International Journal of Nanomedicine

Dovepress
Taylor & Francis Group

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REVIEW

Precise Catalysis and Immune Activation: New Strategies for Tumor Immunotherapy with Cascade Nanozymes

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Abstract: Tumor immunotherapy can activate host antitumor immune responses and specifically eliminate tumor cells, making it a research frontier in tumor therapy. However, its clinical efficacy remains limitations by the immunosuppressive tumor microenvironment (TME) and insufficient tumor immunogenicity. Cascade nanozymes possess the capability to mimic diverse enzymatic activities, catalyze multi-step reactions, regulate the redox equilibrium of the TME, generate reactive oxygen species (ROS) for the eradication of tumor cells, induce immunogenic cell death (ICD), and modulate innate immune signaling pathways. These effects further trigger both innate and adaptive immune responses, thereby suppressing tumor metastasis and recurrence. Nevertheless, achieving selective killing of tumor cells without damaging normal cells via enzymatic reactions and clarifying the underlying mechanisms of cascade nanozyme-based immunotherapy remains a major challenge in cancer treatment. This review summarizes the latest advances of cascade nanozymes in cancer immunotherapy. It critically evaluates the design strategies and mechanisms of cascade nanozymes for immunotherapeutic applications, and highlights the key challenges and future perspectives in this field. It is expected to provide new insights for developing more efficient and targeted tumor immunotherapy strategies.

Keywords: tumor immunotherapy, tumor microenvironment, cascade nanozymes, immunogenic cell death, immune signaling pathways

Introduction

Malignant tumors are characterized by high incidence, high metastatic potential, and poor prognosis, posing a significant threat to human health and life.[1,2] Despite significant progress in tumor treatment, cancer remains a leading cause of death worldwide. Currently, conventional tumor treatments mainly include radiotherapy (RT), chemotherapy, and surgical resection.[3,4] However, these treatments are often limited by severe toxic side effects, long treatment cycles, and tumor drug resistance.[5–7] With the development of nanotechnology, emerging therapeutic strategies such as photothermal therapy (PTT),[8] chemodynamic therapy (CDT),[9,10] immunotherapy,[11,12] and combination therapy[7] exhibit fewer side effects and a low risk of inducing tumor drug resistance.[13] These novel modalities provide new insights into tumor treatment and hold great significance for the research of cancer prevention and clinical therapy.

Nanozymes are a class of nanomaterials with enzyme-like catalytic activity, capable of catalyzing the corresponding substrates under mild conditions.[14] In comparison to natural enzymes, nanozymes possess the merits of high stability, adjustable particle size, low cost, and facile surface modification.[15,16] Based on material composition, nanozymes can be mainly divided into four categories: metal-based nanozymes,[17] metal oxide-based nanozymes,[18] carbon-based nanozymes,[19,20] and MOF-based nanozymes.[21,22] They have been widely applied in biomedical fields, including biosensors,[23] antibacterial therapy,[24] and cancer therapy.[25,26] Cascade reactions are composed of two or more catalytic reactions that occur sequentially. In these reactions, the product of the upstream reaction acts as the substrate for the

https://doi.org/10.2147/IJN.S600885
Received: 3 February 2026
Accepted: 22 June 2026
Published: 21 July 2026

downstream reaction, thereby initiating a series of chemical transformations.[27] These cascade reactions, by modulating the tumor microenvironment (TME), enhance intermediate utilization, optimize catalytic performance, and yield high-purity products.[28] For example, Jin et al designed a nitrogen-doped carbon-supported cerium single-atom nanozyme (Ce SAs@NC).[29] Leveraging its peroxidase-like, oxidase-like, and catalase-like activities, the nanozyme can alleviate tumor hypoxia, generate $O_2^{\bullet-}$ and •OH, and induce lipid peroxidation as well as tumor cell apoptosis and necrosis, thereby achieving effective cancer therapy.

Immunotherapy can activate the host immune system to precisely recognize and attack cancer cells, and form long-term immune memory to prevent tumor recurrence,[30] which attracts widespread attention. However, owing to the limited therapeutic efficacy, low clinical response rates, feeble tumor immunogenicity, and severe adverse effects,[31,32] its clinical application continues to encounter significant challenges. Therefore, developing cascade nanozymes for multidimensional applications in tumor immunotherapy is crucial. Chen et al developed a $Cu_{2-x}O@MnO_2@GOx@HA$ nanozyme.[33] Hyaluronic acid (HA) endows the nanozyme with excellent tumor targeting performance. The $Cu_{2-x}O@MnO_2@GOx@HA$ nanozyme integrates GOx-mediated starvation therapy (ST), Cu-triggered CDT, NIR-II light-mediated PTT, and reactive oxygen species (ROS)-mediated immunotherapy. It enables synergistic and low-toxicity treatment for colorectal cancer. Liu et al developed a cascade reaction platform termed Ir Metallene@LOx@HA (ILH).[34] This platform effectively ameliorated the immunosuppressive TME through the synergistic effects of intratumoral oxygen generation, lactate consumption and photoacoustic effect. These effects promoted the polarization of tumor-associated macrophages (TAMs) from the M2 to the M1 phenotype, thereby activating antitumor immunity. Although several reviews have addressed nanozymes in tumor therapy, only a limited number have systematically concentrated on cascade systems and their immunomodulatory mechanisms. To this end, it is necessary to systematically organize and comprehensively elucidate the catalytic processes of cascade nanozymes and their mechanisms of action in enhancing tumor immunotherapy, with the aim of providing new insights for the rational design of nanozymes and the development of precise tumor immunotherapy strategies.

In this review, we provide a comprehensive overview of the regulatory mechanisms of nanozyme cascade catalysis and the rational design for tumor immunotherapy. First, we summarize the main types of nanozymes and elaborate on their catalytic mechanisms in detail. Second, we briefly recapitulate application examples of cascade catalytic reaction systems in the field of tumor therapy and the research progress in this area. Third, the review particularly highlights strategies based on cascade nanozymes for tumor immunotherapy to enhance the accuracy and efficiency of treatment within the TME. Finally, we discuss the potential applications of nanozymes in biomedicine, as well as the practical challenges they face in clinical tumor immunotherapy, providing a theoretical reference for the rational design of nanozymes and precise tumor immunotherapy.

Catalytic Activity of Nanozymes and Cascade Catalytic

Types of Mimetic Activities by Nanozymes

Nanozymes not only possess catalytic capabilities similar to natural enzymes, but also allow the modulation of their catalytic performance through the unique physicochemical properties of nanomaterials.[35,36] Based on catalytic activity, nanozymes can mainly be divided into two categories: redox-mimicking enzymes and hydrolases.[37] Among them, nanozymes used for tumor therapy usually have redox enzyme-like activity, including peroxidase-like (POD-like), oxidase-like (OXD-like), catalase-like (CAT-like), and superoxide dismutase-like (SOD-like) activities (Figure 1).

POD-Like Nanozymes

POD-like nanozymes are designed to mimic the catalytic functions of natural peroxidases. Under acidic conditions, they can catalyze hydrogen peroxide and other peroxides to produce toxic •OH, thereby causing oxidative stress at tumor sites.[38] Notably, tumor oxidative stress can not only directly damage tumor cells but also trigger immunogenic cell death (ICD), prompting tumor cells to release tumor-associated antigens (TAAs).[39] These antigens can activate dendritic cells (DCs), which in turn promote the proliferation and tumor infiltration of cytotoxic T cells, enhancing the specific antitumor immune response.[40] Currently, nanozymes with POD-like activity such as Au,[41] Fe,[42] Cu,[43] and Pd[44] have been successfully developed and are widely used in environmental remediation[45] and biomedical applications.[46]

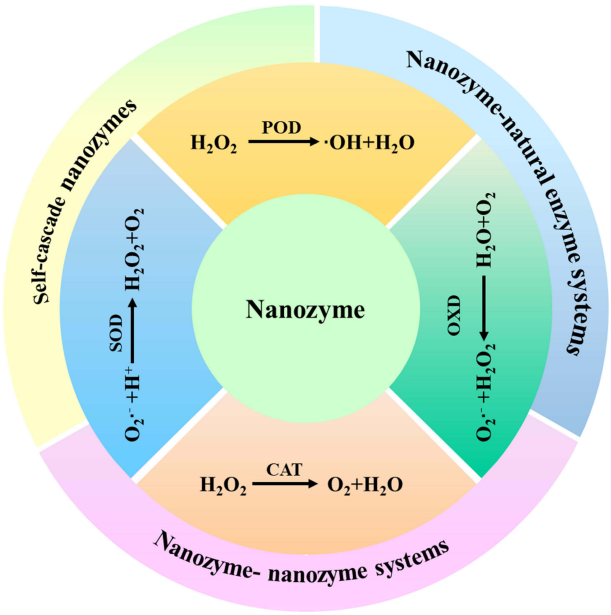

Figure 1 Common classifications of nanozymes and their catalytic mechanisms.

OXD-Like Nanozymes

OXD-like nanozymes primarily use oxygen as the electron acceptor, reducing oxygen to H_2O_2 or H_2O while catalyzing substrate oxidation,[47,48] thereby completing the conversion of energy and matter. Common oxidases include glucose oxidase,[49] polyphenol oxidase,[50] NADPH oxidase,[51] lactate oxidase,[52] xanthine oxidase,[53] and uricase.[54] They are widely used in the quantitative detection of biomacromolecules such as glucose,[55] in the degradation of organic pollutants,[56] and in antibacterial therapy.[57]

Lactate oxidase (LOx) catalyzes the oxidation of lactate within the TME into pyruvate and H_2O_2.[58] It exerts multiple functions, including eliminating immunosuppressive lactate,[59] generating H_2O_2 for CDT,[60] and augmenting the activation of the cGAS-STING pathway.[61] However, as a natural enzyme, LOx has limitations such as poor stability and high cost, which limit its applications. LOx encapsulated in nanomaterials can target lactate consumption and alleviate excessive H_2O_2 accumulation, effectively enhancing the efficacy and safety of immunotherapy.[62] For example, Wang et al combined LOx with Ce6 and Mn through biomineralization, synthesizing LOx-Ce6-Mn (LCM NPs) (Figure 2a).[63] Compared with the control group, the lactate concentrations in the LOx and LCM groups were significantly reduced (Figure 2b), indicating that LOx can still consume lactate in tumor cells after mineralization, cutting off their energy supply. LCM can also provide the H_2O_2 substrate required for POD-like enzyme catalysis, cooperating with other enzyme-like activities to remodel the TME, eliminate tumor cells, and achieve efficient tumor therapy (Figure 2c).

In the presence of oxygen, glucose oxidase (GOx) catalyzes glucose oxidation into D-gluconic acid and H_2O_2.[66] Nutrient depletion by GOx starves tumor cells and ultimately leads to cell death.[67] Xu et al constructed Cu-LDH nanodrug CMGCL loaded with GOx and coated with lung cancer cell membranes.[64] CMGCL exhibits excellent GOx activity, efficiently catalyzing glucose oxidation and triggering starvation stress (Figure 2d). Moreover, compared with normal culture medium, programmed death ligand-1 (PD-L1) expression in LLC lung cancer cells is significantly upregulated in low-glucose (low-glc) medium (Figure 2e). This indicates that it can synergize with cuproptosis and mitochondrial damage, effectively enhancing αPD-L1 immunotherapy. GOx catalysis can synergize with other enzyme activities to realize substrate self-sufficiency and cascade amplification, thereby achieving low-toxicity and high-efficiency tumor therapy and remodeling the TME. Nevertheless, its function relies on high glucose levels in tumors, and its catalytic activity is easily affected by the physiological environment, so its stability needs to be further improved.

