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Progress and prospects of nanozymes for enhanced antitumor therapy

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Nanozymes are nanomaterials with mimicked enzymatic activity, whose catalytic activity can be designed by changing their physical parameters and chemical composition. With the development of biomedical and material science, artificially created nanozymes have high biocompatibility and can catalyze specific biochemical reactions under biological conditions, thus playing a vital role in regulating physiological activities. Under pathological conditions, natural enzymes are limited in their catalytic capacity by the varying reaction conditions. In contrast, compared to natural enzymes, nanozymes have advantages such as high stability, simplicity of modification, targeting ability, and versatility. As a result, the novel role of nanozymes in medicine, especially in tumor therapy, is gaining increasing attention. In this review, function and application of various nanozymes in the treatment of cancer are summarized. Future exploration paths of nanozymes in cancer therapies based on new insights arising from recent research are outlined.

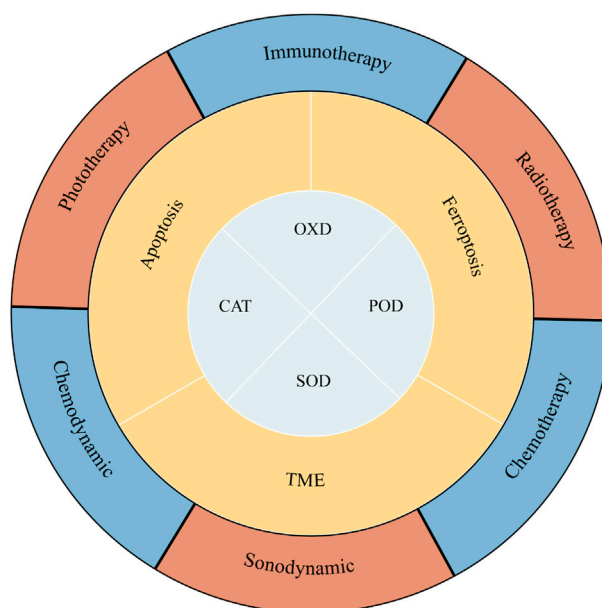
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nanozymes, catalytic therapy, enzyme mimics, cancer therapy, reactive oxygen species

Introduction

Cancer is the main cause of death and has a significant negative impact on both the economy and quality of life (Sung et al., 2021). Although conventional cancer treatment strategies such as radiotherapy, chemotherapy, and immunotherapy have been developed and validated for various types of cancers, the clinical efficacy of these therapies is still restricted. Drug tolerance, toxic side effects, radiation resistance and immune evasion remain formidable obstacles in cancer therapy. As the incidence and mortality of malignancies continue to rise, novel therapeutic agents have long been sought by scientists (Bray et al., 2021).

Enzymes are proteins or nucleic acids synthesized in an organism as a biological catalyst. They can be involved directly or indirectly in a variety of life processes in organisms, including cell metabolism, proliferation, differentiation, and aging. Enzymes have also been shown to contribute to the emergence of diseases. Tyrosinase, for instance, is required for the body to synthesize melanin and its absence can cause albinism (Song et al., 2018; Michaud et al., 2022). Numerous lung illnesses, including asthma and chronic obstructive pulmonary disease, have been linked to nitric oxide synthases (Scott et al.,



SCHEME 1

Nanozymes are engineered to enhance multiple antitumor therapy.

2021). It has been demonstrated that matrix metalloproteinases, which are overexpressed in tumor cells, facilitate cancer metastasis (Shi et al., 2015; Chen et al., 2020). However, protease and ribonuclease easily and quickly break down natural enzymes, making it challenging to store and transport them. On the other hand, the use of enzymes in therapeutic settings is constrained by the strict conditions that natural enzyme catalysis requires, such as a particular pH and temperature.

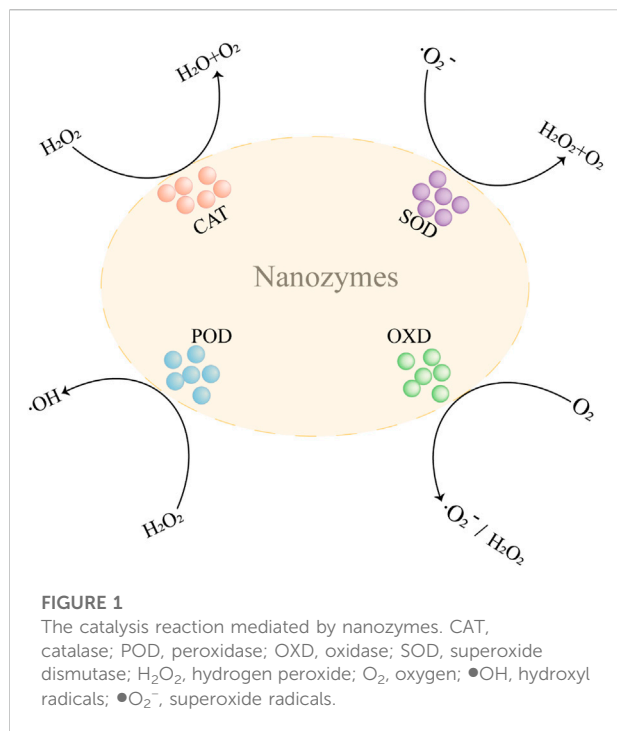
With the rapid development of nanotechnology, nanomaterials which can be manipulated on atomic and molecular scale are applied in medicine (Chai et al., 2022; Wang et al., 2022c; Zhang et al., 2022d; Farheen et al., 2022; Yang et al., 2022). Novel nanomaterials have demonstrated outstanding potentials in clinical applications with diverse functions (Filik et al., 2021; Li et al., 2022b; Kim et al., 2022). Nanozymes are artificial nanomaterials that exhibit intrinsic catalytic properties similar to that of natural enzymes and are attracting a massive attention (Jiang et al., 2019; Liang and Yan, 2019). To date, substantial nanomaterials have been discovered to possess enzyme-like activities, including carbon-based, metal-based, metal oxide-based and metal chalcogenide nanozymes (Robert and Meunier, 2022). By modifying structural composition and surface properties, nanozymes with different enzyme-like activities can be obtained, catalyzing the conversion of substrates into products and speeding up biological reactions under

appropriate physiological circumstances. In contrast to natural enzymes, nanozymes possess the advantages of high stability, simplicity of modification, targeting ability, and low cost (Wang et al., 2019a). As a result, the application trend of nanozymes in tumor treatment has become a hotspot. However, there are few reviews on nanozymes for antitumor therapies.

In this review, the recent research achievements and progress of nanozymes in cancer treatment are highlighted (Scheme 1). Firstly, we summarize the mechanisms underlying the most common antitumor effect of nanozymes. Then the promising applications and defects of nanozyme-based synergistic antitumor strategies are discussed.

