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Review

Application of Multifunctional Nanozymes in Tumor Therapy

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Cite This: *ACS Omega* 2024, 9, 15753−15767

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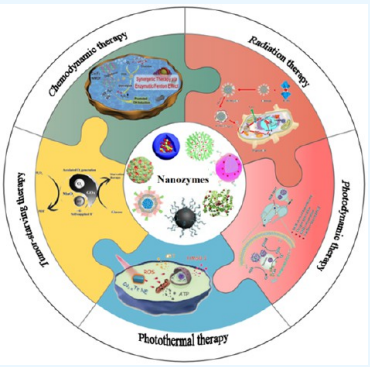
ABSTRACT: Tumors are one of the main diseases threatening human life and health. The emergence of nanotechnology in recent years has introduced a novel therapeutic avenue for addressing tumors. Through the amalgamation of nanotechnology's inherent attributes with those of natural enzymes, nanozymes have demonstrated the ability to initiate catalytic reactions, modulate the biological microenvironment, and facilitate the adoption of multifaceted therapeutic approaches, thereby exhibiting considerable promise in the realm of cancer treatment. In this Review, the application of nanozymes in chemodynamic therapy, radiotherapy, photodynamic therapy, photothermal therapy, and starvation therapy are summarized. Moreover, a detailed discussion regarding the mechanism of conferring physiotherapeutic functionality upon catalytic nanosystems is provided. It is posited that this innovative catalytic treatment holds significant potential to play a crucial role within the domain of nanomedicine.



1. INTRODUCTION

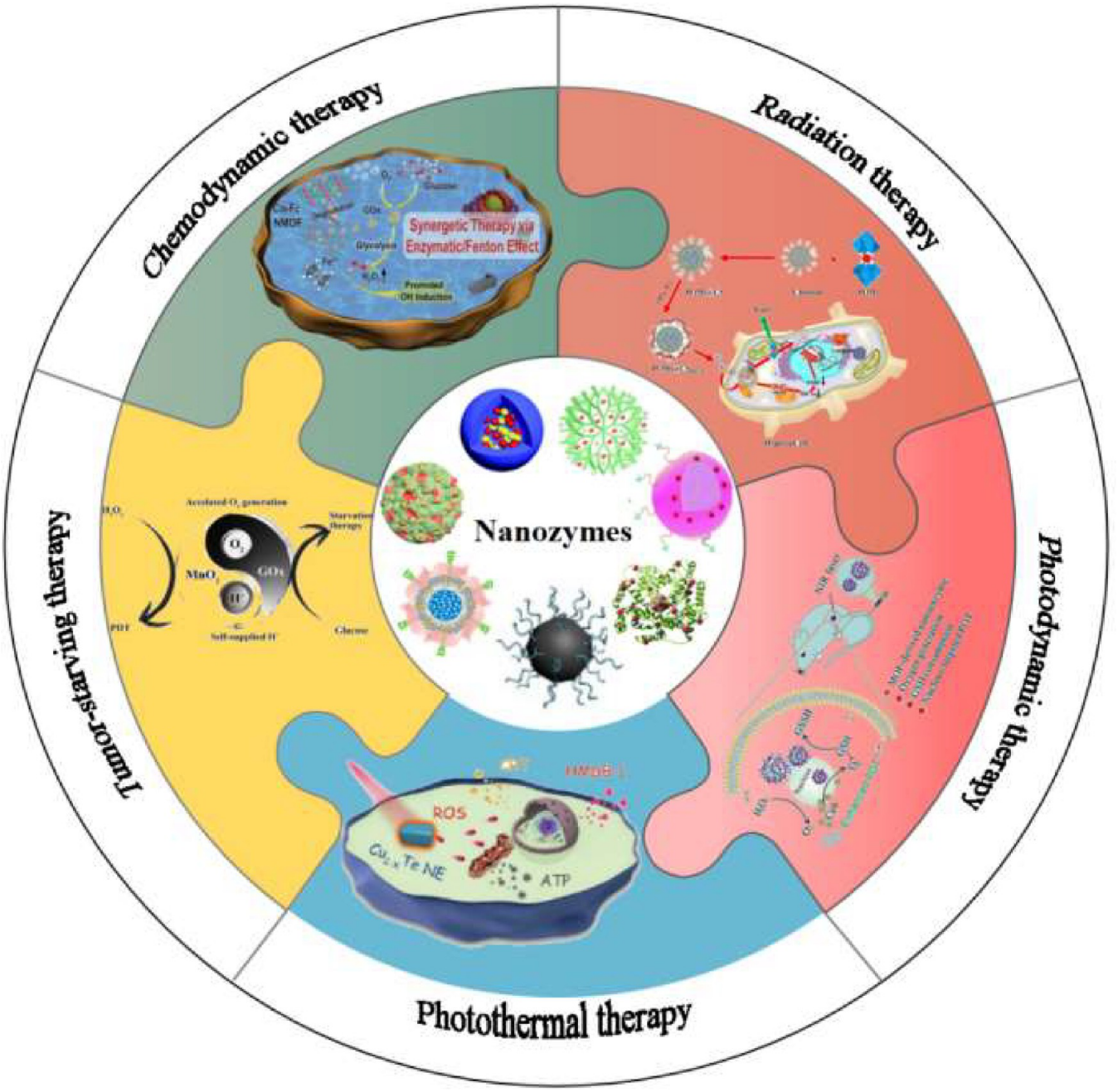
Cancers have become one of the major threats to human health, accompanied by the increasing incidence and mortality rates worldwide.[1] Treatments varies in light of the progression, mainly including surgical resection, chemotherapy, radiotherapy, photodynamic therapy (PDT), sonodynamic therapy (SDT), and immunotherapy.[2] However, therapeutic effects are hindered because of the complicated tumor microenvironment, such as low pH, hypoxia, and the up-regulation of some multidrug resistance-associated proteins and enzymes.[3] Continual exploration and development of novel methodologies remain imperative in the ongoing endeavor to combat cancer effectively.

As biocatalysts, enzymes play integral roles in signal transduction, metabolism, and disease pathogenesis.[4] For instance, some enzymes (such as matrix metalloproteinases, lactate dehydrogenase, and catalase) are involved in tumor progression and are widely considered as potential targets in cancer therapy.[5,6] Furthermore, enzymes hold great potential in cancer treatment due to their high catalytic efficiency and environmental protection.[7,8] Nevertheless, several limitations hinder the widespread application of enzymes. Primarily, enzymes are predominantly comprised of proteins, rendering them susceptible to proteolytic degradation and thereby posing challenges in transportation and storage.[9] Furthermore, exposure to various physical and chemical stressors, such as elevated temperatures or extreme pH conditions, can induce enzyme denaturation and subsequent loss of catalytic activity.[10] Importantly, the recovery of natural enzymes presents logistical and economic challenges. While numerous organisms possess the capacity to produce enzymes, only select animals, plants, and microorganisms serve as economically viable sources, thereby exacerbating issues related to cost-effectiveness and scalability.[11]

As a result, researchers are working on nanomaterials that may mimic various enzyme activities, known as nanozymes. Simply described, nanozymes are nanomaterials that exhibit both simulated enzyme and catalytic capabilities. In comparison to natural enzymes, they are more stable and economical.[12] Nanozymes have great advantages in cancer therapy. Nanozymes can achieve passive targeting of tumor tissues through the enhanced permeability and retention effect (EPR) of blood vessels and increase drug accumulation in tumor tissues.[13] In addition, compared with natural enzymes, the nanodrug delivery system is simple to prepare and holds great stability. In 2007, Yan's group first found that inorganic Fe_3O_4 nanoparticles possessed the biological activity of a natural enzyme (horseradish catalase), which promoted the development of nanozymes.[14] The emergence of nanozymes provides a new idea for the design and development of nanosystems.[15] This is a new interdisciplinary field combining nanotechnology and biomedicine.[16,17] Scientists have developed various nanomaterials with enzyme-like activity, such as Fe_3O_4 nanoparticles, Au nanoparticles, and MnO_2 nanoparticles, which possess the catalytic abilities like catalase (CAT) and superoxide dismutase (SOD).[18−20] Nanozymes can not only be used for tumor treatment but are also useful

Received: January 19, 2024
Revised: February 25, 2024
Accepted: March 13, 2024
Published: March 26, 2024

Scheme 1. Schematic Overview on the Significant Research of Nanozymes in Tumor Therapy[a]



[a]Including chemodynamic therapy, radiotherapy, photodynamic therapy, photothermal therapy, and starvation therapy.

for gene therapy and tumor immunotherapy. Traditional virus vectors are highly immunogenic and can infect people. The advent of biomaterials have piqued people's interest, and their efficient gene delivery vectors can overcome the limitations of viral vectors.[21] Second, existing tumor immunotherapy has limitations, such as limited selectivity, low immunogenicity, insufficient delivery efficiency, and off-target effects. Some biomaterials are utilized to enhance the antitumor immunological response of the immunotherapy and to regulate immune suppression.[22]

Based on the above challenges , in this Review, we mainly concentrate on recent advances regarding the nanozymes in cancer therapy, including chemodynamic therapy, radiotherapy, photodynamic therapy, photothermal therapy, and starvation therapy (Scheme 1), and provide a detailed exploration of the mechanisms that endow the catalytic nanosystems with physiotherapeutic functions.