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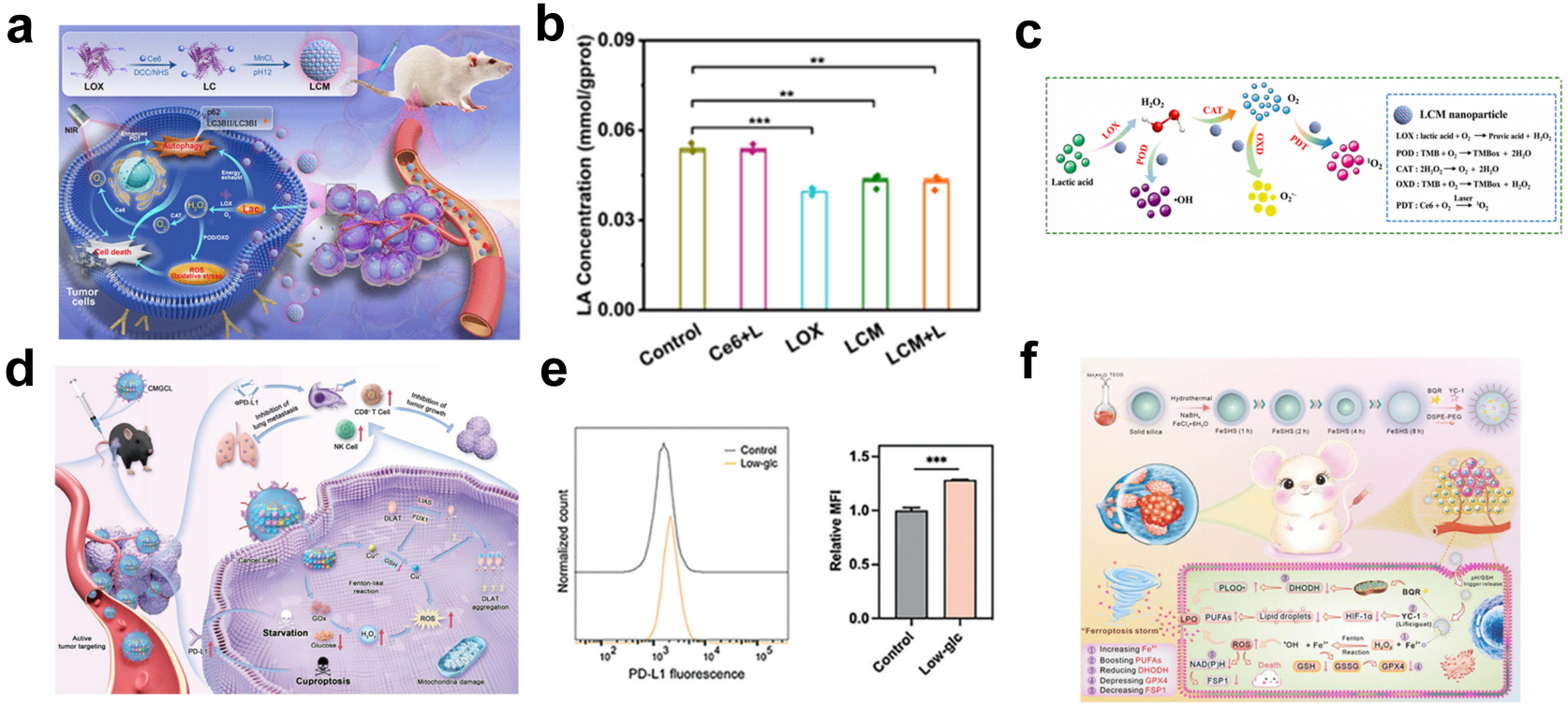

Figure 2 (**a**) Schematic illustration of the synthesis of LCM and LCM-based tumor therapy. Upward arrows indicate up-regulation, downward arrows indicate down-regulation. (**b**) Lactate levels in 4T1 cells after 24 hours of treatment with different solutions. (**c**) Schematic illustration of the cascade catalytic reactions of LCM. **p < 0.01 and ***p < 0.001. Reproduced with permission from ref.[63] (**d**) Schematic diagram of CMGCL for lung cancer treatment. Upward arrows indicate up-regulation, downward arrows indicate down-regulation. (**e**) The synergistically induced PD-L1 upregulation by glucose starvation and cuproptosis. ***p < 0.001. Reproduced with permission from ref.[64] (**f**) Schematic illustration of the synthesis of FeSHS/BQR/YC-1 and its application in tumor therapy. Upward arrows indicate up-regulation, downward arrows indicate down-regulation. Reproduced with permission from ref.[65]

CAT-Like Nanozymes

Natural CAT enzyme is composed of four subunits containing heme prosthetic groups and can promote the decomposition of H_2O_2 into H_2O and O_2.[68] By reducing intracellular H_2O_2 levels, it effectively protects cells from damage caused by oxidative stress and thus activates the immune defense mechanisms within tumors. Compared with natural enzymes, nanozymes not only exhibit high CAT-like activity but also possess advantages such as high stability, low cost, and the ability to modulate enzymatic activity through the regulation of properties like morphology, size, and crystal defects.[69,70] Therefore, CAT-like nanozymes have attracted considerable attention and are anticipated to become effective substitutes for natural enzymes in a variety of applications, particularly in the treatment of tumors.[71]

SOD-Like Nanozymes

SOD-like nanozymes are antioxidant enzymes that use metals as cofactors to catalyze the dismutation of $O_2^{\bullet-}$ into hydrogen peroxide and oxygen.[72] The reported nanozymes with SOD-like activity include Fe, Mn, Pt, Ru, as well as other metals, oxides, carbides, and nitrides.[73–76] In addition, most SOD-like nanozymes also exhibit CAT activity, which can further decompose H_2O_2 into H_2O and O_2. This synergistic effect enables them to effectively regulate cellular H_2O_2 levels and reduce oxidative damage, overcoming the limitations of poor stability of natural SOD and the single function of small-molecule antioxidants, and demonstrating more prominent application potential in the field of immunotherapy.[77]

Other Nanozymes

Glutathione peroxidase (GPx) is an antioxidant enzyme responsible for maintaining the cellular redox balance.[78] In the presence of H_2O_2, it can catalyze the conversion of reduced glutathione (GSH) to glutathione disulfide (GSSG),[76,79] and enhance cellular antioxidant capacity. For example, Xue et al successfully synthesized polyethylene glycol (PEG)-modified hollow iron-doped silica-based nanozymes (FeSHS) loaded with brequinar (BQR) and lificiguat (YC-1), denoted as FeSHS/BQR/YC-1 (Figure 2f).[65] FeSHS/BQR/YC-1-PEG nanozymes exhibit GPx-like activity, which can consume intracellular GSH and downregulate the expression of GPX4, leading to the massive accumulation of lipid peroxides (LPO) that cannot be effectively eliminated. Ultimately, these nanozymes synergize with other enzymatic activities and drug effects to trigger ferroptosis in tumor cells and inhibit tumor growth.

Cascade Catalysis

Biological systems are a coordinated and unified whole, with each unit cooperating to achieve complex life activities. Due to the high catalytic activity and specificity of enzymes, biological cascade catalytic reactions can efficiently and selectively mediate various biological processes within organisms.[80] Inspired by nature, researchers have constructed multi-enzyme cascade systems, where the product of one enzyme directly serves as the substrate for the next enzyme, generating self-sustaining catalytic cycles. On one hand, this system effectively enhances the utilization of intermediates and overall catalytic efficiency by reducing intermediate diffusion between enzymes; on the other hand, through consecutive catalysis by multiple enzymes, a single target substrate can be converted into abundant signaling molecules,[81,82] which can amplify antitumor immune responses and significantly enhance the efficacy of tumor immunotherapy.[83] In this section, we explore and discuss the construction of nanozyme-based cascade catalytic systems, and based on their structure and action mechanism, we classify them into three categories: self-cascade nanozymes, nanozyme-nanozyme cascade catalytic systems, and nanozyme-natural enzyme cascade catalytic systems.

Self-Cascade Nanozymes

Self-cascade nanozymes possess two or more distinct catalytic activities simultaneously. Such nanozymes enable in-situ substrate self-supply and autonomous cascade circulation, circumventing the delivery efficiency limitation of multi-component systems and exhibiting excellent stability.[84] They hold broad prospects in fields such as biocatalysis[85] and disease diagnosis and treatment.[86] For example, Zhong et al designed a Ga/Zn dual-atom nanozyme (Ga/Zn-NC) with POD-like and GSHOx-like activities (Figure 3a).[87] The process of forming Ga-Zn metal bonds is capable of accelerating electron transfer and reducing the reaction energy barrier, thus enhancing catalytic activity. Ga/Zn-NC can catalyze the

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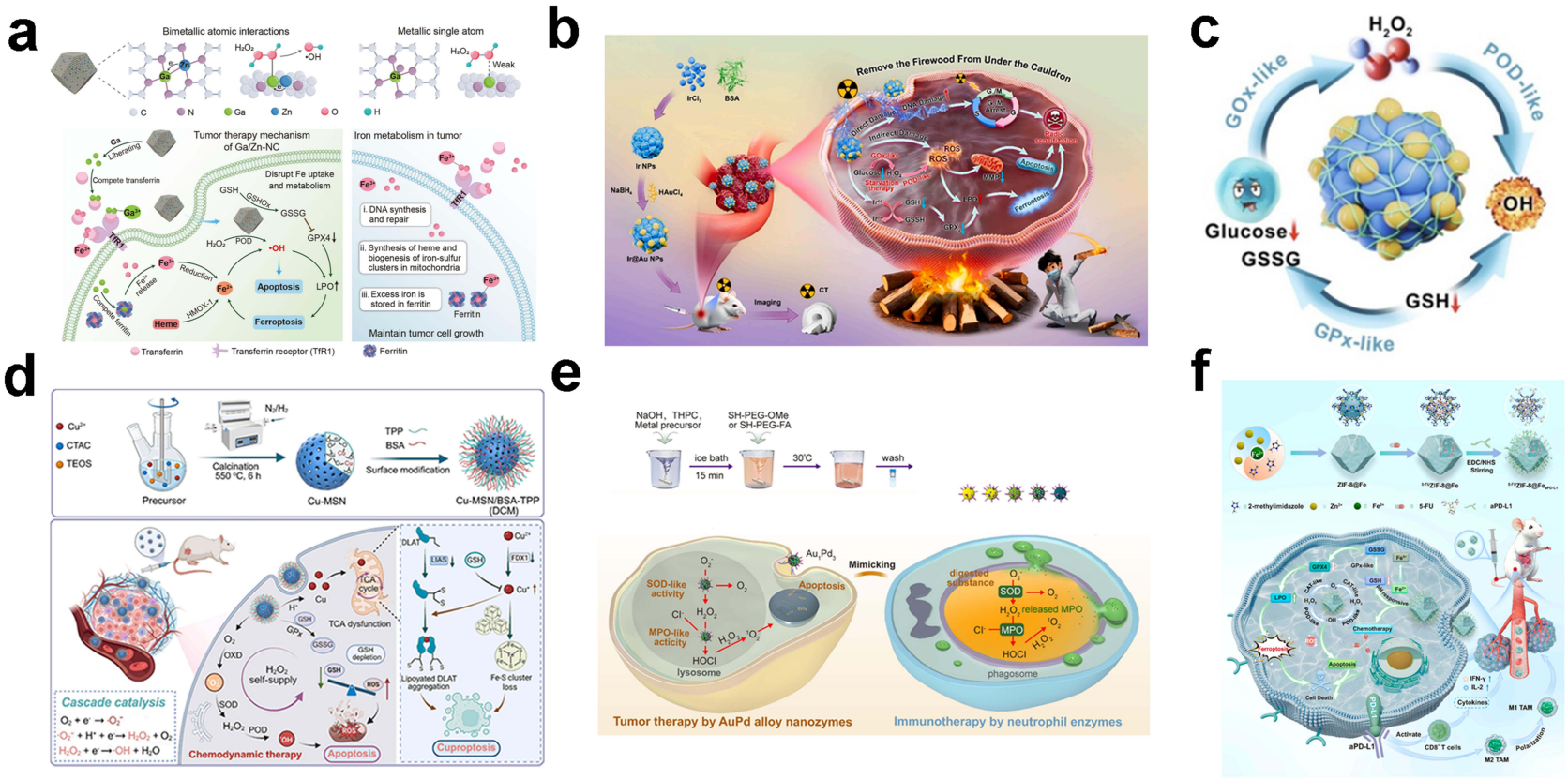

Figure 3 (**a**) Schematic illustration of the specific intracellular mechanism of tumor cell death induced by Ga/Zn-NC. Upward arrows indicate up-regulation, downward arrows indicate down-regulation. Reproduced with permission from ref.[87] (**b**) The synthesis of Ir@Au nanozymes and their antitumor mechanisms. Upward arrows indicate up-regulation, downward arrows indicate down-regulation. (**c**) Schematic representation of the enzyme-like activity of Ir@Au NPs in cells. Upward arrows indicate generation, downward arrows indicate consumption. Reproduced with permission from ref.[88] (**d**) Schematic diagram of the synthesis of DCM and its use in tumor therapy. Upward arrows indicate up-regulation, downward arrows indicate down-regulation. Reproduced with permission from ref.[89] (**e**) Schematic diagram of ultrasmall AuPd alloy nanozyme simulating SOD-MPO enzyme cascade killing function for tumor therapy. Upward arrows indicate generation, downward arrows indicate consumption. Reproduced with permission from ref.[90] (f) Schematic diagram of the synthesis of $^{5\text{-FU}}$ZIF-8@Fe$^{\text{aPD-L1}}$ and its tumor therapy. Upward arrows indicate generation, downward arrows indicate consumption. Reproduced with permission from ref.[91]

generation of cytotoxic •OH as well as deplete the antioxidant GSH. Meanwhile, Ga/Zn-NC can specifically release Ga (III) in the TME, enhancing ferroptosis effects and amplifying catalysis-induced breast cancer cell damage. The diatomic Ga/Zn nanozyme significantly boosts ferroptosis efficiency through POD/GSHOx self-cascade catalysis. However, its ROS generation mechanism is relatively simple, making it insufficient to counteract the complex antioxidant defense systems in tumors.