Antitumor mechanisms of nanozymes

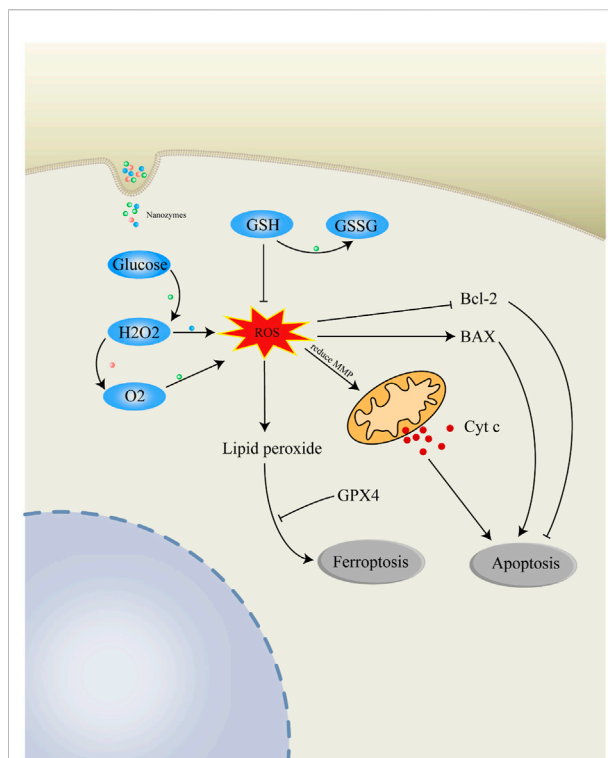
In recent decades, Nanozymes in oncology are compelling hotspots. With the advancement of material science, the design and synthesis of nanozymes is becoming more and more sophisticated (Jiang et al., 2019). Due to their excellent performance, nanozymes have developed into powerful tools for the treatment of tumors. Nanozymes that are more widely used in tumor therapy are peroxidase (POD), oxidase (OXD), catalase (CAT), and superoxide dismutase (SOD) (Figure 1). In this section, we discuss the anticancer mechanisms of nanozymes based on the recent reports (Figure 2).



Apoptosis induction

Apoptosis as a programmed cell death maintains the balance between cell death and cell proliferation, regulating the process of carcinogenesis. One of the characteristics of cancer is evasion of apoptosis, which makes cancer cells live with the ability to keep proliferating and escape cell death (Hanahan and Weinberg, 2011). Due to this characteristic of cancer, apoptosis induction becomes an effective approach for cancer therapy, which can kill malignant cells with no activation of an inflammatory response and little side effects to healthy cells (Chaudhry et al., 2022).

Nanozymes with multiple enzymatic activities can effectively produce reactive oxygen species in the tumor microenvironment through cascade catalytic reactions, thereby promoting the apoptosis of cancer cells (Zhao et al., 2021b; Yao et al., 2022b; Wang et al., 2022f). Ma et al. (2022) designed nanozymes with three nanoceria structures including nanoceria-cube, nanoceria-poly and nanoceria-rod. Among them, nanoceria-rod with highest concentration of surface oxygen vacancies has the highest POD-like and OXD-like enzyme activity. Due to the suitable isoelectric point, nanoceria-rod nanozyme can selectively enter the lysosomes and phagosomes of tumor cells in acidic environments. Then a large amount of ROS is produced and mitochondrial membrane potential is reduced, resulting in malignant cell apoptosis with no toxicity to normal cells.



Typically, the mechanism of nanozymes to induce apoptosis is mainly *via* mitochondrial apoptotic pathway. For example, PP-MnO(x) NPs, an OXD-like nanozyme, can catalyze O₂ to produce abundant ROS and induce the decrease of mitochondrial membrane potential. Meanwhile, PP-MnO(x) NPs activate BAX and Caspase-3, as well as decrease the expression of Bcl-2 (Xi et al., 2021). Moreover, Chu et al. (2020) Synthesized M@AAO@HFe-TA, a nanozyme system with amino acid oxidase (AAO) and POD activity. M@AAO@HFe-TA system induced apoptotic in tumor due to amino acid starvation and cascade Fenton reaction effect. The expression of Bcl-2 was suppressed and the level of BAX was increased, releasing the cytochrome C (cyt C) to the further active caspase 3. These suggest that nanozymes induce ROS generation and oxidative stress to initiate mitochondrial-related apoptosis.

TABLE 1 Nanozymes applied in cancer therapies.

Nanozyme	Activity	Mechanism	Application	References
Single-enzyme activity				
PP-MnO(x)	OXD	generate ROS/induce apoptosis	chemotherapy	Xi et al. (2021)
BN-GDY	POD	deplete GSH/induce ferroptosis	catalytic therapy	Zhang et al. (2022a)
Ce ₆ /Ftn@MnO ₂	CAT	O ₂ supply	photodynamic therapy	Zhu et al. (2022b)
ABTS@PAH-CNts	POD	photothermal effect/tumor target	photothermal therapy	Chen et al. (2021c)
Ni _{0.5} Fe _{0.5} S ₂	POD	generate ROS	photothermal therapy/chemodynamic therapy/photodynamic therapy	Zeng et al. (2022a)
RGD-BPNS@SMFN	CAT	O ₂ supply/tumor target	photothermal therapy/photodynamic therapy	Song et al. (2022)
ChA CQDs	OXD	deplete GSH/immune cells infiltration	immunotherapy	Yao et al. (2022a)
PHCNs	POD	induce apoptosis/activate CART cells	immunotherapy	Zhu et al. (2021)
GDY-CeO ₂	CAT	O ₂ supply/radiosensitizer	radiotherapy	Zhou et al. (2021a)
Mn-Ag ₂ Se-RGD-PEG	CAT	O ₂ supply/tumor target	radiotherapy	Wang et al. (2021)
multi-enzyme activity				
AuNPs@N-HCNs	POD, OXD	generate ROS/induce apoptosis	photothermal therapy	Wang et al. (2022f)
MnMoOx	OXD, CAT	O ₂ supply/generate ROS	photothermal therapy	Zhang et al. (2022f)
Au-FeSAzyme	POD, GOD	consume glucose/generate ROS	photothermal therapy/chemodynamic therapy	Feng et al. (2022)
SSMA/DOX	POD, GOD	consume glucose/generate ROS	chemodynamic therapy/chemotherapy	Zheng et al. (2022)
DOX@HMSN/Mn ₃ O ₄ R	OXD, CAT	deplete GSH/generate ROS	radiotherapy/chemotherapy	Yuan et al. (2022)
PCMGH	GOx,POD	O ₂ supply/generate ROS/photothermal effect	chemotherapy/phototherapy	Yu et al. (2022)
MSNR@MnO ₂ -Au	CAT/GOx	O ₂ supply/generate ROS	radiation therapy/photothermal therapy	Yang et al. (2020)
M@AAO@HFe-TA	POD, AAO	amino acid starvation/Fenton reaction	chemodynamic therapy	Chu et al. (2020)
MFC-Gem	POD, OXD	generate ROS/induce ferroptosis	chemotherapy	Zhang et al. (2022b)
CuPP	POD/CAT/GPx	generate ROS/deplete GSH	immunotherapy	Zeng et al. (2022b)
CDSDM	POD/CAT	O ₂ supply/regulate TME	immunotherapy	Wang et al. (2019b)
Fe ₃ O ₄ /Pt-FLU	POD/CAT	generate ROS and O ₂ /drug deliver	chemotherapy	Nie et al. (2022)
AIMP	CAT/OXD	O ₂ supply/Deplete GSH	sonodynamic therapy	Liu et al. (2021b)

Ferroptosis induction

Ferroptosis is a type of iron-dependent non-apoptotic cell death related to abnormal level of intracellular ferrous iron. Recently, ferroptosis was found to be widely present in many cancers with characteristics of mitochondrial damage and plasma membrane disrepair (Chen et al., 2021b; Tang et al., 2021). The induction of ferroptosis can potentiate the efficacy of chemotherapy, radiotherapy and immunotherapy in drug-resistant cancer (Friedmann Angeli et al., 2019; Ye et al., 2020; Fan et al., 2021), suggesting that targeting ferroptosis strategy is a viable method for cancer treatment (Mou et al., 2019).