2. NANOZYMES IN THE TREATMENT OF TUMORS

Presently, clinical interventions for cancer predominantly encompass three modalities: radiation therapy (RT), surgical resection, and chemotherapy.[2] However, the low targeting to tumor sites and drug resistance lead to poor therapeutic efficacy, even tumor metastasis, and serious side effects, such as alopecia, nausea and vomiting, allergy, bone marrow suppression, and cardiac toxicity. Nanocatalytic system can kill tumor cells through endogenous or exogenous stimulation

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ACS Omega 2024, 9, 15753−15767

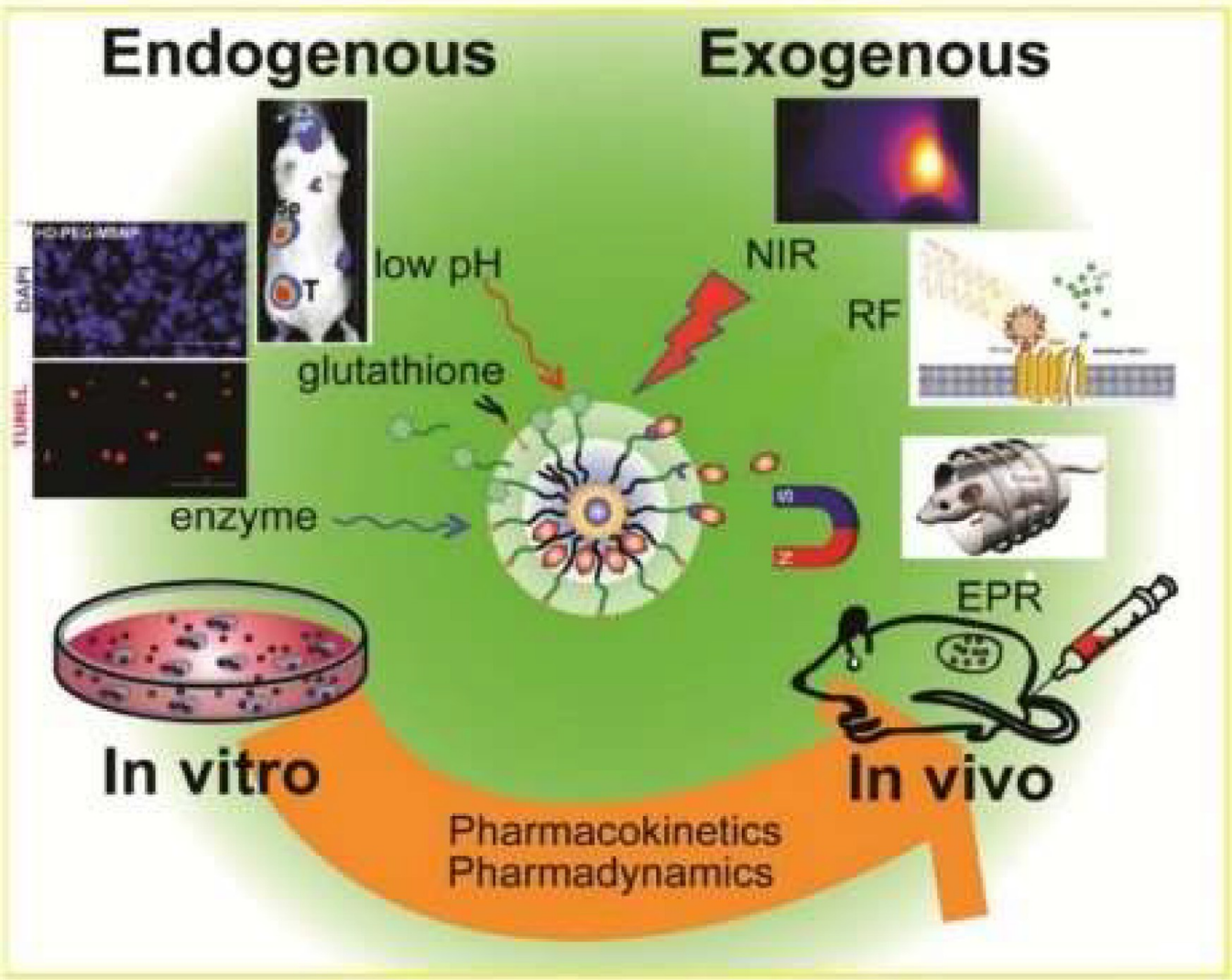

Figure 1. Path of endogenous and exogenous drug release triggered by nanomaterials *in vitro* and in *vivo*. Reprinted with permission from ref 24. Copyright 2013 Nano Today Publishing Group.

to produce toxic substances while protecting normal tissues from damage and have great potential in cancer therapy.[23]

Catalytic nanosystems can be divided into endogenous and exogenous stimulation systems (Figure 1).[24] Briefly, the endogenous stimulation system is triggered by chemical differences in biological systems, which can directly target and precisely deliver drugs to tumor tissues at a molecular level. In the past few years, catalytic nanosystems have been widely explored in chemodynamic therapy (CDT) to produce reactive oxygen species (ROS) in tumors for specific therapy.[25] At the same time, plasma metal Au can also be widely used to enhance chemical and photochemical reaction activity through its surface plasmon resonance (SPR).[26] Additionally, tumors are starved by blocking the supply of nutrients or oxygen, thereby achieving the effect of killing the treated cancer.[27] In contrast, an exogenous stimulation system is triggered by physical magnetic fields, such as light, electricity, and ultraviolet light, to generate locally toxic substances. For example, photodynamic therapy (PDT) and photothermal therapy (PTT) are based on the coordination between the nanocatalyst and physical magnetic stimulation to achieve the therapeutic effect.[28]

In contrast, exogenously assisted therapy offers greater feasibility but entails a series of attendant complexities. In this section, we briefly focus on recent advances regarding the application of nanozymes in cancer therapy, including chemodynamic therapy, radiation therapy, photodynamic therapy, and tumor-starving therapy. Furthermore, the mechanisms underlying the acquisition of physiotherapeutic functionalities by catalytic nanosystems are explored in detail.

2.1. Nanozymes in Chemodynamic therapy (CDT). The escalating incidence of malignancies in recent years underscores the pressing need for novel therapeutic interventions.[29] Throughout tumor progression, a considerable quantity of reactive oxygen species (ROS) is generated, comprising hydrogen peroxide (H_2O_2), superoxide (O^{2-}), and hydroxyl radicals (•OH).[30] Excessive ROS production may precipitate irreversible DNA damage, culminating in severe cellular impairment.[31] However, tumor cells employ various antioxidant defense mechanisms, such as glutathione, to mitigate ROS-induced damage and promote cell survival.[32] Consequently, targeting the redox imbalance represents a promising therapeutic strategy for combating tumors.

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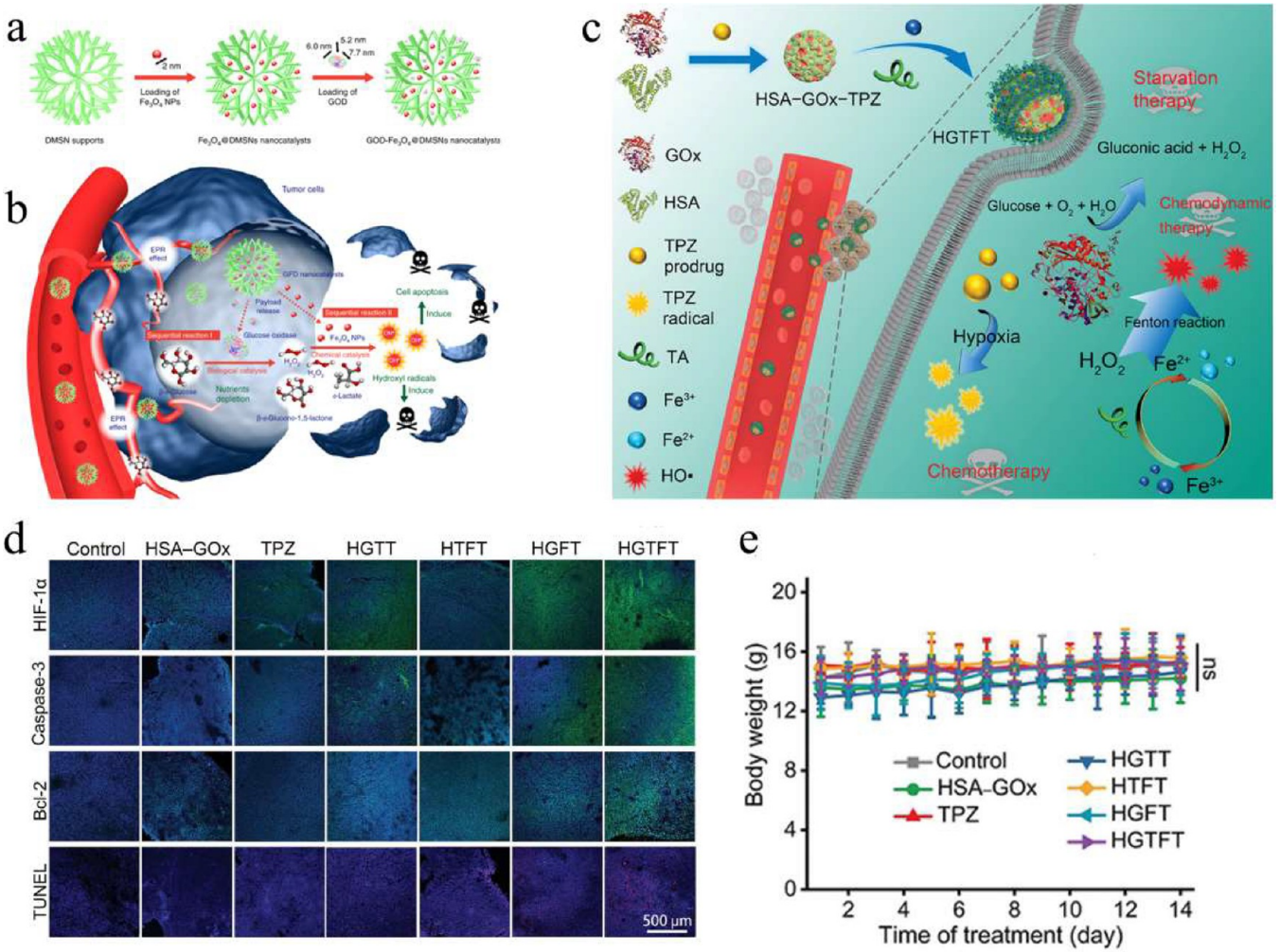