Due to the insufficient generation and rapid depletion of ROS, tumor radioresistance limits the efficacy of RT.[92] Li et al developed Ir@Au nanoparticles (Ir@Au NPs) to enhance tumor radiosensitivity and inhibit the growth of lung adenocarcinoma (Figure 3b).[88] Benefiting from the GOx-like activity of Ir@Au NPs, these nanoplatforms consume glucose at tumor sites, accompanied by H_2O_2 generation and TME acidification (Figure 3c). They also possess POD- and GPx-like activities, promoting the decomposition of H_2O_2 to generate •OH and consuming GSH, thereby disrupting the tumor antioxidant system and inducing apoptosis and ferroptosis in lung adenocarcinoma cells. However, their cascade efficiency is easily affected by fluctuations in intracellular glucose and H_2O_2 levels. To overcome the intrinsic limitation of insufficient H_2O_2 in TME and enhance the catalytic efficiency of POD-like nanozymes, Liu et al developed a triphenylphosphine-functionalized copper-doped mesoporous silica self-cascading nanoplatform (DCM) (Figure 3d).[89] DCM achieves self-sufficient H_2O_2 production through its OXD- and SOD-like activities and uses POD-like activity to produce •OH, inducing apoptosis. Its GPx-like activity allows DCM to effectively consume GSH, further aggravating redox imbalance, promoting cuproptosis, and disrupting the tumor antioxidant defense system.

Meng et al successfully prepared Au_1Pd_3 nanozymes with SOD- and myeloperoxidase-like (MPO) activities (Figure 3e).[90] By simulating the SOD-MPO cascade enzyme killing function of neutrophils, these nanozymes induce DNA damage and tumor cell apoptosis through the generation of hypochlorous acid (HClO) and singlet oxygen ($^1O_2$). Although SOD-MPO biomimetic cascades can specifically kill tumors, they lack regulation of the immune TME, making it difficult to achieve long-lasting antitumor effects. Liu et al developed a $^{5\text{-FU}}$ZIF-8@$Fe_{\alpha PD\text{-}L1}$ self-cascading nanozyme, which was loaded with 5-fluorouracil and surface-functionalized with αPD-L1 (Figure 3f).[91] In the TME, this nanozyme initiates a sequential catalytic cascade to mediate oxygen release, generate •OH, and deplete GSH, thereby alleviating TME hypoxia and inducing tumor cell apoptosis and ferroptosis. These effects trigger the release of immunostimulatory signals, enhance $CD8^+$ T cell infiltration, and promote M1 polarization of TAMs. Combined with αPD-L1, the nanozyme effectively activates systemic antitumor immunity. However, similar to most self-cascading nanozymes, $^{5\text{-FU}}$ZIF-8@$Fe_{\alpha PD\text{-}L1}$ still has critical limitations. It is vulnerable to disruption by biological barriers in vivo, and the magnitude and persistence of its immune activation remain restricted.

Nanozyme-Natural Enzyme Cascade Catalytic Systems

The nanozyme-natural enzyme cascade catalytic system is a novel catalytic framework that integrates nanozymes and natural enzymes. By precisely designing the spatial arrangement and reaction sequence of the two, it can achieve efficient synergistic multi-step catalytic reactions. Natural enzymes have the advantages of strong substrate specificity and high catalytic efficiency but are easily inactivated under varying environmental pH and temperature conditions.[93] Nanozymes, on the other hand, exhibit good stability and tunability, allowing catalytic activity to be optimized by adjusting their size, morphology, and surface electronic states,[94,95] although they are limited by insufficient substrate selectivity.[96] When assembled into a cascade catalytic system, nanozymes can first convert substrates into intermediates through enzyme-like activity, which are then specifically recognized by natural enzymes to complete subsequent reactions; alternatively, natural enzymes can initiate the reaction while nanozymes accelerate the catalytic cycle.[97,98] This effectively solves the inherent drawbacks of poor substrate adaptability and low specificity in cascade catalysis.[99]

Mao et al developed an FeCo/PCP-GOx-DOX nanozyme loaded with GOx and the anticancer drug doxorubicin (DOX) (Figure 4a).[100] GOx consumes glucose to generate H_2O_2. FeCo/PCP-GOx-DOX exhibits POD-like activity for catalyzing the conversion of H_2O_2 into •OH. Combined with DOX-mediated chemotherapy, this cascade system ultimately triggers efficient cancer cell death. To enhance the enrichment of nanozyme-natural enzyme cascades at tumor sites, Li et al constructed an MNPs/GOx@CS/IR820 nanosystem, which integrates Fe_3O_4 nanozymes, IR820 and GOx, and is modified with chitosan.[101] It can actively accumulate at tumor sites under an external magnetic field (Figure 4b). GOx consumes intracellular glucose and produces H_2O_2, initiating a cascade reaction. Fe_3O_4 nanozymes

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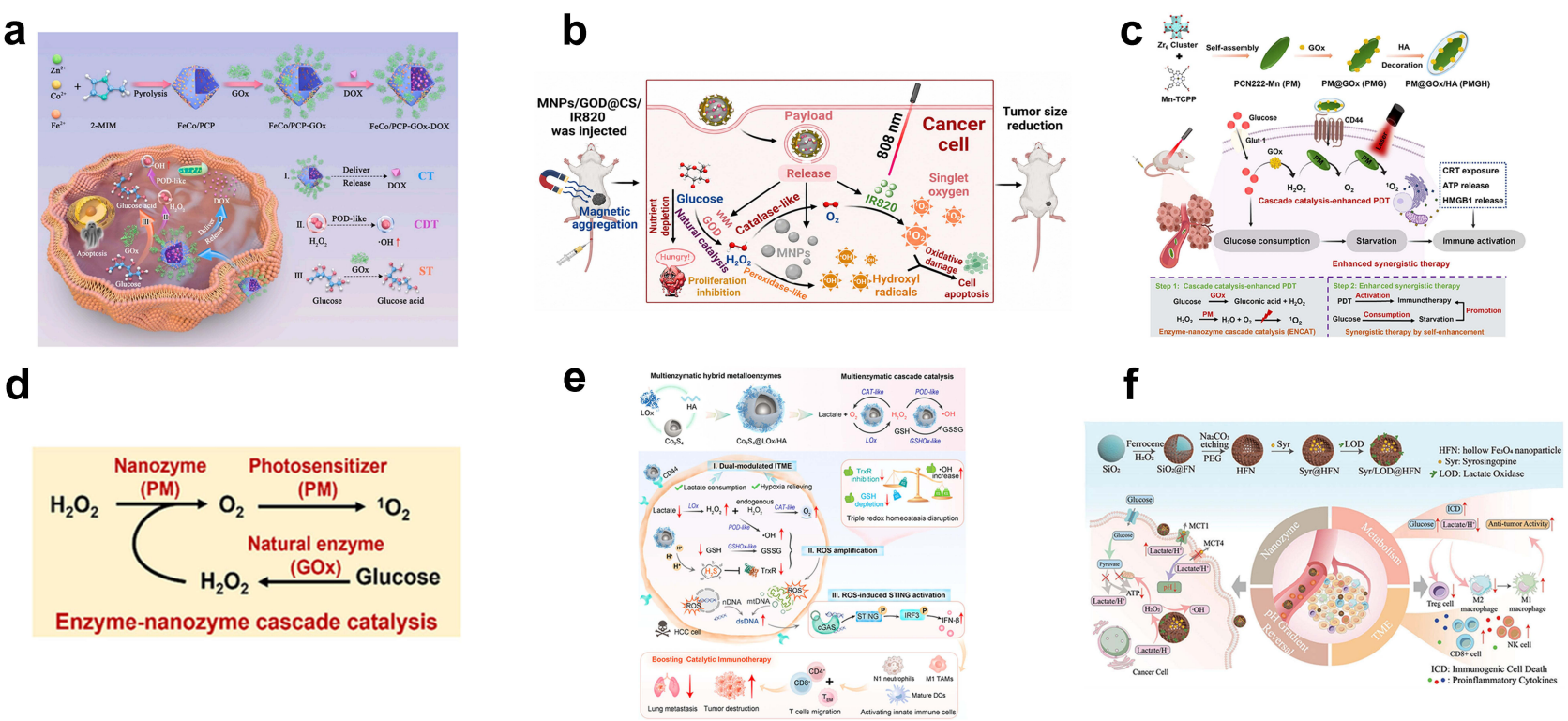

Figure 4 (**a**) Schematic illustration of the synthesis of FeCo/PCP-GOx-DOX nanozyme and its tumor therapy. Upward arrows indicate generation. Reproduced with permission from ref.[100] (**b**) Schematic diagram of MNPs/GOx@CS/IR820 nanosystem for tumor therapy. Upward arrows indicate up-regulation, downward arrows indicate down-regulation. Reproduced with permission from ref.[101] (**c**) Schematic diagram of the synthesis of PCN222-Mn@GOx/HA (PMGH) and its application in tumor therapy. Upward arrows indicate up-regulation, downward arrows indicate down-regulation. (**d**) Schematic description of PMGH cascade catalysis. Reproduced with permission from ref.[102] (**e**) Schematic diagram of the synthesis of Co_3S_4@LOx/HA and its application in tumor therapy. Upward arrows indicate up-regulation, downward arrows indicate down-regulation. Reproduced with permission from ref.[103] (**f**) Schematic diagram of the synthesis of Syr/LOx@HFN and its cancer treatment. Upward arrows indicate up-regulation, downward arrows indicate down-regulation. Reproduced with permission from ref.[104]

catalyze H_2O_2 decomposition to generate highly toxic •OH and O_2. Under near-infrared light excitation, IR-820 converts the generated O_2 into cytotoxic $^1O_2$, inducing tumor cell apoptosis through a synergistic mechanism. Zhou et al synthesized PCN222-Mn (PM) by coordinating porphyrin-manganese (TCPP-Mn) with zirconium clusters, and further modified it with HA and GOx to fabricate PCN222-Mn@GOx/HA (PMGH) (Figure 4c).[102] PMGH can effectively accumulate in tumor sites through both active and passive targeting. GOx consumes intracellular glucose and generates H_2O_2, while PM catalyzes the conversion of H_2O_2 to O_2 through its CAT-like activity (Figure 4d), thereby alleviating tumor hypoxia in situ. In addition, Zr^{4+} in the framework consumes GSH, further amplifying oxidative stress. Ultimately, tumor cell death is induced by glucose depletion and oxidative damage. Although the cascade strategy of nanozymes with natural GOx is easier to scale up, it is overly dependent on acidic environments, limiting the catalytic efficiency in deep tumors.