Ferroptosis is mainly provoked by ROS accretion and unrestricted lipid peroxidation, which is induced by excessive endogenous Fenton reaction and the exhaustion of GSH (Wei

et al., 2020; Yang et al., 2021). Thus, nanozymes with peroxidase-like and glutathione peroxidase-like enzyme activity are designed as ferroptosis inducer for killing cancer cells (Meng et al., 2021). Zhang et al. (2022b) fabricated gemcitabine (Gem)-loaded carbonaceous nanoparticles (MFC-Gem) as peroxidase-like and glutathione oxidase-like nanozymes. The dual-activity MFC-Gem nanozyme effectively catalyzes the Fenton reaction to generate huge ROS and deplete GSH for oxidative damage. Meanwhile, glutathione peroxidase 4 (GPX4), a lipid repair enzyme which can use GSH to detoxify lipid peroxidation, loss activities in MFC and MFC-Gem treated mice, making cancer cells more susceptible to ferroptosis. Similarly, boron and nitrogen cooped graphdiyne (BN-GDY) as a metal-free nanozyme possesses capability to produce •OH in the presence of H₂O₂ and boost GSH depletion, setting the onset of ferroptosis. Interestingly, unlike the most reported enzymes,

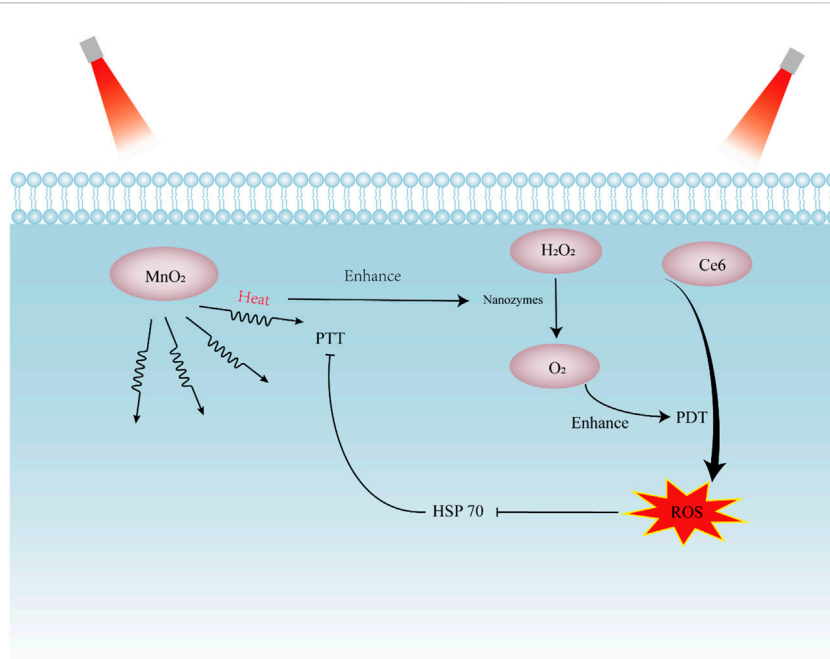


FIGURE 3

Schematic presentation showing the synergistic effect of nanozymes in photothermal therapy (PTT) and photodynamic therapy (PDT). The photosensitizer Ce6 absorb light and generate cytotoxic ROS. MnO_2 act as photothermal agents to converts absorbed light into heat and kill tumor cells via hyperthermia. PDT decreases the expression of HSP70 to increase sensitivity of tumors to PTT. The heat produced by PTT can enhance the activity of nanozymes, augmenting PDT effect. Ce6, chlorin e6; MnO_2 , manganese dioxide; HSP 70, heat shock protein 70; ROS, reactive oxygen species.

the catalytic reaction of BN-GDY undergoes a symbolic sequence Bi–Bi mechanism instead of a ping-pong Bi–Bi mechanism (Zhang et al., 2022a). Moreover, Fenton reaction-independent ferroptosis catalyzed by photothermal nanozyme is a novel insight for ferroptosis-related therapy, due to its satisfactory therapeutic effects in tumor therapy (Xing et al., 2021).

Tumor microenvironment regulation

Due to uncontrolled cell proliferation, aberrant cancer cell metabolism, and abnormal blood vessel development, tumor microenvironment (TME) is generally characterized by hypoxia (Semenza, 2000). The hypoxic TME make tumor cells exhibit increased drug efflux and lessen ROS-induced DNA damage, resulting in strong drug tolerance and radiation resistance (Brizel et al., 1999; Brown and Wilson, 2004; Gacche and Assaraf, 2018; Li et al., 2022a; Li et al., 2022c; Wang et al., 2022e). Nevertheless, the intrinsic hypoxia in TME suppresses the infiltration of anti-tumor immune cells and even induces the polarization of macrophages and T cells to pro-tumor subtype, such as M2 macrophages and regulatory T cells (Zhang et al., 2022c). Therefore, hypoxic TME hinders the efficacy of immunotherapy and augmenting O_2 supply becomes urgent to improve cancer treatment (Kopecka et al., 2021).

Nanozymes with CAT-mimic activity can transfer H_2O_2 to O_2 and supply enough O_2 to reverse hypoxia tumor microenvironment. Combined with GOx-like nanozymes which consume glucose and produced H_2O_2 , self-supply O_2 system is proposed by scientists (Yu et al., 2022).

Yu et al. (2022) modified carbon nitride (C_3N_4) with polydopamine before coating it with MIL-100, Gox, and hyaluronic acid to create a PCMGH nanozyme system. C_3N_4 , as a water-splitting material, catalyzes H_2O to generate O_2 , whereas MIL-100 acts like POD to raise the quantity of ROS. Upon 808 nm irradiation, polydopamine acts as a photothermal agent which convert light energy into hyperthermia to achieve photothermal therapy. The self-supplying O_2 and photothermal effect work synergically to improve the performance of chemotherapy and phototherapy.

The mesoporous silica nanorod was served as nanoplatform to integrate MnO_2 and Au nanoparticles, forming a new biomimetic nanozyme with dual enzyme activities. By decomposing H_2O_2 , MnO_2 can catalyze the production of O_2 , displaying enhanced CAT-like activity. Meanwhile, the Au nanoparticles which exhibit GOx-like activity effectively accelerate the oxidation of glucose and provide enough H_2O_2 for more O_2 production. The alleviation of hypoxic environment surrounding tumor sensitizing tumor cells to radiation therapy and photothermal therapy (Yang et al., 2020).