Figure 2. (a) The preparation of GOD-Fe_3O_4@DMSNs nanocatalysts. (b) Drug release mechanism of GFD nanocatalysts. Reprinted with permission from ref 37. Copyright 2017 Nature. (c) Preparation of the HGTFT nanoreactor and its mechanism in killing tumor cells. (d) Tumor tissues were isolated after 14 days of treatment on 4T1 tumor bearing nude mice for immunohistochemistry (HIF-1α, caspase-3, and Bcl-2) as well as TUNEL staining. (e) Body weight changes of mice during treatments. Reprinted with permission from ref 38. Copyright 2020 Wiley-VCH.

In the treatment of cancer therapies mediated by ROS, Chen's team first proposed the new treatment modality of CDT.[25] This method mainly utilized the Fenton or Fenton-like response to introduce highly toxic •OH in the tumor, which can locally oxidize and damage tumor cells.[33] Nevertheless, owing to the limited iron content within the body and the propensity for most free iron to bind to proteins, only a fraction of free iron is available for participation in the Fenton reaction. Consequently, a higher concentration of iron is required to react with the surplus hydrogen peroxide abundant within tumor cells.[34] Moreover, the weakly acidic microenvironment characteristic of tumors creates an optimal milieu for the Fenton reaction, whereas normal tissue environments do not possess such conditions. This discrepancy serves to protect normal tissues from damage while concurrently augmenting the therapeutic efficacy within tumor sites.[35] In recent years, many nanomaterials, such as Fe^{2+}/Fe^{3+}, Ce^{3+}/Ce^{4+}, Cu^{+}/Cu^{2+}, and Mn^{2+}/Mn^{4+}, with the ability to generate highly toxic •OH have been applied to kill cancer cells by triggering the Fenton reaction or Fenton-like reaction.[30] For instance, Wang's group utilized the reaction between CaO and water to produce H_2O_2, which further reacted with Fe^{2+} in Fe_3O_4 to generate extremely toxic •OH.[36]

Additionally, with the goal of protecting normal tissues from damage while maximizing the therapeutic effect on tumor cells, Huo and his co-workers introduced the concept of sequential catalytic nanomedicine.[37] They constructed a nanoparticle crop carrier of mesoporous silica (GOD-Fe_3O_4@DMSNs) in which natural glucose oxidase (GOD) and Fe_3O_4 nanoparticles with a diameter of 2 nm were sequentially encapsulated (Figure 2a). GOD-Fe_3O_4@DMSNs enables highly efficient enzyme-catalytic reactions and Fenton reactions. First, GOD selectively catalyzes the reaction of intracellular D-glucose and glucose lipid to obtain H_2O_2, which would further serve as the reactant for Fenton reaction. H_2O_2 reacted with Fe_3O_4 in acidic environments to generate highly toxic hydroxyl radicals and thus damages tumor cells, while the generation of oxygen under neutral conditions caused no damage to normal tissues or other organs. This provides a foreground policy for treating tumors, greatly improving tumor specificity, and reducing side effects on normal tissues.

Previous literature indicated that liposomes loaded with hydrogen peroxide can kill tumor cells by the generation of reactive oxygen, but drug leakage impairs therapeutic effects.[11] Therefore, stimulating the generation of H_2O_2 at the tumor site may be a good choice. Guo's group wrapped glucose

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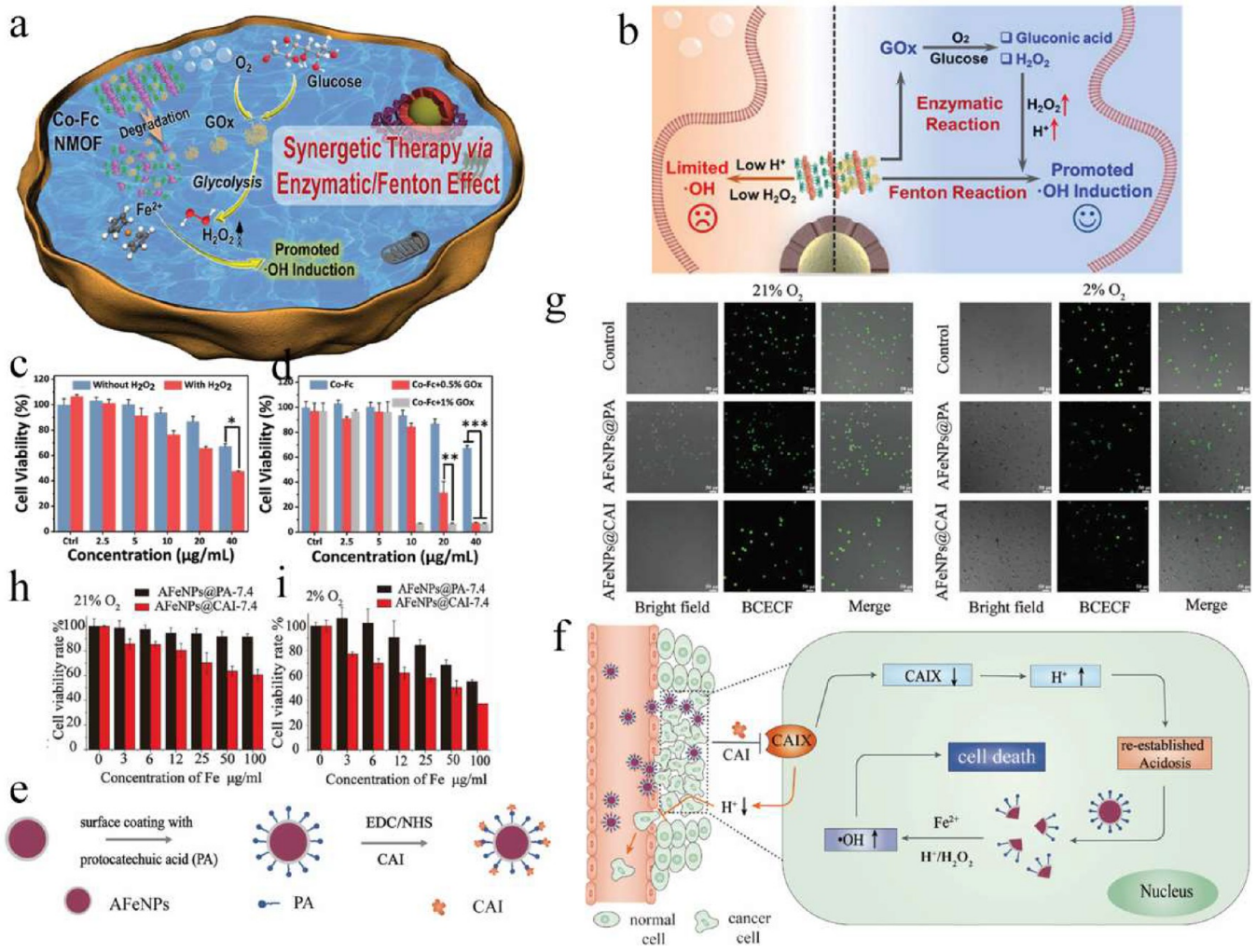

Figure 3. (a) Schematic diagram of Co-Fc@Gox in inducing the generation of •OH. (b) Mechanism of the Fenton reaction in induction of intracellular •OH. (c) Effect of Co-Fc@GOx on 4T1 cells with or without H_2O_2 stimulation. (d) Cell viability of 4T1 tumor cells incubated with different concentrations of GOx in Co-Fc@GOx. Reprinted with permission from ref 40. Copyright 2020 Wiley-VCH. (e) Synthesis of AFeNPs@CAI. (f) Map of the exhibition of mechanisms of enhanced CDT by AFeNPs@CAI. (g) Confocal fluorescence images of BCECF-stained MB231 cells treated with AFeNPs@PA and AFeNPs@CAI. Reprinted with permission from ref 33. Copyright 2019 Wiley-VCH.

oxidase (GOx) and tirapazamine (TPZ) in human serum albumin (HSA) and modified the surface with a metal polyphenol network of Fe^{3+} and tannic acid (TA), which is abbreviated as HAS-GOx-TPZ-Fe^{3+}-TA (HGTFT). H_2O_2 was produced by exogenous stimulation, and TA accelerates the valence conversion between Fe^{3+} and Fe^{2+} so as to achieve a chain reaction in tumor cells (Figure 2c).[38] The HGTFT nanoreactor demonstrates the capability to deplete glucose for starvation-based therapeutic interventions, concurrently elevating the levels of reactive oxygen species (ROS) and exacerbating hypoxic conditions within tumor microenvironments. *In vivo* investigations have additionally corroborated the potent induction of tumor apoptosis and the enhanced biodiversity associated with the HGTFT nanoreactor (Figure 2d and e).