ROS have been confirmed to damage DNA and activate the immune response mediated by the STING pathway. Sun et al developed a novel multi-enzyme hybrid metal enzyme Co_3S_4@LOx/HA (Figure 4e).[103] After being internalized by liver cancer cells, this enzyme generates H_2O_2 and •OH through a cascade reaction, consuming GSH and increasing ROS levels within the TME, thereby triggering antitumor immune responses. During the catalytic process, the consumption of lactate and the generation of oxygen also help reshape the immunosuppressive TME. In vivo experiments validated its efficacy to inhibit liver cancer growth and lung metastasis. Wu et al developed a Syr/LOx@HFN nanoplatform based on hollow Fe_3O_4 nanoparticles, which loads the antihypertensive drug syrosingopine (Syr) and LOx (Figure 4f).[104] LOx converts accumulated lactic acid into H_2O_2, providing substrates for nanozyme-based Fenton reactions, amplifying ROS in situ and triggering ICD, while reversing the acidic TME and enhancing the efficacy of immune checkpoint blockade. However, inhibiting lactate export reverses the acidic TME but fails to establish an efficient substrate conversion cycle, making it susceptible to intracellular lactate accumulation.

Nanozyme–Nanozyme Cascade Catalytic System

Although nanozyme-natural enzyme cascade catalytic systems have made certain progress in the field of antitumor immunotherapy research, challenges including nanozyme aggregation, low loading efficiency, decreased catalytic activity and high cost remain to be addressed.[105] Nanozyme-nanozyme cascade catalytic systems are synergistic catalytic systems constructed from two or more nanozymes with different enzyme-like activities.[28] By regulating the composition of nanozymes and employing reasonable spatial arrangement strategies, efficient coupling of multi-step continuous catalytic reactions can be achieved,[106] offering new prospects for the translational application of cascade catalytic tumor therapy.

Gu et al designed a nanozyme-nanozyme cascade catalytic system, Au@COF@MnO_2.[107] MnO_2 can be reduced by GSH to Mn^{2+}, which can catalyze H_2O_2 to generate •OH, synergistically amplifying ferroptosis (Figure 5a). The gold nanozyme decomposes glucose to produce H_2O_2 and remodels the acidic TME. In addition, glucose depletion can downregulate the expression of heat shock proteins in tumor cells, thereby markedly improving antitumor efficacy. Li et al synthesized Cu_2O@Au nanozymes, achieving efficient integration of the GOx-like activity of gold nanozymes, the POD-like activity of Cu_2O, and GSHOx-like activity, thereby realizing a GOx-POD-GSHOx continuous cascade reaction (Figure 5b).[108] The GOx-like activity consumes glucose and generates H_2O_2 in situ while acidifying the TME; the POD-like activity catalyzes H_2O_2 to produce •OH; the GSHOx-like activity continuously consumes GSH and enhances oxidative stress. The Cu_2O@Au nanozyme cascade operates without exogenous substrates or natural enzymes. It affords efficient intermediate conversion and excellent structural stability. This work provides an important reference for designing high-efficiency nanozyme cascade catalytic systems.

Zhang et al constructed Pt@CNDs nanocomposites by integrating carbon nanodots (CNDs) with SOD-like activity and platinum nanoparticles (PtNPs) with CAT-like activity, achieving efficient SOD-CAT nanozyme-nanozyme cascade catalysis (Figure 5c).[109] CNDs first disproportionate $O_2^{\bullet-}$ into H_2O_2, and PtNPs immediately decompose H_2O_2 in situ into water and oxygen, completing a sequential antioxidative cascade reaction. The carbonyl and hydroxyl groups present on the surface of CNDs have been shown to bind with PtNPs, thereby facilitating electron transfer between PtNPs and CNDs. This process has been demonstrated to result in Pt@CNDs exhibiting enhanced catalytic performance, dispersibility, and stability. Such nanozymes can target mitochondria and efficiently scavenge multiple ROS, providing a typical paradigm for designing high-performance cascade antioxidative systems. To further enhance the tumor targeting and

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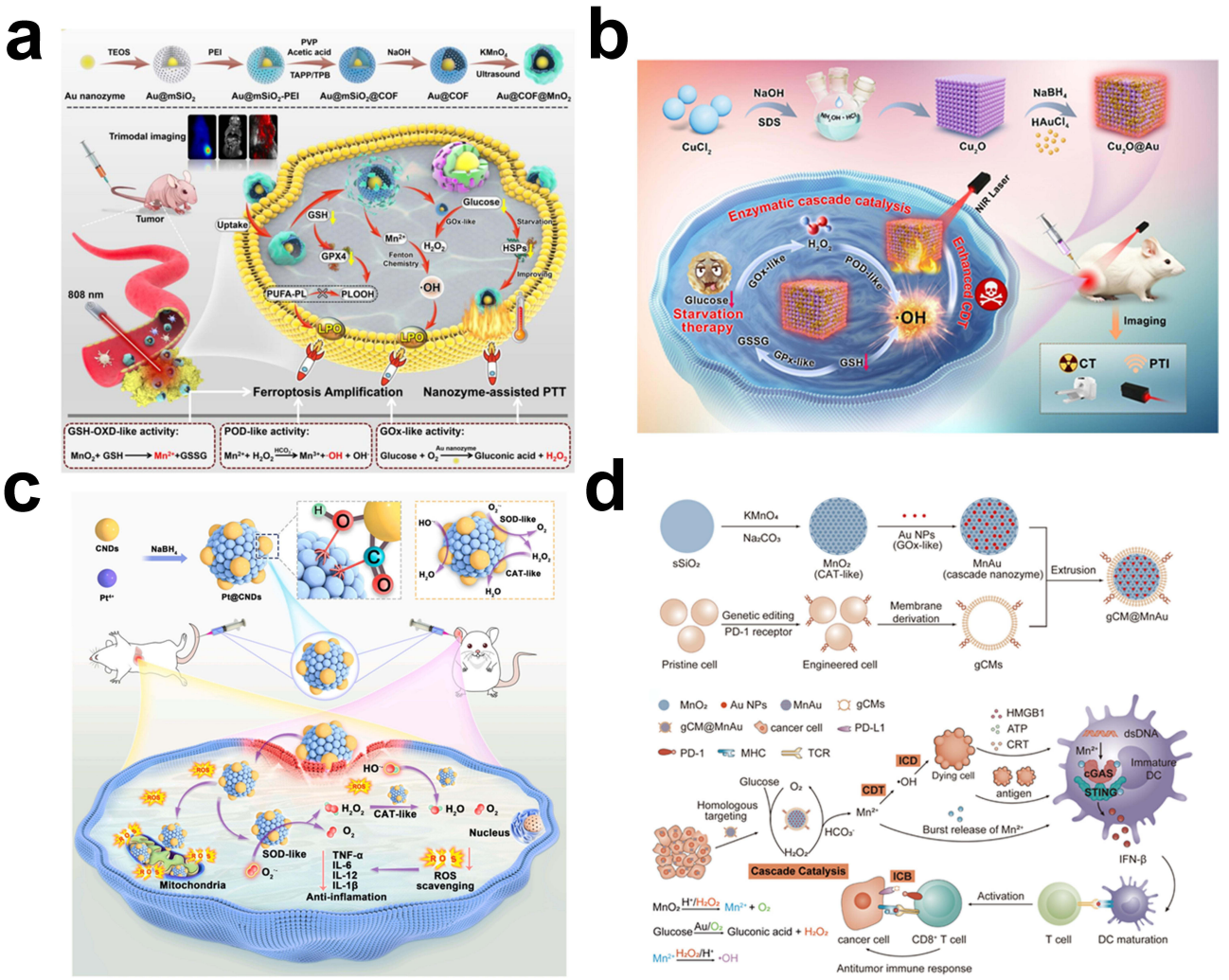

Figure 5 (**a**) Schematic diagram of Au@COF@MnO_2 nanocomposite synthesis and its application in tumor therapy. Upward arrows indicate up-regulation, downward arrows indicate down-regulation. Reproduced with permission from ref.[107] (**b**) Schematic diagram of the synthesis of Cu_2O@Au nanozyme and its anti-tumor mechanism. Upward arrows indicate generation, downward arrows indicate consumption. Reproduced with permission from ref.[108] (**c**) Schematic diagram of the synthesis process of Pt@CNDs nanocomposites and their application in intracellular antioxidant therapy. Upward arrows indicate up-regulation, downward arrows indicate down-regulation. Reproduced with permission from ref.[109] (**d**) Schematic diagram of the synthesis of gCM@MnAu and its enhanced cancer immunotherapy. Upward arrows indicate up-regulation, downward arrows indicate down-regulation. Reproduced with permission from ref.[110]

immunomodulatory capabilities of the system, Zhang et al constructed genetically engineered cell membrane-coated gCM@MnAu nanoreactors (Figure 5d).[110] This system is composed of MnO_2 with CAT-like activity and Au nanoparticles with GOx-like activity. It achieves substrate self-sufficiency via a sequential GOx-CAT cascade reaction, generates •OH in situ, and induces antitumor immune responses. The gCM@MnAu nanoreactor integrates cascade catalysis, targeted delivery, and immune regulation, featuring favorable biocompatibility and tumor-targeting ability, thereby effectively inhibiting tumor growth and lung metastasis. However, this system suffers from cumbersome preparation procedures and its catalytic activity being highly dependent on the acidic TME, which limits its further clinical translation.

In summary, the three types of cascade catalytic systems exhibit distinct advantages and disadvantages for in vivo tumor immunotherapy. Self-cascaded nanozymes feature mature fabrication procedures, favorable in vivo biological stability and low immunogenicity, thus possessing high potential for clinical translation. Nevertheless, their inherent reaction pathways are inflexible, hindering the realization of multidimensional dynamic functional regulation. Nanozyme-natural enzyme cascade systems show superior substrate recognition specificity, and their catalytic activities can be precisely modulated via exogenous stimuli to achieve excellent regulatory performance. However, natural enzyme

components are prone to metabolic clearance in vivo, accompanied by high risk of immune rejection and unsatisfactory in vivo circulation stability. By contrast, nanozyme-nanozyme cascade systems can integrate diverse catalytic activities to trigger synergistic cascade responses within the TME and exert comprehensive immune activation effects. Nonetheless, these systems suffer from uneven mass transfer efficiency among different components and difficulties in accurate regulation of interfacial synergistic effects, which pose prominent obstacles to large-scale practical applications.

Mechanism of Cascade Nanozyme Regulation of Tumor Immune Response

Immunotherapy achieves tumor-specific clearance by activating the body's immune system and has become an important direction in cancer treatment.[111] However, issues such as the TME, low immune response rates, and tumor heterogeneity severely limit its clinical efficacy.[112] Cascade nanozymes are a new type of nanoplatform that integrates multiple enzyme catalytic activities. They can kill tumor cells directly and activate immunotherapy through various regulatory mechanisms, such as inducing ICD, remodelling the TME and activating immune signalling pathways. They show great potential in tumor immunotherapy for breast cancer, colorectal cancer, bladder cancer and others (Table 1).

