications of specially designed nanozymes in pan-cancer treatment, from catalytic therapy to improved traditional methods like chemotherapy, radiotherapy, and sonodynamic therapy, specifically analyzing the anti-tumor mechanisms of different therapeutic combination systems. Through rational design, these biomimetically designed nanozymes not only deepen the understanding of the regulatory mechanisms of nanozyme structure and performance but also adapt profoundly to tumor physiology, optimizing therapeutic effects and paving new pathways for innovative cancer treatment.

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1. Introduction

Nanozymes represent a groundbreaking and distinctive class of nanomaterials that have come to the forefront with the evolution of nanoscience. These materials showcase the ability to catalyze reactions, much like enzymes, challenging the old view of nanomaterials as merely inert in biological systems.[1,2] Now, they stand on par with proteins and nucleic acids as key players in biological catalysis. What sets nanozymes apart from traditional synthetic enzyme mimics is their unique nanostructure, which is the key to their high and adjustable catalytic efficiency. Research has consistently shown that tweaking these nanostructures, such as size and shape, can dramatically boost their catalytic performance.[3] The versatility of these structures also allows some nanozymes to possess multiple enzymatic activities. The hallmark of nanozymes lies in their multifunctionality, blending their catalytic prowess with the distinct physical and chemical properties of nanomaterials, like magnetic and photothermal features. This fusion makes nanozymes a versatile tool with promising applications in the realm of biomedical science.

Nanocatalysis in medicine is an exciting field that links nanomaterials, chemistry, enzymology, and medicine,[4] and is progressively being applied in research areas ranging from *in vitro* testing to the diagnosis and treatment of cancer,[5] inflammation,[6] infectious diseases,[7] and degenerative diseases.[8] These interdisciplinary studies between medicine and

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engineering have validated the feasibility of utilizing nanocatalysis to intervene in the pathophysiology of diseases. Thanks to a deep understanding of tumor oxidative stress regulation mechanisms and the characteristics of the tumor microenvironment (TME), nanocatalytic therapy, by modulating intracellular and extracellular redox levels, induces reactive oxygen species (ROS) including hydroxyl radicals ($^{\bullet}OH$), singlet oxygen ($^1O_2$), and superoxide radicals ($O_2^{\bullet-}$), thereby directly killing tumor cells.[9] This opens a new paradigm for cancer treatment. However, the effectiveness of solo nanocatalytic therapy is limited, with weak anti-tumor responses, and it cannot fundamentally suppress the development, and recurrence of tumors.[10] Recent research indicates that there are complex biological interactions between cancer cells and the TME. Tumors can alter the TME, and the TME can also affect the growth and invasion of tumors.[11] Tumor cells have an antioxidant system that can resist and adapt to oxidative stress damage through pentose phosphate pathway, either by producing more nicotinamide adenine dinucleotide phosphate (NADPH) or upregulating antioxidant transcription factors.[12,13] The unique biochemical and metabolic characteristics of the TME,[14] such as hypoxia, lower pH, high concentrations of glutathione (GSH), as well as immune tolerance and immunosuppressive mechanisms in the immune cells of the TME.[15] These conditions significantly reduce the stability, sustainability, and effectiveness of nanocatalytic therapy. Therefore, the ideal nanocatalysts for future anti-tumor therapy should improve catalytic activity, control reaction stability and sustainability, and possess multifunctionality to enhance tumor specificity, alleviating tumor hypoxia, blocking immune checkpoints, and re-regulating tumor metabolism to enhance the therapeutic effect of nanocatalytic therapy.

Developing effective strategies for designing high-performance nanozymes has always been a central issue in nanozyme research. Unlike natural enzymes, nanozymes can be synthesized from scratch, offering the advantage of controlled design and synthesis.[16] In recent years, driven by practical applications, the design and synthesis of nanozymes have gradually evolved bionic design strategies by deeply analyzing and understanding the key structural sites, spatial conformations, mechanisms of reaction processes, and the catalytic activity and specificity involved in natural enzymes.[17,18] Drawing inspiration from the structure of natural enzymes, biomimetic single-atom nanozymes have been engineered to mimic their metal–N_x active sites.[19] These nanozymes boast customizable geometrical structures and electronic coordinations, distinctive quantum size effects, and optimal atomic utilization.[20] Additionally, biological enzyme cascade reactions are known for their high substrate concentration, efficient mass transfer, and minimized intermediate breakdown.[21] This has guided the development of biomimetic cascade reaction systems using nanozymes, focusing on their catalytic processes.[22,23] However, understanding nanozyme catalytic activity and physical–chemical properties indicates that merely enhancing their enzyme-like functions is not enough to tackle the complexities of the TME effectively.[24,25] It is also essential to combine the inherent characteristics of nanomaterials to endow nanozymes with new biomimetic functional requirements, such as combining with other treatment methods[26] or reshaping the TME[27] through catalytic reactions to build a cyclic reaction system.[28] Ultimately, this improves the specificity and effectiveness of cancer treatment. To our knowledge, a theoretical summary of the design and application of nanozymes based on biomimetic design strategies is still lacking.

Therefore, this review focuses on nanozymes capable of biomimetic design from *de novo*, systematically summarizing the design strategies of structural biomimetics, process biomimetics, and functional biomimetics of nanozymes, as well as their application progress in anti-tumor diagnosis and treatment. We believe that a deep analysis of the relationship between structural components, reaction processes, multifunctionality, and catalytic therapy performance in the biomimetic design philosophy of nanozymes will lay a theoretical foundation for the evidence-based biomimetic design of nanozymes for cancer diagnosis and treatment. This is of great significance in breaking through the bottleneck in the biomedical transformation research of nanozymes.

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2. Biomimetic design of nanozymes

The strategy of biomimetic design has proven to be both viable and efficient in enhancing the enzyme-like catalytic activity and therapeutic efficacy of nanozymes.[29,30] Initially, nanozyme research primarily depended on arbitrary synthesis and sequential activity testing to discover highly active nanozymes.[31] However, due to lacking solid theoretical guidance and high-throughput screening techniques, turned out to be cumbersome and inefficient, and it did not significantly advance the catalytic efficiency of nanozymes.[32] Moreover, the diverse composition, complex structure, and unclear catalytic

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sites of nanomaterials have left the mechanism of nanozymes in catalytic reactions still unclear. Past studies suggested that higher catalytic activity in nanozymes often requires a smaller size, larger surface area, higher specific surface area, more open and exposed crystal faces and dangling bonds, higher nanozyme density, unsaturated surface coordination, high-energy surfaces, low surface energy, and specific surface modifications.[33,34] In recent years, backed by research into the catalytic mechanisms of nanozymes, researchers have started designing and optimizing nanozymes for specific applications from scratch by mimicking the structure, process, and function of natural enzymes.[35,36] This approach in structural biomimetics, process biomimetics, and functional biomimetics has paved new ways for designing and synthesizing nanozymes with enhanced catalytic activity, specificity, and selectivity.[17] The concept of biomimetic design is expected to actively expand the application of nanozymes in the biomedical field, especially in integrated platforms for anti-tumor diagnosis and therapy.

2.1. Structural biomimicry of nanozymes

Reactive enzymes in living organisms have gradually evolved into the most compatible substrate-active center-specific catalytic pairs over a long period. The intrinsic catalytic activities of natural enzymes are highly dependent on their structures. For example, *N*-acyl homoserine lactones amide hydrolase has a hydrophobic substrate-binding pocket that confers C12 fatty acid-like chain recognition.[37] Lignin peroxidase can catalyze substrate oxidation with a high redox potential, as in the case of the low electron density heme active site.[38] This characteristic of natural enzymes has inspired the structural biomimetic design of artificial nanozymes. We believe that biomimetic-based enzyme structure design is function-guided rather than the trial-and-error approach of random synthesis and batch screening of nano-enzymes. Currently, the widely reported methods for structural bionics can be classified into three categories: active center engineering, surface modifications, as well as geometric and chiral structure modulation (Fig. 1). Meanwhile, multiple biomimetic approaches are often combined in practical synthesis in pursuit of better results.[39–42] This chapter focuses on biomimetic designs inspired by the structures of natural enzymes, with emphasis on the aforementioned three kinds of strategies.

2.1.1. Active site engineering. Mimicking the active center structure of a natural enzyme is one of the most widely reported strategies for structural biomimetic design. Active centers can be metallic or non-metallic elements, and the dispersed active sites generated by defective structures can also collaborate to assist the catalytic reaction.

2.1.1.1 Classical metallic and non-metallic site structures. Metal sites in enzymes play important roles in catalysis, such as stabilizing charge, stabilizing free radicals, increasing system acidity, and so on.[43] A class of porous nanomaterials possessing a structure similar to that of metalloproteinases in biomass are metal–organic frameworks (MOFs), which consist of metal ions or metal clusters connected by organic linkers. In addition to the biomimetic structures, MOFs also have some inherent characteristics that can aid the improvement of the catalytic performance, such as high specific surface area, tunable pore size, abundant and uniformly dispersed active sites, and multiple interconnected channels.[44]

MOFs such as those based on iron,[45] copper,[46] and zirconium[47] have been developed as biomimetic nano-enzymes and the catalytic ability can be enhanced by doping various metal elements or incorporating multi-element alloy nanoparticles as active sites.[48] We can either mimic the MOF system for better catalytic performance or take full advantage of its robust restriction framework as a carrier for biomimetic enzymes. MOFs with copper centers are often developed as biomimetic nano-enzymes. By mimicking the trinuclear isocenter structure of natural catechol oxidase, Li *et al.*[49] prepared MOF-818, which selectively and efficiently catalyzes the oxidation of catechol to the corresponding *o*-quinone structure, illustrating its superiority to conventional oxidases (OXDs) (Fig. 2A). In addition to traditional crystalline MOFs, Liang *et al.*[46] synthesized an amorphous multicopper-centered MOF nano-enzyme using nucleotides as ligands, which structurally and functionally mimics the natural multi-copper metalloenzymes, namely laccases. The nucleotide itself as a ligand brought about asymmetry and the high flexibility of copper ions, resulting in a partially amorphous MOF structure. Compared to natural laccases, this MOF-based laccase-mimic exhibited a higher catalytic rate, better stability over long-term storage, and stronger robustness in harsh conditions, such as extreme pH, temperature, and salt. MOFs also play an important role as a carrier, where enzymes are dispersed within the frameworks to achieve high reaction activity and stability. Scaffolds for natural enzymes are usually composed of biomolecular polymers such as peptides. They provide a relatively confined environment, support the active sites, and provide specific spatial organization. The solid support of MOF allows the enzyme to exert better activity. For example, Wang group anchored Pt single atoms as active catalytic sites in MOFs and encapsulated them to bring about high catalase (CAT) mimetic activity.[50]

We believe that constructing MOF structures will continue to be an important approach for future nanozyme mimicry and there is huge room awaiting to be explored. For example, the pore structure of MOFs can be further modified to improve mass transfer capacity, and multi-catalytic centers can be constructed to achieve synergistic effects, or amorphous and crystalline MOF heterostructure can also be attempted to synthesize.

Unlike traditional complex enzyme systems, single-atom nanomaterials with well-defined geometries and electronic structures can mimic the highly evolved catalytic centers of natural enzymes to achieve the highest atom utilization efficiencies, such as iron-nitrogen core single-atom nanozymes that mimic the local coordination environment of heme.[51] They usually exist in the form of isolated active metal centers anchored to suitable carriers, which allows the catalytic potential of the mimetic enzyme to be fully realized. It is important

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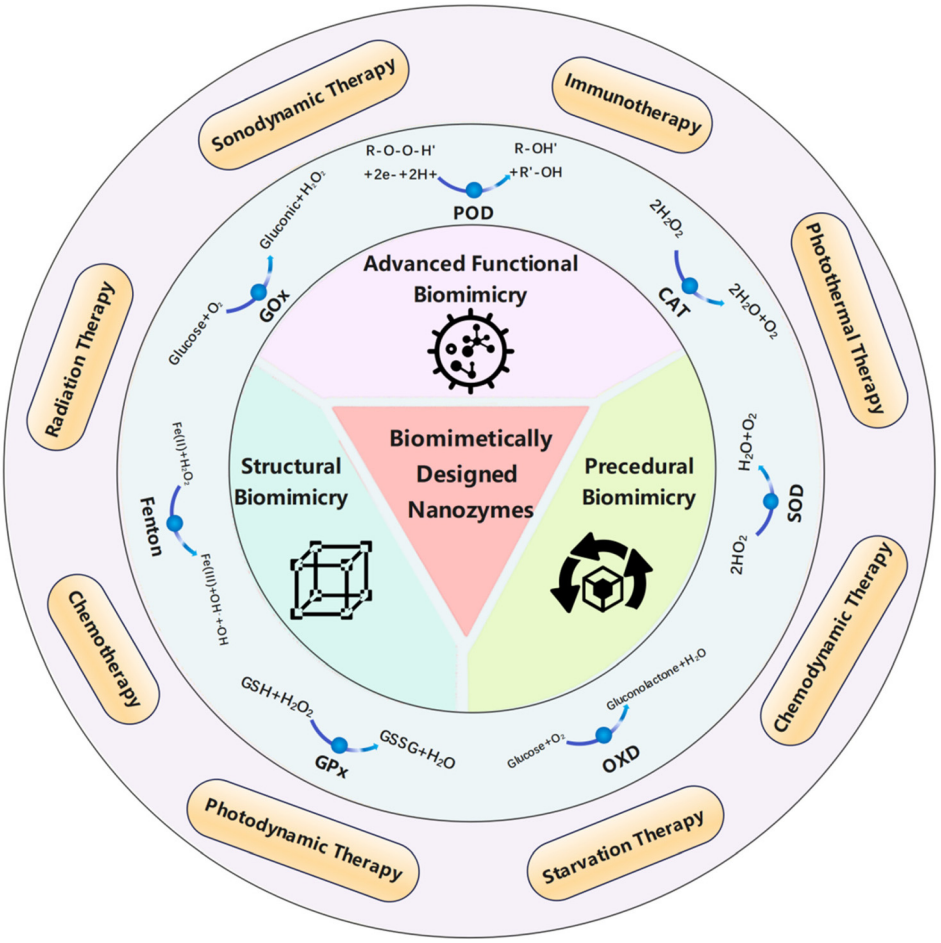

Fig. 1 Basic aspects of the structure, procedure and advanced functions of biomimetically designed nanozymes and their biomedical applications in anti-tumor treatments.

to note that the active centers of single-atom nanozymes are not simply zero-valent metal atoms, but rather the metal centers are coordinated with other atoms (such as nitrogen and phosphorus) of the carrier. The final microstructure formation of single-atom nanozymes is inextricably linked to the synthesis process, and the carriers should ensure close integration with the enzyme body and have a certain degree of stability. For example, Liu *et al.*[40] prepared Fe single-atom nanozymes by using $Fe(NO_3)_3$@ZIF-8 as the precursor and subsequent carrier for better iron source adsorption and site distribution. Huang *et al.*[51] developed an oxidoreductase-like single-atom nanozymes with a FeN_5 active center (FeN_5 SA), which resembles the structure of a cellular P450 active center. Specifically, a carbon nano-framework was used to restrict the formation of Fe sites, which were further reconstructed into FeN_4 at high temperatures, and ligated to form thermodynamically stable FeN_5/C sites. Similarly, Xu *et al.*[52] just replaced the nitrogen source to obtain the FeN_5 structure directly. In addition to single N coordination, other non-metallic elements such as B[53] and P[54] can be introduced to bring more variable microstructures.

Various metals have been explored as the active centers of single-atom nano-enzymes in addition to Fe and Cu that are common in biological enzymes, such as Ir,[55] Zn,[53] and Mn.[56] As shown in Fig. 2B, Zhang group[55] prepared RhN_4 and VN_4 single-atom nano-enzymes, which displayed much higher CAT-like and glutathione peroxidase (GPx)-like activities compared with the corresponding natural enzymes, respectively.

Carbon materials are excellent candidates for single-atom nanozyme carriers. For example, environmentally friendly and biocompatible carbon dots have abundant dangling bonds, such as $-NH_2$, –OH, and C═O, thus can easily anchor metal ions and prevent the agglomeration of metal sites. Zhang *et al.*[57] used carbon dots as carriers and developed Pt single-atom nano-enzymes that can be easily assembled and disassembled. N-doped hollow carbon spheres can be used as carriers for Cu single-atom nanozymes, in which the active center is CuN_4, as demonstrated in the work of Lu *et al.*[58]

There are also some interesting structures derived from traditional metal-site structured enzymes or single-atom nanozymes. For example, inspired by the natural heme copper oxidase with a dinuclear active site, Jiao *et al.*[59] made the first

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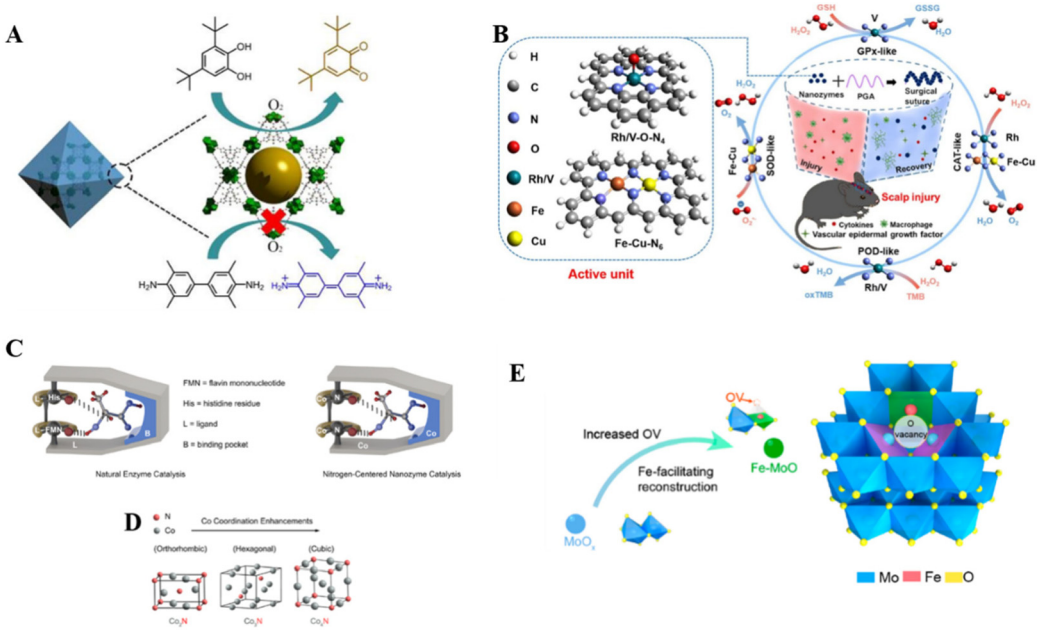

Fig. 2 Active site engineering. (A) Schematic illustration of selective catalysis by biomimetic MOF-818 nanozymes. Reproduced from ref. 49 with permission from American Chemical Society, copyright 2022. (B) Rh/V–O–N_4 and Fe–Cu–N_6 active unit. Reproduced from ref. 55 with permission from Springer Nature, copyright 2022. (C) Comparison of natural enzyme catalytic models and N-center nano-enzymatic catalytic models; (D) crystallographic transition due to change in Co coordination number. Reproduced from ref. 61 with permission from the American Chemical Society, copyright 2023. (E) Fe doping causes substitution defects and oxygen vacancies (OVs) in Fe–MoOv nanozymes. Reproduced from ref. 62 with permission from the American Chemical Society, copyright 2021.

attempt to construct the Fe_2NC diatomic nanozymes, which have an Fe_2N_6 active site that accelerates the O–O cleavage. The Fe–Cu–N_6 active unit synthesized by Jana *et al.*[60] is a large expansion of traditional single-atom nanozymes, because the lattice strain as well as the electron coordination effect brought about by such alloying contributes to the enhancement of the enzyme-like activity and the increase in the number of reaction sites.