In addition to biodegradable dendritic silica nanoparticles (DMSNs), metal organic frameworks (MOFs) have a feasible microstructure for drug loading. MOFs are interconnected by self-assembly with bridging organic ligands at inorganic metal centers (metal ions or metal clusters), forming a class of porous crystalline materials with periodic network structures. They are characterized by high porosity, large specific surface area, and adjustable pore size, as well as the rigidity of inorganic materials and ttoughness of organic materials.[39] Due to these advantages, nanosized MOFs (NMOFs) are widely applied in cancer therapy and show great potential. A cofrequency metal organic framework was synthesized by Cao's group and combined with GOx to construct a cascade enzyme/Fenton catalytic platform (Co-Fc@GOx) for enhanced tumor therapy.[40] GOx transformed glucose into gluconic acid and H_2O_2, which are both conducive to the generation of ROS through an oxidative stress reaction, resulting in cell death (Figure 3a–d).

However, tumor microenvironment is characterized by an acidic extracellular pH (6.5) and a mildly alkaline intracellular pH (7.2), providing an innate response condition for CDT.[33] Therefore, an effective method of improving the curative effect of CDT is to increase the degree of intracellular acidification to reconstruct tumor acidosis. Chen's group constructed unique amorphous iron nanoparticles (AFeNPs) loaded with carbonic anhydrase IX inhibitor (CAI).[33] CAIX, as a zinc metalloenzyme, is overexpressed in tumors and can undergo a rather slow reversible reaction that is capable of interconverting carbon dioxide and bicarbonate to maintain the acid–base

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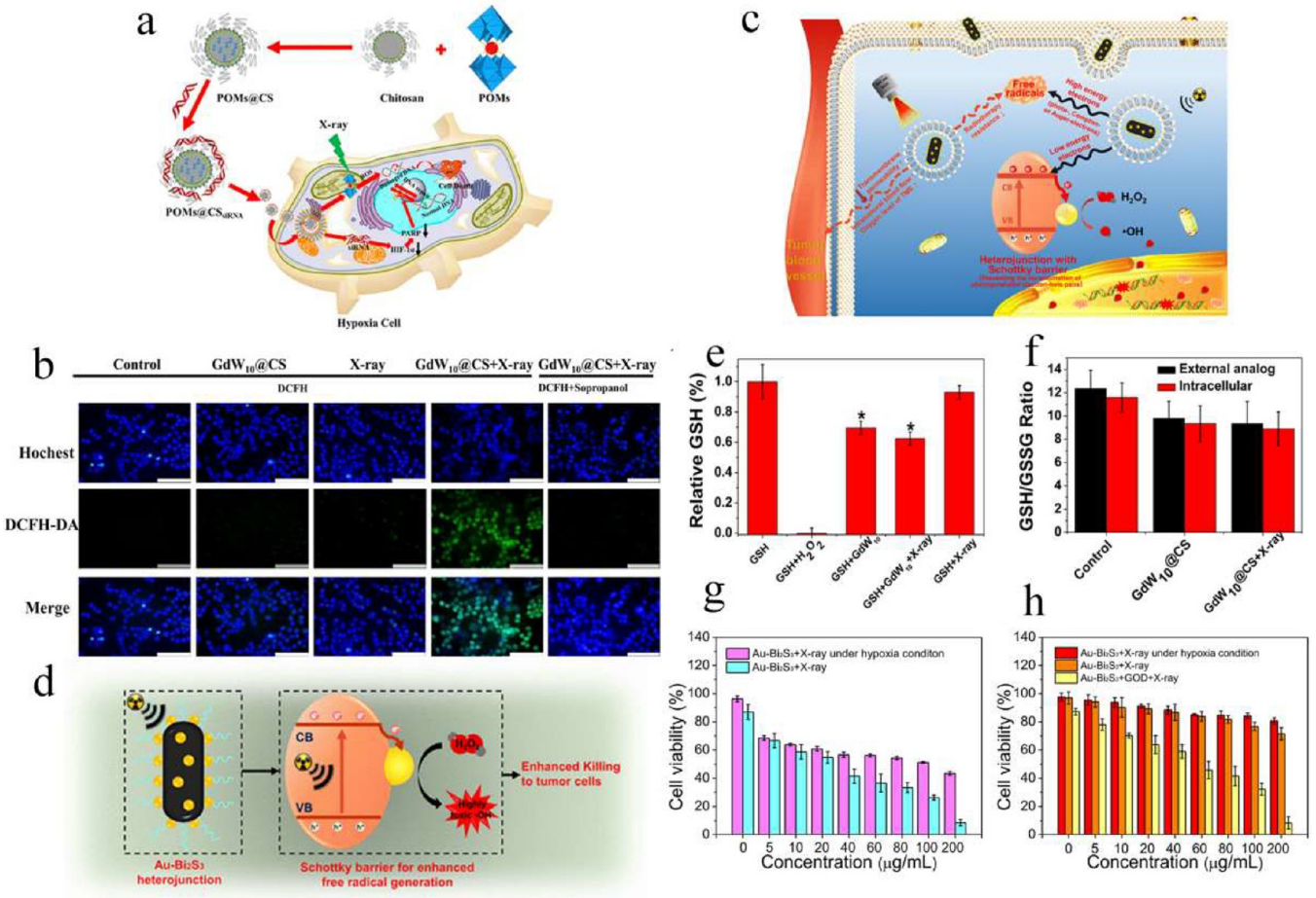

Figure 4. (a and b) Preparation and principle schematic illustration of Au−Bi2S3 HNSCs. (c) Cell viability of HeLa cells and HUVECs after treatment with the Au−Bi_2S_3 HNSCs nanomaterial. (d) The preparation process of nanosphere GdW10@CS for radiosensitizing radiotherapy to hypoxic tumor cells. (e) Cell viability of Hela cells after different treatments. (f) γ-H2AX fluorescent spot numbers after treatment with different groups. Reprinted with permission from ref 47. Copyright 2019 American Chemical Society.

balance in blood and other tissues, accelerating the invasion and metastasis of tumors. The inhibition of CAI disrupts the balance between CO_2 and HCO_3^-, resulting in the accumulation of H^+. CAI was loaded in AFeNPs to further improve the performance of CDT, which recovered the intracellular acid environment. This reconstruction of acid environment in tumor cells contributes to the optimization of CDT and furthers the development the new antitumor methods (Figure 3e−g).

Additionally, the overexpression of glutathione (GSH) in tumor cells impairs the therapeutic effect of CDT. Ma's group[41] studied fabricated two-dimensional metal−organic frameworks to enhance the induction of mitochondrial targeting. The metal−organic framework was modified with folic acid (FA) and triphenylphosphine (TPP) to enhance the induction of mitochondrial targeting. A Fenton-like reaction triggered by $Cu^{2+}$and MnO_2 in nanomaterials consumes intracellular GSH and H_2O_2 to generate highly toxic •OH, while Cu^{2+} could also undergo Russell reaction to generate cytotoxic singlet state oxygen. With the sequential targeting of FA/TPP, a highly efficient CDT effect was achieved, which also provided a strategy for the development of CDT based on polymetallic organic frameworks.

Chemodynamic therapy (CDT), which has undergone rapid development in recent years, represents one of the quintessential therapeutic modalities for tumors. The above discussion of CDT is mainly about nanomaterials that utilize the EPR effect of a tumor based on the activity of one kind of enzyme to produce toxic substances through endogenous stimulation. Presently, a novel class of nanoscale metallic glass has been discovered to possess notable attributes, such as high thermal stability and electromagnetic characteristics. This material exhibits a propensity for rapid accumulation within tumor sites and facilitates prompt material ionization, thereby augmenting the efficacy of CDT through its disordered atomic arrangement.[36] Merely capitalizing on the EPR effect of tumors is deemed insufficient, thus necessitating the development and design of novel nanomaterials to further enhance therapeutic specificity.