Induction of Immunogenic Cell Death

ICD serves as an effective strategy to boost immunotherapeutic efficacy. It facilitates the release of TAAs and damage-associated molecular patterns (DAMPs) into the TME, activates innate immune cells such as DCs and macrophages, promotes DC maturation and initiates innate immune responses to accomplish antigen recognition, uptake and preliminary immune activation. Mature antigen-presenting cells further process and present antigens to trigger specific T cell immune responses. Among them, $CD4^+$ and $CD8^+$ T cells are specifically activated via antigen presentation, which can not only precisely eliminate tumor cells, but also establish immune memory to exert long-lasting and stable antitumor immune effects.[127] Although ICD can be induced by chemotherapy, radiotherapy, and phototherapy, its efficacy is severely limited due to the constraints of the TME.[128] Therefore, constructing an ICD amplifier to activate the immune system is one of the effective methods for treating tumors and preventing cancer metastasis or recurrence. Cascade nanomaterials, by generating ROS, induce ICD while regulating the release of DAMPs to enhance immunogenicity, holding promise to significantly improve the efficacy of antitumor immunotherapy.[129]

Yan et al developed an iron-based benchmark MOF nanozyme, Q-MIL-53 (Fe), which can catalyze ROS generation in a cascade, deplete GSH, induce mitochondrial dysfunction, promote LPO accumulation, and trigger ferroptosis.[130] Ferroptosis further induces ICD, accompanied by the release of DAMPs including CRT, HMGB1, and ATP. These DAMPs act on innate immune cells, promoting the maturation of DCs and driving the polarization of TAMs toward the M1 phenotype. Meanwhile, they recruit and activate adaptive immune cells, enhancing the infiltration and cytotoxicity of $CD4^+$/$CD8^+$ T cells. This system significantly boosts antitumor efficacy when combined with αPD-L1 antibody, yet its in vivo delivery efficiency and duration of action still require further optimization. Besides iron-based MOF nanozymes, copper-based single-atom nanozymes exhibit superior catalytic activity and dual cell death-inducing capacity, emerging as a novel direction for catalytic immunotherapy. For example, Zhang et al used N-acetyl-L-cysteine (NAC) as a ligand to coordinate with copper ions and self-assemble onto the surface of 2D Ti_3C_2 to synthesize a Cu SAzyme (CuNTD) (Figure 6a).[131] CuNTD consumes GSH and explosively generates ROS through multi-enzyme cascade catalysis, and simultaneously induces ferroptosis and cuproptosis. The resulting oxidative stress and mitochondrial damage further trigger ICD. By releasing DAMPs including ATP, HMGB1, and exposing CRT, tumor cells effectively activate innate immune cells such as DCs, and further initiate the $CD8^+$ T cell-dominated adaptive immune response. This system highly integrates single-atom catalysis, dual cell death pathways, and ICD, exhibiting remarkable immune activation efficacy. However, the potential toxicity of copper ions and insufficient long-term immune memory still limit its clinical translation potential.

To address the inadequate tumor-targeting capability of metal nanozymes, researchers have employed passive targeting carriers for surface modification, which effectively improves their tumor accumulation efficiency. Lu et al successfully synthesized an Elesclomol@Cu(II)-MOF modified with polyethylene glycol (PEG) (Figure 6b).[132] ES@Cu(II)-MOF possesses both POD-like and GPx-like activities. It generates •OH through catalysis, depletes GSH, and converts Cu^{2+} into highly toxic Cu^+, triggering abnormal aggregation of mitochondrial lipoylated DLAT protein,

Table 1 Cascade Nanozymes in Immunotherapy for Different Tumors

Cascade Nanozyme	Catalytic Mechanism	Mechanism of Immune Response	Tumor Model	References
BiOCl:Ce-Pt@PGA[a] (Bismuth-based nanocatalyst)	POD, CAT	Induced ICD	Breast cancer	[113]
SS-MSN[b]@Au-BOM[c] (BOM-camouflaged self-oxygenating cascade catalytic nanozyme system)	GOx, POD, CAT	Remodeled the TME, induced ICD	Breast cancer	[114]
CGNPs (Copper-doped GOx-loaded Mesoporous silica Nanoparticles modified with silane-PEG-tLyp1)	GOx, POD, OXD, CAT	Remodeled the TME, induced ICD, activated of the cGAS-STING pathway	Breast cancer	[115]
FeCo-DA (Iron-cobalt dual-single-atom nanozyme)	POD, CAT, GSHOx	Induced ICD	Pancreatic cancer	[116]
$ZnFe_2O_4$@Pt@PEG-GOx	POD, CAT, OXD, GOx, GSHOx	Remodeled the TME, induced ICD	Prostate cancer	[117]
Cu SA-DOX[d]@COD[e] (Cu-based Single-Atom Nanozyme loaded with Doxorubicin and Cholesterol Oxidase)	CAT, POD, GSHOx	Remodeled the TME, induced ICD	Prostate cancer	[118]
FBFO[f]@HM[g]@aOPN[h] (Bioengineered hybrid dual-targeting nanoparticles)	POD, CAT	Remodeled the TME, induced ICD, activated the cGAS-STING and NF-κB pathways	Glioblastoma	[119]
$Mo_{0.2}Fe_{2.8}O_4$@CeO_x/FA[i] (Dual-magnetically actuated nanozyme)	POD, GSHOx, CAT	Remodeled the TME, induced ICD	Glioblastoma	[120]
FeCP@PDA[j]-GOx (Multifunctional and multi-enzyme active nanosystem)	GOx, POD, OXD, CAT	Remodeled the TME, induced ICD	Melanoma	[121]
Pt/Co BNzyme (Platinum-cobalt bimetallic nanozyme)	POD, GPx	Remodeled the TME, induced ICD	Hepatocellular carcinoma	[122]
MSaG[k] (Mesoporous single-atom enzyme with GOx)	GOx, POD	Induced ICD	Bladder cancer	[123]
CuOTeDsP (CuO-based nanotherapeutic co-loaded with Terbinafine, Disulfiram and PEGylated)	POD, CAT, GPx	Remodeled the TME, induced ICD	Bladder cancer	[124]
CuSR4M ($Cu(OH)_2$-based hybrid nanozyme loaded with COH-SR4 and coated with cancer cell Membrane)	POD, GPx	Remodeled the TME, induced ICD	Bladder cancer	[125]
Fe/Cu-HPC[l]@GOx/PEG (Fe/Cu-embedded hierarchical porous carbon loaded with GOx and PEG)	GOx, POD, CAT	Remodeled the TME, induced ICD	Bladder cancer	[126]

Notes: References cited in this table are listed in the main reference list.
Abbreviations: [a]PGA, polyglutamic acid; [b]SS-MSN, mesoporous silicon nanoparticles doped with disulfide bonds; [c]BOM, bacterial outer membrane; [d]DOX, doxorubicin hydrochloride; [e]COD: CHOL oxidase, [f]FBFO, Fe_3O_4@$BiFeO_3$; [g]HM, the fusion of bacterial outer membrane vesicles and M1-like macrophage-derived exosomes; [h]aOPN, anti-OPN; [i]FA, folic acid; [j]PDA, polydopamine; [k]MSaG, GOx loaded with Fe-SAE; [l]Fe/Cu-HPC, iron/copper-embedded hierarchical porous carbon.

thereby inducing cuproptosis. Cuproptosis induces ICD through oxidative stress and mitochondrial damage, promoting CRT membrane externalization, HMGB1 extracellular release, and ATP secretion. These signals first activate innate immunity, recruiting and activating macrophages and dendritic cells; subsequently, they initiate adaptive immunity. Furthermore, PEG enables passive tumor targeting via the enhanced permeability and retention effect, effectively

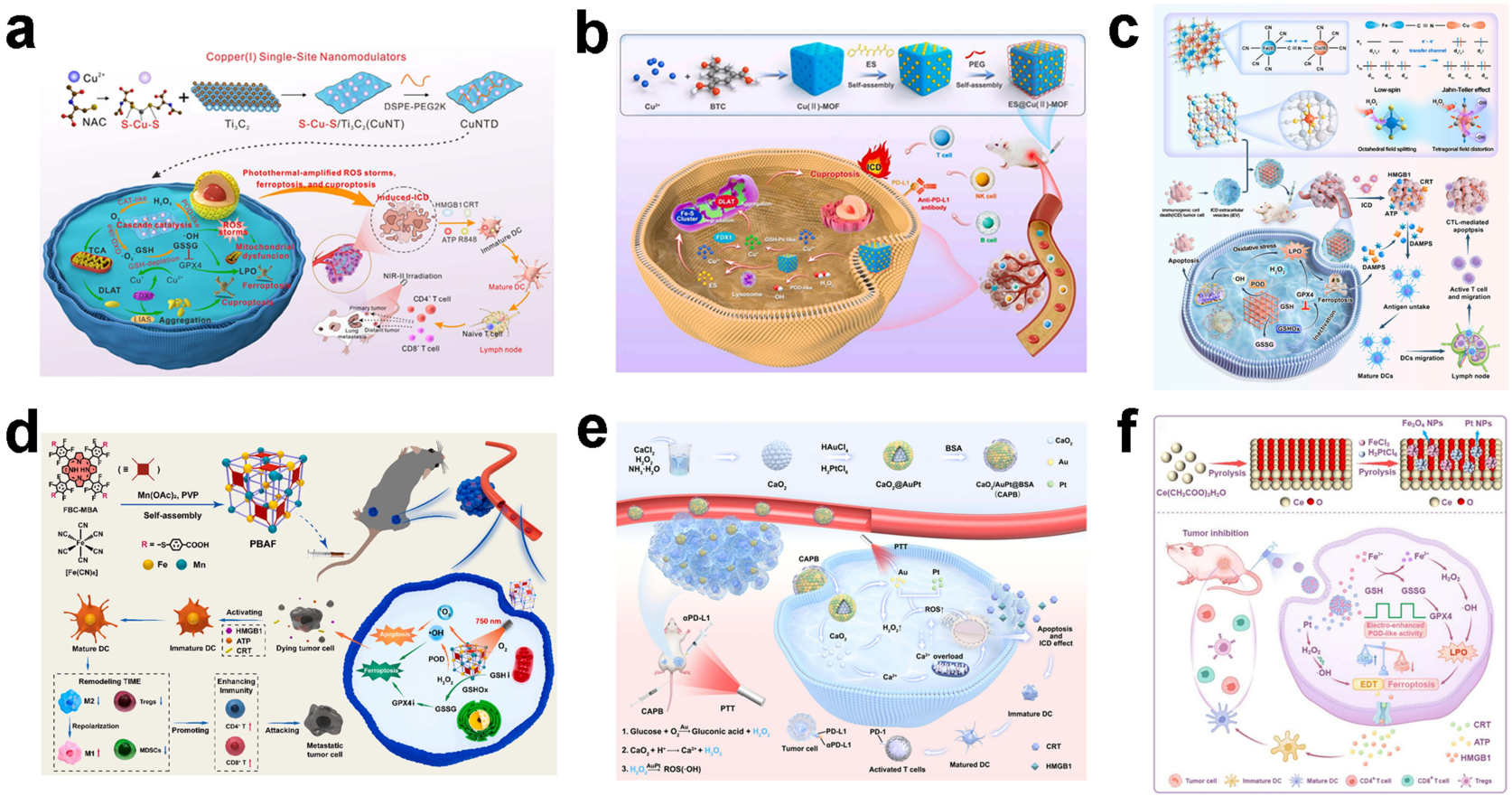

Figure 6 (**a**) Schematic illustration of the preparation of CuNTD single-atom copper enzyme and its enhanced tumor immunotherapy effect. Reproduced with permission from ref.[131] (**b**) Schematic of the synthesis of ES@Cu(II)-MOF and its application in tumor immunotherapy. Reproduced with permission from ref.[132] (**c**) Schematic diagram of the catalytic mechanism of SANE and intracellular therapeutic mechanism of iEV@SANE. Reproduced with permission from ref.[133] (**d**) Schematic diagram of the synthesis of PBAF nanozyme and its application in tumor therapy. Upward arrows indicate up-regulation, downward arrows indicate down-regulation. Reproduced with permission from ref.[134] (**e**) Schematic diagram of the synthesis of CaO_2/AuPt@BSA (CAPB) nanozyme and its application in tumor therapy. Upward arrows indicate generation, downward arrows indicate consumption. Reproduced with permission from ref.[135] (**f**) Schematic diagram of the synthesis of FePt/CeO_2 nanozyme and its application in immunotherapy. Downward arrows indicate consumption. Reproduced with permission from ref.[136]

https://doi.org/10.2147/IJN.S600885

improving tumor accumulation and reducing off-target effects, thereby simultaneously enhancing the biosafety and antitumor efficacy of the system. However, this system lacks active targeting capability for tumor recognition and cannot completely inhibit tumor recurrence and metastasis, thus still failing to meet the requirements for clinical applications. Consequently, researchers have further shifted towards more efficient design strategies based on polymetallic synergy and coupling with immune biological carriers. Wu et al constructed a cyano-bridged bimetallic single-atom nanozyme $Cu_2[Fe(CN)_6]$ (SANE), which was modified with immunogenic exosomes (iEV) to achieve efficient catalytic immunotherapy.[133] The nanozyme triggers a ROS burst and depletes GSH through dual POD and GSHOx enzymatic activities, and inhibits GPX4 and induces ferroptosis (Figure 6c). Ferroptosis promotes tumor cells to release DAMPs such as CRT, HMGB1 and ATP, activating innate immunity and initiating adaptive immunity. DAMPs further activate dendritic cells, upregulate CD80/CD86, and promote $CD8^+$ T cell infiltration and the secretion of pro-inflammatory cytokines including IFN-γ. This work precisely clarifies the relationship between electronic structure regulation and ICD, providing an important direction for the subsequent catalytic-immune synergistic design of bimetallic nanozymes.