In addition to directly enhance the efficacy of antitumor treatment such as chemotherapy, phototherapy and radiotherapy, increasing O_2 level *in vivo* can change the expression of genes linked with tumor metabolism, proliferation and metastasis *via* regulating hypoxia-inducible factor 1 (HIF-1) pathway. Au-Pt nanozymes are reported to relieve the hypoxic TME and suppress the expression of HIF-1 α , thus reducing lung metastasis (Shen et al., 2022).

Nanozyme-based enhanced cancer therapies

Though traditional treatments for cancer such as chemotherapy, radiotherapy and Immunotherapy have been widely practiced. Low response rate, drug resistance and toxic side effects still are obstacles that have not yet been overcome. In recent years, nanozymes are employed in multiple cancer treatments due to their various mimic enzyme activities. In this section, we focused on the synergy of nanozymes and conventional cancer therapy (Table 1).

Nanozymes in phototherapy

Phototherapies including photothermal therapy (PTT) and photodynamic therapy (PDT) are considered as novel strategies employed widely in tumor treatment, due to their advantages of highly selective, negligible side effects, and minimally invasive (Vieyra-Garcia and Wolf, 2021). PDT provides oxidative damage on the tumor primarily through singlet oxygen, which is converted from triplet molecular oxygen by the photosensitizer as part of the photoconversion reaction (Zheng et al., 2022). While PTT initiates tumor cell death predominantly through hyperthermia *via* plasmonic dissipation, which is converted by the energy of photons absorbed on the photothermal agent under near infrared (NIR) laser irradiation (Figure 3). However, strict conditions such as oxygen leakage, acidic condition and overexpression of GSH in the tumor microenvironment (TME) constrain the photothermal conversion efficacy and ROS production of Phototherapies (Song et al., 2022). Photosensitive nanozymes which can remodel the restricted environment in tumor are intensively studied by scientists to achieve better phototherapeutic efficiency (Wang et al., 2022a; Tang et al., 2022).

In fact, the ROS generation in PDT often ceases with oxygen depletion. To solve this dilemma, an intelligent nanoplatform $Ce_6/Ftn@MnO_2$ with the ability of O_2 self-supply was constructed, which can reverse unfavorable hypoxia conditions and decrease the expression of hypoxia-inducible factor (HIF)-1 α . With adequate O_2 , $Ce_6/Ftn@MnO_2$ produced a significantly higher cytotoxic 1O_2 amount. The enhanced photodynamic effect

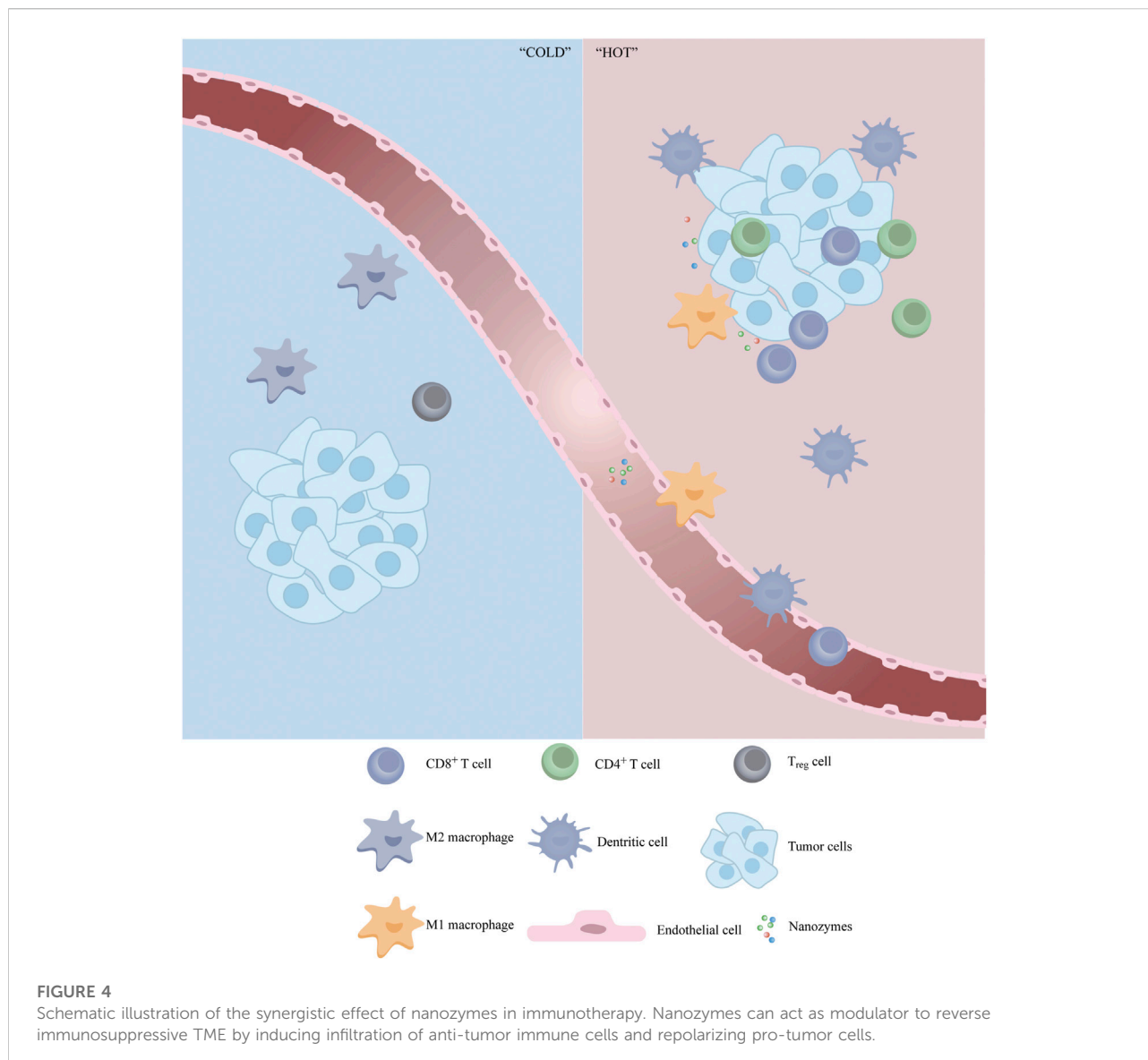
of $Ce_6/Ftn@MnO_2$ caused reduction of mitochondrial membrane potential and disruption of lysosome integrity, resulting in tumor cell death (Zhu et al., 2022b). To achieve profound photothermal therapeutic efficacy and minimized side effects, a “dual lock-and-key” type tumor-specific nanozyme (ABTS@PAH-CNTs) was designed with higher selectivity. Activated under both H_2O_2 and acidic pH, ABTS@PAH-CNTs present remarkable photothermal effect, with negligible off-target hyperthermic damage to normal tissues (Chen et al., 2021c).