Furthermore, to advance the anticancer effectiveness of chemodynamic therapy (CDT) and facilitate its translation into clinical practice, it is imperative to explore strategies for maximizing the exploitation of the tumor microenvironment. Such endeavors aim to optimize catalytic efficiency and enhance tumor targeting while minimizing collateral damage to normal tissues, thereby advancing the overarching objective of tumor treatment.

2.2. Nanozymes in Radiation therapy (RT). As one of the three major antitumor treatments, radiation therapy (RT) kills tumor cells though DNA damage and ROS generation caused by the high-energy X-ray or γ-ray.[42] However, the high

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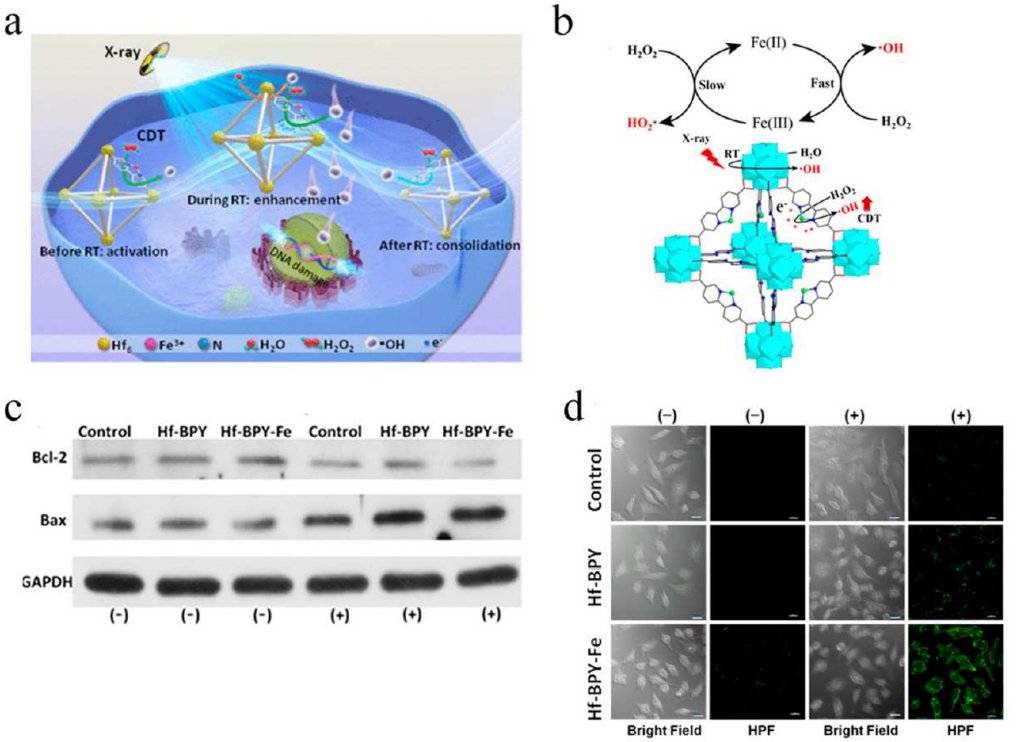

Figure 5. (a and b) Schematic illustration of the interaction between Hf-BPY-Fe in radiosensitization and the Fenton reaction. (c) Expression of Bcl-2 and Bax after different treatments. (d) Immunofluorescent staining of DNA double-strand breaks. Reprinted with permission from ref 49. Copyright 2017 American Chemical society.

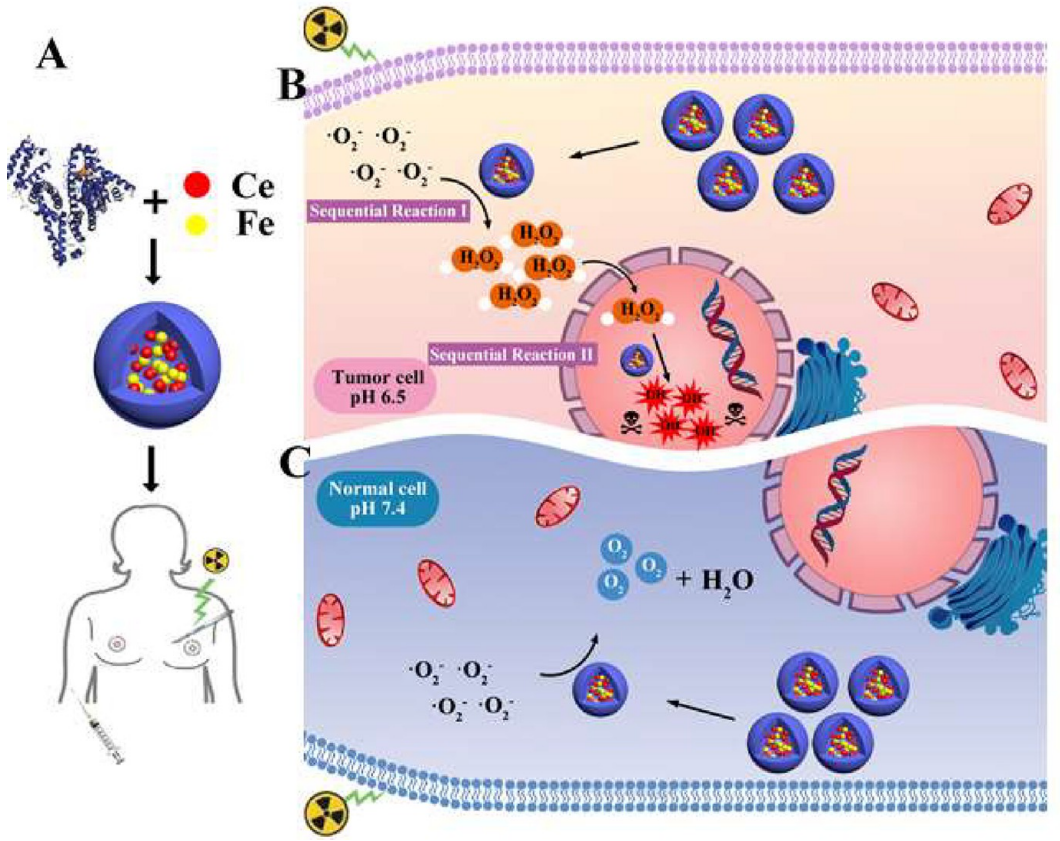

Figure 6. A mechanical explanation of nanozymes for radiosensitivity and radioprotection. Reprinted with permission from ref 52. Copyright 2022 Royal Society of Chemistry.

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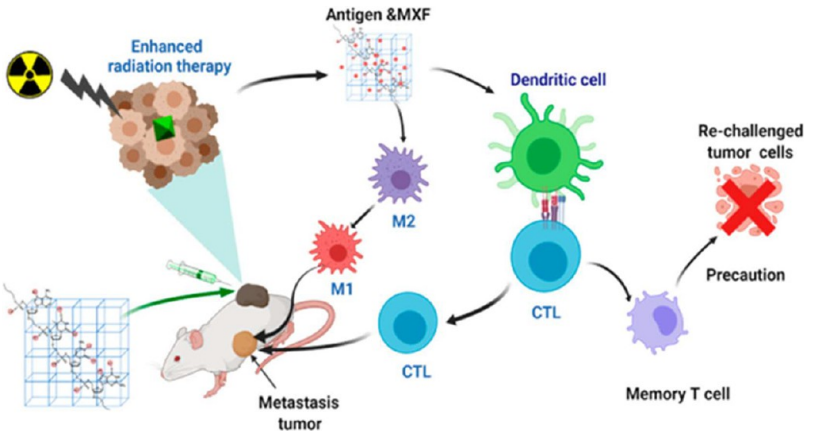

Figure 7. Mechanisms of radiotherapy-induced antitumor immune responses. Reprinted with permission from ref 53. Copyright 2016 Springer.