Remodel the TME

The accumulation of GSH in the TME, along with hypoxia and infiltration of immunosuppressive cells, can inhibit T cell proliferation, promote M2 macrophage polarization, and weaken immunotherapy efficacy.[137,138] Cascade nanozymes can efficiently and orderly catalyze multiple biochemical reactions at tumor sites by mimicking the synergistic action of natural cascade enzyme systems, eliminating immunosuppressive factors, and effectively regulating the TME to create conditions for activating immune responses.[139] For example, Zheng et al synthesized a PBAF nanozyme covalently assembled from the organic bridging ligand ($[FeIII(CN)_6]$), manganese ions, pentafluorophenyl bacteriochlorin with benzoic acid (FBC-MBA), and biocompatible polyvinylpyrrolidone (PVP) (Figure 6d).[134] PBAF displays GSHOx-like activity, which specifically depletes intratumoral GSH, disrupts cellular redox homeostasis, and induces ferroptosis. Meanwhile, PBAF possesses POD-like activity to consume intratumoral H_2O_2 and generate •OH. Moreover, PBAF is capable of producing $^1O_2$ under 750 nm laser irradiation, further amplifying oxidative stress and remodeling the TME. By inducing ICD, PBAF promotes DC maturation, facilitates M1 phenotypic polarization of TAMs, and reduces the infiltration of Tregs and MDSCs. It markedly increases the intratumoral infiltration of cytotoxic T lymphocytes and activates both innate immunity and adaptive antitumor immunity, thereby effectively inhibiting tumor recurrence and metastasis. Although this photosensitive nanozyme can remodel the TME and boost T cell infiltration via oxidative stress, its immune activation is heavily dependent on external light stimulation. In contrast to endogenously responsive nanozymes with autonomous cascade amplification capacity, this material fails to achieve sustained TME remodeling.

Liu et al constructed a CaO_2/AuPt@BSA (CAPB) nanozyme encapsulated with bovine serum albumin (BSA) (Figure 6e).[135] AuPt exerts GOx- and POD-like activities, consuming glucose and self-supplying H_2O_2 to generate abundant ROS. Meanwhile, CaO_2 decomposes to release Ca^{2+}, triggering calcium overload. Together, these effects induce ICD, promoting CRT externalization and the release of HMGB1 and ATP, which facilitates DC maturation and activates innate immunity. Mature DCs further initiate adaptive immunity, enhancing $CD8^+$ T cell infiltration and cytotoxicity. Combination with αPD-L1 blocks immune escape and enables synergistic amplification of innate and adaptive immunity, providing important insights for subsequent research on immune regulation by cascade nanozymes. On the basis of autonomous cascade catalysis, the introduction of defect engineering and electronic structure modulation can further enhance the synergistic catalytic-immunotherapeutic effect of nanozymes. Yang et al fabricated a FePt/CeO_2 cascade nanozyme with boosted POD-like activity via defect engineering and electronic modulation (Figure 6f).[136] This nanozyme initiated a self-amplified cascade cycle to reshape the TME, including ROS burst, ferroptosis-driven GSH depletion, and catalytic self-enhancement. It effectively activated innate immunity and further triggered adaptive antitumor immunity. It induced ICD with the release of ATP, CRT, and HMGB1. It promoted dendritic cell maturation, activated $CD8^+$/$CD4^+$ T lymphocytes, drove tumor-associated macrophage polarization from M2 to M1 phenotype, and decreased the infiltration of Tregs and MDSCs. However, this strategy does not directly activate immune pathways such as STING and exerts weak direct regulation of immune cells, making it difficult to elicit a strong antitumor response.

Activation of Immune Signaling Pathways

Innate immunity, as the first line of defense in the body's immune system, can trigger broad-spectrum antitumor immune responses when its signaling pathways are activated.[140] Cascade nanozymes can activate immune signaling pathways and alleviate immunosuppression either through catalytic reaction products or by directly acting on signaling molecules.[141] Liu et al successfully constructed a Cu-SAs/C_2N copper single-atom cascade nanozyme (Figure 7a).[142] Cu-SAs/C_2N efficiently mimics both POD- and OXD-like activities, triggering an ROS burst in the TME. ROS inhibit the phosphorylation and activation of the PI3K-AKT pathway via oxidative stress-mediated interference with upstream regulatory molecules, thereby downregulating the antiapoptotic protein Bcl-2 and upregulating Bax to trigger tumor cell apoptosis. Apoptotic tumor cells not only drive macrophage polarization toward the M1 phenotype and activate NK cells to strengthen innate immune clearance, but also promote $CD8^+$ T cell infiltration and alleviate immune exhaustion, initiating adaptive antitumor immune responses. This system exhibits a significant synergistic effect when combined with PD-1 inhibitors. This work provides a novel strategy for catalytic therapy combined with immune checkpoint blockade, yet its in vivo translation is still limited by targeting efficiency, metabolic clearance rate, and long-term biosafety.

To further improve the targeting ability and immune regulatory specificity of nanozymes, researchers have incorporated biological molecules such as nucleic acid aptamers into nanozymes to construct multifunctional synergistic systems. Li et al developed a bifunctional cascade Pt single-atom nanozyme (PCFP@H-TDN) modified with a hairpin tetrahedral DNA nanostructure (H-TDN) (Figure 7b).[143] The PD-L1 nucleic acid aptamer on the surface of H-TDN directly blocks the recognition and binding of PD-1 and PD-L1 at the cell membrane level, relieving the immune checkpoint inhibitory signal. Furthermore, H-TDN can targetedly deliver PD-L1 antisense oligonucleotides, which degrade PD-L1 mRNA via the RNase H1 pathway and downregulate total protein expression, thereby targeting and regulating the PD-1/PD-L1 pathway through dual mechanisms. While relieving tumor hypoxia through cascade oxygen production, this system induces ICD, releasing DAMPs such as ATP, CRT, and HMGB1. It significantly activates innate immunity, increases $CD4^+$/$CD8^+$ T cell infiltration, enhances T cell killing function, and further initiates adaptive antitumor immunity. However, this system is highly dependent on 660 nm external laser triggering, and its deep tumor penetration capability is still limited. Moreover, it does not directly activate key innate immune pathways such as cGAS-STING, and the intensity and duration of immune activation need to be further improved.

Zhang et al developed a BMP-Au nanoadjuvant via integrating gold nanoparticles (Au NPs) with biomineralized manganese phosphate (BMP) nanosheets (Figure 7c).[144] Through the cascade catalysis of GOx-like activity of Au NPs and POD-like activity of Mn^{2+}, it consumes glucose and generates ROS in tumor cells. ROS induce DNA damage, leading to the accumulation of cytoplasmic double-stranded DNA (dsDNA) (Figure 7d). The dsDNA is recognized by cGAS, which catalyzes the production of 2'3'-cGAMP. 2'3'-cGAMP binds to the adaptor protein STING, triggering its translocation and activating the transcription factors IRF3 and NF-κB, thereby driving the expression of type I interferons and pro-inflammatory cytokines and activating the cGAS-STING pathway. In addition, ROS also triggers ICD, causing tumor cells to expose CRT and release DAMPs including ATP and HMGB1, activating both innate and adaptive immune responses, offering a new paradigm for breast cancer therapy. To further enhance the cascade catalytic efficiency and immune activation potency of manganese-based materials, Zhang et al modified Cu-MOF with MnO_2 and GOx to synthesize Cu-MOF@MnO_2/GOx (CMG) (Figure 7e).[145] After CMG is endocytosed by cells, it can be degraded by GSH, releasing Cu^{2+}, Mn^{2+}, and GOx (Figure 7f). GOx consumes glucose, reprogramming tumor metabolism and making cells sensitive to copper toxicity. The released Cu^{2+} and Mn^{2+} trigger Fenton-like reactions, generating ROS, inducing cuproptosis. Cuproptosis disrupts the tricarboxylic acid cycle and promotes the release of mitochondrial DNA (mtDNA) into the cytoplasm (Figure 7g). As a natural double-stranded DNA ligand for cGAS, mtDNA is recognized and bound by cGAS, initiating the catalytic synthesis of the second messenger cGAMP. Meanwhile, Mn^{2+} acts as an allosteric activator that directly binds to the cGAS protein, alters its conformation, and markedly enhances the DNA-binding affinity and catalytic activity of cGAS. Through a synergistic mechanism of "substrate supply plus enzymatic potentiation", mtDNA and Mn^{2+} co-activate the cGAS-STING pathway, strongly stimulating the STING-TBK1-IRF3 signaling cascade. This ultimately drastically promotes the secretion of type I interferons and pro-inflammatory cytokines, potently activating innate immunity and further driving adaptive antitumor immune responses.

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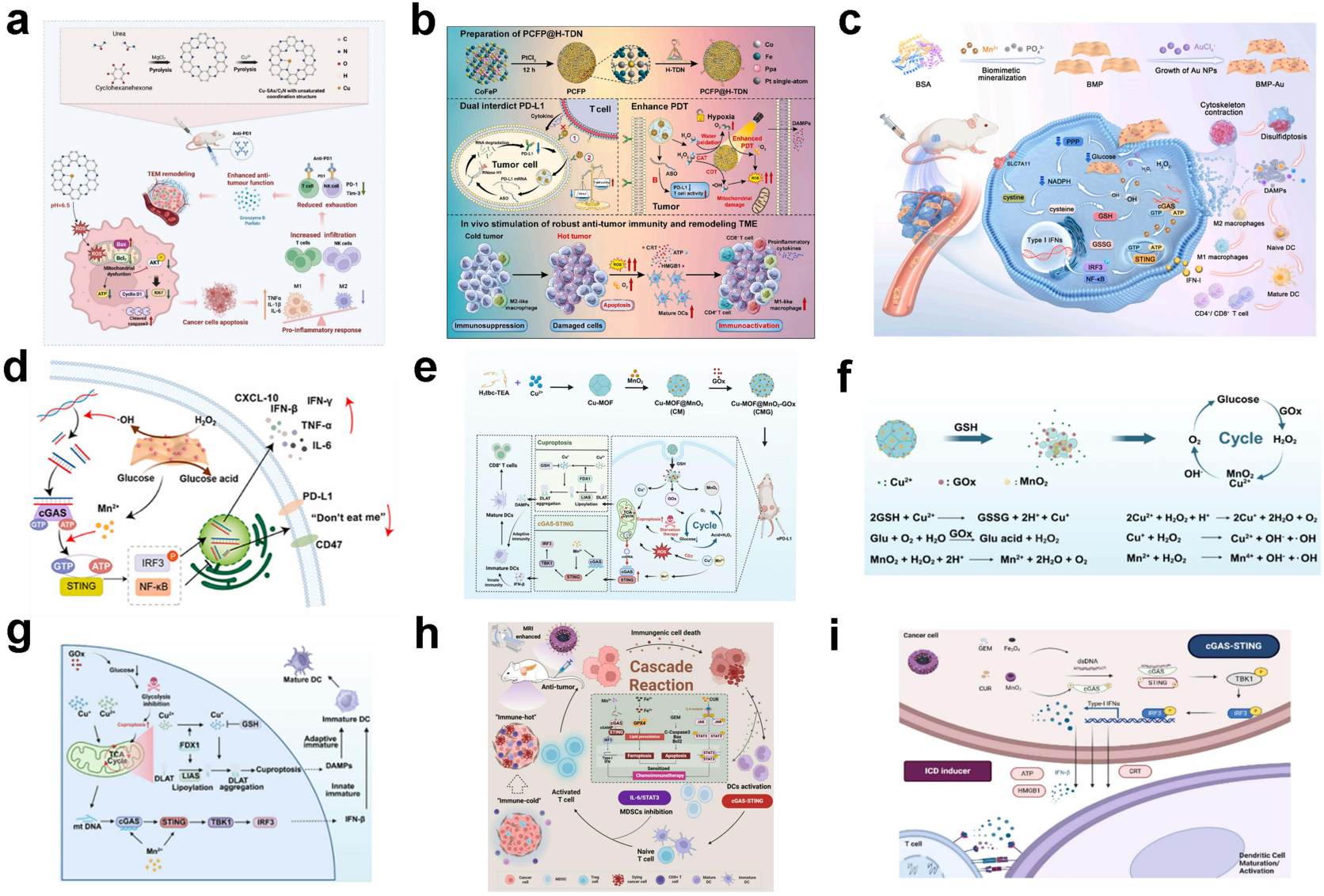