Although most enzymes use metallic elements as active centers, some enzymes use non-metallic elements as catalytic centers, such as lactate oxidase (LOX). Given that the nitrogen atom plays an important role in natural enzymes as a catalytic center with electron-rich properties, Zhao *et al.*[61] were inspired to optimize the electronic configuration around the N center (Fig. 2C), and the performance of LOX was sufficiently approached by adjusting the number of Co atoms coordinated to the N center. As shown in the simulated model in Fig. 2D, N-centered components borrowed from the structure of natural enzymes, and underwent different lattice transitions, causing changes in electronic structure. This non-metallic element center mimicry enriches the family of mimetic nanozymes.[31]

2.1.1.2 Defect-derived multiple active sites. Defects usually have higher energy than conventional ordered structures, and the artificial introduction of vacancies, substitutions, or dopants in nanomaterials can effectively mimic the distribution of active sites in natural enzymes and their spatial cooperation.[31] Unlike the well-defined structural metallic or non-metallic sites discussed in the previous section, defect engineering brings about highly dispersed active sites, which act synergistically with each other to trigger multiple enzyme activities. Wu *et al.*[63] discussed in detail and summarized the implementation strategies of nano-enzyme defect engineering, such as the formation of OVs, metal element doping, and amorphization of the enzyme to make the man-made enzyme mimic the binding and catalytic properties of the natural enzyme. Among them, the construction of OVs can effectively regulate various free radicals, so that these ROS can efficiently kill cancer cells.[64] Specifically, oxygen vacancy defects bring about an optimized energy band structure that can interact with oxygen-containing substances, assisting the production of ROS and greatly enhancing the catalytic effect.

Yu *et al.*[62] pioneered in utilizing defect engineering to develop structural biomimetic nano-enzymes, which provided the cognitive basis for subsequent defect-based studies. They used MoO_x as a starting material to prepare Fe-MoOv nanozymes with substitution defects and OVs by Fe doping (Fig. 2E). Similarly, Cu doping has also been reported.[39] The OVs acted as substrate pockets, and the Fe-substituted metal sites promoted the optimization of the adsorption energy of the ROS intermediates, which ultimately resulted in enhanced redox catalysis. Dong's team[41] also used defect engineering to integrate active sites. They doped CeO_2 with Fe to obtain a Fe–CeOv defective structure, in which Fe and O act as key synergistic active centers. Unlike the previous work, they used a hollow mesoporous structural template, and subsequently additional

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modifications were made. At the same time, such as doping and vacancy-induced defects, the mechanistic explanation of their promotion of catalytic reactions often requires the aid of theoretical DFT. In future work, multiple defect construction methods could be used jointly to obtain higher defect density and catalytic efficacy.

2.1.2. Surface modification

2.1.2.1 Loading of functional groups. The surface of nanozymes is the main site where catalytic reactions occur. Surface functional groups determine the affinity for the substrate substance and the nature of the enzyme surface charge. Loading functional groups on the enzyme surface by physical adsorption or chemical bonding is an intuitive and easy way to mimic the natural enzymes.

Modification groups can considerably increase the reaction rate by enhancing the interaction between substrates and reaction sites. For instance, Fan *et al.*[35] carried out pioneering work on surface modification mimicry. By mimicking the catalytic mechanism of horseradish peroxidase (HRP), in which imidazole His42 assists the substrate to reach the active site cavity for subsequent reaction through hydrogen bonding, they introduced histidine residues as modifying groups on the surface of Fe_3O_4 nanozymes, which brought about hydrogen bonding to help the adsorption of hydrogen peroxide (H_2O_2) on the enzyme and the cleavage of the O–O bond of H_2O_2, thus significantly enhancing the hydroperoxide affinity on the enzyme. Consequently, the H_2O_2 affinity as well as the catalytic efficiency were significantly improved (Fig. 3A and B). The flexible state of surface modifiers affects the effectiveness of the modification, and past studies have shown that ligands with an upright conformation on the nanomaterial surface achieve the maximum distribution density and improve the bioactivity.[65] Zhou group[66] made the first attempt to use deoxyribonucleic acid (DNA) modification to functionalize CuO nanozymes and achieved controlled polar adsorption of DNA (Fig. 3C). The fluorescence quenching ability of CuO in this study promoted DNA loading, and DNA fragments not only possess the flexibility to curl up to achieve high distribution density, but also stabilize CuO colloids, resulting in better enzyme stability.

Enzymes for oncology therapy need to be highly biocompatible, a property that can be conferred by the modifying groups on the surface. Most of the works use amino acid-based modifying groups for better biocompatibility.[67,68] Other modification groups are also available. Zeng *et al.*[69] used polypyrrole doped with copper and then polyethylene glycolised to produce nano-enzymes that fully bind to immune checkpoint blockers and exhibit strong immune efficacy (Fig. 3D).

Folic acid, as an appealing tumor-targeting molecule, was used by Nwahara *et al.*[70] for modification of phthalocyanine nanozymes, where the enzyme outer liposomes could be selectively conjugated with folic acid to improve *in vitro* photodynamic therapy (PDT) activity under hypoxic conditions. This is an example of a surface modification that improves the selectivity of the reaction. To take it a step further, the enantioselectivity of the enzyme can likewise be complemented by the introduction of appropriate surface modifiers.[71–74] It is worth noting that this kind of selectivity usually originates from a chiral structure, some chiral amino acids or metal ionic organics are commonly used to introduce chirality. Chen *et al.*[74] self-assembled thiols containing chiral zinc ion-binding head-

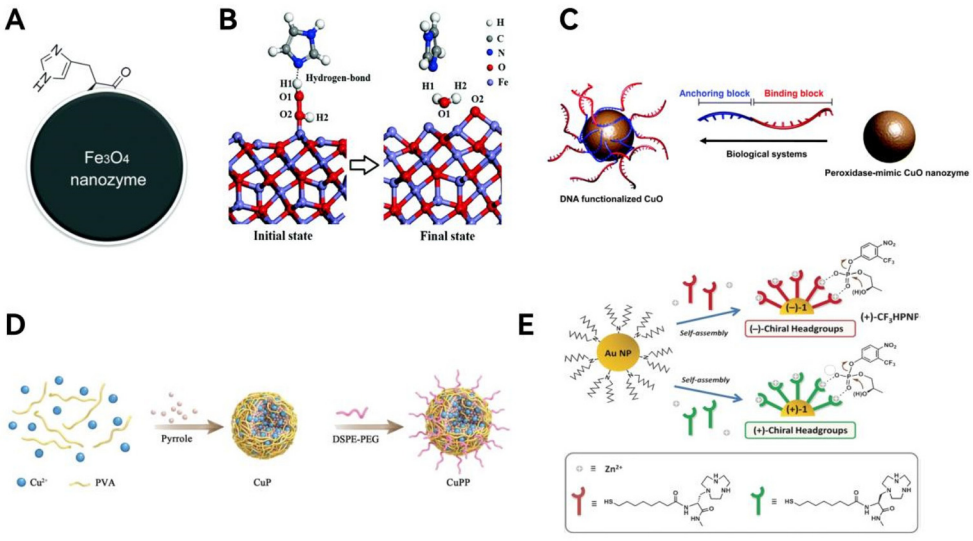

Fig. 3 Loading of functional groups. (A) Macroscopic schematic of histidine-modified nanozymes; (B) mechanistic simulation diagram of the catalytic effect of histidine. Reproduced from ref. 35 with permission from The Royal Society of Chemistry, copyright 2017. (C) Schematic diagram of dual DNA-functionalized CuO nanozymes. Reproduced from ref. 66 with permission from The Royal Society of Chemistry, copyright 2021. (D) Schematic introduction of surface modifying groups by polyethylene glycolization. Reproduced from ref. 69 with permission from Wiley-VCH, copyright 2022. (E) Modification of surface with chiral zinc ion complexes to form chiral selective nanozymes. Reproduced from ref. 74 with permission from Wiley-VCH, copyright 2016.

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groups on Au nanoparticles to obtain nanozymes possessing a chiral Au–Zn bimetallic catalytic site, which can subsequently enantioselectively discriminate and catalyze substrates, producing opposed activities for different chiral substrates (Fig. 3E). In another research, Chen *et al.*[73] used arginine as a capping agent to obtain chiral ruthenium nanozymes (denoted as D/L-arginine@Ru), which mimic both OXD and nitric oxide (NO) synthase activities and thus can simultaneously produce sufficient ROS and NO to induce tumor cell apoptosis and ferroptosis. It was found that L-arginine@Ru was more effective in this study because of the chirality-induced higher natural homology, catalytic activity, and cellular uptake.

In conclusion, surface modifications aim to improve enzyme catalytic reaction kinetics, stability, biocompatibility, and enantioselectivity. The selection of the modifying moiety can draw on the optimal interaction between the enzyme and substrate to achieve a biomimetic effect. We believe that surface modification will become an important part of biomimetic design by the simple post-treatment process.

2.1.2.2 Encapsulation in membranes. Apart from modifying the nano-enzyme surface with individual molecules, surface modification can also be achieved by wrapping nano-enzymes in integrated membranes. This biomimetic structural design is mainly inspired by the structure of biological cell membranes, which can bring about good biocompatibility and aid antitumor drug delivery. Meanwhile, this coated membrane can enhance the adhesion of the enzyme on tumor tissues, thus improving therapeutic stability.

The surface cladding can firstly enhance the target recognition ability and bring precise treatment. Such modifications can enable nanozymes that do not have targeting capabilities but have other advantages to show unexpected therapeutic effects. A representative work is that Duo *et al.*[75] wrapped the hollow MnO_2 enzyme in a circulating platelet (PLT) membrane to form a complete enzyme–membrane system. This PLT-wrapped MnO_2 enzyme fully combines the high drug-loading characteristics of the hollow material with the *in vivo* tumor-targeting ability of the membrane to enable the MnO_2 enzyme to play a greater role, and this modification work is easy to operate (Fig. 4A).

Besides, the cell membrane encapsulation structure can protect the encapsulated nano-enzymes from being cleared by the immune system, thus achieving long-lasting tumor therapy to a certain extent, as cell membranes possess certain biorecognition information.[40,76,77] The mechanism of this protection is the communication of endogenous information through cell membranes, which has a camouflaging effect and thus slows down metabolism and clearance in the body. Specifically speaking, Liu *et al.*[40] synthesized an iron-monoatomic type nano-enzyme encapsulated by A549 cell membranes, and this was used for the treatment of tumors in a long-lasting manner. The enhanced biocompatibility of the enzyme encapsulated by A549 cell membranes is reflected in the fact that it can achieve homologous binding to tumor tissues, preventing premature clearance by the body (Fig. 4B). In another case, the membrane spontaneously bends to fit the

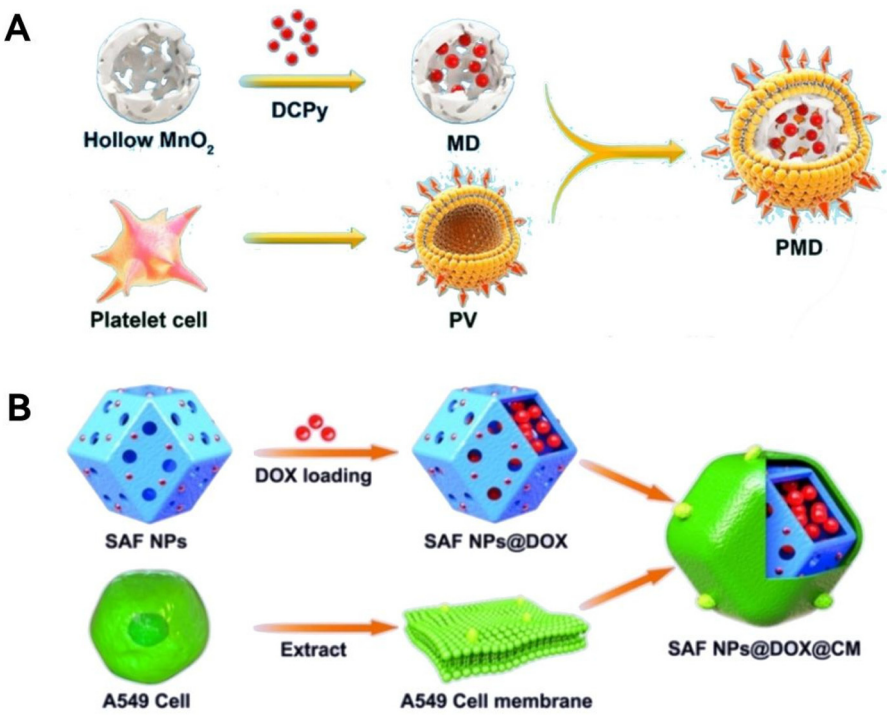

Fig. 4 Encapsulation in membranes. (A) A Scheme showing platelet cell membrane coated hollow MnO_2 that combines long-lasting therapeutic effect and high drug loading characteristics. Reproduced from ref. 75 with permission from American Chemical Society, copyright 2022. (B) Schematic representation of the single-atom nanozymes encapsulated in cell membranes. Reproduced from ref. 40 with permission from European Chemical Societies Publishing, copyright 2021.

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shape of the enzyme during synthesis. The structural design of cell membrane-encapsulated nanozyme is undoubtedly an excellent example of bionics, and this encapsulated structure brings enhanced targeting ability, therapeutic stability, and long-lasting efficacy, which is worth further development.

As shown in the diagram of Fig. 4B, the extraction of the cell membrane from the cell and the coating of the cell membrane onto the body of the nano-enzymes are two key steps in the realization of membrane coating, and it is particularly important to confirm the adaptability of different cell membranes for the extraction and the coating effect. It is also important to note that when surface modification is performed, the catalytically active sites should not be overly covered and obstructed, which can lead to a decrease in enzyme activity.[78] How to make a balance between wrapping and ensuring the number of active sites is a challenge for future work. Besides, the modifying agents need to be firmly anchored onto nanoparticle surface, otherwise they may gradually fall off as nanozymes circulate in the human body. Finally, the modifying agents need to be rationally selected in order to circumvent the involvement of harmful elements and substances to the human body.

2.1.3. Geometric structure mimicry. Natural enzymes have different morphologies depending on their functions, and these geometric characteristics determine their specific recognition function to some extent. For example, HRP activity is highly correlated with structural changes induced by the number of α-helical structures.[79]

The geometry of the mimetic enzyme should be designed in such a way that the active site is in a pocket of the substrate channel so that the center of redox can be spatially separated from the host solution.[80] Qileng *et al.*[81] attempted to construct a Pt nano-enzyme in which the active site is distributed in an internally segregated substrate channel, which exhibits a concave half-moon shape, and the reaction channel is artificially constructed by chemical etching (Fig. 5A and B). In addition to enzyme-specific geometries, the geometric features of microscopic organisms can also be mimicked. Inspired by the process of viral invasion into cells, Zhao *et al.*[42] modified silica matrix nano-enzymes into the shape of viruses to enable rapid response and meanwhile utilize the dense tentacles to achieve large specific surface area for high drug loading and drug delivery efficiency (Fig. 5C). The shape of the virus is suitable for cell adhesion and will aid cancer therapy. To summarize, specific geometries bring about specific confinement effects or specific biological interactions.

Chirality, as an element of geometric symmetry and a significant bio-structural analytical feature, is also included in the biomimetic design of nanozymes. Chirality is prevalent in nature, and the chirality of enzymes endows them with stereo-

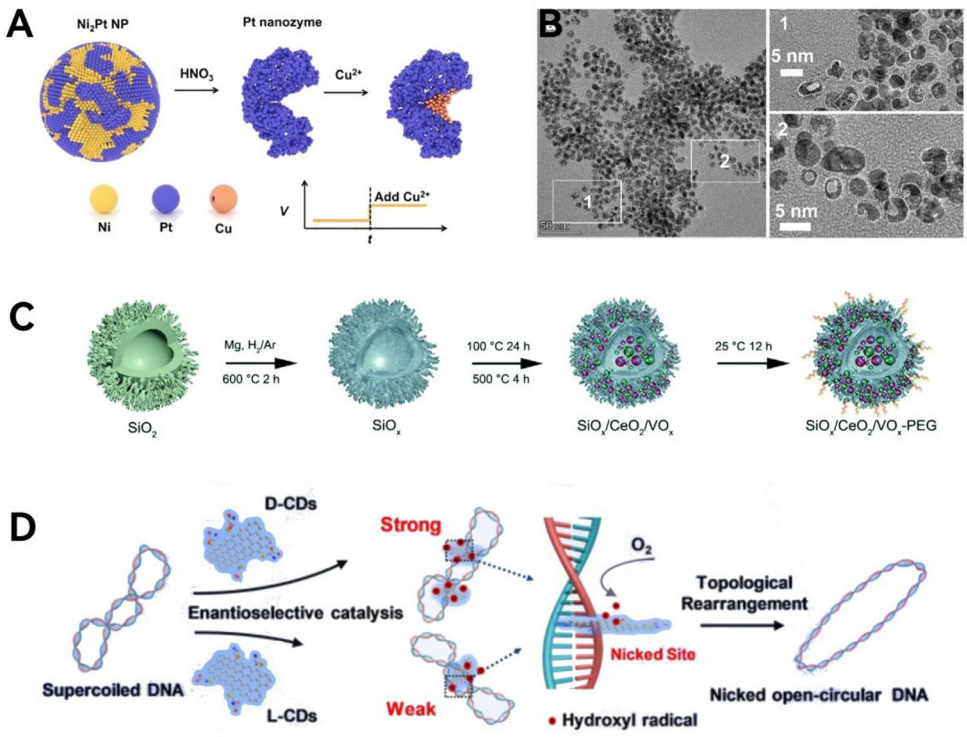

Fig. 5 Geometric structure mimicry. (A) Mimicking the concave side of the meniscus in natural enzymes. (B) Scanning electron microscope (SEM) images of the half-moon geometry structure. Reproduced from ref. 81 with permission from Elsevier, copyright 2022. (C) Schematic diagram of nano-enzymes modified into the shape of a virus. Reproduced from ref. 42 with permission from The Royal Society of Chemistry, copyright 2022. (D) Schematic illustration of the enantioselective chiral carbon dot mediated topological rearrangement of supercoiled DNA. Reproduced from ref. 83 with permission from Wiley-VCH, copyright 2020.

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specificity, which allows the enzyme to selectively act on only one specific stereoisomer when faced with different stereoisomers.[82] This property can be utilized to selectively kill tumor cells without attacking normal cells, so the study of chirality and geometrical mimicry has practical medical applications. Most of the chiral introduction methods of nanozymes are based on surface modification of chiral ligands and achieve good enantioselective catalytic effects, which have been discussed above.[71–73] In addition, Li *et al.*[83] demonstrated that chiral carbon dots, synthesized from cysteine, exhibit topoisomerase I mimetic activity. These carbon dots can mediate the topological rearrangement of supercoiled DNA in an enantioselective manner (Fig. 5D). More specifically, the intercalative binding of D-CDs with DNA double helix is stronger than that of L-CDs, thus D-CDs perform more efficiently in catalyzing the rearrangement of DNA. In summary, structural chirality has been introduced into nano-enzymes to improve the low enantioselectivity of the original artificial enzyme, thus achieving artificially controllable selective catalysis.

Unfortunately, geometrical mimicry of enzymes is relatively less studied at present compared with other mimicry strategies, partly because of the difficulty in investigating the mechanism of enhanced catalytic activity, and partly due to the complexity of synthesizing sophisticated structures. However, it is still valuable to biomimetic design some natural enzymes with well-defined geometrical conformational relationships and pay attention to their morphological changes during catalysis.

2.2. Procedural biomimicry of nanozymes

In biological systems, an enzyme often participates in multiple catalytic reactions, or various enzymes form complexes to create complex catalytic networks,[84] which carry out a series of crucial biochemical reactions, ensuring the normal physiological functions of the organism. For example, human cells contain various antioxidant enzymes like superoxide dismutase (SOD), CAT, and GPx, which together establish a comprehensive defense system based on antioxidant enzymes.[85] This system is essential for maintaining the redox balance within cells and protecting the body from oxidative damage.

Inspired by enzyme cascade reactions, nanozymes are designed to replicate the complex enzyme systems found in organisms, generating a series of synergistic and cascading enzymatic reactions.[86] This approach, known as process biomimicry, involves participating in and simulating specific life processes. Nanozymes with process biomimetic characteristics are based on multi-enzyme systems and often possess the synergistic catalytic activities of multiple enzymes,[87] mediating cascading catalytic reactions[88] or responding to specific environmental factors to regulate the catalytic process.[89] Compared to nanozymes with single enzyme activity, the concept of process biomimetic design offers tighter spatial structures and shorter diffusion paths for multi-enzyme catalytic reactions.[22] This broadens the types of catalytic reactions, facilitates smooth transitions between reaction steps, improves catalytic efficiency, and enhances therapeutic effects.