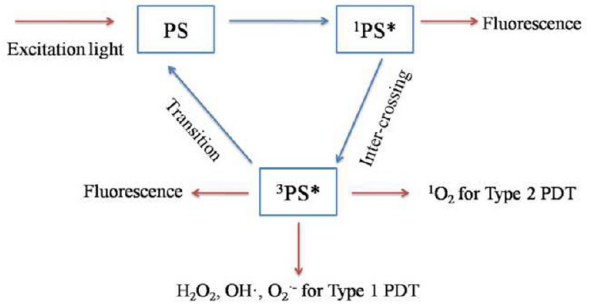

Figure 8. Photodynamic reaction mechanisms of PDT. Reprinted with permission from ref 57. Copyright 2020 Wiley-VCH.

level of radiation can also result in damage to normal tissues, which limits the development of radiotherapy.[43]

In order to improve the efficiency of radiotherapy and reduce damage to normal tissues, the development of new methods has attracted wide attention. One of the main strategies is to combine a radiosensitizer with radiotherapy, which can make tumor cells more sensitive to radiotherapy.[44] Traditional chemosensitizers mainly include renal inhibitors, oxygen utilization inhibitors, and electrophilic radiosensitizers, although they lack targeting activity. Hence, nanomaterials are preferred carriers of chemosensitizers and therapeutics due to their favorable physicochemical properties, simple and green preparation, and good stability both *in vivo* and *in vitro*.[45]

Recently, studies are increasingly developed on the application of nanoparticles in radiation sensitization.[46]

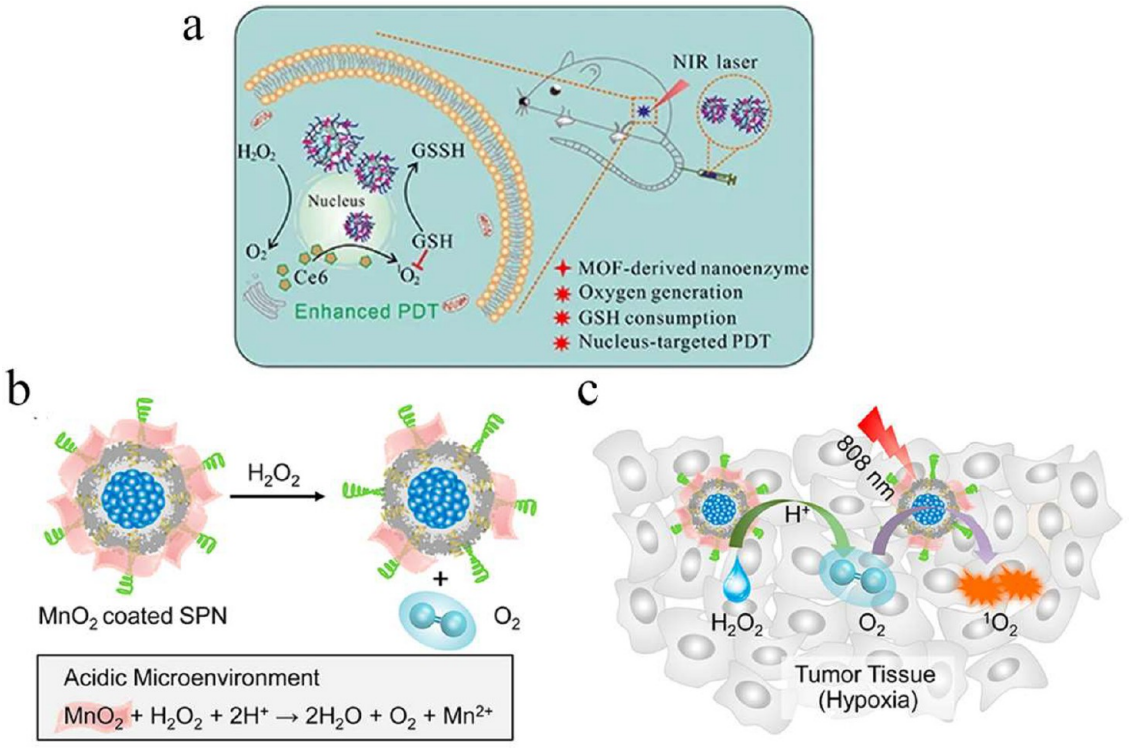

Figure 9. (a) The reaction mechanism of Mn_3O_4-PEG@C&A nanomaterials. Reprinted with permission from ref 59. Copyright 2019 Springer. (b and c) The reaction mechanism of nanomaterials and the whole process in which nanomaterials play a role under acidic and hypoxic conditions. Reprinted with permission from ref 62. Copyright 2018 American Chemical Society.

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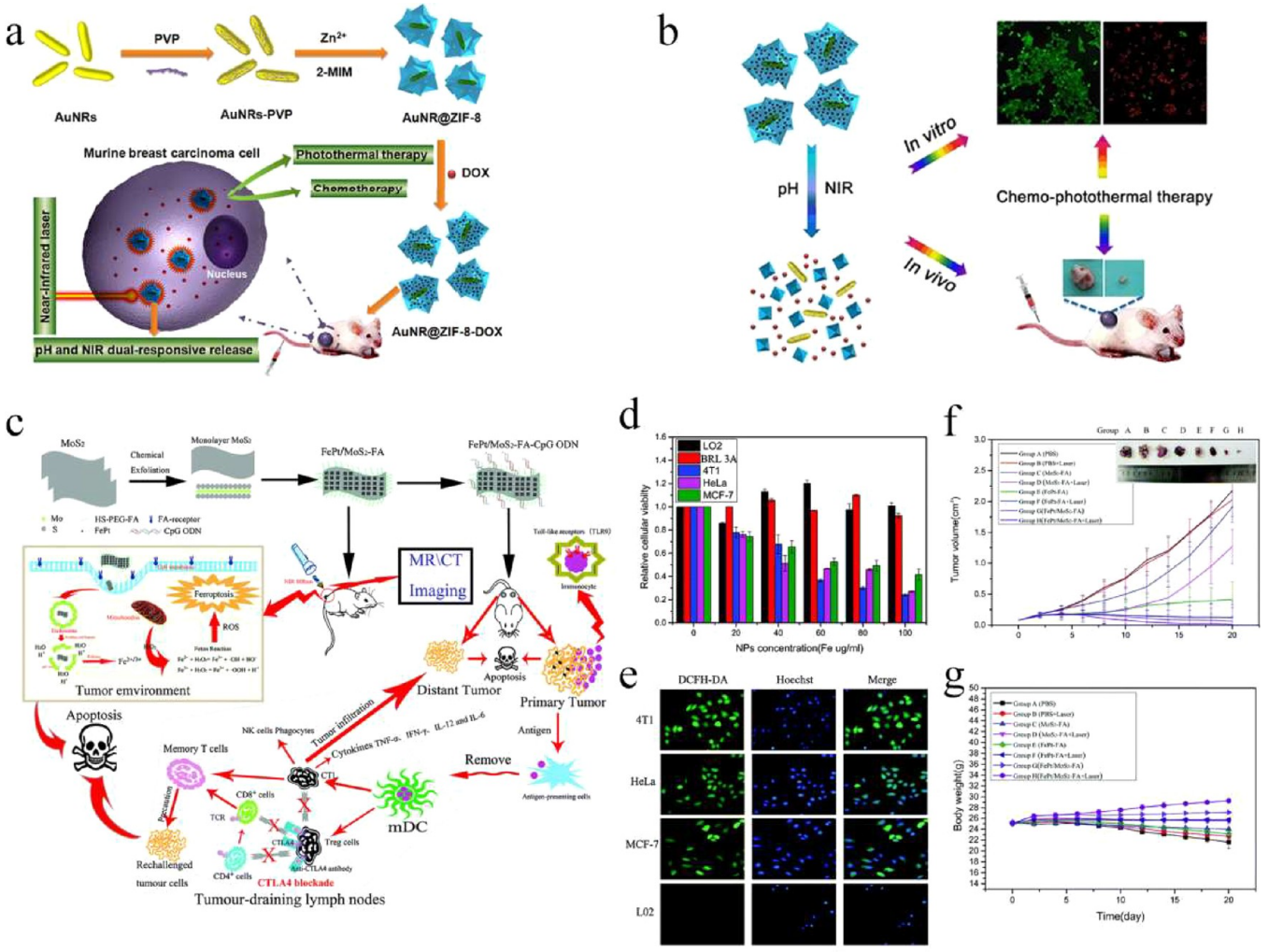

Figure 10. (a and b) Construction and mechanism of a novel multifunctional nanoplatform AuNR@ZIF-8. Reprinted with permission from ref 64. Copyright 2018 Springer. (c) Scheme of the catalytic-therapeutic mechanism of FePt/MoS_2-FA nanocomposites. (d) Viabilities of different cell lines after treatment with different concentration of FPMF NPs for 8 h. (e) Fluorescence microscopy images of DCFH-DA-labeled 4T1, Hela, MCF-7, and L-02 cells. (f) The tumor growth curves changes of mice during treatments. (g) Body weight changes of mice during treatments. Reprinted with permission from ref 65. Copyright 2019 Royal Society of Chemistry.

When nanoparticles loaded with metal elements with high atomic numbers are introduced into tumor tissue and irradiated by high-energy radiation, a variety of effects (such as the photoelectric effect and Compton effect) will occur.[11] Therefore, researchers utilize nanomaterials with high-atomic-number metal elements such as gold, bismuth, tantalum, and other rare earth elements as sensitizers to enhance the effect of RT. Wang's group identified a novel Schottky-type heterostructure consisting of metallic Au and bismuth sulfide (Bi_2S_3). The hypoxic conditions within tumor environments typically diminish the efficacy of radiation therapy. However, the engineered structure significantly enhances X-ray utilization in oxygen-deprived settings, leading to the generation of oxygen-independent reactive oxygen radicals. Furthermore, electrons would be generated under X-ray irradiation and gathered in Au to form empty electron pairs for Bi_2S_3 pairing with excess H_2O_2 in tumor cells (Figure 4a–h).[47]

Additionally, in tumor therapy, excessive GSH in tumor cells weaken the therapeutic effect of ROS produced by radiotherapy, so the consumption of GSH is a crucial factor to inhibit tumor growth.[48] Yong et al. applied a simple ionotropic gelation technique to prepare GdW_{10}@CS that can be developed as HIF-1 α siRNA nanocarrier.[49] In the presence of X-ray, GdW10@CS downregulated the expression of HIF-1α siRNA, and reduced the production of PARP by inhibiting DNA fragmentation repair. Moreover, GdW10@CS triggered the oxidation of GSH to produce more ROS, thus significantly improving the efficiency of radiotherapy (Figure 5a and b).