Figure 7 (**a**) Schematic diagram of the synthesis of Cu-SAs/C_2N nanozyme and its application in tumor therapy. Upward arrows indicate up-regulation, downward arrows indicate down-regulation. Reproduced with permission from ref.[142] (**b**) Synthesis of PCFP@H-TDN cascade nanozyme and its catalytic mechanism in tumor therapy. Upward arrows indicate up-regulation, downward arrows indicate down-regulation. Reproduced with permission from ref.[143] (**c**) Synthesis of BMP-Au nanoadjuvants and their mechanisms for tumor therapy. Downward arrows indicate consumption. (**d**) Schematic diagram of the cGAS-STING pathway activated by BMP-Au. Reproduced with permission from ref.[144] (**e**) Schematic diagram of CMG synthesis and its application in enhanced cancer immunotherapy. Red upward arrows indicate activation. (**f**) Schematic diagram of the CMG cascade reaction. (**g**) Schematic diagram of the cGAS-STING pathway activated by CMG. Reproduced with permission from ref.[145] (**h**) Schematic diagram of FMGC nanozyme for cancer immunotherapy. (**i**) Diagram illustrating the inherent immunomodulatory actions of FM in ICD induction and DC maturation. Reproduced with permission from ref.[146]

Compared with the CMG nanoplatform that only focuses on cuproptosis and cGAS-STING pathway activation, cascading nanozymes can further achieve systematic regulation of tumor immunotherapy through multi-pathway synergy. Zhao et al engineered Fe_3O_4 cores and MnO_2 shells (FM) nanozymes loaded with the chemotherapeutic drug gemcitabine and the immune adjuvant curcumin, synthesizing the FMGC nanozymes to enhance immunotherapy for pancreatic cancer (Figure 7h).[146] FM can deplete GSH, induce ferroptosis, catalyze H_2O_2 to produce •OH, thereby enhancing the chemotherapy effect and promoting the release of immune antigens. Gemcitabine induces DNA double-strand breaks in tumor cells, and MnO_2 responsively releases Mn^{2+}. As an allosteric activator, Mn^{2+} binds to cGAS, improves its affinity and catalytic activity toward cytoplasmic DNA, and synergistically hyperactivates the cGAS-STING pathway with DNA damage, promoting DC maturation and type I interferon secretion (Figure 7e). Meanwhile, curcumin directly inhibits the IL-6/STAT3 signaling pathway by blocking JAK phosphorylation downstream of the IL-6 receptor, reducing MDSC recruitment and activation and relieving their immunosuppression on $CD8^+$ T cells. This work achieves quadruple synergy of ferroptosis, chemotherapy, STING activation, and MDSC regulation, providing important insights for the immune regulation and clinical translation of multifunctional nanozymes in the future.

In brief, cascade nanozymes are capable of inducing ICD in tumor cells, remodeling the TME and effectively regulating signaling pathways. ICD rapidly releases immune-stimulatory signals to initiate host immune responses. TME remodeling alleviates hypoxia and immunosuppression, achieving the most sustained and stable therapeutic effects. The regulation and activation of signaling pathways can potently amplify antitumor immune responses with higher therapeutic efficiency. The synergistic action of the above three approaches strengthens immunotherapeutic effects and facilitates the improvement of overall efficacy in tumor immunotherapy.

Application of Cascade Nanozymes in Tumor Immunotherapy

In tumor treatment, monotherapy is often limited by the complexity of TME and tumor heterogeneity.[147] Immunotherapy can activate the body's antitumor immunity, but its response rate is relatively low due to high PD-L1 expression and immune suppression in the TME. Therefore, various strategies need to be explored to improve the efficiency of immunotherapy. Although CDT, PT, SDT, RT and other treatment methods can directly kill tumors, they may cause damage to surrounding normal tissues and even lead to unnecessary tumor metastasis and spread. Research has shown that the synergistic therapeutic effect of immunotherapy and the above-mentioned tumor treatment strategies can compensate for their respective shortcomings and improve the efficacy of tumor treatment.[148]

Chemodynamic Therapy @ Immunotherapy

The chemodynamic therapy @ immunotherapy synergistic strategy mediated by nanozymes can not only catalyze the Fenton-like reaction via CDT to convert H_2O_2 into •OH for specific killing of tumor cells, but also trigger ICD to release TAAs and DAMPs.[149] These phenomena facilitate immunotherapeutic efficacy. For example, Jiao et al designed a DNA origami (DO)-based enzymatic cascade nanoreactor (DOECN) that integrates AuNPs and Fe_2O_3.[150] DOECN can promote the generation of H_2O_2, consume GSH, and amplify the Fenton-like reaction to enhance the efficacy of CDT. CDT directly kills tumor cells through in-situ burst generation of ROS. Simultaneously, CDT triggers ICD and releases DAMPs including CRT, ATP, and HMGB1, converting "cold tumors" into "hot tumors". This not only provides sufficient tumor antigens for subsequent immunotherapy, but also addresses the core limitations of monotherapy, including inadequate antigen supply and impaired initiation of adaptive immunity. To further trigger innate immunity at the source and reinforce the efficacy of immune priming, Zhang et al successfully developed an OMV-DFA nanoplatform by encapsulating bacterial outer membrane vesicles (OMVs) with a DaFe shell and incorporating Au nanoparticles (Figure 8a).[151] OMV-DFA can catalyze GSH oxidation, trigger ST, promote DaFe depolymerization and release Fe^{3+}, and improve CDT efficacy. ST combined with CDT synergistically exacerbates tumor oxidative stress and energy depletion, further strengthening the ICD effect. Meanwhile, as natural immune agonists, OMVs directly activate innate immunity, compensating for the shortcomings of single immunotherapy, such as insufficient initiation of innate immunity and difficulty in reversing the immunosuppressive TME.

By integrating TME-responsive self-supply and self-depletion designs, such strategies can further break through the limitations of catalytic efficiency and achieve deeper and more durable remodeling of the TME. Li et al fabricated the

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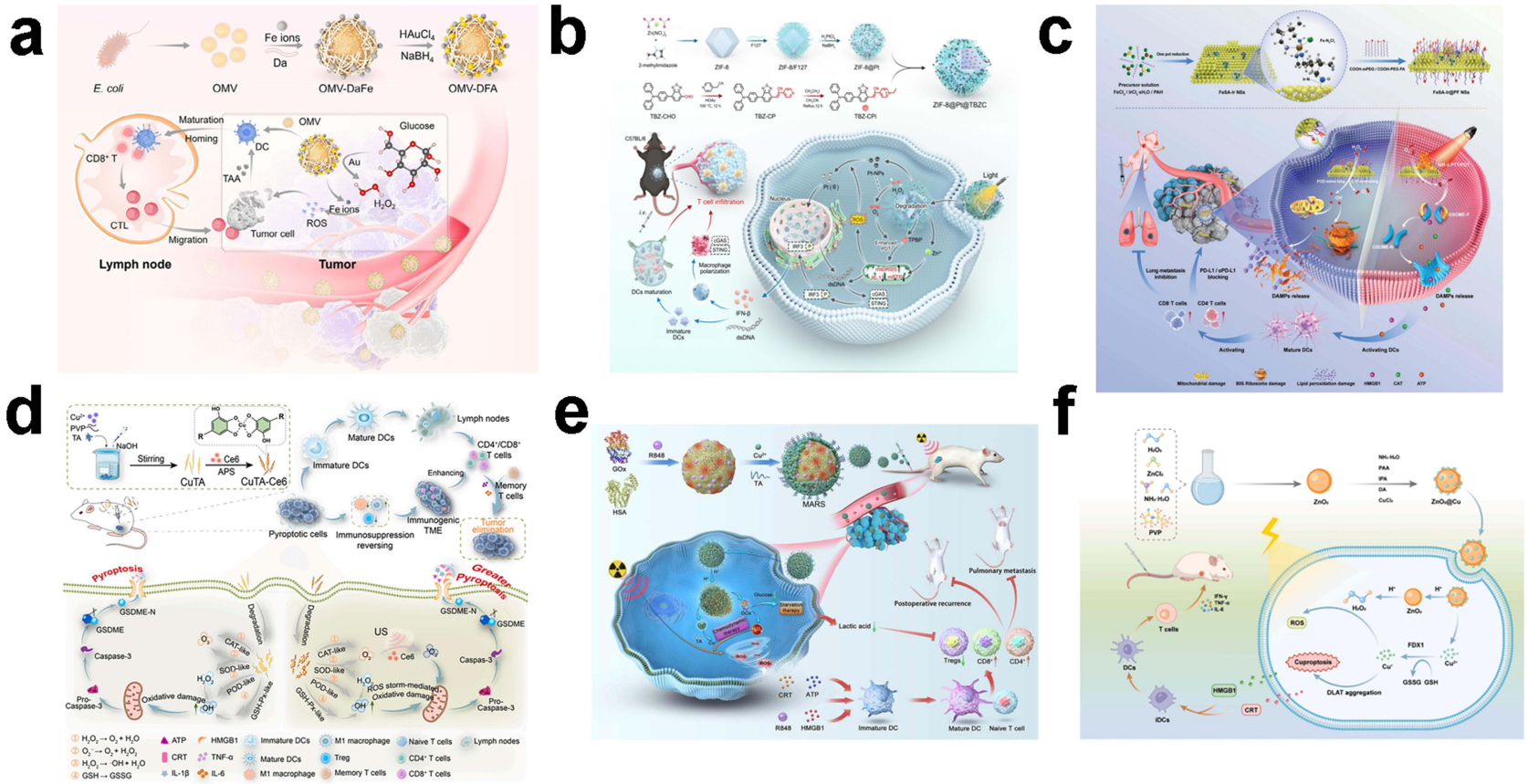

Figure 8 (**a**) Schematic diagram of OMV-DFA preparation and its cascade effect in cancer therapy. Reproduced with permission from ref.[151] (**b**) Synthesis of ZIF-8@Pt@TBZC NPs and its mechanism for colorectal cancer treatment. Reproduced with permission from ref.[152] (**c**) Schematic illustrations showing the fabrication and tumor therapy of FeSA-Ir@PF NSs. Reproduced with permission from ref.[153] (**d**) Schematic diagram of the synthesis of CuTA-Ce6 and their dual activation and amplification effect mediated by US and TME-targeted ferroptosis. Upward arrows indicate an increase. Reproduced with permission from ref.[154] (**e**) Schematic diagram of the preparation of MARS nanoparticles and their application in tumor therapy. Upward arrows indicate activation, and downward arrows indicate inhibition. Reproduced with permission from ref.[155] (**f**) Schematic diagram of ZnO_2@Cu preparation and its cascade reaction-based enhancement of radiotherapy immunotherapy. Reproduced with permission from ref.[156]

chlorogenic acid (CA)-loaded CA@ZIF-8/MnO_2 (CZM) nanoreactor. The nanoreactor achieves cascade catalysis of CDT via GSH depletion and endogenous H_2O_2 self-supply.[157] The degradation of the MnO_2 shell simultaneously achieves GSH scavenging and Mn^{2+} release, which not only enhances the Fenton reaction efficiency but also activates the cGAS-STING innate immune pathway. CA continuously converts superoxide anions into H_2O_2, addressing the bottleneck of insufficient substrates in conventional CDT. The resulting strong oxidative stress further induces ICD, promotes M1 phenotypic polarization of macrophages, and remodels the TME. These effects overcome multiple limitations of single immunotherapy, including low immunogenicity, hypoxia-induced drug resistance, enrichment of immunosuppressive cells, and insufficient T cell infiltration, ultimately yielding superior antitumor therapeutic outcomes.