It is worth noting that PTT can be used to integrate with PDT to get better synergistic antitumor effect. For instance, $Ni_{0.5}Fe_{0.5}S_2$ efficiently converts near-infrared light energy into heat for realizing the photothermal therapy. Moreover, the peroxidase-like property of $Ni_{0.5}Fe_{0.5}S_2$ triggers formation of cytotoxic $\bullet OH$ and 1O_2 to further enhance the efficiency of PDT (Zeng et al., 2022a). Similarly, Song et al. (2022) generated a PTT-PDT dual mode nanoplatform of RGD-BPNS@SMFN, which had self-synergetic behavior and enhanced photonic response than single PDT and PTT. The key self-synergetic mechanism is the PTT promoted temperature-dependent CAT-like activity, which alleviates the hypoxia microenvironment and further encourages the PDT behavior. Indeed, PTT induced hyperthermic temperature can accelerate enzyme-catalyzed ROS generation, which enhances the further PDT therapeutic performance (Zhou et al., 2022). On the other hand, ROS produced by PDT decreases the expression of heat shock protein 70 (HSP70), which was found to protect cells from the damage of heat, thus augmenting photothermal effect (Sun et al., 2021b). Taken together, the combination of PTT and PDT achieves strikingly therapeutic efficacy.

Nanozymes in immunotherapy

In recent decades, immunotherapy is a hot topic in cancer therapy which revolutionizes cancer treatment because of its striking tumor ablation effect. Multiple immunotherapeutic strategies, including cancer vaccines, immune checkpoint blockade (ICB), and adoptive cell transfer, have been developed by scientists (Rudd, 2019; He and Xu, 2020). However, the application of cancer immunotherapy is limited by low response rates and individual differences mainly due to immunosuppressive TME and heterogeneity. Nanozymes can act as a modulator to reverse immunosuppressive TME by degrading immunosuppressive molecules, inducing infiltration of anti-tumor immune cells and repolarizing pro-tumor cells (Wang et al., 2022b). Thus, nanozymes can be utilized as adjuvant therapeutics to boost immunotherapy efficacy.

The ChA CQDs nanozyme, formed by carbon quantum dots and chlorogenic acid, was reported with GSH oxidase-like activities and induction of cell ferroptosis. In addition to directly inducing cancer cell death through catalytic therapy, ChA CQDs activated the tumor immune microenvironment and



converted the “cold tumor” to “hot tumor” by recruiting CD4⁺/CD8⁺ T cells, macrophages, and NK cells (Figure 4). The increase in immune cells provides an important basis for subsequent immunotherapy, changing the situation that immunotherapy is ineffective in several types of cancer (Yao et al., 2022a).

A novel nanozyme (CuPP) with trienzyme-like activities has been proposed to efficiently modulate immunosuppressive TME by releasing O₂ and •OH but consuming glutathione (GSH). With the reversion of hypoxic microenvironment, macrophages in tumor site were repolarized from pro-tumoral M2 to anti-tumoral M1 phenotype, accompanied by the upregulation of IL-12 and the downregulation of IL-10. Moreover, the ratio of CD4⁺ and CD8⁺ T cells was elevated by further combining with αPD-L1, exhibiting strong immune responses (Zeng et al., 2022b). Except for αPD-L1, the synergistic effect is also achieved by

combining nanozymes with CTLA-4 blockade. CaO₂/DOX@SiO₂/DOX-MnO₂ (CDSMDM) nanozyme reactor was reported with self-oxygenation and alleviation of hypoxia-adenosinergic signaling. Through the positive immune modulation of CDSMDM NRs, the infiltration of cytotoxic T cells was facilitated and the population of immunosuppressive regulatory T cells was decreased. On the other hand, the DOX in CDSMDM NRs promoted the maturation of antigen-presenting dendritic cells. Thus, the reversion of the immunosuppressive TME is expected to favor CTLA-4-mediated immunotherapy (Wang et al., 2019b).

HA@Cu₂-xS were synthesized by hyaluronic acid, CuCl₂ and Na₂S, which were further modified by PEG to form HA@Cu₂-xS-PEG nanozymes (PHCNs). The PHCNs nanosystem effectively triggers apoptosis of tumor cells due to its dual

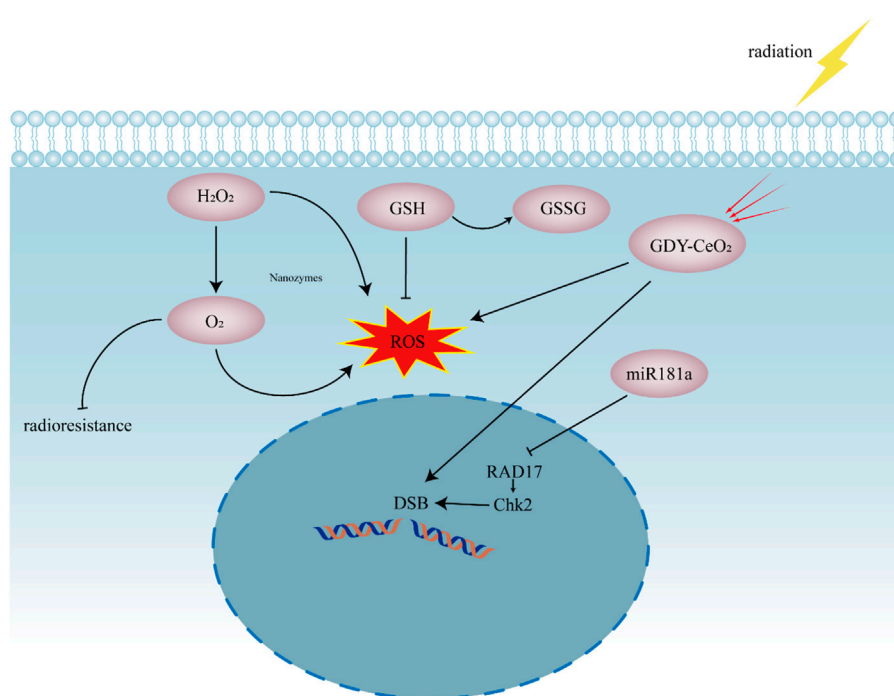


FIGURE 5

Schematic presentation showing the synergistic effect of nanozymes in radiotherapy. Nanozymes supply O_2 to reduce radioresistance of tumor cells. The production of ROS enhances the effect of radiotherapy. GDY– CeO_2 act as radiosensitizer to enhance the intracellular radiation energy deposition. miR181a can regulate RAD17/Chk2 pathway to suppress DNA repair. DSB, DNA double-strand break; GDY, 2D graphdiyne; CeO_2 , Cerium oxide, miR181a, miR181a-2-3p; RAD17, Cell cycle checkpoint protein RAD17; Chk2, Serine/threonine-protein kinase Chk2, ROS, reactive oxygen species; H_2O_2 , hydrogen peroxide; O_2 , oxygen; GSH, glutathione; GSSG, glutathione disulfide.

photothermal and peroxidase-like catalytic properties. Tumor-specific antigen released from dead tumor cells facilitates the infiltration and activation of chimeric antigen receptor (CAR) T cells, presenting a synergistic effect with CAR T-cell therapy (Zhu et al., 2021).