Multi-enzyme synergistic activity and multi-enzyme cascade reactions are classified based on the number of enzymes involved in the reaction. Multi-enzyme synergistic activity depends on one enzyme that exhibits two types of activities to convert substrates into products. Multi-enzyme cascade reactions involve two or more enzymes that catalyze different types of reactions, which can be categorized into five main types: linear, parallel, orthogonal, cyclic, and triangular. While current understanding of how nanozymes exhibit multi-enzyme catalytic activities is still evolving. The catalytic capabilities of nanozymes are influenced by various intrinsic characteristics, such as size, shape, surface modifications, and composition. Nanomaterials with multiple catalytic abilities can be customized for specific purposes through from-scratch design. An effective method for developing multi-enzyme mimetic nanocatalysts with varied activities is to hybridize two or more different materials. For example, graphene quantum dots/silver nanoparticles hybrids have shown high peroxidase (POD)-like activity and OXD properties. A hollow mesoporous Mn/Zr co-doped CeO_2 tandem nanocatalyst (PHMZCO-AT) exhibits tunable multi-enzymatic activities, specifically enhanced SOD- and POD-like activities while inhibiting CAT-like activity.[90] By encapsulating bimetallic nanocatalysts (Fe_2NC) within a selenium MOF (Se-MOF) shell, a bimetallic nanocatalyst with multi-enzymatic cascade capabilities has been constructed.[91]

Biomimetic design principles offer a clue: by studying the active centers of natural enzymes and applying these insights to the rational design of nanozymes, it is feasible to combine the active centers of various nanozymes into one. This innovative approach holds promise for creating nanozymes that demonstrate targeted synergistic activities, sequential cascade catalysis, and adaptability to environmental changes. Such advancement in nanozyme technology could significantly enhance their functionality and application potential in anti-tumor treatment fields.

2.2.1. Multi-enzyme synergistic activity. Nanomaterials with two or more enzyme-like functions are called multi-enzymatic nanozymes.[86] Back in 2012, Fan's team[34] made a pioneering discovery regarding Fe_3O_4 nanozymes. They found these nanozymes exhibit dual enzymatic activities, akin to POD and CAT, which are dependent on pH levels. Remarkably, these nanozymes can catalyze distinct reactions with the same substrate, H_2O_2, just by varying the pH conditions. This groundbreaking discovery opened up new possibilities in understanding and utilizing nanozymes in various scientific and medical applications. They can imitate the complexity and versatility of natural enzyme systems. Multi-enzymatic nanozymes, especially when compared to their single-enzyme counterparts, can significantly boost catalytic efficiency and exhibit synergistic effects (Fig. 6A), such as the combination of glucose oxidase (GOx) and POD, demonstrating stronger ROS generation capabilities. Designing these multi-enzymatic nanozymes is a more intricate process, involving the integration of various nanomaterials through methods like doping, hybridizing, or assembling to achieve the desired multi-enzymatic properties.

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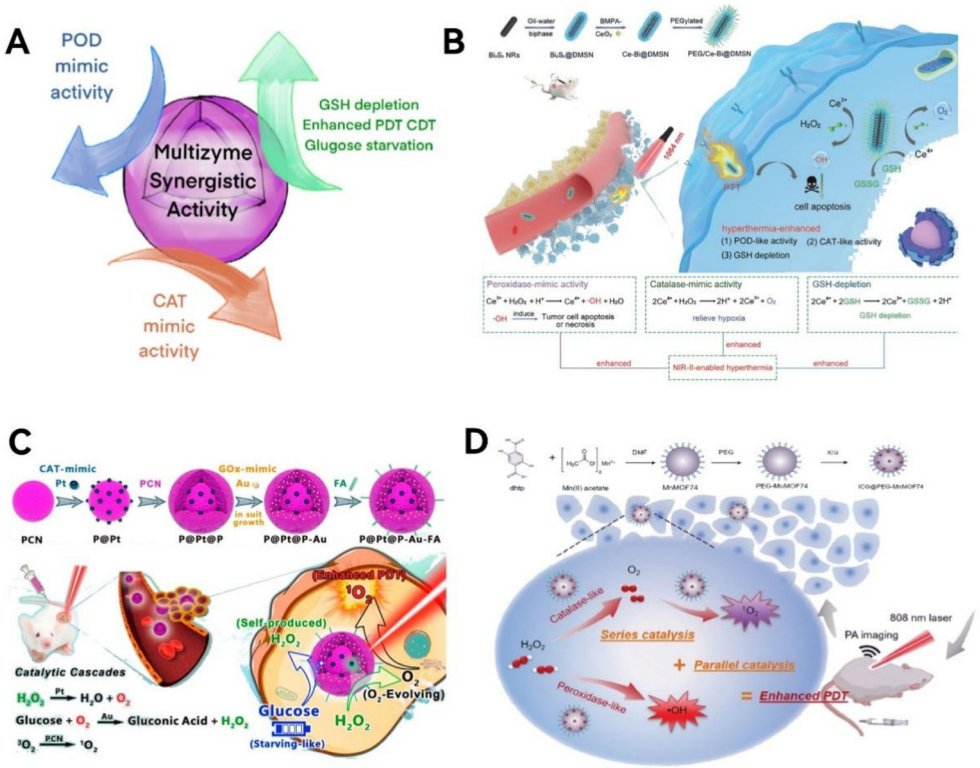

Fig. 6 Multi-enzyme synergistic activity. (A) Scheme illustration of the mechanism of multi-enzyme synergistic activity. (B) The PEG/Ce-Bi@DMSN nanozymes, featuring synergistic dual enzyme-mimic catalytic activities and GSH depletion, are designed for *in vivo* synergistic photothermal-enhanced nanocatalytic cancer therapy. Reproduced from ref. 92 with permission from WILEY, copyright 2020. (C) Pt NPs effectively reduce tumor hypoxia by catalyzing H_2O_2 into O_2, enhancing oxygen-dependent PDT, and are complemented by Au NPs that accelerate β-D-glucose consumption, synergizing with H_2O_2 for improved starvation therapy. Reproduced from ref. 94 with permission from the American Chemical Society, Copyright 2019. (D) The synthesis process of ICG@PEG-MnMOF74 nanoparticles with improved PDT capabilities that are realized through a series–parallel catalysis process. Reproduced from ref. 95 with permission from WILEY, copyright 2021.

Lin group[92] has developed a novel approach by first coating Bi_2S_3 nanorods with dendritic mesoporous silica (Bi_2S_3@DMSN) and then infusing these structures with ultra-tiny cerium dioxide nanozymes (Fig. 6B). This innovative design endows the nanozymes with the ability to mimic two key enzymes: POD and CAT. These nanozymes are particularly effective in adjusting the TME in acidic conditions. They have the dual capability of increasing oxidative stress while simultaneously reducing hypoxia, offering a promising strategy for targeted cancer therapy. Chen group[93] has created a $LaFeO_3$ perovskite nanozyme with a unique set of capabilities, mimicking four different enzymes: OXD, POD, GPx, and CAT. This nanozyme triggers a series of reactions that not only reverse the low-oxygen conditions often found in tumors but also deplete the natural antioxidant, GSH in cancer cells. This process leads to a continuous production of harmful ROS, effectively inducing cell death in densely packed breast cancer cells through pyroptosis.

To targeting overexpressed H_2O_2 and glucose within tumors. Liu *et al.*[94] investigated the potential advantages of platinum nanoparticles (Pt NPs) mimicking CAT and ultra-small "exposed" gold nanoparticles (Au NPs) mimicking GOx in tumor synergistic catalytic therapy (Fig. 6C). The porous porphyrin metal organic framework (PCN) with PDT and fluorescence imaging capabilities is the cornerstone supporting synergistic catalytic activity of non-toxic nanozymes. The production of ample oxygen by Pt NPs, catalyzed by endogenous H_2O_2, enhances the generation of cytotoxic $^1O_2$ during PDT induced by PCN under light exposure. This process also hastens the oxygen-dependent decomposition of glucose in tumors by Au NPs. Furthermore, catalytic therapy synergizes with starvation therapy by using the self-generated H_2O_2 as a substrate for the Pt NPs. The deployment of PCN-supported dual nanozyme systems to simulate catalytic reactions is poised to provide enhanced, TME-specific, and synergistic therapeutic outcomes.

To provide sufficient oxygen in the relatively hypoxic TME, Roy and colleagues[95] developed a Mn-doped MOF-based nanozyme, indocyanine green (ICG)@PEG-MnMOF74, composed of three key components: Mn-doped MOF74, the photosensitizer ICG, and the stabilizer polyethylene glycol (PEG) (Fig. 6D). It exhibits catalytic activities similar to POD and CAT, not only supplying oxygen for the production of $^1O_2$ in PDT but also generating $^{\bullet}OH$, thereby inducing Fenton reactions to enhance

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anticancer effects. This synergistic 'series–parallel catalytic pathway' significantly improves the therapeutic efficiency of PDT.

2.2.2. Multi-enzyme cascade catalysis. In biological organisms, multi-enzyme driven biocatalytic cascade reactions are crucial for maintaining normal physiological functions. A typical biocatalytic cascade involves at least two reactions, with each subsequent reaction starting only after the completion of the previous one (Fig. 7A), depending on the close coordination of multiple enzymes within the cascade system.[84] The main advantages of enzyme cascade reactions include high atom economy, reduced diffusion barriers, minimized reaction

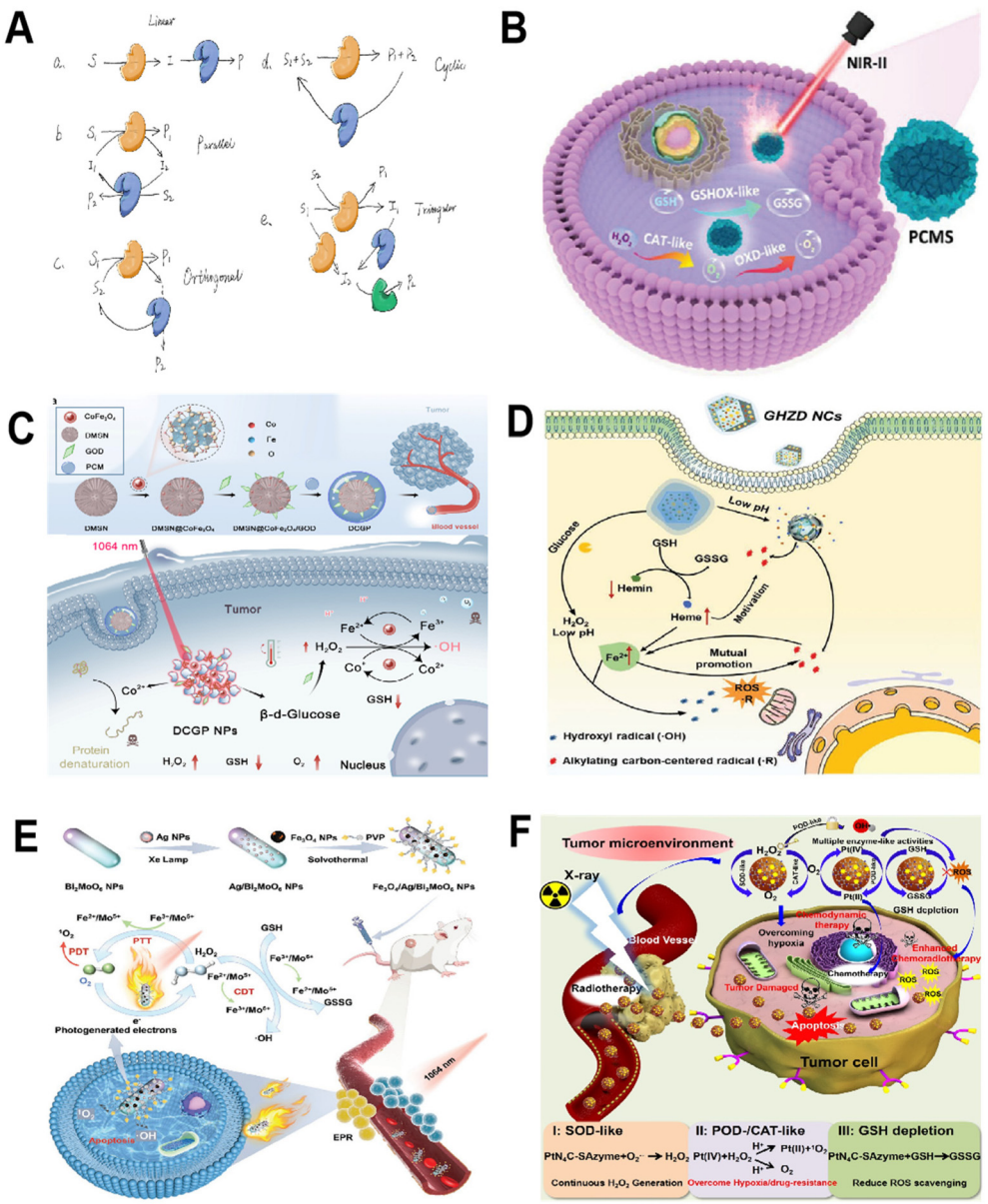

Fig. 7 Multi-enzyme cascade catalysis. (A) Scheme illustration of the reaction types of cascade catalysis system. (B) The mechanism of PCMS for photothermal-enhanced cascade catalytic therapy. Reproduced from ref. 96 with permission from WILEY, copyright 2023. (C) Under NIR-II illumination, $CoFe_2O_4$ nanozymes initiate a cascade catalytic reaction. Within this Co/Fe dual-cycle system, highly toxic ˙OH are produced. This reaction sequence is further intensified by the *in situ* consumption of GSH and the alleviation of hypoxia within the tumor environment, leading to a significant amplification of oxidative stress. Reproduced from ref. 97 with permission from American Chemical Society, Copyright 2022. (D) GHZD NC nanozymes significantly amplify endogenous oxidative stress within the TME by facilitating cascade reactions. This strategic augmentation of biocatalytic therapy, when used in conjunction with checkpoint blockade therapy, effectively orchestrates an anti-tumor immune response. Reproduced from ref. 98 with permission from WILEY, copyright 2021. (E) Fe_3O_4/Ag/Bi_2MoO_6 NPs utilize their multiple nanozyme activities and photodynamic properties to initiate and sustain cascade nano-catalytic reactions in the TME. Reproduced from ref. 99 with permission from WILEY, copyright 2021. (F) PtN_4C-SAzyme and its cascaded catalytic reaction in TME for synergistic enhanced CDT and chemoradiotherapy of tumor. Reproduced from ref. 100 with permission from Ivyspring International Publisher, copyright 2022.

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waste, and the increased local concentration of intermediates, which facilitates simple and efficient enzyme-catalyzed reactions.

Inspired by natural enzyme cascades, researchers are trying to design nanozymes with biomimetic cascade reaction characteristics. Nanozymes with multi-enzymatic activities are the material basis for simulating multi-enzyme cascade catalysis. Since different reactions in these cascades naturally lack affinity under identical conditions, immobilizing enzymes become a vital step in constructing these systems. Numerous effective enzyme immobilization techniques have been developed, including physical adsorption, covalent grafting, and *in situ* encapsulation.

Liu group[96] developed a polyethylene glycolated $Cu_xMn_yS_z$ (PCMS) featuring multiple oxidation states of manganese ($Mn^{2+/3+/4+}$) and copper ($Cu^{1+/2+}$) (Fig. 7B). PCMS showcases remarkable CAT-like and OXD-like cascade catalytic activities, efficiently converting endogenous H_2O_2 into O_2 and subsequently catalyzing O_2 in the TME to generate toxic $O_2^{\bullet-}$. Furthermore, PCMS possesses GOx-like activity, capable of depleting GSH, which amplifies its chemodynamic therapy (CDT) effectiveness. Remarkably, under near-infrared II (NIR-II) 1064 nm laser exposure, PCMS achieves an impressive photothermal conversion efficiency of 56.7%, enhancing its catalytic performance. *In vivo* studies have demonstrated PCMS's ability to effectively suppress tumor growth, highlighting its potential as a multifaceted agent for cancer therapy. Additionally, Yang and his team[97] developed an innovative nano-platform (DMSN@$CoFe_2O_4$/GOD-PCM) that integrates nanozymes and natural enzymes (Fig. 7C). This platform is crafted by embedding cobalt ferrite ($CoFe_2O_4$) bimetallic oxide nanozymes and GOx, a natural enzyme, into the pores of dendritic mesoporous silica (DMSN). When subjected to NIR-II illumination, the $CoFe_2O_4$ nanozymes produce heat. This heat, in turn, triggers the phase change material to release GOD. Upon its release, GOD initiates changes in the TME through the modulation of glucose metabolism pathways. This alteration leads to highly acidic conditions and the production of a significant amount of H_2O_2, setting off a series of catalytic reactions that can target tumor cells. Furthermore, Lin group[98] introduced an innovative approach by developing a novel nanozyme–drug conjugate known as GHZD NCs. They ingeniously combined GOx, trivalent iron protoporphyrin (hemin, Fe^{3+}), and dihydroartemisinin (DHA) within a zeolitic imidazolate framework 8 (ZIF-8) using a one-pot reaction method (Fig. 7D). This unique combination endows GHZD NCs with sustained enzymatic activities, including POD-, GOx-, and GPx-like functions. These activities are particularly effective in cancer cells that rely on glucose as their energy source. The GOx-driven glycolysis generates adequate H_2O_2 to sustain the creation of toxic $^{\bullet}OH$. Fe^{3+} serves a dual role, both as a POD generating $^{\bullet}OH$ and as a consumer of the GSH, crucial for GPx. This process transforms Fe^{3+} into ferrous (Fe^{2+}), disrupting iron balance and triggering DHA to produce carbon-centered radicals. This cascade, fueled by tumor-activated Fe^{2+}, perpetuates a lethal cycle of accumulating carbon-centered radicals. The resulting depletion of GSH and the formation of radicals amplify oxidative stress, intensifying the immunogenic cell death (ICD) effect and combating immunosuppressive tumors. This customized strategy improves the targeted action and efficacy in treating particular cancer cells. It refines the accuracy of ROS-mediated treatments while simultaneously reducing the inadvertent oxidative damage to healthy cells and tissues.

The effectiveness of catalytic therapy largely stems from the synergistic interplay between cascade nano-catalytic reactions and multi-enzymatic activities. This coupling ensures that the cascade reactions are both sustainable and capable of self-replenishment, crucial for maintaining their therapeutic efficiency. To address the challenge of sustaining cascade reactions within the TME, in an innovative approach, Dong and colleagues[99] developed a multifunctional nanoparticle, denoted as Fe_3O_4/Ag/Bi_2MoO_6 NPs. This particle showcases a range of nanozyme actions, emulating the functions of enzymes like POD, CAT, SOD, and GOx (Fig. 7E). Triggered by the TME, a series of nanocatalytic reactions continuously produce cytotoxic $^{\bullet}OH$ and $^1O_2$. The sustainability and self-replenishing nature of these reactions are ensured through a synergy of light activation, catalytic reactions, nanozyme activities, and the dynamic interchange between Fe^{2+}/Mo^{5+} and Fe^{3+}/Mo^{6+} ions. Moreover, Yong and colleagues[100] proposed a novel TME-responsive PtN_4C single atom nanozyme (SAzyme), capable of continuously self-replenishing H_2O_2, promoting the release of O_2 and Pt^{2+}, and depleting GSH, for tumor-specific cascade catalytic therapy (Fig. 7F). This system has the following advantages: (a) SAzyme can significantly enhance the production of OH and O_2 through POD- and SOD-like activities, as well as X-ray deposition capability, which helps oxygenate the TME for intensified CDT and O_2-dependent radiochemotherapy; (b) simultaneously, the self-recycling valence state change of Pt(IV) and Pt(II) leads to the continuous depletion of overexpressed GSH in cells and the release of a large amount of Pt^{2+}, ultimately overwhelming the antioxidant defense and enhancing tumor-specific therapy; (c) more importantly, PtN_4C SAzyme can also convert $O_2^{\bullet-}$ into H_2O_2, achieving sustainable replenishment of H_2O_2 at the tumor site, which can further react with PtN_4C SAzyme to realize the cyclic accumulation of $^{\bullet}OH$ and O_2.

To sum up, it is recognized that nanozymes, crafted from metal elements or amino acids that facilitate electron transfer, can replicate the catalytic reactions facilitated by various oxidoreductase enzymes.[101] The oxidation states of these metal elements play a crucial role in determining the multi-enzymatic activities of nanozymes.[102] A deeper understanding of these multi-enzyme mechanisms will be instrumental in designing nanozymes with enhanced activity and catalytic efficiency. Such advancements will not only boost the efficiency of nanozyme catalysis but also bolster their use in biomimetic processes, providing a strong theoretical foundation for future applications.

2.2.3. Microenvironmental response initiation. The exploration of the feasibility of synergy and cascade reactions

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mediated by multi-enzymatic nanozymes *in vivo* also requires consideration of the biological environmental factors affecting their biomimetic design.[103] This is due to the incompatibility of nanozyme catalytic conditions with physiological environments. Natural biological barriers in tissues and cells, such as vascular endothelium, cell membranes, lysosomal membranes, *etc*., could become barriers to the flux of substrates or products, hindering material transport and concentration maintenance, and limiting the continuous progress of cascade reactions.[104] With an increasing understanding of tumor cells and the TME, the physicochemical factors inside and outside the tumor and their changes could serve as mediums to help nanozymes achieve highly selective tumor-specific catalytic therapy. Thus, using environmental responses to regulate and activate specific enzyme-like activities of multi-enzymatic nanozymes is a viable strategy.[105,106] By applying or responding to specific stimuli, one can precisely and specifically regulate the onset and intensity of the nanozyme catalytic activities to accommodate the complex and varied environments inside and outside tumor tissues.[107] Therefore, the design of process-mimetic nanozymes needs to focus on enhancing environmental responsiveness, biological targeting, and spatiotemporal controllability.