However, the insufficient accumulation of nanoparticles at the tumor site results in unsatisfactory therapeutic efficacy, and scientists are urgently seeking novel methods to improve tumor accumulation as well as therapeutic efficacy through cascading reactions. The emergence of hafnium-based nanoscale metal–organic frameworks (Hf-nMOFs) provides a new idea for the research institute, which is a kind of hybrid material composed of Hf^{4+} and organic bridging ligands. This organic framework structure possesses unique characteristics of X-ray energy absorption and conversion capability.[50] In 2020, Gong's group constructed Hf-BPY-Fe with Fe^{3+} and Hf-nMOFs to improve the effect of radiotherapy through a multilevel mechanism, and Fe^{3+} can induce an intracellular Fenton reaction leading to continuous ROS stress.[51] X-ray is sensitive to cells in the G2/M phase, and the increase of ROS reduces the proliferation rate of cancer cells and hinders the

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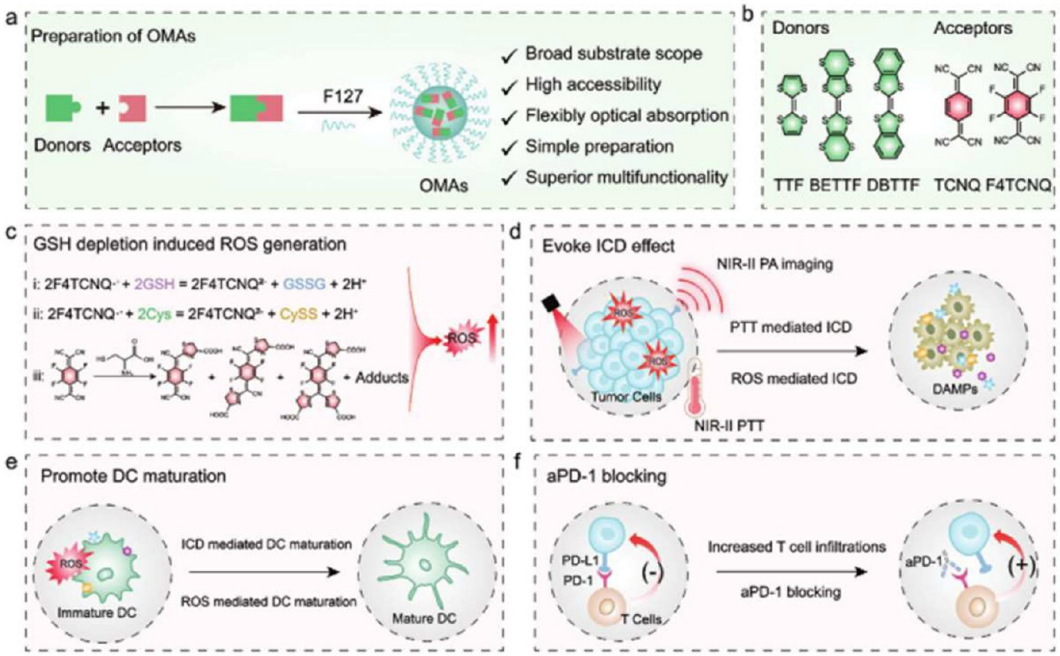

Figure 11. Schematic diagram of organometallic-nanoadjuvant-mediated NIR-II photothermal immunotherapy. Reprinted with permission from ref 66. Copyright 2022 Wiley-VCH.

cell cycle in the G2/M phase, which greatly improves the apoptosis of cancer cells. During RT irradiation, Hf-BPY-Fe activated the sustained ROS froemd by the *in situ* Fenton reaction, resulting in the increased sensitivity of the tumor to photon radiation. Hf^{4+} in Hf-BPY-Fe produced a large number of electrons to convert H_2O into •OH. At the same time, these aggregated electrons converted Fe^{3+} to Fe^{2+} and further promoted the generation of •OH in the process of the Fenton reaction (Figure 5). The synergistic treatment of CDT and RT improved the limitations of chemokinetic therapy and enhanced the sensitivity of cancer cells to X-ray in radiotherapy, which provided a reliable direction to achieve the synergistic treatment in our later stage.

Long-term radiation therapy causes side effects in healthy tissue and needs to be combined with other treatments to produce a synergistic effect. In our previous study, we developed an ultrasmall bionic multifunctional nanozyme (BSA@CNPs/Fe^{2+}) that combined the dual functions of radiation sensitization and radiation protection against breast cancer[52] (Figure 6). BSA@CNPs/Fe^{2+} effectively converted superoxide produced by ionizing radiation into H_2O_2 under an acidic tumor environment, while the produced H_2O_2 could be catalyzed by an incorporated Fe^{2+}-mediated Fenton reaction to produce highly toxic hydroxyl radicals to induce cell death. In normal tissues, it converted a superoxide anion into water and oxygen to reduce the production of reactive oxygen species and minimize the damage for normal tissues. Meanwhile, multifunctional BSA@CeO/Fe^{2+} exhibited superior biocompatibility and safety *in vitro* and *in vivo*.

Yang's group developed metal "X" frameworks (MXFs) with crystalline structures and various functions formed via coordination interactions between metal ions and biomacromolecules ("X components").[52] Composed of Hf^{4+} and CpG oligodeoxynucleotides, Hf-CpG MXF performed high Z element enhanced photon irradiation as well as activated powerful tumor-specific immune responses, demonstrating effective tumor suppression capabilities (Figure 7)

2.3. Nanozymes in Phototherapy. Photodynamic therapy (PDT) and photothermal therapy (PTT), collectively known as light therapy, have been broadly applied in the treatment of malignant cancers.[53] PDT means that photosensitizers (PSs) are excited under the irradiation of specific wavelength to produce large amounts of ROS to kill target cells.[54,55] PTT utilizes materials with high photothermal conversion efficiencies to convert light energy into heat energy to kill tumor cells upon irradiation by an external light source such as NIR light.[56]

2.3.1. Nanozymes in Photodynamic Therapy (PDT). Photosensitizer, oxygen, and light are three key factors in photodynamic therapy. The photosensitizer can be irradiated by laser to interact with molecular oxygen.[49] Due to the high reactivity and short lifetime of ROS, only the molecules and structures near the PS localization region can be destroyed by PDT (Figure 8).[57]

A novel PDT mode for deep tumor treatment combining nanomaterials with traditional PS is being developed to overcome those shortcomings.[58] In 2019, Zeng's group first reported the application of MOF-derived nanoparticles in nucleus-targeted PDT.[59] They fabricated a novel nanozymes (Mn_3O_4-PEG@C&A) with the ability of catalase. Due to their larger pore size compared to natural MOF particles, more photosensitizers were encapsulated. In addition, Mn_3O_4-PEG@C&A can decompose H_2O_2 to O_2 via nuclear targeting and simultaneously consume GSH to improve the efficacy of photodynamic therapy, resulting in significant tumor inhibition *in vivo* (Figure 9a).

Photodynamic therapy, radiotherapy or other treatments are all inseparable from oxygen, but the tumor microenvironment often presents as hypoxic, which greatly reduces the efficacy of treatments.[60,61] Therefore, it is necessary to combine photodynamic therapy, imaging, and photodynamic nanodissection