Nanozymes in radiotherapy

Radiotherapy occupies an essential position in cancer treatment and has been widely applied for solid tumors in the clinic. However, radioresistance, mainly caused by hypoxia and antioxidant environment around tumor, constrains the efficacy of radiotherapy (Dai et al., 2022). On the one hand, tumor cells overexpress the DNA repair proteins, making them more enduring than normal cells (Roos et al., 2016). On the other hand, the toxicities of the radiation to normal tissues can cause gastrointestinal damage, lung fibrosis, and cognitive impairment in patients, preventing them from being given at high enough doses (Stone et al., 2003). Thus, how to improve the radiation sensitivity of tumors and protect normal tissues from radiation damage has drawn considerable attention (Gong et al., 2022a; Gong et al., 2022b). Therefore, highly selective and

multifunctional radiosensitizers are urgently needed for radiotherapy enhancement. To address this issue, nanozymes that can target the tumor and improve hypoxia are promising strategies (Li et al., 2021; Zeng et al., 2021).

The tumor ablation effect of radiotherapy mainly relies on the radiation-induced DNA damage and toxicity of radiation-induced ROS. By coating pyrite (FeS_2) with cancer cell-derived exosomes, a nanozyme system with homologous targeting abilities, GSH-OXD and POD-like properties was created. The dual enzyme activities of FeS_2 reduce intracellular GSH levels and generate huge $\bullet OH$ to disrupt redox homeostasis and mitochondria integrity, thus significantly reducing radiotherapy resistance of cancer cells and amplifying the radiotherapeutic efficacy (Huang et al., 2021a).

GDY– CeO_2 nanozyme are synthesized by 2D graphdiyne (GDY) anchoring to the Cerium oxide (CeO_2) nanoparticles. The sustainable catalase activity of GDY– CeO_2 can decompose H_2O_2 and elevate O_2 concentration in TME, while high-Z element cerium in GDY– CeO_2 act as a radiosensitizer to enhance the intracellular radiation energy deposition (Figure 5). Moreover, combining miR181a with the GDY– CeO_2 further regulates the Serine/threonine-protein kinase Chk2 pathway and destroy the

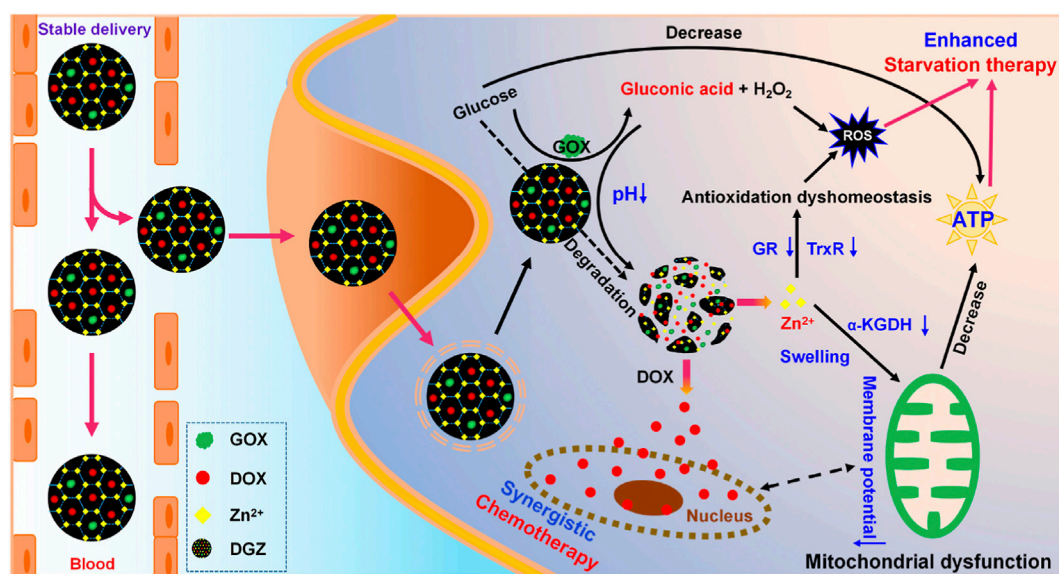


FIGURE 6

Schematic illustration of the synergistic effect of nanozymes in chemotherapy. Adapted with permission from (Huo et al., 2022). Copyright 2022 American Chemical Society.

DNA repair system in cancer cells, strikingly reinforcing the effect of radiotherapy (Zhou et al., 2021a).

A novel nanoprobe (Mn-doped Ag_2Se QDs) are engineered by doping Mn (II) ions into Ag_2Se quantum dot, using Mn (II) ions as CAT mimic to translate H_2O_2 into O_2 and Ag_2Se QDs as a radiosensitizer and NIR-II fluorescent materials to enhance radiation energy deposition and NIR-II imaging. By conjugating arginine-glycine-aspartate (RGD) tripeptides and polyethylene glycol (PEG) with Mn-doped Ag_2Se QDs, Mn-doped Ag_2Se -RGD-PEG nanoprobe were formed showing great biocompatibility and tumor specificity. The specific tumor-targeting and NIR-II-emitting abilities of the nanozymes enable precise NIR-II imaging-guided radiotherapy with negligible damage to normal tissues, which can be applied to boost the efficacy of RT (Wang et al., 2021).