Nanozymes with multi-enzymatic activities are more likely to exhibit environmentally responsive catalytic activities. Combining the characteristics of nanomaterials, they can mediate changes in enzyme-like catalytic reactions based on physicochemical factors such as pH, temperature, light, or magnetism.[108–111] Moreover, ideally, these nanozymes are designed to be highly selective, and activated by specific triggers related to the TME or external stimuli. This targeted approach enables them to precisely attack tumors or specific cancer cells, thus reducing the possibility of damaging healthy cells or tissues. Deng group[112] conducted pioneering work in introducing nitrogen-doped graphene materials (N-GNM) as catalysts to biomedical fields. The N-GNM they developed are characterized by strong biocatalytic properties and specifically tailored for targeted catalytic therapy of tumors (Fig. 8A). N-GNM functions as a nanozyme that emulates POD, boasting a unique structure and robust catalytic activity. It is designed to be activated in response to the mildly acidic TME and react specifically to endogenous H_2O_2 concentrations of 100 μM to 1 mM. This specificity allows N-GNM to utilize endogenous H_2O_2 to generate $^{\bullet}OH$, selectively inducing tumor cell death at minimal lethal doses. In acidic conditions, N-GNM demonstrates the catalytic behavior of POD mimics and actively engages in modifying the TME, while it remains inert in normal tissues with neutral pH.

Qian group[113] has innovated a straightforward polyol method to create $AgBiS_2$ nanozymes with a unique hollow structure. These nanozymes, made up of small, poorly crystalline nanoparticles, become highly active under near-infrared light as well as without it. This is achieved through a rapid formation and ion exchange process in a mildly polar solvent, leading to a targeted toxic effect on cancer cells. The approach effectively lowers the energy barrier for producing highly reactive $^{\bullet}OH$ in the TME. Thanks to the surface-catalyzed conversion of abundant H_2O_2 in the TME into reactive $^{\bullet}OH$, the $AgBiS_2$ hollow-structured nanozymes demonstrate a marked increase in their ability to specifically target and kill cancer cells, a result that has been proven both in lab settings and within living organisms, particularly when subjected to NIR laser illumination at 808 nm.

Developing smart nanozymes that accurately perform in the TME without harming nearby normal tissues is a formidable challenge. Drawing inspiration from the fact that the activity of

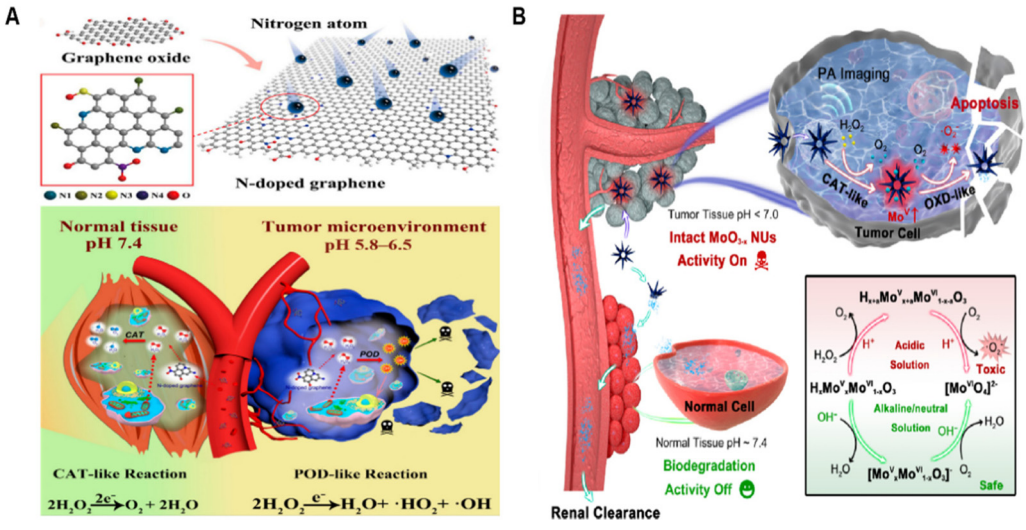

Fig. 8 Microenvironmental response initiation. (A) The synthesis process of N-GNMS and the application for pH-triggered tumor-specific catalytic treatment. Reproduced from ref. 112 with permission from MDPI, copyright 2021. (B) Biodegradable and enzyme-activity-tunable MoO_{3-x} NUs exhibit high specificity for tumor tissues due to their multi-enzymatic stepwise cascade catalysis in the acidic TME. Reproduced from ref. 114 with permission from American Chemical Society, copyright 2020.

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biological enzymes is tied to their specific structures, researchers have developed a method to control the active/inactive states of nanozymes by altering their nanostructures through biodegradation. This technique paves the way for catalytic therapies that are responsive to tumors, capable of differentiating between diseased and healthy states, thereby ensuring compatibility with normal tissues. Ling group[114] innovated by creating MoO_{3-x} nanourchins (NUs), whose enzymatic activities are dependent on their structure (Fig. 8B). Characterized by their expansive active surface and the presence of numerous Mo^{5+} species, these MoO_{3-x} NUs exhibit remarkable CAT-like behavior in the acidic milieu of tumors. They efficiently convert H_2O_2 into oxygen, followed by activation of OXD-like properties that facilitate electron transfer to oxygen, resulting in the formation of harmful $O_2^{\bullet-}$. Crucially, these NUs rapidly lose their enzymatic properties in the physiological pH of 7.4, undergoing pH-responsive biodegradation. This process leads to the formation of kidney-clearable and biocompatible molybdate ions. This rapid biodegradation in normal physiological conditions allows MoO_{3-x} NUs to target tumors with highly specific cascading catalytic activity while preserving the integrity of normal tissues.

2.3. Advanced functional biomimicry of nanozymes

Due to various adverse factors in the dynamically changing TME, there are limitations to the expected catalytic therapeutic effects of nanozymes. For instance, high levels of intracellular GSH (about 10×10^{-3} M) can neutralize the produced ROS, and the typically low levels of H_2O_2 are insufficient to sustain enzyme reactions.[14,115] To overcome these obstacles, the biomimetic design of nanozymes, in addition to achieving basic functional biomimicry, *i.e.*, mimicking the catalytic activity of natural enzymes and enhancing catalytic performance through the aforementioned structural and process biomimicry, still needs to develop advanced nanozymes with more profound and comprehensive biomimetic functions.

Based on the understanding of tumor biology, biomimetic nanozymes applied for anti-tumor therapy need to meet the following new advanced functional requirements: (a) reshape the microenvironment through biocatalysis to obtain better anti-tumor therapeutic effects; (b) disrupt the balance of the oxidative stress regulation network in the TME to achieve cyclical catalytic reactions; (c) construct biologically orthogonal catalytic systems for *in situ* synthesis of biological prodrugs. All these advanced functional biomimetics highlight key regulatory mechanisms in the realm of nanozyme-mediated anti-tumor therapy. They form the cornerstone for enhancing the efficacy of nanozyme-catalyzed therapies, combined with drug delivery, conventional or novel anti-tumor treatments, or regulating the TME. Such comprehensive methods are essential in profoundly expanding our understanding of the synergistic roles and underlying mechanisms of nanozymes in combating cancer.

2.3.1. Metabolism imbalanced function. In contrast to normal cells, tumor cells undergo metabolic adaptations to support their rapid proliferation, such as increased biomass production.[116] Cancer cells have a high demand for regenerating electron acceptors like nicotinamide adenine dinucleotide (NAD^+) to support the biosynthesis of proteins and nucleic acids.[117] This involves processes like glycolysis and the tricarboxylic acid cycle. Tumor cells exhibit the Warburg effect, characterized by heightened glycolytic activity and reliance on lactate dehydrogenase (LDH) for continual NAD^+ regeneration from NADH. Coupled with upregulated synthetic metabolism and the constraining TME, tumor cells face increased oxidative stress. To combat this, tumor cells employ antioxidant mechanisms, including GSH and thioredoxin systems, hence genetic and metabolic changes bolstering these defenses are common in tumors.[118] Additionally, tumor cells alter their metabolism to manage oxidative stress, maintaining antioxidants for ROS scavenging.[13] Despite the impressive catalytic capabilities of various biomimetic nanozymes, therapies leveraging tumor endogenous O_2 and H_2O_2 face limitations. Designing biomimetic nanozymes that disrupt tumor resistance can solve substrate scarcity in enzyme-catalyzed therapy and provide multi-enzymatic nanozymes the ability to break the tumor redox and energy metabolism balance. This approach ensures a self-sustaining cascade reaction system in nanozymes, enabling substrate and product autonomy, and profoundly disrupting tumor metabolism to maximize anti-tumor therapy effectiveness in the body.

Yang group,[119] inspired by the enhanced activity achieved by adding axial nitrogen coordination in single-atom catalysts, created an innovative Ir–N_5 single-atom nanozyme (Ir–N_5 SA) (Fig. 9A). This nanozyme not only emulates the activities of natural OXDs, POD-like, and CAT-like enzymes but also possesses the ability to convert NADH into H_2O_2, similar to nitric oxide synthase (NOS). Its effective CAT-like traits enable the conversion of H_2O_2 into oxygen at tumor sites, relieving tumor hypoxia. At the same time, Ir–N_5 SA, which functions similarly to NOS, catalyzes the conversion of NADH into H_2O_2. It also blocks the mitochondrial electron transport chain and hinders aerobic respiration, thereby reducing the consumption of oxygen within cells. This combined effect notably increases both oxygen and H_2O_2 concentrations at tumor locations, boosting the nanozyme's capacity to produce ROS, leading to irreversible oxidative harm to tumor cells. Importantly, NADH and NAD^+ are essential redox coenzymes in fundamental metabolic processes. The consumption of NADH disrupts their equilibrium, hindering adenosine triphosphate (ATP) synthesis through both glycolysis and oxidative phosphorylation. While Ir–N_5 SA interferes with the energy metabolism of tumor cells, these cells can adapt through metabolic reprogramming, relying on fatty acid oxidation (FAO) for survival in the nutrient-depleted TME. To address this adaptation, cerulenin (Cer), an inhibitor of fatty acid synthase, was integrated into Ir–N_5 SA to further weaken the FAO metabolism in tumor cells. In summary, the combined Ir–N_5 SA/Cer formulation substantially enhances tumor treatment by significantly upsetting the tumor's redox balance and metabolic homeostasis.

In cancer cells, H_2O_2 levels are delicately balanced between production and elimination, regulated by the antioxidant

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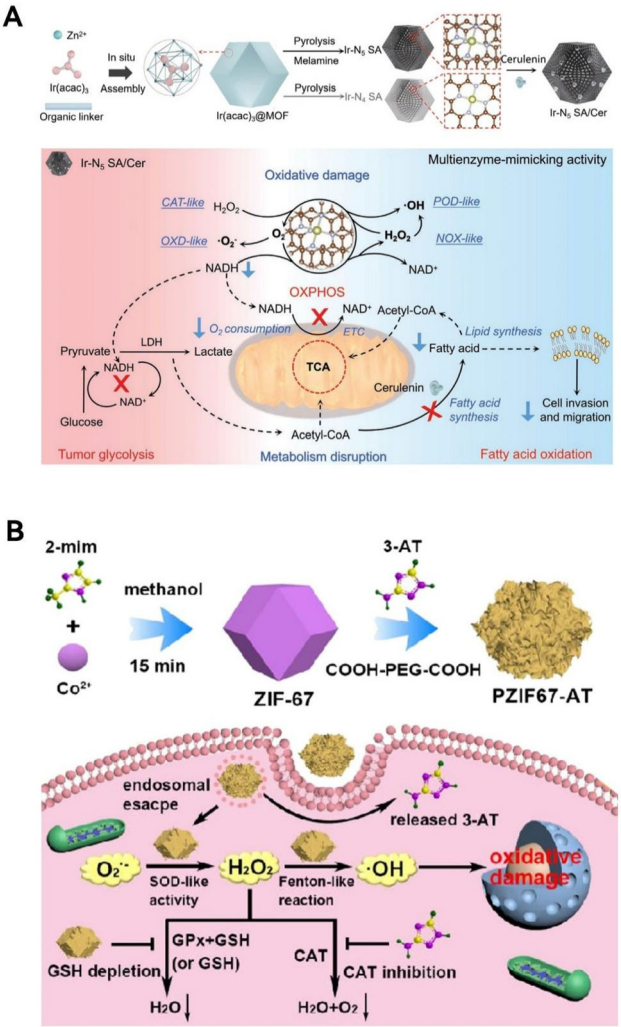

Fig. 9 Metabolism imbalanced function. (A) The Ir–N_5 SA/Cer nanozyme has the capability to disturb both the redox balance and the metabolic equilibrium within tumor regions through emulating a series of enzymatic cascade reactions. Reproduced from ref. 119 with permission from WILEY, copyright 2022. (B) The PZIF67-AT nanozyme enhances intracellular H_2O_2 levels by promoting H_2O_2 production and inhibiting its elimination, thereby intensifying CDT. Reproduced from ref. 121 with permission from American Chemical Society, Copyright 2020.

system that includes enzymes like SOD, CAT, GPx, and molecules such as GSH.[120] Capitalizing on these findings, the research team led by Qu[121] has engineered a novel H_2O_2 disruptor, termed PZIF67-AT. This disruptor is an innovative modification of zeolitic imidazolate framework 67 (ZIF-67) nanoparticles, achieved by incorporating 3-amino-1,2,4-triazole (3-AT) and PEG (Fig. 9B). These nanoparticles are structured by the interlinking of 2-methylimidazole (2-mim) with cobalt ions, resulting in a sodalite zeolitic formation. This newly created nanozyme demonstrates SOD-like behavior, effectively converting $O_2^{\bullet-}$ into H_2O_2 and thereby promoting its accumulation. Moreover, under slightly acidic conditions, it releases molecules that inhibit CAT, reducing H_2O_2 decomposition. Significantly, the disruptor exhausts GSH, hindering GSH-mediated H_2O_2 clearance irrespective of GPx presence. By targeting the H_2O_2 homeostasis in tumor cells and disturbing this balance, this study achieves H_2O_2 accumulation in cancer cells, thereby enhancing CDT effectiveness through the Fenton reaction.

2.3.2. Biorthogonal catalytic function. Biorthogonal chemistry is an emerging tool that allows for the observation of biochemical reactions within living organisms without interfering with their biological systems.[122] It utilizes synthetic chemistry to achieve transformations that are beyond the capabilities of biological systems. Some nanozymes are capable of catalyzing these non-natural bioprocesses, a phenomenon known as biorthogonal catalysis.[123] Biorthogonal catalysis, through the amplification effect of nanozymes in biological reactions, provides a platform for substrate transformation and is widely used in the study of drug precursors, *in vivo* imaging, and bioengineering.

Biorthogonal reactions could produce therapeutic drugs *in situ*, greatly minimizing off-target effects. Despite the challenges posed by the lysosomal membrane, which serves as a cellular barrier impeding drug delivery to targeted sites.[124] Sun group[125] has made a groundbreaking advancement (Fig. 10A). They developed a protein-based nanozyme platform incorporating transition metals, alongside a novel cage-like composite fluorophore group system. This innovative system facilitated the screening of compatible nanozyme/protective group pairs. By integrating various transition metal nanoparticles directly into protein frameworks, they were able to create a comprehensive library of nanozymes. This library proved to be an excellent resource for selecting the ideal pairs for cleavable bonds in nanozyme-driven processes. Among their discoveries, a Pd-based nanozyme exhibits activities akin to mutant P450(BM3), which specifically targets propargyl ether groups. Leveraging a multi-enzyme synergistic strategy, this Pd nanozyme achieves *in situ* biorthogonal catalysis and can permeate the lysosomal membrane due to its POD-like properties. This innovation has been effectively utilized in the development of prodrugs for cancer treatment, laying a foundational framework for the creation of lysosome-targeted prodrugs in oncological therapies.

Transition metal catalysts show promise in activating prodrugs, but their constant 'always-on' catalytic state and struggle to operate in complex cellular environments have raised concerns about their safety and effectiveness in therapy.[126] To address these issues, Qu and team[127] ingeniously used programmable DNA molecules to modify nanozyme-Pd^0, creating a DNA-gated, self-protective biorthogonal catalyst (Fig. 10B). This innovation has been effectively applied in synthesizing drugs within cells and treating cancer. The catalyst single DNA layer serves a dual purpose: it targets cancer cells specifically and also acts as a 'gatekeeper', selectively triggering prodrugs in these cells. Additionally, the graphite nitrogen-doped carbon nanozymes, which mimic GPx and CAT enzymes, help create a more favorable environment for the catalyst inside cells. This prevents the catalyst from becoming inactive and increases the effectiveness of sub-

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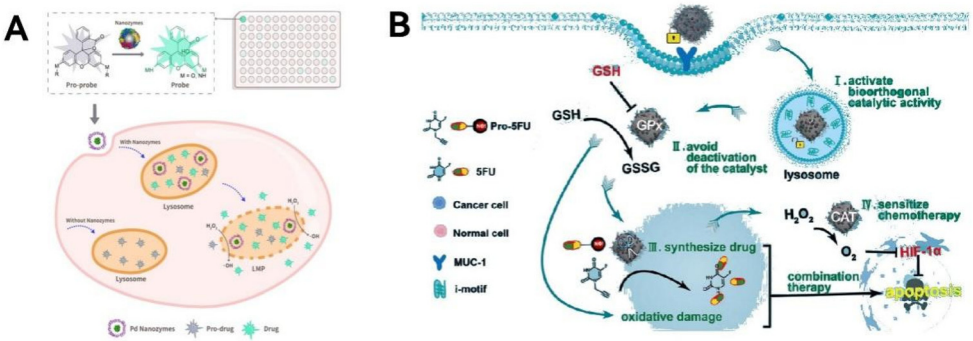

Fig. 10 Biorthogonal catalytic function. (A) The prodrugs are activated by the biorthogonal catalysis of the Pd nanozymes, thereby significantly boosting effective drug delivery to target cancer cells. Reproduced from ref. 125 with permission from WILEY, copyright 2022. (B) A DNA-gated and self-protected biorthogonal catalyst is crafted by utilizing highly programmable DNA molecules to modify the nanozyme Pd^0. Reproduced from ref. 127 with permission from WILEY, copyright 2023.

sequent chemotherapy treatments. This research represents a significant step forward in developing safe and efficient nanozyme-based biorthogonal catalysis systems for medical applications.

2.3.3. Environment reprogramming function. In the past 20 years, cancer therapy has made significant progress. Avoidance of immune destruction, promotion of tumor inflammation, non-mutational epigenetic reprogramming, and polymorphic microbiomes are newly identified tumor markers, closely related to the occurrence, growth, and metastasis of tumors.[116] Hence, the epigenetic plasticity of the TME in malignant solid tumors is deem to be a major obstacle that hinders the further enhancement of catalytic therapeutic efficacy and the expansion of anti-cancer treatment applications by nanozymes. Directly targeting and regulating these characteristic nodes of the TME might become a new Achilles' heel in cancer therapy. For example, manipulating the microbiome[128] and immune-suppressive factors[129] in tumor tissues through nanozymes could potentially enhance anti-tumor effects.

Overcoming the immunosuppressive environment within tumors ranks among the toughest challenges in cancer treatment.[130] Tumor-associated macrophages have been recognized for their role in advancing malignant tumor growth, drug resistance, and unfavorable outcomes.[131] Drawing inspiration from natural bodily responses, Liu's team[73] has innovatively used arginine, a precursor to NO, as a capping agent to create two types of chiral ruthenium nanozymes (D/L-arginine@Ru) (Fig. 11A). These nanozymes mimic both OXD and NOS activities, rapidly producing $^1O_2$ and O_2. They then catalyze arginine to generate enough NO, which plays a crucial role in boosting macrophage M1 polarization, a key factor in reversing the immune suppression in tumors. Moreover, these chiral Ru nanozymes harness the combined anti-tumor powers of $^1O_2$ and NO, leading to a 'cocktail therapy' effect that triggers tumor cell death through apoptosis and ferroptosis. This research paves the way for new approaches in tumor catalytic therapy, offering a viable strategy to modulate the immune microenvironment by leveraging self-catalytic cascade reactions that activate macrophage M1 polarization *via* ROS and NO. Zeng group[69] has created an innovative copper-doped polypyrrole nanozyme (CuP) possessing three enzyme-like activities: CAT, GPx, and POD (Fig. 11B). This nanozyme distinctively increases O_2 and $^{\bullet}OH$ levels *via* a straightforward process, simultaneously decreasing GSH within the TME. This mechanism results in irreversible oxidative damage to tumor cells, disrupting their redox balance. The CuP nanozyme enhanced with polyethylene glycol, denoted as CuPP, is particularly effective in reversing the immunosuppressive nature of the TME. It alleviate tumor hypoxia and converts M2 macrophages, which promote tumor growth, back into the M1 phenotype that combats tumors. Crucially, CuPP also demonstrates enhanced catalytic and immunomodulatory activities when combined with thermotherapy. When used alongside the immune checkpoint inhibitor PD-L1, CuPP facilitates potent immune responses and delivers outstanding anti-tumor results.