Phototherapy @ Immunotherapy

In the field of minimally invasive tumor therapy, phototherapy (PT) possesses high controllability and reduces damage to normal tissues,[158] making it a research hotspot in tumor treatment. PT mainly includes photodynamic therapy (PDT) and photothermal therapy (PTT).[159] PDT can kill tumor cells and damage tumor blood vessels under specific light and photosensitizers, but hypoxia in the TME can limit its efficacy.[160] PTT can use photothermal agents to convert light energy into heat energy for local high-temperature ablation,[161] but suffers from insufficient photothermal conversion efficiency and limited deep tissue penetration, resulting in incomplete treatment.[162,163] Therefore, there is an urgent need to combine other cancer treatment strategies to improve tumor-specific therapeutic efficacy.

Zhu et al designed a cascade nanoplatform denoted as ZIF-8@Pt@TBZC NPs (ZPT NPs). Pt NPs and the photosensitizer TBZ-CPi (TBZC) were loaded on zeolitic imidazolate framework-8 (ZIF-8) (Figure 8b).[152] Platinum nanoparticles catalyze H_2O_2 to produce oxygen, relieve tumor hypoxia, and improve PDT efficiency. The TBZC photosensitizer targets mitochondria and causes mitochondrial DNA damage. The oxidized Pt (II) induces nuclear DNA breakage. Dual DNA damage strongly activates the cGAS-STING innate immune pathway. This process promotes DC maturation, $CD8^+$ T cell infiltration, and macrophage M1 polarization, as well as inducing ICD. This combination effectively overcomes the limitations of monotherapy, including insufficient T cell infiltration, difficulty in reversing the immunosuppressive TME, and low response rates, providing a new strategy for direct tumor killing and long-term antitumor immunity. Building on these findings, subsequent studies have focused on developing integrated strategies that combine PDT with immunotherapy to achieve more potent and systematic antitumor efficacy. For example, Fan et al successfully constructed a self-oxygenated photodynamic system named Fe-TCPP-R848-PEG (FeMOF-RP), which integrates Fe-TCPP metal-organic frameworks and R848 agonists.[164] This system achieves synergistic antitumor effects through the combination of PDT, CDT and immunotherapy. Upon excitation by 660 nm laser irradiation, TCPP generates $^1O_2$ via type-II photodynamic reactions and produces ROS including superoxide anions and •OH via type-I reactions, directly killing tumor cells and inducing ICD. This process releases DAMPs, converting "cold tumors" into "hot tumors" and supplying sufficient antigens for immunotherapy. Meanwhile, PDT alleviates tumor hypoxia, downregulates immunosuppressive cells such as M2-type macrophages and MDSCs, and restores the function of effector immune cells. From the dual dimensions of antigen supply and TME remodeling, this system overcomes the limitations of monotherapy including insufficient antigens, weak innate immune activation, and irreversible immunosuppression. Furthermore, cascade nanozymes achieve a closed-loop amplification effect of oxygen supply, ROS generation, and GSH depletion through multi-enzymatic cascade reactions, further enhancing the efficacy of combination therapy.

Yang et al developed FeSA-Ir@PF nanosheets constructed with supramolecularly encapsulated Fe single atoms and iridium metallene, which achieved synergistic antitumor effects through PTT and single-atom cascade catalysis (Figure 8c).[153] Under NIR-II light irradiation, PTT not only directly ablates tumor cells via hyperthermia but also enhances the cascade catalytic efficiency of nanozymes to generate ROS, thereby inducing ferroptosis and pyroptosis and releasing DAMPs. This process effectively initiates both innate and adaptive immune responses. This system successfully addresses the limitations of single immunotherapy, including insufficient tumor antigen release, low DC maturation, and poor effector T cell infiltration. Meanwhile, it remodels the TME via ROS-mediated oxidative stress and efficiently inhibits tumor lung metastasis when combined with αPD-L1. In addition to the synergistic antitumor effect of single-atom cascade catalysis and PTT, multi-enzyme-like composites loaded with immune adjuvants and functional metal ions also enable photothermal-immunological synergistic therapy. Zhang et al synthesized MCMSFT using Cu_2MoS_4 as the

carrier to encapsulate the immune adjuvant MET, Fe^{3+}, and tannic acid (TA).[165] This material exhibits triple enzyme-like activities of CAT, POD, and GPx, which induce tumor cell apoptosis and ferroptosis. Meanwhile, photothermal ablation and ferroptosis trigger ICD, promoting DC maturation and T cell activation. This strategy effectively overcomes the bottlenecks of pure immunotherapy, such as tumor hypoxia, strong immunosuppression, and the lack of positive immune feedback. Furthermore, MET downregulates PD-L1 expression, overcomes tumor cell apoptosis resistance and immune escape, promotes tumor regression, and suppresses metastasis and recurrence. To accurately identify osteosarcoma, Cheng et al encapsulated these nanospheres with indocyanine green (ICG) and grafted RGD peptide onto the surface of mCu&Ce nanospheres to obtain an mCu&Ce@ICG/RGD nanoplatform.[166] After the nanoplatform enters osteosarcoma cells, the photothermal effect significantly enhances the Cu/Ce-based Fenton-like reaction, amplifies ROS cascades, induces ICD, and activates effector T cells, eliciting systemic and specific antiosteosarcoma immune responses. In addition, this platform enables early diagnosis of osteosarcoma via NIR-II fluorescence and magnetic resonance dual-mode imaging, providing a novel paradigm for precision immunotherapy of bone tumors.

Sonodynamic Therapy @ Immunotherapy

Sonodynamic Therapy (SDT) is a non-invasive tumor ablation method that uses ultrasound (US) to activate sonosensitizers and generate cytotoxic ROS.[167,168] The resulting ROS can trigger cell apoptosis and necrosis, induce ICD, and promote TAAs release to activate DCs and CTLs, providing a new strategy to improve the therapeutic efficacy of immune checkpoint blockade.[169] For example, Zhao et al synthesized a CD@H-MnO_2 heterojunction platform with multiple enzymatic activities.[170] Upon ultrasound irradiation, this system generates massive ROS, directly inducing ICD and releasing tumor antigens. As a cascade nanozyme, CD@H-MnO_2 decomposes H_2O_2 via CAT-like activity to produce oxygen, relieving tumor hypoxia and enhancing SDT efficiency. Meanwhile, it depletes GSH, further amplifying oxidative stress and ICD effects. This strategy overcomes the limitations of single immunotherapy, such as hypoxia-suppressed SDT and impaired immune cell activation, thereby achieving potent antitumor efficacy.

To further exploit the synergistic potential of SDT and immunotherapy, cascade nanozymes with diverse compositions are developed to boost synergistic antitumor efficacy. Wang et al successfully synthesized a CuTA-Ce6 pyroptosis amplifier integrating the photosensitizer chlorophyll e6 (Ce6) and copper-tannic acid (CuTA), which exhibits dual activation and amplification effects mediated by US and TME-targeted ferroptosis (Figure 8d).[154] CuTA can activate and disrupt the tumor antioxidant system in the TME, and Ce6-mediated SDT further enhances pyroptosis. The two synergistically generate ROS, thereby inducing TAMs polarization, DC maturation, and T cell immune response. This approach addresses the key challenges of immunotherapy alone, including abundant immunosuppressive cells and insufficient T cell infiltration. Building on the synergy between SDT and immunotherapy, multi-enzyme-active nanomaterials can further amplify the superiority of ultrasound-triggered immunotherapy via the regulation of signaling pathways. Luo et al developed an ECHO nanosheet incorporating Mn^{2+} as metal nodes to connect meso-tetra (4-carboxyphenyl) porphine Cu (TCPP(Cu)) while simultaneously loading niclosamide (Nic).[171] Ultrasound-driven SDT generates ROS to trigger DNA damage, and ECHO acts as a cascade nanozyme to sustain ROS supply and maintain oxidative stress. Simultaneously, ECHO releases Mn^{2+} to activate the STING pathway and Nic to inhibit STAT3, realizing asynchronous regulation of STING and STAT3 signaling. This system not only sensitizes cells to DNA damage and suppresses intrinsic DNA repair but also strongly activates systemic innate antitumor immunity, advancing cascade nanozymes from "catalytic synergy" to "dual regulation of immunity and DNA repair".

Radiotherapy @ Immunotherapy

Radiotherapy (RT), as a commonly used clinical modality, can directly kill tumor cells through ionizing radiation,[172] yet it inevitably damages adjacent normal tissues. Cascade nanozymes, with their tunable enzymatic activities, have become an ideal bridge between RT and immunotherapy. They can remodel the TME through catalytic reactions, enhance the tumor-killing efficacy of RT, and promote the activation of immune pathways, providing a new strategy for synergistic RT-immunotherapy.[173] Bai et al constructed MARS nanoparticles containing GOx, Cu^{+}-based POD-like nanozyme, and R848 agonist (Figure 8e).[155] Radiotherapy directly eradicates tumor cells via ionizing radiation and induces ICD to release TAAs. As a cascade nanozyme, MARS catalyzes glucose to produce H_2O_2 via GOx-like activity for ST, supplies

substrates for POD-mediated Fenton-like reactions, and produces abundant ROS, which synergize with RT to amplify ICD. In addition, the combined treatment of RT and MARS can effectively inhibit local tumor growth and reduce lung metastasis and postoperative recurrence rates by nearly 90%. This overcomes the limitations of the weak abscopal effect and high risk of postoperative recurrence and metastasis in radiotherapy alone.

On this basis, the new-generation cascade nanozymes further incorporate ion interference and cuproptosis mechanisms, enhancing the synergy of RT-immunotherapy. Zhong et al designed core-shell structured nanoparticles ZnO_2@Cu (Figure 8f).[156] Radiotherapy causes DNA damage and triggers ICD. As a cascade nanozyme, ZnO_2@Cu dissociates in the acidic TME to release Cu^{2+} and ZnO_2. Cu^{2+} efficiently depletes GSH to weaken tumor antioxidant defenses, catalyzes H_2O_2 to generate ROS for radiosensitization, and induces cuproptosis. The co-activation of multiple cell death pathways further promotes antigen release, strongly activating innate immunity and significantly boosting adaptive immune responses. This overcomes the limitations of insufficient immunogenicity and poor efficacy in eliminating residual lesions in single-agent immunotherapy.

Conclusions and Perspectives

Nanozymes integrate the catalytic activity of natural enzymes and the inherent advantages of nanomaterials, and have been widely used in tumor therapy, biosensing and other research fields. Based on nanozymes, cascade catalysis can establish multi-step continuous catalytic systems to elevate catalytic efficiency, reduce the loss of intermediate products, alleviate side reactions and realize multifunctional regulation.[174] Different from conventional tumor therapies, immunotherapy exerts therapeutic effects by regulating the immune system. It shows prominent curative effects in certain patients and reduces tumor recurrence risks,[175] whereas its application is greatly restricted by the TME and individual immune status. Benefiting from superior catalytic activity, cascade nanozymes provide novel strategies to break the bottlenecks of immunotherapy. They can amplify ROS production and consume GSH within the TME via cascade reactions, thereby inducing ICD of tumor cells and promoting the release of DAMPs. Meanwhile, they can modulate immune cell functions and ameliorate the immunosuppressive TME,[176] which creates favorable conditions for the action of immune effector cells.

In summary, this review focuses on the applications of cascade nanozymes in tumor immunotherapy, illustrates the antitumor mechanisms of three types of cascade catalytic systems, and deeply explores the immunoregulatory mechanisms of cascade nanozymes in remodeling TME, activating immune signaling pathways and triggering ICD. These approaches can ultimately achieve the dual effects of improving local therapeutic efficacy and activating systemic antitumor immunity, providing innovative research concepts to overcome the limitations of traditional immunotherapy. Nevertheless, their clinical translation still faces many core challenges, including insufficient in vivo tumor targeting ability, poor delivery and penetration capacity towards solid tumors, lack of research on long-term immune effects, and unclear biosafety mechanisms. Future studies should focus on optimizing the tumor targeting capability of nanozymes, improving the deep penetration efficiency in solid tumors, establishing evaluation systems for long-term immune effects and perfecting biosafety assessment systems, so as to promote cascade nanozymes to evolve into practical and multifunctional novel strategies for clinical tumor immunotherapy.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the Shandong Provincial Natural Science Foundation (grant no. ZR2023MH370).

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The authors report grants from Department of Science & Technology of Shandong Provincial, during the conduct of the study.

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