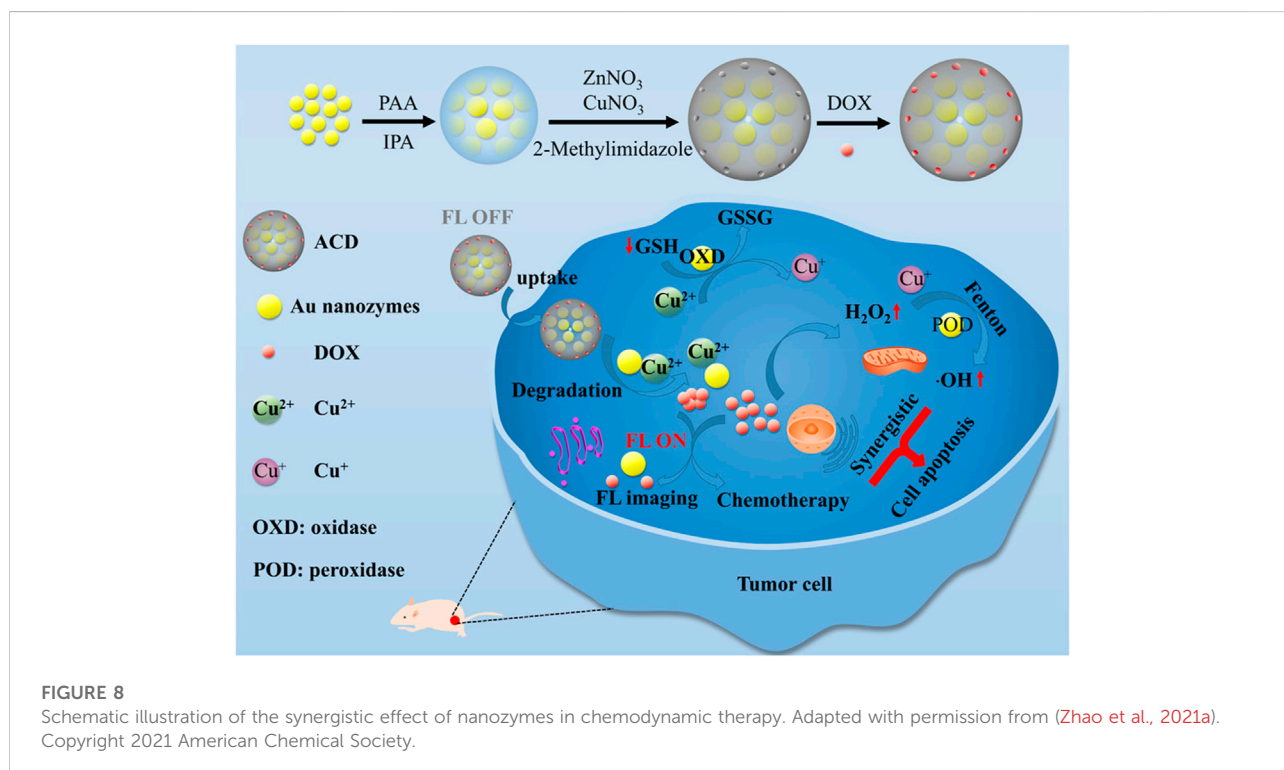
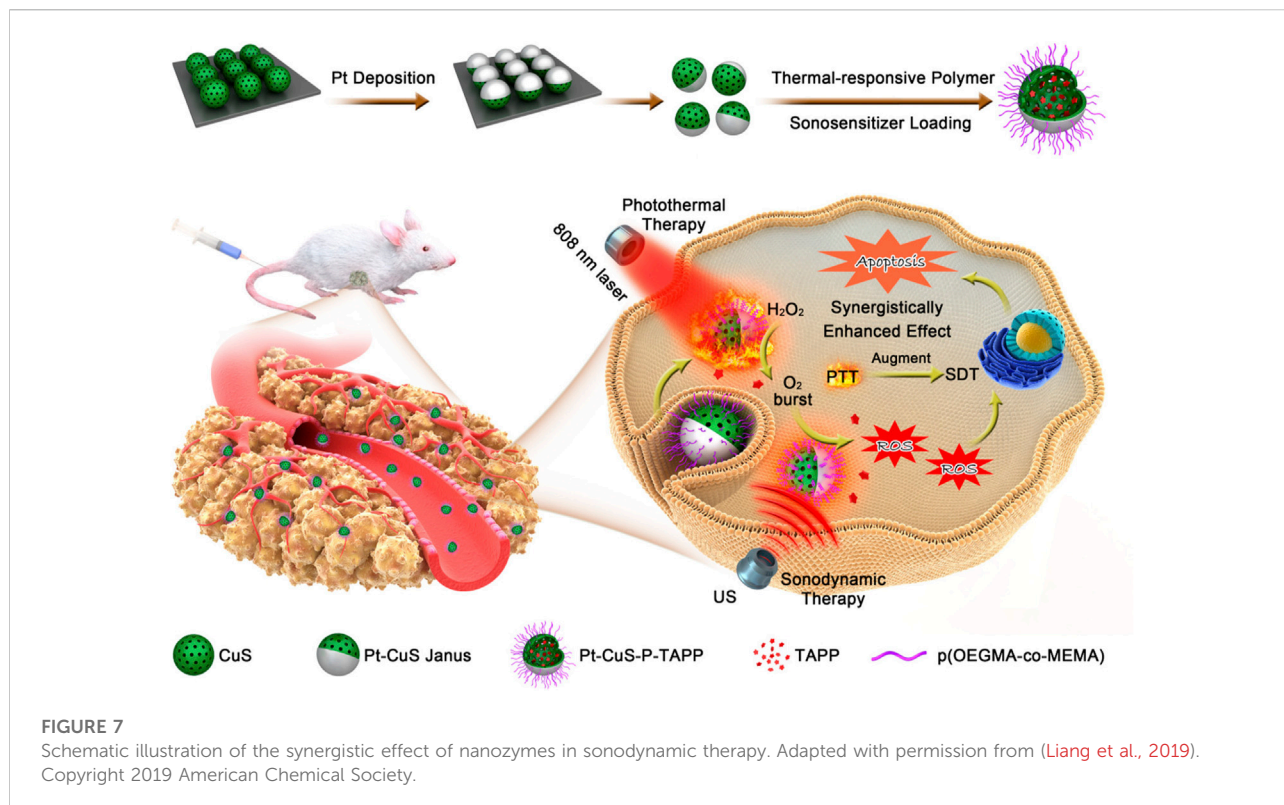
Nanozymes in chemotherapy

Conventional tumor chemotherapy, which is most commonly applied as first-line therapy for cancer in the clinic, remains a formidable challenge due to the severe side effects and drug resistance (Alkhatib et al., 2022; Zhu et al., 2022a; Wang et al., 2022d; Kang et al., 2022). Through tremendous research by scientists, multifunctional nanozymes are proven to be a promising avenue to achieve higher tumor elimination efficacy in synergistic chemotherapy and catalytic therapy.

On the one hand, nanozymes have the advantage of their enzyme-mimic activities to catalyze abundant ROS generation, which cause redox homeostasis disruption and damage to the cell membrane (Yuan et al., 2022). The direct effect of nanozymes can alleviate drug resistance and even kill cancer cells. On the other hand, nanozymes as nanoparticles can encapsulate chemotherapy drugs and release them in the tumor position (Ning et al., 2021). The specific targeting tumor property of nanozymes loaded drug system makes it possible to get better tumor elimination with a lower dose of chemotherapy drugs and less normal tissue injury (Han et al., 2022).

Zeolitic imidazolate framework (ZIF)-based nanoparticles co-loaded with glucose oxidase (GOX) and doxorubicin (DOX) were created to synergistically enhance chemotherapy. GOX activity of DOX/GOX-loaded ZIF (DGZ) effectively consumes glucose and generates adequate H_2O_2 , restraining the mitochondrial energy metabolism and promoting ROS production. As degradation of DGZ, Zn^{2+} was released to break antioxidation homeostasis in cancer cells via inhibiting reductase systems such as glutathione reductase and thioredoxin reductase. In case of energy shortage and ROS accumulation, the therapeutic effects of DOX delivered by DGZ get greatly enhanced. More importantly, DGZ releases DOX drug only in the weak acid environment surrounding tumor rather than in normal tissue (Figure 6). This high degree of targeting makes it possible to use higher doses of chemotherapy drugs to get better therapeutic outcomes with fewer side effects (Huo et al., 2022).

The hypoxia-related drug resistance and the lack of potential uptake of drugs also hamper chemotherapy application in tumor



treatment. Zheng et al. fabricated $\text{Fe}_3\text{O}_4/\text{Pt-FLU}$ nanozymes by loading Pt nanozymes and 5-fluorouracil on the Fe_3O_4 nanospheres to achieve improvement in the treatment of breast cancer. The POD-like and CAT-like activities of $\text{Fe}_3\text{O}_4/\text{Pt-FLU}$ alleviate the hypoxia environment in TME by increasing the level of ROS and O_2 , which leads to the reduction of drug resistance of cancerous tissue. Furthermore, $\text{Fe}_3\text{O}_4/\text{Pt-FLU}$ specifically delivers 5-fluorouracil to the tumor site in a pH-sensitive drug release manner. The drug carrier role of $\text{Fe}_3\text{O}_4/\text{Pt-FLU}$ significantly increases the stability of 5-fluorouracil and reduces the cytotoxicity in off-target tissues. The catalytic/chemotherapy double-modality therapy shows great therapeutic outcome for tumor elimination (Nie et al., 2022).