Reversing the immunosuppressive nature of the TME and reactivating the capability of immune system to fight tumors is a key therapeutic strategy.[132] Certain immune cells in the TME, like T cells, dendritic cells, and macrophages, become dysfunctional upon sensing high extracellular lactate levels through MCT1 and MCT2.[133] LDH, crucial in the lactate metabolism pathway, catalyzes the conversion of lactate to pyruvate.[134] Wang and colleagues[135] harnessed this by synthesizing SnSe nanosheets (SnSe NSs) with lactate adsorbed on their surface, creating an effective adsorption structure. SnSe NSs were found to mimic LDH, efficiently consuming lactate both in lab settings and in living organisms. Importantly, the lactate degradation facilitated by SnSe NSs effectively counteracts the immunosuppression induced by elevated lactate levels in the TME, leading to the inhibition of tumor growth in different mouse models. This suggests that SnSe NSs play a significant role in enhancing the acidic and immunosuppressive TME. They achieve this by promoting the consumption of lactate within tumors, which in turn revitalizes the immune system's ability to combat cancer.

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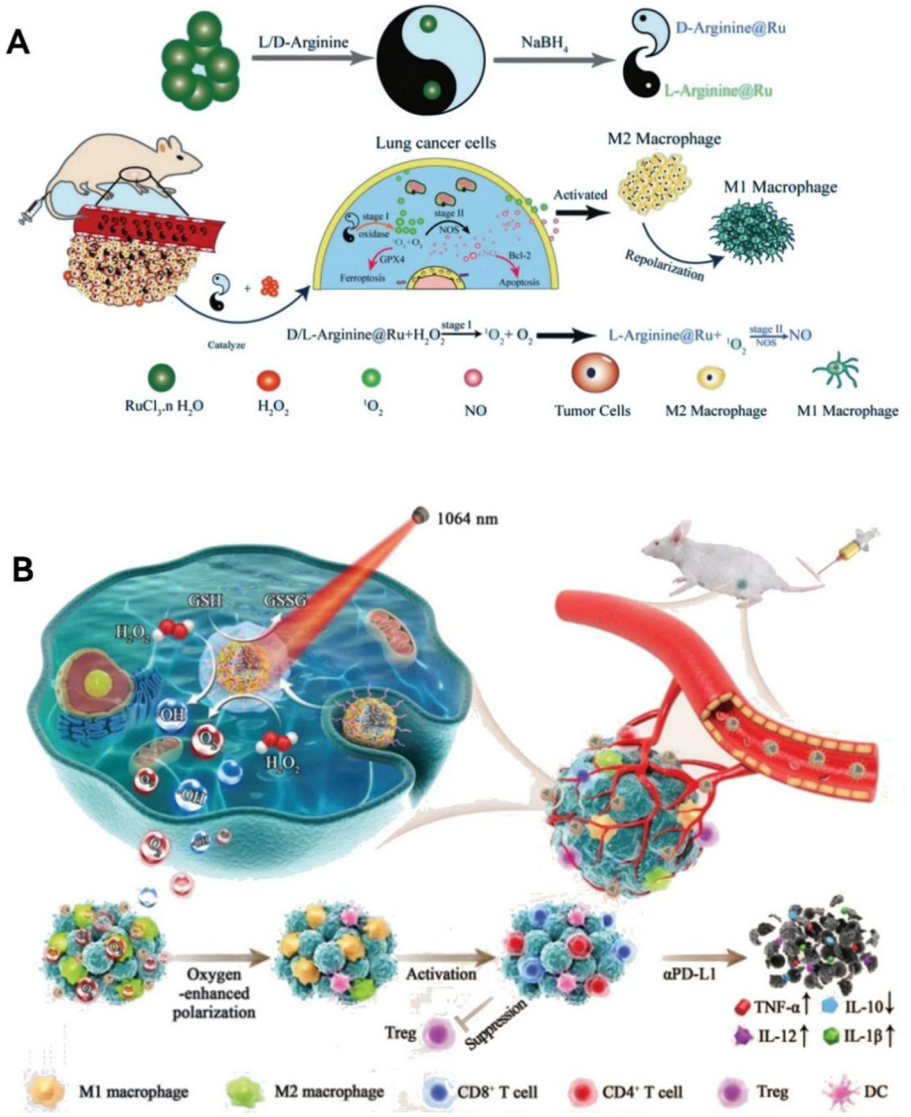

Fig. 11 Environment Reprogramming Function. (A) Chiral ruthenium nanozymes (D/L-arginine@Ru) with OXD- and NOS-mimic activities play a crucial role in enhancing the M1 polarization of macrophages, thereby reversing the immunosuppressive environment in tumors. By leveraging the combined anti-tumor effects of $^1O_2$ and NO, these chiral Ru nanozymes induce apoptosis and ferroptosis in tumor cells. Reproduced from ref. 73 with permission from WILEY, copyright 2023. (B) CuP nanozymes specifically promote an increase in O_2 and $^{\cdot}OH$, and a decrease in GSH, causing oxidative stress damage to tumor cells and reversing the redox balance. CuPP overcomes tumor hypoxia and re-educates macrophages from M2 to M1 phenotype, reversing the immunosuppressive TME. Reproduced from ref. 69 with permission from WILEY, copyright 2022.

3. Applications in cancer treatment

The TME is a sophisticated network comprising tumor cells, stromal cells, and the extracellular matrix, which profoundly influences tumor development, growth, and spread. This influence is exerted through metabolic, secretory, immune, structural, and functional changes, making the TME a pivotal factor in the distribution and biological effects of nanoparticles. In the TME, hypoxia arises not only from the rapid proliferation of tumor cells, which drastically increases their oxygen demand but also from the inadequate oxygen supply due to the abnormal vasculature of tumor.[115] This lack of oxygen is further compounded by an imbalance in pH levels, a direct consequence of altered glucose metabolism.[136] In such hypoxic conditions, tumor cells shift towards glycolysis, resulting in distinct pH values both inside and outside the cells. Moreover, the TME is characterized by elevated levels of ROS, H_2O_2, and GSH.[137] Tumor cells adapt by enhancing their antioxidative systems to effectively manage these increased internal ROS levels. This unique feature of the TME, with its higher redox potential compared to normal tissues, presents an opportunity for nanozyme-catalyzed therapeutic strategies, offering targeted and efficient options for tumor therapy.

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Reflecting these mechanisms, extensive research has been conducted on the use of nanozymes with biomimetic designs in anti-tumor treatments, encompassing both single-type and multi-enzymatic nanozymes. This section will delve into the advancements in research on various cancers, as well as the integration of catalytic therapy with other complementary therapies like radiotherapy, PDT, and sonodynamic therapy (SDT), in the realm of tumor catalytic therapy.

3.1. Catalytic therapy

The therapeutic action of nanozymes in cancer treatment is largely driven by their ability to induce the production of ROS, which are key in killing tumor cells. The main members of the ROS family are $O_2^{\bullet-}$, $^1O_2$, and $^{\bullet}OH$. Based on the number of enzyme-like catalytic activities mediated, nanozyme-based catalytic therapy can be categorized into single-enzyme activity catalysis and multi-enzyme activity catalysis, with the latter further classified into bi-enzymic, tri-enzymic, and quarter-enzymic nanozymes. Most single-enzyme activity nanozymes generate or scavenge reactive ROS based on their inherent POD, SOD, CAT, OXD, GOx, and GPx mimetic activities. For multi-enzyme activity nanozymes, the nanomaterials may exhibit stronger ROS-producing or clearing effects through synergistic or cascading catalytic reactions of multi-enzyme-like activities, displaying more complex functionalities. This could lead to more effective outcomes in the application of anti-tumor diagnosis and therapy.

3.1.1. Lung cancer. Lung cancer continues to exhibit alarmingly high rates of occurrence and mortality, while the chances of patient survival remain notably low.[138] The situation is further compounded by increased recurrence rates and growing resistance to therapeutics, casting a shadow over patient outcomes.[139] Current therapeutic options for lung cancer are limited in their effectiveness, making the search for advanced and combined treatment strategies, as well as the pursuit of breakthroughs in lung cancer detection technology, critical areas of ongoing research.

Zhang *et al.*[140] synthesized ultrasmall Pt (nPt) nanozymes within the restricted domains of the worm-like pore channels of gold–nanobipyramide–mesoporous silica nanocomposites to prepare AP-mSi nanozyme carriers with photo-enhanced POD ability (Fig. 12A). Next, based on the prepared AP-mSi, a nanozyme probe (AP-HAI) for lung cancer therapy was prepared by removing SiO_2, modifying human serum albumin, and loading atovaquone molecules and IR780. Upon irradiation with near-infrared light, the internal Au particles and IR780 interact in a photothermal process, thereby promoting a POD-like catalytic process of H_2O_2. The photo-enhancing ability of IR780 nanozyme for PDT and nPt PODs gives the probe high ROS performance, which can be used to induce anti-tumor immune responses that destroy tumor tissue.

Addressing the pivotal challenge of effectively promoting M1 macrophage polarization in lung cancer treatment, due to the critical role of macrophages in tumor-mediated immunosuppression, has led to significant advancements. Drawing inspiration from natural biochemical processes, Chen *et al.*[73] innovated a dual-activation approach for M1 macrophage polarization, harnessing the synergistic effects of ROS and NO through a self-propagating cascade reaction. This method employs NO precursor-arginine as a capping element, facilitating the creation of two distinct enantiomeric forms of ruthenium-based nanozymes (D/L-arginine@Ru). These chiral Ru nanozymes are adept at rapidly generating $^1O_2$ and O_2, simultaneously mimicking OXD and NOS activities. Subsequently, they catalyze arginine, leading to the production of ample NO, thereby boosting M1 macrophage polarization and counteracting tumor immunosuppression.

3.1.2. Breast cancer. Breast cancer, accounting for about a quarter of all female cancer cases, has become the most diagnosed cancer among women as of 2020, with approximately 2.3 million new cases. Despite advances, preventing recurrence and metastasis remains a challenge, with up to 30% of invasive cases recurring. Most breast cancer deaths are due to metastatic disease.[141] In response to these challenges, the evolving fields of nanoscience and nanotechnology are spearheading new diagnostic and therapeutic approaches to tackle breast cancer.

As oxygen deprivation is a major obstacle to hypoxia-related theranostics, much research has been done to develop methods to utilize the hypoxic response properties of nanoparticles to deliver oxygen.[142] Nonetheless, effectively achieving nanoparticle penetration into the hypoxic zones of tumors remains an unresolved issue. In a recent study, Gao *et al.*[143] developed a biomimetic ferritin nanocages with CAT-like activity and can penetrate into a hypoxic region in tumor tissue to deliver oxygen based on a catalytic response in the TME (Fig. 12B), which significantly alleviated tumor hypoxia by almost three times compared to untreated tumor tissue. Moreover, this nanosystem facilitates multimodal tumor imaging and alters the TME, enhancing PDT through a series of therapeutic agents. The result is a marked improvement in inhibiting tumor growth and preventing lung metastasis.

Nanomaterials with enzyme-like activity have been identified as potentially important self-therapeutic nanomedicines. Zeng *et al.*[144] have pioneered a novel biodegradable boroxynitride (BON) based POD nanozyme for an advanced, multimodal approach to breast cancer treatment (Fig. 12C). This BON nanozyme efficiently produces cytotoxic $^{\bullet}OH$, leading to a significant reduction in 4T1 cancer cell viability—up to 82% within 48 hours. *In vivo* studies revealed that this nanozyme curbs breast tumor growth by 97% over a 14-day treatment period, outperforming inert and B-releasing boron nitride nanospheres and by 10 times and 1.3 times, respectively. This study underscores the potential of integrating BON nanoclay within the boron nitride nanomedicine framework for breast cancer treatment.

3.1.3. Glioblastoma. Treating aggressive glioblastoma (GBM), a primary brain tumor, remains a daunting challenge due to its heterogeneous nature, an immunosuppressive TME, and the blood–brain barrier that hinders chemotherapeutic agents from accessing the central nervous system.[145] However, nanocarrier-based drug delivery and nanotechnological

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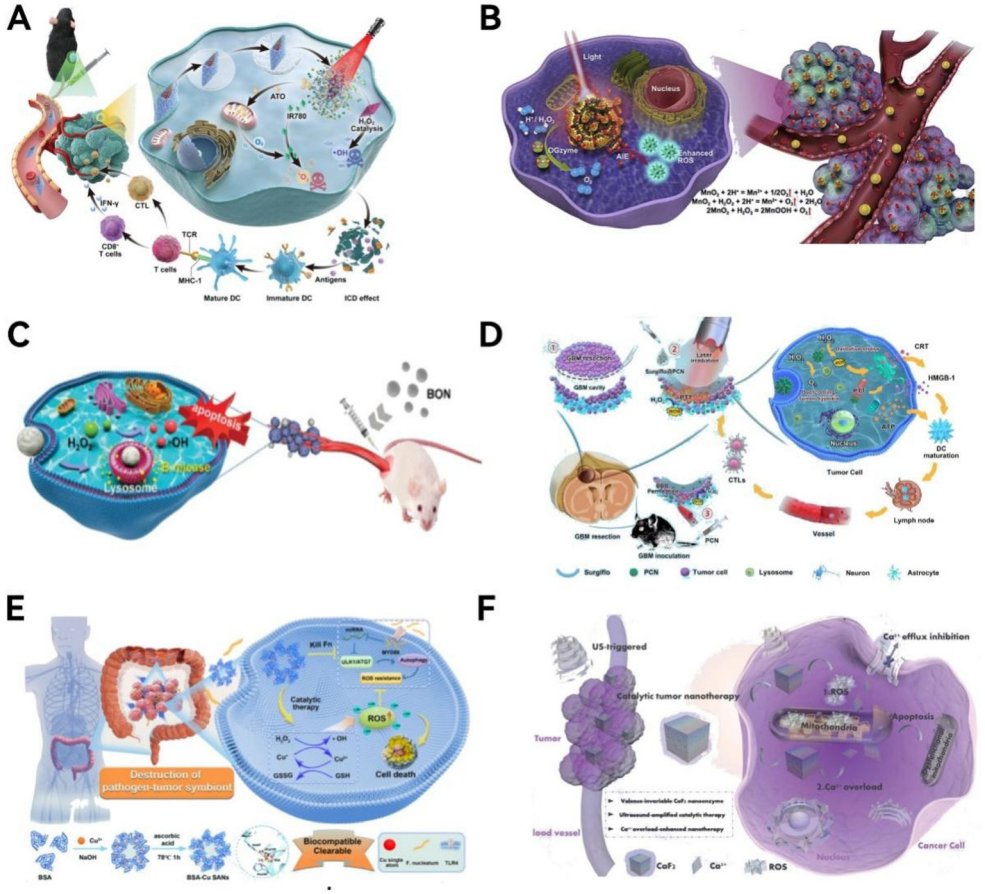

Fig. 12 Biomimetic-designed nanozymes for caner catalytic therapy. (A) Under near-infrared light irradiation, the internal Au particles and IR780 with photo-enhancing ability work synergistically to promote the POD-like catalytic process of H_2O_2. Reproduced from ref. 140 with permission from WILEY, copyright 2023. (B) Nanozymes possess POD-like activity and can efficiently penetrate directly into the hypoxic areas of tumor tissues to provide oxygen based on catalytic reactions within the TME. Reproduced from ref. 143 with permission from Elsevier Ltd, copyright © 2020. (C) BON nanozymes catalyze the production of cytotoxic $^{\bullet}OH$, inducing apoptosis in 4T1 cancer cells. Reproduced from ref. 144 with permission from WILEY, copyright 2021. (D) The catalytic and photothermal therapeutic effect of Surgiflo@PCN in GBM treatment. Reproduced from ref. 146 with permission from American Chemical Society, copyright 2023. (E) The catalytic therapeutic effect of BSA-Cu SAN in killing colorectal cancer cells. Reproduced from ref. 150 with permission from Springer Nature, copyright 2023. (F) The (CaF_2) nanozyme with ultrasound-enhanced POD-mimicking activity are used for hepatoma therapy. Reproduced from ref. 153 with permission from WILEY, copyright 2022.

advances offer promising avenues in addressing the formidable obstacles in GBM treatment. Nie *et al.*[146] developed a novel nanozyme-based hemostatic matrix (Fig. 12D), designed for *in situ* application in the tumor cavity post-surgical resection of GBM. This matrix, acting as a photothermal agent, not only induces immunogenic cell death but also bolsters antitumor immunity, thereby delaying tumor recurrence. The system, known as Surgiflo@PCN, incorporates Surgiflo with a multi-space structure, enabling it to adapt to various shaped tumor cavities and prevent post-operative bleeding. Additionally, it contains porous palladium–copper nanoclusters (PCNs) with regulated enzymatic activities (OXD, PDT, CAT), producing ROS under near-infrared laser irradiation (808 nm). Upon entry into the excised tumor cavity, Surgiflo@PCN combats glioma cells *via* ROS and photothermal therapy (PTT) from PCNs. This approach not only directly targets tumor cells but also counters the immunosuppressive TME and strengthens anti-tumor immune responses through oxidative stress and PTT-induced immunogenic cell death. Moreover, Carvalho *et al.*[147] developed a nanozyme using cobalt-doped iron oxide nanoparticles stabilized with carboxymethylcellulose ligands (Co-MION), which acts on GBM cancer cells with a POD-like biocatalytic effect. This nanozyme effectively kills U87 brain cancer cells by first generating $^{\bullet}OH$ directly at the tumor site and producing toxic ROS, which ultimately leads to apoptosis (programmed cell death) and ferroptosis (lipid peroxidation). Their research offers hope for treating this aggressive cancer.

3.1.4. Colorectal cancer. Fusobacterium (F.) nucleatum is commonly found in colorectal cancer tissues, playing a pivotal role in the pathogenesis, progression, metastasis, and poor prognosis of the disease.[148] The mechanism of cancer development is associated with the activation of FadA adhesion and TLR4/AKT signaling pathways. A previous study revealed that

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the load of *F. nucleatum* decreases in mice with colorectal tumors treated with the antibiotic metronidazole, leading to reduced tumor growth.[149] Therefore, eliminating *F. nucleatum* within tumors could be beneficial for the treatment of colorectal cancer.

Wang *et al.*[150] developed an innovative approach to target and eradicate the intratumoral pathogen *F. nucleatum*, thereby disrupting its symbiotic relationship with colon cancer cells (Fig. 12E). This method employs a novel monoatomic protein-assisted copper nanozyme (BSA-Cu SAN), designed based on natural enzyme structures with metal elements as active sites. The BSA-Cu SAN demonstrates catalytic efficiency by producing ROS and degrading GSH. This action leads to the elimination of the pathogenic *F. nucleatum* within the tumor, disrupting its symbiotic interactions and effectively contributing to the destruction of colorectal cancer cells.

Zhu *et al.*[151] successfully synthesized hollow Ru@CeO_2 nanozymes (Ru@CeO_2YSNs) utilizing a one-pot synthesis method. They innovatively loaded both the anticancer drugs ruthenium complex (RBT) and resveratrol (Res) into these Ru@CeO_2YSNs. A dual-layered structure was then created by incorporating polyethylene glycol, forming a sophisticated dual drug delivery system (Ru@CeO_2-RBT/Res-DPEG) designed for controlled drug release. This double outer layer structure not only enhanced the biocompatibility of Ru@CeO_2YSNs but also significantly extended their circulation time in the bloodstream. The efficacy of Ru@CeO_2-RBT/Res-DPEG was demonstrated in reducing tumor hypoxia and in the inhibition of metastasis and recurrence in both orthotopic and subcutaneous models of colorectal cancer.

3.1.5. Hepatoma. Hypoxia is an important factor in the development of multidrug resistance, recurrence, and metastasis in solid tumors.[152] The response of nanozymes to the TME is a novel and effective strategy for tumor-specific therapy. The anticancer mechanism of nanozymes is primarily related to their ability to generate ROS caused by a change in the valence of metallic elements. However, the enzymatic activity of metal compounds with variable valence is still poorly understood.

Dong *et al.*[153] ingeniously engineered a calcium fluoride (CaF_2) nanozyme with varying valences, featuring ultrasound-enhanced POD-like activity (Fig. 12F). This innovation marks the first instance of calcium-based nanozymes being used in catalytic cancer therapy. The design leverages the release of exogenous Ca^{2+} ions from CaF_2 nanocrystals, coupled with the generation of harmful ROS amplified by the POD-mimicking effects of ultrasound. This mechanism promotes intracellular calcium accumulation, leading to Ca^{2+} overload and subsequent mitochondrial dysfunction, which is instrumental in the therapeutic effectiveness.

The Hepatitis C virus (HCV) stands as a primary contributor to various liver-related conditions, including chronic hepatitis, cirrhosis, and hepatocellular carcinoma.[154] Presently, the prevalent interferon-based treatments only successfully eradicate the virus in roughly half of the patients and are not specifically tailored to HCV, leading to considerable side effects. Given the lack of an effective vaccine, there is an urgent need for more targeted antiviral treatments. RNA interference plays a crucial role in gene regulation through the RNA-induced silencing complex. Wang *et al.*[155] highlighted that a specially engineered nanoparticle complex can adeptly imitate the cellular RISC, facilitating targeted RNA cleavage. Their findings reveal that this nanozyme, custom-designed for combating HCV, can precisely and effectively slice HCV RNA in a sequence-specific way.

The use of exosome-expressed proteins as liquid biopsy biomarkers for cancer diagnosis has shown considerable promise.[156] Nevertheless, profiling these exosomal proteins accurately is still technically challenging. Di *et al.*[157] introduced a novel approach called the nanozyme-assisted immunoassay (NAISA) for the sensitive, rapid, and multiplexed profiling of exosomal proteins. This innovative NAISA system employs POD-like nanozymes attached to the phospholipid membranes of exosomes, eliminating the requirement for post-labeling with detection antibodies. Thanks to the NAISA nanozyme, the efficient profiling of a wide range of exosomal proteins has been made possible, potentially revolutionizing early detection of hepatocellular carcinoma and other cancers.

3.1.6. Other cancer types. Osteosarcoma, a serious bone cancer primarily affecting children and teenagers, presents a challenging prognosis in clinical practice,[158] highlighting the urgent need for novel strategies to improve outcomes and reduce side effects. Liang *et al.*[159] have developed bimetallic RhRu/Ti_3C_2Tx nanoenzymes on 2D Ti_3C_2Tx nanosheets. These nanoenzymes combine the catalytic properties similar to POD and CAT provided by rhodium (Rh), with the photothermal conversion capabilities, alongside ruthenium (Ru) which, under near-infrared light, transforms O_2 into $^1O_2$. Theoretical calculations using density functional theory (DFT) show a strong electron transfer between RhRu and Ti_3C_2Tx, enhancing the absorption of H_2O_2, crucial for boosting enzyme-like activity. Leveraging the synergistic effects of Rh and Ru, this dual-metal nanoenzyme on Ti_3C_2Tx exhibits exceptional catalytic and photothermal activities, effectively generating $^1O_2$. This combination results in a significant anti-tumor impact through a tri-modal therapy approach combining CDT, PTT, and PDT therapies in treating osteosarcoma, showing promise for deep cancer treatments.

Cutaneous squamous cell carcinoma (cSCC) ranks as the second most prevalent form of non-melanoma skin cancer, contributing to 20% of all skin cancer deaths. Lately, local PDT has gained favor for its safety and effectiveness against non-melanoma skin cancers.[160] Yet, the therapy's impact is often curtailed by the poor skin penetration and bioavailability of photosensitizers. Addressing this, Tao and colleagues[161] have introduced a microneedle patch containing MnO_2/Cu_2O nanosheets and Cabotegravir A4, designed for precise drug delivery to tumors. The innovative use of MnO_2/Cu_2O enables the catalysis of glucose into H_2O_2, which, in combination with released copper, triggers a Fenton-like reaction to produce $^{\bullet}OH$, offering an effective CDT approach. Additionally, the ability of MnO_2/Cu_2O to convert light into heat not only

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directly attacks cancer cells but also boosts the Fenton-like reaction's efficiency, presenting a promising multi-modal treatment strategy for enhancing cSCC therapy.

3.2. Combination therapy

Anti-tumor treatments encompass conventional methods like surgery, chemotherapy, and radiotherapy, alongside novel approaches such as immunotherapies, targeted treatments, PDT, and PTT. However, they usually lack targeted and sustained drug release, and the accompanying drug resistance and enrichment with systemic toxicity limit their application.[138,162] Owing to the constraints inherent in single-modality therapies, current research is increasingly directed towards multi-modal approaches for enhanced, synergistic tumor treatment.[163] In this context, nanozymes are gaining prominence for their augmented therapeutic impact across various cancer treatments. With superior catalytic activity, enhanced stability, and greater ease of modification compared to natural enzymes, nanozymes have made significant strides in diverse treatment modalities including chemotherapy, radiotherapy, phototherapy, immunotherapy, CDT, PDT, sonodynamic therapy, and starvation therapy.

3.2.1. Chemotherapy. While chemotherapy remains a cornerstone in cancer treatment, its efficacy is frequently compromised by the growing problem of multidrug resistance.[164] Factors such as hypoxia, elevated H_2O_2 levels, glucose scarcity, and acidic environments can significantly impede chemotherapy effectiveness and outcomes.[165] Furthermore, chemotherapy is notorious for its various adverse side effects, such as hair loss, bone marrow suppression, mucositis, nausea, and vomiting, all of which can substantially impact a patient's quality of life. Balancing the eradication of cancer cells with minimizing systemic side effects presents a critical challenge.[166] In tackling this challenge, nanozymes are emerging as a revolutionary approach to cancer chemotherapy.[167,168]

The TME is characterized by a mildly acidic nature, an excess of H_2O_2, hypoxic conditions, and reduced activity of specific enzymes like CAT.[169,170] These factors are instrumental in fostering the nourishment, proliferation, and metastatic progression of cancer cells, as well as aiding their escape from immune-mediated destruction.[171,172] Consequently, leveraging nanozymes to modulate the TME presents a promising strategy for cancer therapy. Nanozymes can induce notable alterations in the TME *via* various established or potential mechanisms. These include catalyzing Fenton-like reactions, converting prodrugs into active chemotherapeutics locally, breaking down tumor-promoting oncogenes, and boosting the function of enzymes such as CAT.[103,173,174] Such nanozyme-mediated adjustments to the TME can either directly eradicate cancer cells or augment the efficacy of other treatments like chemotherapy, PTT, and PDT. Cai *et al.*[103] have identified that combining TME cascade catalytic therapy with chemotherapy offers a promising avenue for effective tumor treatment (Fig. 13A). They engineered a unique single-atom nanozyme specifically designed to initiate a series of enzymatic reactions within the TME, targeting tumor cells precisely. This nanozyme, a single-atom cobalt structure supported on N-doped porous carbon (Co-SAs@NC), exhibits CAT-like properties, breaking down endogenous H_2O_2 in cells to produce O_2. It then demonstrates OXD-like activity by transforming O_2 into toxic $O_2^{\bullet-}$, which are highly effective in eradicating tumor cells. Additionally, incorporating doxorubicin (DOX) into this treatment protocol markedly enhances its antitumor efficacy *in vivo*. Furthermore, Li *et al.*[175] engineered an innovative nanosystem, H-MnO_2-DOX-Col NPs, using mesoporous manganese dioxide (H-MnO_2) as a base, encapsulating DOX within its core, and coating the surface with collagenase (Col) (Fig. 13B). Additionally, these NPs were enveloped in a fusion membrane (FM) composed of RAW264.7, an inflammation-specific cell membrane, and pH-sensitive liposomes, creating a biomimetic structure termed MP@H-MnO_2-DOX-Col. The study findings suggest that MP@H-MnO_2-DOX-Col enhances the effectiveness of DOX while significantly reducing its cardiotoxicity. This is achieved through its multifunctional capabilities, including efficient tumor tissue penetration, TME hypoxia reduction, pH-responsive drug release, and targeted DOX delivery. This comprehensive strategy not only amplifies DOX therapeutic impact but also markedly diminishes the risk of cardiac damage often associated with the drug. Song *et al.*[47] constructed Zr/Ce-MOFs/DOX/MnO_2, which serves as a new type of nanosome for combined chemotherapy and catalytic treatment (Fig. 13C). Zr/Ce-MOFs can produce $^{\bullet}OH$ to mimic TME, and MnO_2 on the surface can deplete GSH, further stimulating $^{\bullet}OH$ production. The dual stimulation of pH/GSH accelerates the release of the anticancer drug DOX into tumor tissue to enhance cancer chemotherapy.

Fan *et al.*[176] addressed the challenge posed by low H_2O_2 levels in the TME, which often limits the effectiveness of POD nanozyme therapy. They developed a mesoporous nanozyme with dual functionality: it not only demonstrates POD-like activity but also carries an anti-tumor drug, thereby facilitating synergistic cancer treatment. This nanozyme consists of iron-doped mesoporous silica nanoparticles (FeMSN). Iron inclusion imbues FeMSN with POD-like properties, allowing it to break down H_2O_2 into OH^- in acidic environments. Additionally, the mesoporous structure of FeMSN serves as a carrier for the chemotherapeutic agent DOX, enhancing the chemotherapy by generating H_2O_2 and creating a synergistic effect that improves overall cancer treatment efficacy. Wu *et al.*[177] tackled the challenge in chemotherapy of utilizing Fenton chemistry in the TME for ROS generation, which is often hindered by low H_2O_2 levels and insufficient acidity in tumors. They engineered a MOF containing iron, integrating a cisplatin prodrug (Pt(IV) prodrug) and incorporating a GOx biocatalyst, resulting in the MOF-Pt(IV)@GOx nanozyme designed for cascade reactions (Fig. 13D). In this arrangement, the Pt(IV) prodrug attached to the MOF significantly enhances GOx loading and chemotherapy. The abundant GSH in the TME reduces Fe(III) to Fe(II) for the Fenton reaction and transforms the Pt(IV) prodrug into active cisplatin, which targets DNA and generates H_2O_2. Additionally, the GOx-catalyzed glucose oxidation not only depletes glucose for starvation therapy but

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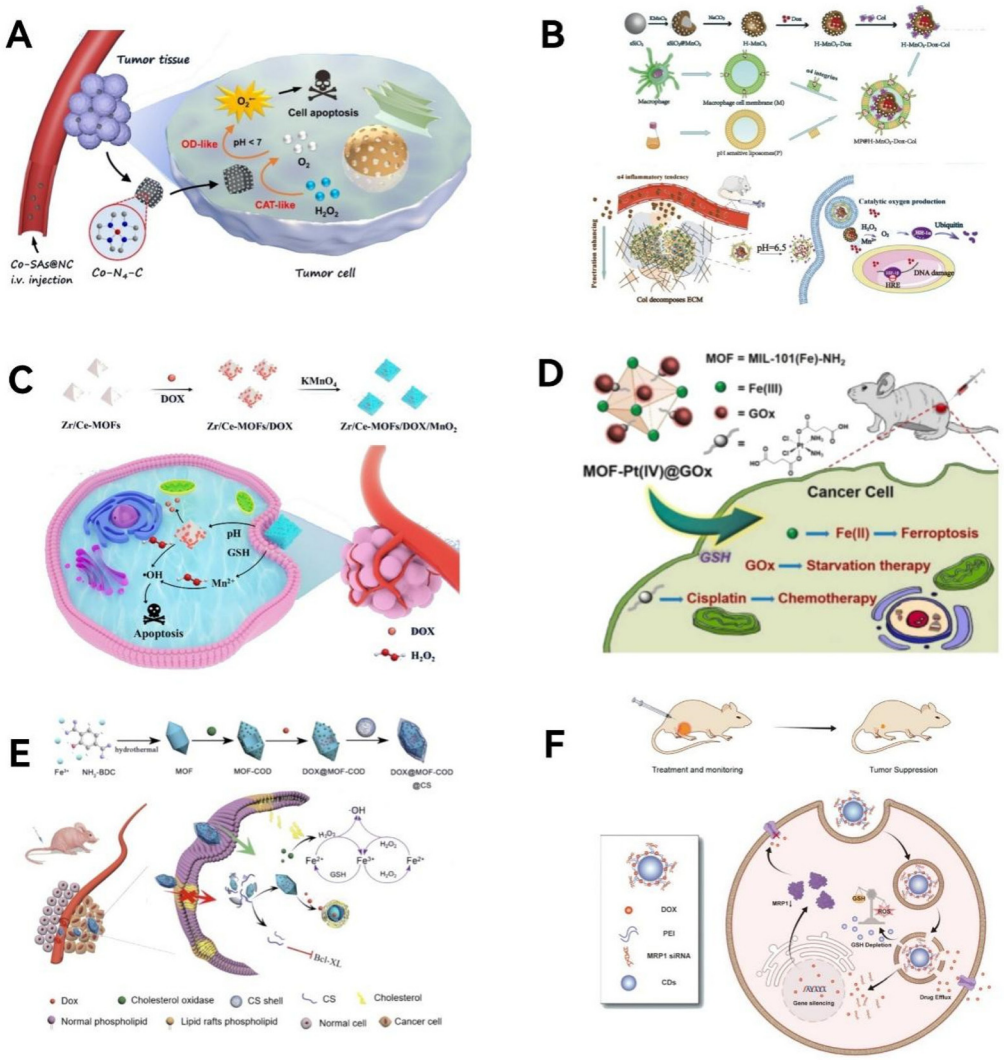

Fig. 13 Biomimetic-designed nanozymes for cancer chemotherapy. (A) The Co-SAs@NC nanozyme with dual enzymatic activities are paired with the chemotherapy drug DOX for effective cancer therapy. Reproduced from ref. 103 with permission from WILEY, copyright 2022. (B) The H-MnO_2-DOX-Col nano-system possesses multifunctional capabilities that maximize the therapeutic efficacy of DOX. Reproduced from ref. 175 with permission from Springer Nature, copyright 2023. (C) The Zr/Ce-MOFs/DOX/MnO_2 nanosystem serves as a new type of nanosome for combined chemotherapy and catalytic treatment. Reproduced from ref. 47 with permission from Royal Society of Chemistry, copyright 2023. (D) The MOF-Pt(IV)@GOx nanozyme provides remarkable anti-tumor efficacy through synergistic trimodal therapy with ferroptosis, starvation therapy, and chemotherapy. Reproduced from ref. 177 with permission from Elsevier, copyright 2023. (E) By immobilizing cholesterol oxidase (COD) onto an NH_2-MIL-88B MOF through an amide reaction, this system can catalyze the conversion of cholesterol into H_2O_2, which then leverages the POD-like activity of the MOF to generate toxic $^{\bullet}OH$. Reproduced from ref. 178 with permission from Springer Nature, copyright 2022. (F) CD-PEI is capable of loading and delivering siMRP1 and DOX into tumors, increasing DOX accumulation and significantly enhancing the cell vitality inhibition induced by CD-PEI-DOX to counteract chemotherapy resistance. Reproduced from ref. 179 with permission from Dove Press, copyright 2023.

also amplifies intracellular acidity and H_2O_2 availability, thus boosting the Fenton reaction. Both *in vitro* and *in vivo* experiments demonstrate that MOF-Pt(IV)@GOx achieves remarkable tumor inhibition through a synergistic tri-modal approach combining ferroptosis, starvation therapy, and chemotherapy.

Multiple resistance remains a barrier to cancer treatment. Most research focuses on the inhibition of *P*-glycerin activity during drug transport, but its effect is also very unsatisfactory. Du *et al.*[178] developed an enzyme-driven DOX@MOF-COD@CS nanosystem (Fig. 13E). This system carries the drug DOX on MOF-COD nanoparticles, where a chondroitin sulfate (CS) shell with disulfide bonds reacts with GSH, triggering drug release, catalyzing a series of reactions, and causing cell death. The focus of the study is on overcoming drug resistance by using cholesterol oxidase to reduce cholesterol in resistant cell membranes, enhancing drug absorption. Furthermore, cholesterol oxidase converts cholesterol into H_2O_2, which is then transformed into $^{\bullet}OH$ by MOF nanozymes, aiding in combating resistance and effectively destroying cancer cells. Finally, the CS shell suppresses the production of COX enzymes,

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leading to a reduction in the levels of the anti-apoptotic protein Bcl-XL, making tumor cells more susceptible to chemotherapy. Yu and team[179] employed a CD-PEI system for loading siRNA aimed at MRP1, addressing the resistance of lung cancer to DOX treatment (Fig. 13F). They utilized siRNA to lower MRP1 levels, curtailing drug expulsion and boosting the drug concentration within lung cancer cells. The CD-PEI simultaneously transports siRNA and chemotherapeutic drugs to tumors, enhancing drug absorption in cells by blocking the drug outflow channels and managing oxidative stress, thus concentrating more drugs near the nucleus. Crucially, the co-delivery system combats MRP1 activity by promoting GSH suppression through increased oxidation and ROS. Their approach of delivering DOX *via* CD-PEI, alongside a dual strategy of MRP1 inhibition and GSH depletion, underscores the significant potential of this combined system in improving the efficacy of chemotherapy and siRNA treatments for challenging lung cancer.

3.2.2. Radiotherapy. Radiation therapy stands as a pivotal cancer treatment modality.[180] However, radiotherapy also has various side effects. This is mainly because the radiation kills not only the cancer cells but also the surrounding normal tissue. In addition, there are other problems such as insufficient deposition of radiation in the tumor tissue, increased hypoxia in the TME, *etc*.[181] Vascular abnormalities in the TME also contribute to hypoxia, and hard tumor tissue leads to radioresistance.[182] In response to these limitations of radiotherapy, nanozymes can improve sensitivity to radiotherapy, protect the normal tissue around the tumor, and reduce the side effects of radiotherapy.

To overcome these radiotherapy resistance that may lead to local recurrence and treatment failure,[183] Zhou *et al.*[184] reported the synthesis of a covalent organic framework (COF) saturated with iodine and ferrocene (TADI-COF-Fc) at room temperature to improve the efficacy of radiotherapy in the treatment of radioresistant oesophageal cancer (Fig. 14A). Iodine atoms in the COF scaffold not only directly affected radiotherapy and increased X-ray absorption to enhance the therapeutic effect, but also promoted aqueous radiolysis, which increased ROS generation. In addition, ferrocene surface finishing increased the levels of hydroxyl and lipid peroxyl radicals and decreased intracellular antioxidants, which disrupted redox homeostasis.

Ionizing radiation therapy often leads to H_2O_2 radiolysis, generating substantial ROS that can alter DNA.[185] However, the hypoxic conditions in solid tumors can diminish the effectiveness of radiotherapy due to the reduced capacity of oxygen to facilitate DNA damage and ROS generation.[186] Addressing these challenges, new strategies have been developed. For instance, Yuan *et al.*[187] devised a TME-sensitive DOX@HMSN/Mn_3O_4(R) nanosome. This nanosome, responding to the TME, undergoes an *in situ* Mn^{3+}/Mn^{2+} transition, disrupting redox balance and catalyzing excessive ROS production (Fig. 14B). It also interacts with excess GSH in the TME to produce oxidized glutathione (GSSG), neutralizing ROS. The OXD-like activity of nanosome fosters $^{\bullet}OH$ from O_2 and enhances the TME oxidative state.[188] When combined with radiotherapy, the outer layer electrons of the nanosome are excited by high-energy X-rays, contributing to the OXD-like reaction and further boosting ROS levels, thereby amplifying the efficacy of radiochemotherapy. Besides, an innovative BiPt-PFA nanocomposite was created by embedding platinum nanoparticles into a mesoporous bismuth (Bi)-based nanomaterial, followed by acid modification with amphiphilic polyethylene glycol (PFA) (Fig. 14C). BiPt-PFA functions as an effective radiosensitizer, enhancing X-ray absorption specifically in tumor areas and responding to the TME due to the material accumulation in these regions. During its action, the Bi component of the nanocomposite interacts with GSH, disrupting the oxidative stress equilibrium through resonance. Simultaneously, the platinum nanoparticles facilitate the breakdown of H_2O_2 into O_2, thereby mitigating the hypoxic state of the tumor. Li *et al.*[189] introduced porous platinum nanoparticles as an innovative single-agent nanomedicine platform, addressing dual challenges in cancer treatment (Fig. 14D). Leveraging the high atomic number and oxygen generation capabilities of these nanoparticles, they significantly enhance radiation-induced DNA damage, ROS stress, and cell cycle arrest in cancer cells by effectively concentrating X-ray energy. Moreover, these porous platinum nanoparticles boost tumor oxidation by transforming endogenous H_2O_2 into O_2, thus markedly enhancing the efficacy of radiotherapy while demonstrating no apparent *in vivo* toxicity in animal models.