Nanozymes in sonodynamic therapy

Ultrasound (US)—triggered sonodynamic therapy (SDT) is mainly based on low-intensity US and sonosensitizers, which can induce the generation of cytotoxic ROS for tumor elimination (Chen et al., 2021a; Huang et al., 2021b). Compared with traditional therapy, SDT has the advantage of noninvasiveness, high tissue-penetrating capability, and safety, showing promising applications in new generation antitumor treatment (Pan et al., 2018; Son et al., 2020; Sun et al., 2021a). However, the ROS yield of sonosensitizers requires adequate O_2 assistance which is strongly hampered by hypoxia of TME. Thus, synergistic therapy with nanozyme-based O_2 supply and SDT may be a practical strategy (Gong and Dai, 2021).

AIMP, a multifunctional nanozyme, is formed by linking Angiopep-2 (Ang) with PLGA, in which IR780 and MnO_2 are encapsulated. Through the function of Ang and IR780, AIMP can target cancer cells and remain inside the mitochondria. Upon low-intensity US irradiation, IR780 behave as sonosensitizer to produce ROS and cause damage to cancer cells. On the other hand, enzyme-like activity of MnO_2 is responsible for O_2 release and GSH depletion, thereby boosting the production of ROS and enhancing SDT effect (Liu et al., 2021b).

The Pt-CuS Janus loaded with tetra-(4-aminophenyl) porphyrin (TAPP) as a sonosensitizer is designed to facilitate SDT-based synergistic therapeutic modality. Upon exposure to US, TAPP are released from the hollow Pt-CuS Janus and interact with O_2 to produce $^1\text{O}_2$. Meanwhile, Pt possesses CAT-like activity for the degradation of H_2O_2 and production of O_2 , which provides an O_2 source for SDT-induced ROS production (Figure 7). Importantly, the photothermal effect of Pt-CuS elevates the Pt catalytic activity for O_2 generation and facilitates SDT efficacy (Liang et al., 2019).

Nanozymes in chemodynamic therapy

Chemodynamic therapy (CDT) is an emerging therapeutic strategy that can destroy cancer cells through catalyzing the

endogenous H_2O_2 into lethal hydroxyl radical by Fenton reaction or Fenton-like reaction (Zhou et al., 2021b; Jia et al., 2022). CDT takes advantage of high selectivity, low side effects and no requirement for exogenous stimulus. However, the limited concentration of endogenous H_2O_2 and excessive antioxidant GSH hinder the application of CDT. Supplying sufficient intratumoral H_2O_2 and depleting endogenous GSH are necessary to improve the efficiency of CDT. Recently nanozyme cascade platforms have been extensively studied and widely applied to enhance the antitumor effect of chemodynamic therapy (Zhang et al., 2021; Zhang et al., 2022e).

The cascade reaction systems ACD is fabricated by loading copper ion-doped ZIF-8 with ZIF-8 doped with Au nanozymes and doxorubicin hydrochloride (Zhao et al., 2021a). The POD-like activity of Au nanozymes can catalyze H_2O_2 to $\cdot\text{OH}$ for CDT. While Au can also serve as an oxidase to deplete the GSH. Moreover, the Cu^{2+} ions released from ACD could consume the GSH *via* redox reactions and the generated Cu^+ can produce $\cdot\text{OH}$ by Fenton-like reaction. Thus, the increased ROS and exhaustion of GSH can effectively amplify the antitumor effect of CDT. On the other hand, doxorubicin hydrochloride not only act as chemotherapeutic drug to kill cancer cells but also supply sufficient H_2O_2 to boost the effect of CDT (Figure 8). Herein, the application of nanozymes in CDT can achieve better treatment effects and are promising for tumor elimination.

Apart from increasing ROS production and promoting GSH depletion, strengthening the tumor targeting ability of nanodrug is another way to augment the effect of CDT. Au-DNA-Fe, a microRNA-triggered nanozyme cascade platform is fabricated for enhanced tumor-specific chemodynamic therapy. Au nanozyme as glucose oxidase-like nanozyme catalyze Glucose into gluconic acid and H_2O_2 , while the produced H_2O_2 is subsequently catalyzed by Fe_3O_4 nanoparticles to generate hydroxyl radicals for CDT. Interestingly, Au and Fe_3O_4 nanoparticles are modified by two different single-stranded DNA which are complementary to each part of miRNA-21. Due to the overexpression of miRNA-21 in cancer cells, the nanozyme Au-DNA-Fe can trigger the cascade reaction specifically in cancer cells with negligible side effects on normal tissues (Liu et al., 2021a).

Conclusion and perspectives

Nanozyme is a breakthrough in the treatment of cancer, and their extremely small size, good modifiability and applicability provide endless opportunities to design multi-program cancer therapy strategies. A lot of research has generated a large number of feasible solutions for nanozymes involved in cancer treatment, mainly *via* inducing oxidative stress by catalyzing ROS production and disrupting the function of tumor cells by altering the

metabolism. The imbalance in redox homeostasis caused by excessive ROS induces apoptosis or ferroptosis, which both result in tumor death. In addition to the direct killing of tumor cells, modification of the tumor microenvironment by nanozymes effectively reduces the resistance of tumor cells to therapy, including drug resistance, radiation desensitization, or immune evasion. This creates an amazing synergy when used in conjunction with other classical therapies such as phototherapy, immunotherapy, radiotherapy, and chemotherapy.

Despite the promising future, many hurdles remain to be overcome in the application of nanozymes in cancer therapy. Oxidases, catalase and hydrolases already exist in numerous applications in the treatment of cancer, but the study of other enzymes such as transferases and lysates are new direction and relatively empty areas of research. Exploration of novel enzymatic nanoparticles can help us establish a multi-enzyme nanoparticle therapeutic system. Due to their diverse catalytic activities, different enzyme types can synergistically address the difficulties that exist in aberrant tumor environments and play a more effective role in tumors.

On the other hand, the catalytic activity of nanozymes needs to be improved. Although there is a small subset of nanozymes with greater catalytic activity than natural enzymes. However, achieving optimal catalytic efficiency in a complex tumor microenvironment remains a challenge. Most importantly, good biocompatibility is a pre-requisite for nanozymes to be used in the clinic. There is an urgent demand to reduce nanozymes inherent toxicity or design nontoxic nanozymes, for which ensuring that nanozymes remain effective at low doses is a viable method. Thus, it is the key to improving the targeting ability of nanozymes, as well as the ability to deliver them into the bloodstream in a sustained manner. The construction of a nanozymes-system with good biocompatibility and high target efficiency will be future development trend in new generation cancer therapy.

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As nanotechnology continues to develop and cancer treatment improves, nanozymes with high catalytic efficiencies, excellent biocompatibility, specificity, and multiple functionalities in combination with traditional anticancer therapy are expected to emerge in the future.

Author contributions

YY performed a literature search, interpreted the data, and wrote the manuscript. RL, XY, and WZ supervised and contributed to the writing process. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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.

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