Nanocatalysts can be engineered to "reprogram" the TME by changing how certain biomolecules are expressed, leading to significantly improved radiotherapy outcomes. The designed multifunctional nanocatalyst system, CuPy-Au@EM, which mimics tumor cell exosomes, acts as a radiosensitizer.[190] Its exosome membrane proteins on the surface ensure targeted delivery to tumor sites, with a core made of CuPy nanocatalyst embedded with gold nanoparticles (AuNPs). These AuNPs boost H_2O_2 levels in a manner similar to GOx, while CuPy-Au@EM further lowers cellular GSH and through its GPx and POD activities, generates a vast number of $^{\bullet}OH$, expanding the effectiveness of radiotherapy. Additionally, an innovative method uses AuNPs-modified iron SOD-mimic (FeSAE@Au) for a self-propelling catalytic effect in radiotherapy.[191] In this dual-nanocatalyst strategy, AuNPs serve as a GOx mimic, enabling FeSAE@Au to produce H_2O_2, which boosts its POD-like activity. This leads to a marked increase in $^{\bullet}OH$ within cells, thereby enhancing radiotherapy's effectiveness.

The effectiveness of conventional radiotherapy is often limited by inadequate radiation energy deposition and collateral damage to healthy tissues.[192] To address these issues, recent advancements have focused on multifunctional nanoformulations and synergistic therapies, aiming to boost both the efficacy and safety of radiotherapy. Hu *et al.*[192] introduced a bimetallic nanozyme, RuCu NPs (copper-modified ruthenium nanoparticles), incorporating the high atomic number element ruthenium as a novel radiosensitizer. This nanozyme demonstrates ultrasensitive POD-like and CAT-like activities, offering an ideal approach for radiotherapy sensitization. DFT

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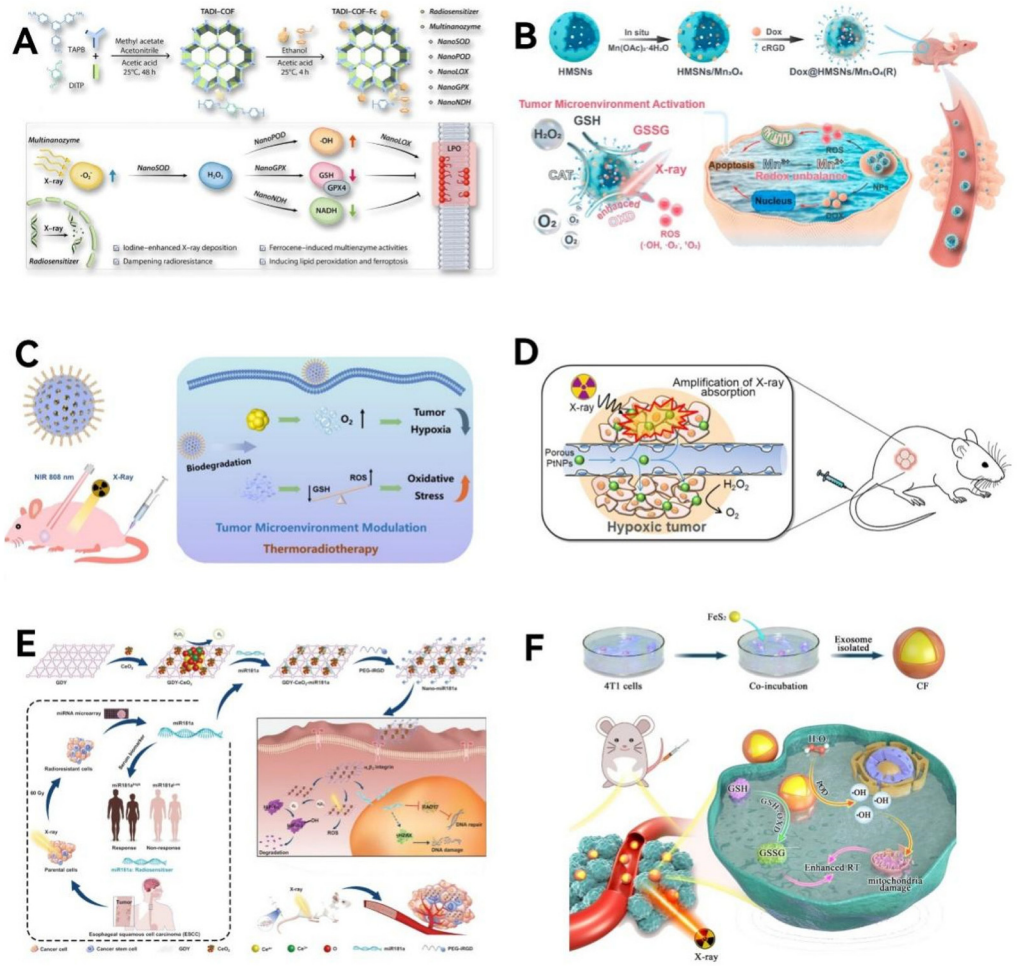

Fig. 14 Biomimetic designed nanozymes for cancer radiotherapy. (A) The TADI-COF-Fc is used to enhance the radiotherapy efficacy for esophageal cancer therapy. Reproduced from ref. 184 with permission from American Chemical Society, copyright 2023. (B) A TME-sensitive DOX@HMSN/Mn_3O_4(R) nanosome for effective radio-chemotherapy. Reproduced from ref. 187 with permission from Elsevier Ltd, copyright 2022. (C) BiPt-PFA acts as a radiosensitizer to enhance the absorption of X-rays at tumor sites, also triggering reactions related to the TME. Reproduced from ref. 188 with permission from American Chemical Society, copyright 2020. (D) Porous platinum nanoparticles exhibit the ability to deposit X-ray radiation energy effectively within cancer cells and enhance tumor oxygenation. Reproduced from ref. 189 with permission from Elsevier Ltd, copyright 2019. (E) The POD-mimicking GDY-CeO_2 nanocomposites, integrated with miR181a, are conjugated to iRGD-grafted polyoxyethylene glycol, augmenting their radiotherapeutic efficacy. Reproduced from ref. 194 with permission from WILEY, copyright 2021. (F) A biomimetic nanozyme system (CF) was developed by encapsulating FeS_2 into exosomes derived from tumor cells, designed to enhance low-dose radiotherapy. Reproduced from ref. 193 with permission from Springer Nature, copyright 2021.

calculations further elucidated the optimal POD-like catalytic ratio of RuCu NPs and shed light on its superior catalytic activity. Under X-ray irradiation, RuCu NPs coated with PEG effectively enhanced ROS production and alleviated tumor hypoxia in the acidic TME, showing significant therapeutic efficacy in the MDA-MB-231 breast cancer model. Besides, Huang *et al.*[193] developed a biomimetic nanozyme system (CF) by encapsulating pyrite (FeS_2) into tumor-derived exosomes (Fig. 14F). This CF system endows FeS_2 with immune evasion and homologous targeting capabilities. Post-administration, CF, exhibiting both GSH-OXD and POD activities, notably reduces GSH content in tumors and catalyzes intracellular H_2O_2 to generate abundant $^{\bullet}OH$, disrupting intracellular redox balance and destroying mitochondria, thus mitigating radiotherapy resistance. Both *in vivo* and *in vitro* studies have demonstrated that CF, combined with radiotherapy (2Gy), significantly curbs tumor proliferation.

3.2.3. Immunotherapy. Over the last few years, cancer immunotherapy has drastically changed how we treat tumors by triggering a sustained immune surveillance that reactivates the body's defense against tumors. Notably, immune checkpoint blockade (ICB) therapy using monoclonal antibodies, which targets the programmed cell death protein 1/programmed cell death 1 ligand 1 (PD-1/PD-L1) pathway, has shown promise in revitalizing exhausted T cells, allowing them to fight a variety of cancers effectively. Despite its potential, ICB therapy's success is limited, benefiting only a select group of patients due to poor T cell infiltration and the low immuno-

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genic nature of tumor tissues. An emerging alternative strategy involves inducing ICD to transform the tumor immune microenvironment (TIME), offering new hope for enhancing treatment efficacy.[195]

Building on the complex yet effective link between immunotherapy and tumor catalytic therapy, Yang group introduced a groundbreaking tumor treatment method,[77] this approach combines MnO_x nanocatalysts that mimic multiple enzymes, coated with tumor cell membranes (CM@Mn), and PD-1 monoclonal antibodies (αPD-1) (Fig. 15A). The aim is to kickstart the TME for a manganese-enhanced catalytic immunotherapy that works in tandem with PD-1 checkpoint inhibition. These CM@Mn nanocatalysts are capable of generating a significant amount of ROS to eliminate tumor cells and counteract tumor hypoxia *via* CAT activity, thereby transforming the tumor immune microenvironment. Additionally, the release of DAMPs by tumor cells boosts the tumor's immunogenicity. The TME facilitates the generation of Mn^{2+}, further boosting immune activation within the tumor. Ultimately, with the support of PD-1 checkpoint inhibition, this strategy can unleash a robust anti-tumor response, converting an immunosuppressive TME into an immune-activated environment.

Current trends in immunotherapy, particularly its combination with chemotherapy and radiotherapy, aim to enhance treatment outcomes. However, the adverse effects of chemotherapy and radiotherapy necessitate the discovery of safer, more effective complementary methods. In this context, Xu *et al.*[196] devised a technique to trigger tumor cell pyroptosis and modulate the expression levels of PD-L1 by controlling tumor glycometabolism (Fig. 15B). They synthesized nanoparticles with dual enzymatic activities using a biomineralization-like approach. These nanoparticles are capable of self-amplifying the regulation of tumor cell glycometabolism, inducing pyroptosis, and elevating PD-L1 expression in tumor cells. When these nanoparticles are used in conjunction with anti-PD-L1 therapy, there is a significant suppression in tumor growth and a notable increase in the survival rates of mice. This combination therapy not only demonstrates a pronounced immunological memory effect but also effectively prevents tumor recurrence and metastasis.

Accurately triggering antitumor immune responses is a complex challenge. Nguyen *et al.*[197] developed a novel nanocomposite polymer immunomodulator, the drug-free polypyrrole–polyethyleneimine nanozyme (PPY-PEI NZ). This nanozyme specifically responds to the B-cell lymphoma TME, aiming for precise cancer immunotherapy. It rapidly binds to various B-cell lymphoma cells due to early endocytosis, effectively inhibiting B-cell colony growth *in vitro* and inducing cytotoxic apoptosis. PPY-PEI NZ-triggered cell death involves mitochondrial dysfunction, downregulation of antiapoptotic proteins, and caspase-dependent apoptosis, with altered AKT and ERK signaling pathways contributing to apoptosis. Additionally, these nanozymes can disrupt lysosomal membranes while preventing endosomal acidification, offering protection against lysosomal apoptosis. Notably, PPY-PEI NZs can selectively target and eliminate malignant B cells in mixed cultures with healthy leukocytes, showing effectiveness *ex vivo* without harming wild-type mice. *In vivo*, they significantly inhibit the growth of B-cell lymphoma-driven nodules in a xenograft model.

Moreover, a cold-activated artificial enzyme based on $Bi_2Fe_4O_9$ nanosheets (NSs) is introduced (Fig. 15C).[198] These NSs exhibit glutathione oxidase-like activity at low temperatures due to their pyroelectric properties. They induce tumor cell death *via* apoptosis and ferroptosis while minimizing toxicity to normal tissues. An innovative device also allows for the intelligent, remote control of the enzymatic activity of $Bi_2Fe_4O_9$ NSvia a smartphone. Serving as an *in situ* vaccine, these NSs activate systemic antitumor immunity, effectively suppressing metastasis and relapse. Blood biochemistry and histological analyses confirm the high biosafety of $Bi_2Fe_4O_9$ NSs for *in vivo* use.

3.2.4. Chemodynamic therapy (CDT). Recognizing the unique challenges of the TME, which includes low oxygen, high H_2O_2 levels, and acidic conditions, Bu *et al.*[199] introduced CDT. This innovative therapy transforms the chemical energy present in tumors into ROS, avoiding issues like photosensitivity and limited tissue penetration that come with PDT. The effectiveness of nanozymes in CDT is closely linked to their active sites, and ultrafine nanozymes with more active sites and larger surface areas have shown improved anti-tumor effects. Another crucial aspect of CDT is boosting intracellular H_2O_2 levels, which in turn increases the production of toxic ROS, a process regulated by enzymes and antioxidants.

However, CDT has been constrained by the demanding conditions of Fenton reaction (pH = 3–4) and slow kinetics. To address this, Jana's team[60] introduced a minuscule trimetallic alloy nanozyme (PCF-a NE), comprising Pd, Cu, and Fe (Fig. 16A). This nanozyme leverages dynamic active site synergy, enabling cascading GPx and POD-like activities at a neutral pH. Notably, PCF-a NE exhibits photothermally enhanced POD characteristics and an impressive photothermal conversion efficiency of 62%, aiding in the apoptosis of tumor cells. Furthermore, ultrasound application can boost the mass transfer at the nanozyme active sites, speeding up the tumor-specific CDT through a Fenton-like reaction. This innovation outlines a biomimetic approach to designing alloy nanozymes that amplify ROS within tumors in response to external stimuli, showing marked efficiency in suppressing tumor growth both in lab settings and live models.

Yang's team[48] advanced this field by creating ultrafine, evenly distributed nanozymes within MOF structures for CDT in cancer. Using high-intensity ultrasound, they produced various ultrafine alloy nanoparticles like Ni–Ru@MIL-101 and Cu–Pd@MIL-101 (Fig. 16B). Among these, the Cu–Pd@MIL-101 modified with a 9.5% alloy (Cu–Pd@MIL-101-PEG, or CPMP) showed exceptional ability in generating toxic $^{\bullet}OH$ and depleting GSH, making it highly effective in CDT. Both lab and animal studies confirmed that Cu–Pd@MIL-101-PEG was highly effective in producing toxic radicals within the TME, leading to tumor cell death, and hindering tumor

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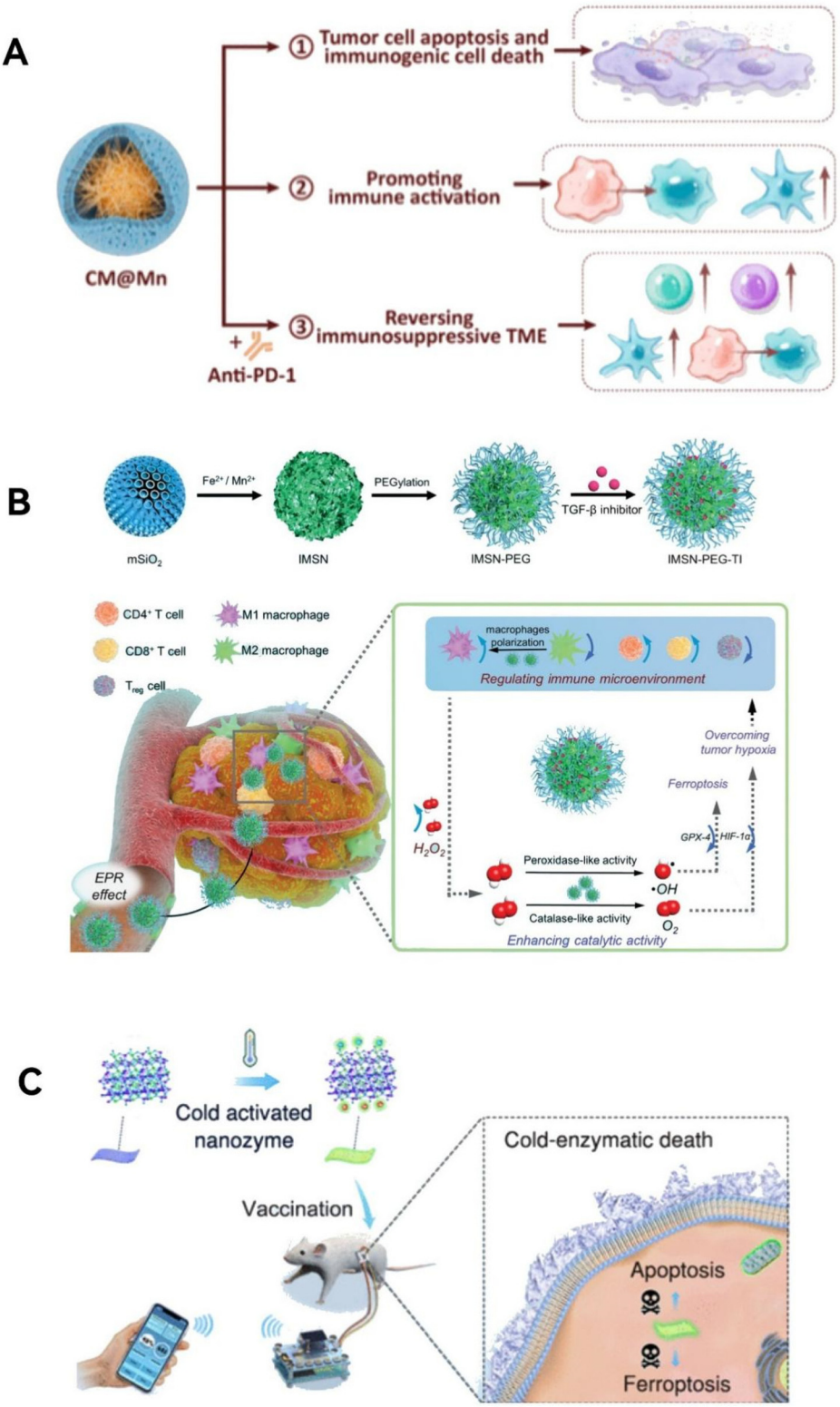

Fig. 15 Biomimetic-designed nanozymes for cancer immunotherapy. (A) In the acidic TME, the CM@Mn nanozyme, exhibits POD and OXD-like activities, designed for killing tumor cells killing and evoking immunogenic cell death. Reproduced from ref. 77 with permission from American Chemical Society, copyright 2020. (B) The IMSN-PEG-TI nanozyme, exhibiting both POD-like and CAT-like activities in the acidic TME, facilitates a synergistic interaction between nanozyme efficiency and TME modulation, significantly enhancing immunotherapy outcomes. Reproduced from ref. 196 with permission from WILEY, copyright 2020. (C) $Bi_2Fe_4O_9$ nanosheets, serving as *in situ* vaccines, successfully activate systemic anti-tumor immunity, effectively inhibiting tumor metastasis and recurrence. Reproduced from ref. 198 with permission from American Chemical Society, copyright 2022.

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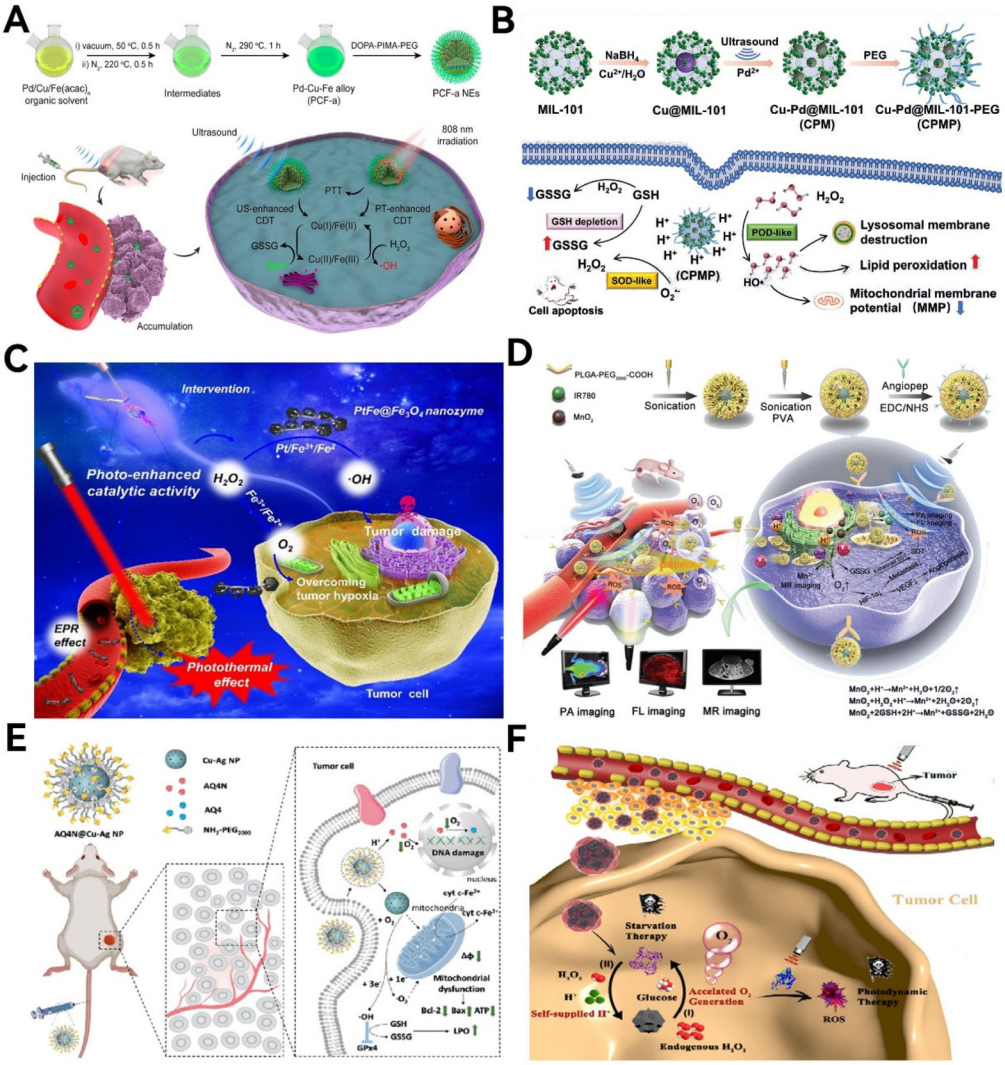

Fig. 16 (A) PCF-a NE targets cancer with a two-pronged approach: one method boosts CDT using ultrasound and depletes GSH, and the other enhances CDT through heat generated by PTT while also reducing GSH. Reproduced from ref. 60 with permission from American Chemical Society, copyright 2021. (B) PEG-modified Cu–Pd@MIL-101 (Cu–Pd@MIL-101-PEG, CPMP) exhibits the highest POD-like and SOD-like activities, as well as GSH depletion characteristics, demonstrating strong tumor CDT effects. Reproduced from ref. 48 with permission from WILEY, copyright 2021. (C) PtFe@Fe_3O_4 significantly enhances catalytic activity under near-infrared laser irradiation, and by utilizing a photointervention device, implements an *in situ* photo-enhanced catalytic therapy combined with a photothermal effect strategy. Reproduced from ref. 200 with permission from American Chemical Society, copyright 2022. (D) AIMP nanoparticles are designed for crossing the blood–brain barrier (BBB) and specifically targeting tumors and mitochondria, offering deep tissue penetration and improved SDT outcomes. Reproduced from ref. 201 with permission from Royal Society of Chemistry, copyright 2021. (E) Nanozymes made of a copper–silver alloy, carrying AQ4N, have the unique capability to trigger cell starvation, induce ferroptosis, and deliver targeted prodrug treatments all at once. Reproduced from ref. 202 with permission from WILEY, copyright 2022. (F) rMGB achieves self-supply of H^+ and accelerates the generation of O_2, alleviating tumor hypoxia, enhancing PDT, and starvation therapy for hypoxic tumors. Reproduced from ref. 203 with permission from American Chemical Society, copyright 2022.

growth. Additionally, these ultrafine nanoparticles were found to be biocompatible and safe for biological use.

3.2.5. Photodynamic therapy (PDT). Motivated by the progress in phototherapy, incorporating a NIR laser has been proposed to boost both the catalytic activity and therapeutic potential of nanozymes. On one front, nanocatalysts can facilitate the generation of ROS under light exposure, aided by direct electron transfer and a light-augmented Fenton reaction. Concurrently, the photothermal properties of nanozymes can substantially enhance ROS production. This dual mechanism suggests that the light-strengthened catalytic function and photothermal impact of nanozymes could be effectively harnessed to synergize tumor catalytic therapy with PTT, offering a well-integrated therapeutic approach.

Li's team[200] introduced an innovative nanozyme (PtFe@Fe_3O_4) that showcases dual enzymatic-like activities, offering a promising approach for effective tumor catalytic therapy (Fig. 16C). In the acidic milieu of the TME, PtFe@Fe_3O_4

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demonstrates intrinsic photothermal effects alongside light-amplified POD and CAT activities. This dual functionality enables it to efficiently eliminate tumor cells and address the issue of tumor hypoxia. Furthermore, their research delved into the electron transfer dynamics between PtFe nanorods, Fe_3O_4 nanoparticles, and H_2O_2 molecules to explore the potential light-enhanced synergistic catalytic mechanism.

3.2.6. Sonodynamic therapy (SDT). Sonodynamic therapy (SDT) is a promising cancer treatment method, but its efficacy is severely hindered by the low specificity of sonosensitizers and the adverse characteristics of the TME. Liu's team[201] developed a multifunctional nanozyme (Ang-IR780-MnO_2-PLGA, AIMP) by encapsulating IR780 and MnO_2 in PLGA and linking Angiopep-2 (Ang), enhancing SDT effectiveness (Fig. 16D). The design of AIMP enables better penetration of the blood–brain barrier and targeted delivery to gliomas, while IR780 enhances mitochondrial targeting in cancer cells. When exposed to low-intensity focused ultrasound, AIMP produces ROS and triggers tumor cell apoptosis. The mitochondrial targeting capability of IR780 amplifies the sonodynamic impact, resulting in heightened sensitivity of mitochondria to ROS. MnO_2 in AIMP acts like an enzyme, reacting with abundant H^+, H_2O_2, and GSH in the TME to continuously generate oxygen and deplete GSH, boosting SDT efficacy. This research demonstrates that AIMP NPs, activated by LIFU, significantly suppress tumor growth and metastasis by leveraging multifaceted mechanisms like targeted action, deep penetration, localized oxygen provision, and GSH depletion, thereby enhancing the overall therapeutic impact of SDT.

3.2.7. Starvation therapy. One of the key hallmarks of cancer is its abnormal cellular metabolism and the intense consumption of nutrients. The strategy of cancer starvation therapy, targeting the disease by cutting off the blood supply and depleting essential tumor nutrients like glucose and oxygen, has gained considerable attention in research. This approach is emerging as a compelling method in the arsenal of cancer treatment options. Cao *et al.*[202] showcased a copper–silver alloy nanozyme infused with AQ4N that effectively delivers a triple-mode therapy involving starvation, ferroptosis, and targeted prodrug activation (Fig. 16E). Their extensive research, encompassing both lab and live studies, revealed how this Cu–Ag nanozyme, by imitating the cytochrome c oxidase, leverage the excess cytochrome c in cancer cells. It acts as an electron donor, transforming oxygen into cell-damaging superoxide and $^{\bullet}OH$, thereby intensifying the lack of oxygen in tumors. This action, combined with the collapse of mitochondrial function and cellular respiration, blocks ATP production, paving the way for an innovative starvation therapy approach. The nanozyme also triggers ferroptosis by inhibiting glutathione peroxidase 4 and activates prodrugs in severely hypoxic conditions, ensuring targeted cancer treatment. This study underlines the multifaceted capabilities of copper–silver nanozyme in conducting efficient, specific, and minimally side-effective starvation therapy, along with its potential to enhance cancer treatment through nanocatalysis.

Sun's team[203] developed an innovative biomimetic hybrid nanozyme, rMGB, by harnessing GOx and BSA-Ce_6 on MnO_2 nanoparticles, forming the cornerstone of this hybrid nanozyme system (Fig. 16F). They cleverly utilized a red blood cell membrane coating on the MGB NPs to minimize the systemic toxicity associated with GOx and MnO_2. The rMGB is particularly effective against hypoxic tumors, catalyzing the conversion of endogenous H_2O_2 and H^+ into O_2 right at the tumor site. This process supplies the necessary oxygen for GOx, thereby facilitating cancer starvation therapy. Additionally, H^+ production by GOx aids MnO_2 in further boosting oxygen generation, mitigating tumor hypoxia, and consequently amplifying the effectiveness of PDT. Therefore, rMGB, through the synergistic action of GOx and MnO_2, significantly improves the efficacy of PDT and starvation therapy for hypoxic tumors by enhancing oxygen production in the tumor environment.

4. Perspectives

4.1. Catalytic specificity

Nanozymes, while offering synergistic and multifunctional enzyme-like activities, lack the precise catalytic specificity and pathway selectivity of natural enzymes.[204] This restricts their use in highly selective applications, especially in critical biological processes. The variety and number of nanozymes known for catalytic activity are significantly fewer than natural enzymes. Progress in enhancing nanozyme selectivity is notable, yet it falls short of the stringent specificity found in natural enzymes. Enhancing the catalytic selectivity of nanozymes is crucial, especially for targeted and personalized approaches in cancer therapy.

Improving nanozyme specificity hinges on boosting the ability of their structural domains to specifically recognize substrates and finely control catalytic sites. Unlike natural enzymes, many nanozymes have exposed catalytic sites, lacking the specific binding sites and precise environments needed for effective substrate interaction and catalysis. Selecting appropriate ligands as binding domains can increase substrate recognition and binding, thereby enhancing activity for particular substrates. For example, lactate, a key signaling molecule, is crucial in the progression of tumor malignancy, blood vessel formation, immune suppression, and resistance to treatment. Targeting lactate has emerged as a promising approach to improve cancer therapies. Developing nanozymes with effective LOX mimicry could advance lactate-responsive cancer treatments, yet oxidizing the α-C–sp^3–H bond of lactate to generate pyruvate under gentle conditions remains a complex challenge. Drawing inspiration from nature, advancements in nanozymes mimicking LOX should focus on enhancing the electronic configuration near electron-rich nitrogen (N) sites. Zhao group[61] introduced a strategy that mimics LOX by adjusting the electronic characteristics of the N center in Co (x)–N nanocomposites, by controlling the number of Co atoms near the N. This results in Co_4N/C having specific sites for accurately recognizing lactate and its intermediates, fine-

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tuning the absorption energy of intermediates, thus facilitating the conversion of lactate's α-C–sp^3–H bond into a ketone. This optimized nanozyme markedly improves its anti-cancer properties by altering the TME high lactate and immunosuppressive conditions, leading to significant inhibition of tumor growth and metastasis.

Future research should aim at designing nanozymes that closely mimic enzyme active sites for selective substrate interaction and high catalytic efficiency. Understanding the structure–activity relationships of nanozymes that dictate substrate transformation pathways is also vital. These research directions are key to enhancing substrate selectivity and determining the specificity of nanozyme-catalyzed reactions.

4.2. Functional versatility

Nanozymes offer distinct advantages over natural enzymes: they are cost-effective, stable, easily modifiable, and can self-assemble. Their activity can be tuned through size and structural factors. Crucially, nanozymes blend the unique physical and chemical properties of nanomaterials into their functionality.[205] For example, Fe_3O_4 nanozymes not only act as PODs but also have superparamagnetic features.[206] Similarly, molybdenum disulfide (MoS_2) nanoparticles combine catalytic activity with near-infrared photothermal properties, making nanozymes versatile in function.[207] In cancer therapy, this allows for an innovative approach: beyond just combining catalytic treatments with other cancer therapies, the catalytic properties of nanozymes can be integrated with their physical and chemical attributes. This fusion opens up new, groundbreaking possibilities for unified cancer diagnostics and treatment strategies, leveraging the multifaceted nature of nanozymes. For instance, Song group[208] have developed an innovative manganese semiconductor polymer-based nanozyme (MSPN), designed for specific cancer treatment in acidic tumor environments. What sets MSPN apart is its ability to self-report its activity, providing real-time near-infrared fluorescence-photoacoustic (NIRF-PA) feedback. The core of MSPN is a mix of manganese oxide (MnO_x) and semiconductor polymer (PFODBT), linked to oxidase-responsive molecules (ORM) through amide bonds. In acidic conditions, MnO_x triggers the breakdown of ORM, which changes the emission signals at 695 nm and 825 nm due to effective fluorescence resonance energy transfer between PFODBT and ORM. Importantly, MSPN maintains a consistent internal PA signal at 680 nm while the responsive PA signal at 780 nm drops, creating a distinct PA signal ratio (PA680/PA780). This functionality allows MSPN to not only actively treat cancer in the body but also to monitor the efficiency of its OXD-like catalysis in real-time through dual-mode NIRF-PA imaging. This cutting-edge method merges nanozyme catalysis with tumor imaging, providing a novel strategy for evaluating and tracking the success of cancer treatments.

Multifunctional nanozymes are adept at combining diagnostic and therapeutic functions. Chen group[209] developed a versatile Ti_3C_2–MXene–Au nano-platform. This platform integrates photothermal, enzymatic, and anti-tumor immune therapies for treating triple-negative breast cancer (TNBC) by coupling Ti_3C_2–MXene–Au nanodrugs with OX40 mAb. Thanks to the nanostructure's enhanced permeability and retention effect, the Ti_3C_2–MXene–Au nanocomposite specifically accumulates at tumor sites post-intravenous injection. It also facilitates thermal/PA dual-mode imaging within the body. Upon laser exposure, the localized heating at the tumor site not only ablates the tumor but also boosts catalytic reactions to produce $^{\bullet}OH$, leading to tumor cell death. Furthermore, introducing OX40 mAb strengthens T-cell-mediated anti-tumor immunity and mitigates immune suppression caused by tumor cells.

Multifunctional nanozymes, serving as versatile molecules, hold potential in areas like medical diagnosis, therapy, and monitoring. Given the broad and yet-to-be-fulfilled clinical needs for diagnosing and treating diverse diseases, exploring and applying the multifaceted capabilities of nanozymes is a key focus for future research. Moreover, before these nanozymes can be clinically applied, it's crucial to rigorously investigate and test them, particularly concerning issues like their clinical safety, stability, and how their catalytic processes work. This thorough examination is vital to ensure their efficacy and safety in medical applications.

4.3. Artificial intelligence-aided design

AlphaFold, a ground-breaking artificial intelligence (AI) program by DeepMind, has revolutionized the field with its ability to predict human protein structures, a long-standing challenge in biology and medicine.[210] This achievement underscores the immense potential of AI in advancing medical research. More than just handling vast datasets, this cutting-edge technology can unravel complex biological patterns that elude direct human observation. Inspired by this, AI-driven data analysis and performance prediction have become essential tools for assessing material properties and spearheading new material developments.[211,212] In contrast to the traditional, resource-intensive methods of developing nanozymes —relying on trial and error or intuition and experience, which are often inefficient and costly. Using AI algorithms, including machine learning (ML) and deep learning (DL), presents a more effective alternative.[212] leveraging existing data through artificial intelligence algorithms such as ML and DL as a reliable tool can uncover the hidden relationships between the physicochemical characteristics of nanozymes and their enzyme-like functions. This approach holds tremendous research and practical value, opening new frontiers in material science.[213]

Researchers are finding innovative uses of ML in pinpointing the best activities for nanozymes. At the outset, ML helps sift through nanozymes by examining their kinetic features—like K_M, V_{max}, k_{cat}, and k_{cat}/K_M ratios—offering a clear picture of their performance and specificity.[213] ML also steps in to forecast the energy barriers and thermodynamic aspects of nanozyme-catalyzed reactions, evaluating how challenging it is to these reactions.[214] Such thermodynamic insights, typically gleaned from DFT computations that demand high-perform-

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ance computing and significant time,[215] can now be more efficiently predicted by ML. This leap is possible because ML models, trained on precise quantum or experimental data, might even outperform hybrid DFT analyses in accuracy.[216] Moreover, the scope of ML extends to classifying nanozymes based on their enzymatic actions.[213] It does so by digitizing their catalytic activities and leveraging intrinsic and extrinsic nanozyme markers for direct predictions, or by using physical descriptors to foretell the enzyme type and specificity.[217] ML is also viable for analyzing the biomimetic structures of nanozymes. For instance, ML can predicate the spatial arrangement and the type and distribution of metal atoms at SAN active sites, which are key to their catalytic process, showcasing the broad applicability of ML in advancing nanozyme research.

Li group[218] applied an innovative approach, combining stochastic surface walking technology based on global neural network potentials and DFT calculations, to fast-track exploring the global potential energy surface of catalysts. Through this method, they successfully mapped out the phase diagrams for PdAg catalysts, both in bulk and on surfaces, under actual reaction conditions. This exploration shed light on how variations in phase composition and surface structures influence the catalyst effectiveness. From their findings on how *in situ* surface structures affect PdAg catalysts, they developed a new catalyst, Pd_1Ag_3, supported by rutile. This catalyst exhibited exceptional performance, achieving a remarkable 496% conversion rate and 485% selectivity, setting a new standard in catalytic efficiency. Moreover, Huang's group[213] conducted a detailed analysis on a diverse dataset of nanozymes, extracted from over 300 research papers. They focused on datasets that included at least one variable from the Michaelis–Menten equation, aiming at further refinement for data mining purposes. The analysis highlighted eight key internal factors, namely, the type and valency of metals, the quantity of metals, size, shape, non-metal elements, surface modifications, and types of enzyme mimicry. Additionally, external conditions such as buffer pH, temperature, and substrate type were identified as critical variables influencing nanozyme characteristics. The researchers then developed 14 sophisticated deep neural network (DNN)-based models, both qualitative and quantitative, designed to accurately predict the enzymatic activities of nanozymes. The classification models were tasked with identifying the types of enzyme mimetics, whereas the quantitative models focused on measuring the levels of enzymatic activity. Remarkably, the predictions made by these models were found to align closely with actual observed data, showcasing the potential of DNN in advancing nanozyme research. In summary, these studies reveal the strength of ML in the development of nanozymes.

5. Conclusion

In summary, this review provides a comprehensive overview of the pioneering research in the field of nanozymes, specifically those that are biomimetically engineered from the ground up for anti-tumor treatment. It emphasizes the intricate processes involved in their creation, including structural biomimicry, process biomimicry, and the nuances of advanced functional biomimicry. This exploration sheds light on the fundamental mechanisms that amplify their catalytic properties and examines their extensive biomedical applications in the fight against tumors, thereby underscoring the remarkable progress achieved in this cutting-edge area of study.

Abbreviations

2-mim	2-Methylimidazole
3-AT	3-Amino-1,2,4-triazole
ATP	Adenosine triphosphate
Ang	Angiopep-2
AI	Artificial intelligence
BON	Boroxynitride
CAT	Catalase
Cer	Cerulenin
CDT	Chemodynamic therapy
CS	Chondroitin sulfate
CuP	Copper-doped polypyrrole nanozyme
COF	Covalent organic framework
DL	Deep learning
DNN	Deep neural network
DMSN	Dendritic mesoporous silica
DFT	Density functional theory
DNA	Deoxyribonucleic acid
DHA	Dihydroartemisinin
DOX	Doxorubicin
FAO	Fatty acid oxidation
Fe^{2+}	Ferrous
FM	Fusion membrane
GBM	Glioblastoma
GOx	Glucose oxidase
GSH	Glutathione
GPx	Glutathione peroxidase
Fe^{3+}	Hemin
HCV	Hepatitis C virus
HRP	Horseradish peroxidase
H_2O_2	Hydrogen peroxide
$^{\bullet}OH$	Hydroxyl radicals
ICB	Immune checkpoint blockade
ICD	Immunogenic cell death
ICG	Indocyanine green
FeMSN	Iron-doped mesoporous silica nanoparticles
LDH	Lactate dehydrogenase
LOX	Lactate oxidase
ML	Machine learning
MOFs	Metal–organic frameworks
NPs	Nanoparticles
NUs	Nanourchins
NAISA	Nanozyme-assisted immunoassay
NIR-II	Near-infrared II
$NADH/NAD^+$	Nicotinamide adenine dinucleotide
NADPH	Nicotinamide adenine dinucleotide phosphate

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NO	Nitric oxide
NOS	Nitric oxide synthase
N-GNM	Nitrogen-doped graphene materials
OXD	Oxidase
GSSG	Oxidized glutathione
O_2	Oxygen
OVs	Oxygen vacancies
PCNs	Palladium–copper nanoclusters
POD	Peroxidase
PDT	Photodynamic therapy
PTT	Photothermal therapy
PLT	Platelet
PEG	Polyethylene glycol
PD-1/PD-L1	Programmed cell death protein 1/programmed cell death 1 ligand 1
ROS	Reactive oxygen species
Rh	Rhodium
Ru	Ruthenium
SAzyme	Single atom nanozyme
$^1O_2$	Singlet oxygen
SOD	Superoxide dismutase
$O_2^{\bullet-}$	Superoxide radicals
TNBC	Triple-negative breast cancer
TIME	Tumor immune microenvironment
TME	Tumor microenvironment
ZIF	Zeolitic imidazolate framework

Conflicts of interest

There are no conflicts to declare.

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