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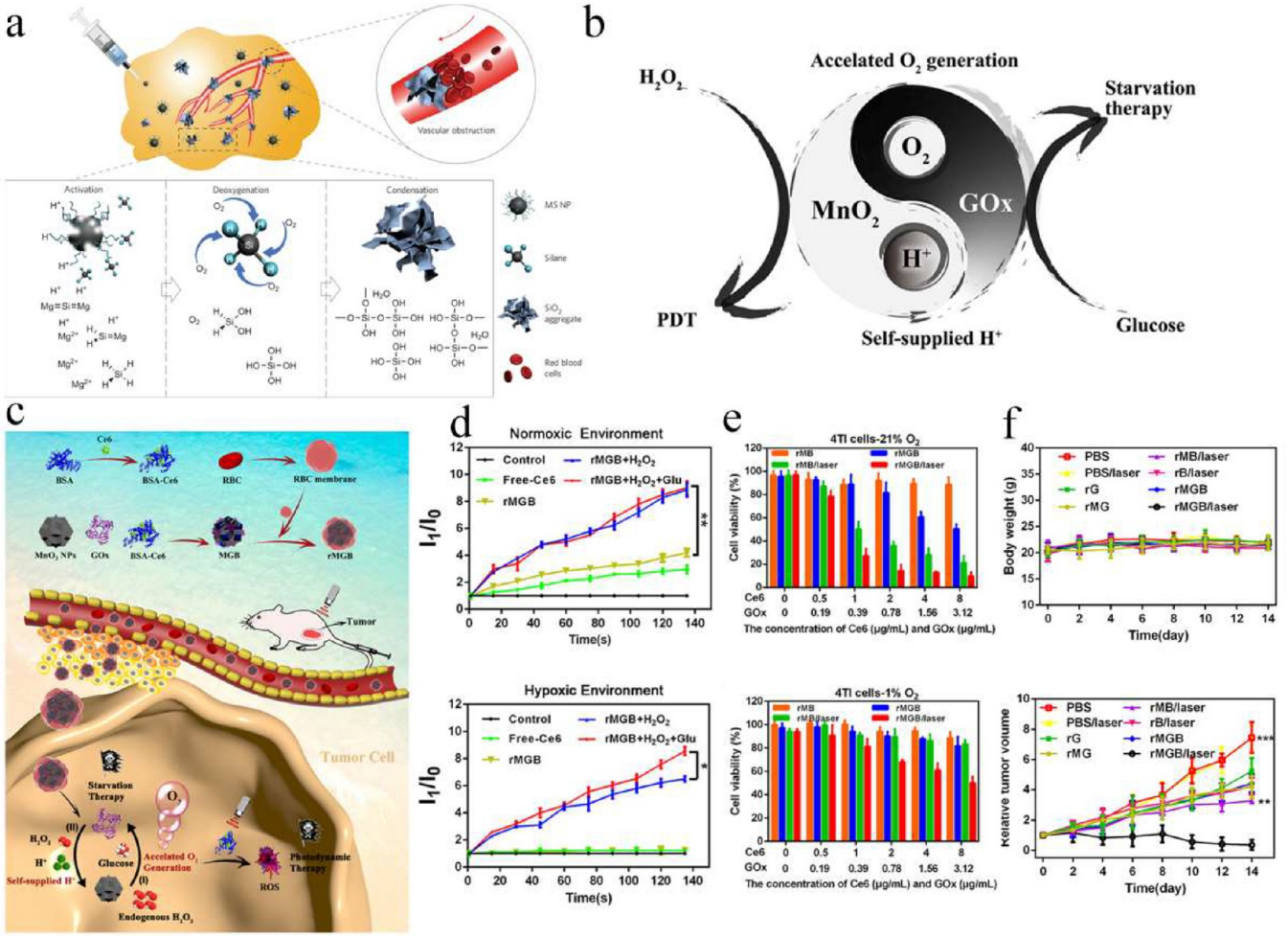

Figure 12. (a) Mechanism of Mg_2Si NPs for cancer-starving therapy. (b and c) Schematic diagram of the reaction mechanism of biomimetic hybrid nanozymes rMGB. Reprinted with permission from ref 72. Copyright 2017 Nature. (d) Different samples after irradiation in normoxic environment and hypoxic environment. (e) The survival of 4T1 cells with different nanostructured materials by MTT assay. (f) Tumor growth curves and mouse body weights in 14 days of different treatments. Reprinted with permission from ref 73. Copyright 2019 American Chemical Society.

to improve the therapeutic efficacy. Last year, a group at Nanyang Technological University[62] discovered hybrid core−shell semiconducting nanoparticles (SPN-Ms) that can undergo O_2 transformation in hypoxic tumor. They reported the utilization of an inorganic shell formed by an organic photoelectric semiconductor polymer SPN core and manganese dioxide (MnO_2), followed by high NIR absorption of a conformational agent and photosensitizer poly(cyclopentadithiene-*o*-benzothiazole) (PCPDTBT) encapsulated into the shell to form the core. In the acidic tumor microenvironment, MnO_2 in its outer shell reacts with H_2O_2 to provide O_2 for PDT. Irradiating the tumor site with a specific wavelength, the photosensitizer transfers the energy to the surrounding oxygen, generating the highly active singlet oxygen. Singlet oxygen undergoes an oxidative reaction with nearby biomacromolecules, leading to cell damage (Figure 9b and c).

2.3.2. Nanozymes in Photothermal Therapy (PTT). Based on the characteristics of the tumor microenvironment (TME), including acidity, hypoxia, inflammation, and hydrogen peroxide overload, combined with emerging nanotechnology, designing nanoplatforms with TME specificity/responsiveness for tumor treatment is a promising nanotherapy strategy. Nanoenzymes containing gold ions are used for effective photothermally enhanced cascade catalytic synergistic therapy of tumors.[63]

In photothermal therapy, photothermal agents are indispensable as they absorb light energy to generate localized hyperthermia, leading to apoptosis or necrosis to realize effective tumor ablation.[57] However, the therapeutic effect of single photothermal therapy is unsatisfactory, and there are many cases reports of photothermal therapy combined with other therapies to improve the therapeutic effect. Li et al.[64] constructed a core−shell nanostructure (AuNR@ZIF-8), which combined photothermal therapy and photodynamic therapy (Figure 10a and b). They introduced a crystalline zeolitic imidazolate framework-8 (ZIF-8) as a support to interact with single gold nanorods (AuNRs), forming a pore structure to encapsulate DOX. In the formation and breaking of coordination bonds, a high drug loading of doxorubicin hydrochloride (DOX) was achieved. DOX was released under dual-stimulation of low pH and NIR light. Compared with chemotherapy alone, AuNR@ZIF-8 reduced toxicity to normal tissues, improved specificity toward tumor sites, eliminated the primary tumor, and prevented tumor recurrence.

Zhang's group[65] introduced multifunctional nanoparticles with MoS_2 nanosheets, which can efficiently convert light energy into heat energy. Folic acid (FA) and FePt nano-

https://doi.org/10.1021/acsomega.4c00258
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particles were attached to MoS_2. FA endowed the nanomaterials with the ability to target tumor cells, and MoS_2 nanosheets catalyzed the Fenton reaction to generate ROS. In addition, the combination of cytosine guanine oligodeoxynucleotides (CpG ODNs), antibodies against CTLA4 and systemic checkpoint blockade therapy produced a strong immunological memory effect and effectively eliminated tumor metastasis (Figure 10c−g).

The latest research shows that PTT can not only cause damage to tumor tissue but also stimulate immune function by inducing tumor cell immunogenic cell death (ICD). However, the low immunogenicity and immune response of tumor cells limit the efficacy of PTT. Consequently, the combination of PTT and immunotherapy may achieve synergistic antitumor effects. Zhu's group achieved supramolecular assembly by regulating different electron acceptors and electron donors to obtain organometallic nanoparticles (OMAs) with the capability of NIR-II photothermal and photoacoustic imaging (Figure 11). In addition, OMAs oxidized glutathione and cysteine, which hindered the synthesis of GSH, and further disturbed the balance between GSH and ROS, resulting in the accumulation of intracellular ROS.[66] Through the synergistic therapy of GSH depletion and NIR-II photothermal therapy, OMAs not only promoted the ICD effect and enhanced the immunogenicity of tumor cells but also promoted the maturation of dendritic cells and increased the infiltration of T cells. Moreover, cooperating with immune checkpoint inhibitor (aPD-1) effectively cleared the *in situ* tumor, further inhibited the distal tumor, and produced an effective photothermal and immunotherapy effect. This concept not only provides a successful strategy for improving photothermal immunotherapy efficacy but also directs the creation of organometallic libraries to fulfill the varied demands in tumor therapy.

As photocatalytic therapeutic modalities, the basic factors of catalytic reaction of PTT and PDT have been utilized to adjust the design of various nanoparticles in cancer therapy. It is expected that the discovery of photocatalysis will contribute to the further development of PDT in clinical application.

2.4. Nanozymes in Tumor-Starving Therapy. In the clinic, PDT, RT and CDT are major treatments, but they are highly oxygen-dependent.[67,68] However, the hypoxic environment of most solid tumors promotes the proliferation and metastasis of cancer cells, leading to poor therapeutic effect.[69,70] Hence, tumor starvation therapy is a potential adjuvant therapy to inhibit tumor growth by consuming oxygen and nutrition in tumor.[71]

In 2017, Zhang[72] reported an injectable Mg_2Si nanoparticle modified with polyvinylpyrrolidone (PVP) to achieve specific tumor starvation treatment (Figure 12a and b). As the equation indicated, SiH4 was obtained by Mg_2Si in the acidic tumor microenvironment and subsequently reacted with oxygen to generate insoluble SiO_2. SiO_2 blocks the capillaries of the tumor, thus cutting off the supply of oxygen and nutrition to the tumor and achieving the goal of "starving cancer cells".

$$Mg_2Si + 4H^+ \rightarrow 2Mg^{2+} + SiH_4(\text{dissolved}) \quad (1)$$

$$SiH_4 + 2O^{2-} \rightarrow 2H_2O + SiO_2 \quad (2)$$

However, this kind of material should be biocompatible and possess the characteristics of great deoxidation efficiency, long-range deoxidation, and tumor-targeting. In 2019, Yang[73] developed a novel biomimetic hybrid nanozyme (rMGB), which integrates the characteristics of nanozymes MnO_2 and natural enzyme GOx. As shown in Figure 9, under the hypoxic tumor environment, MnO_2 reacts with endogenous H_2O_2 to generate O_2, which improves the enzymatic activity of GOx for accelerating the consumption of glucose. On the other hand, GOx oxidizes glucose into gluconic acid, providing an acidic environment for the catalysis of MnO_2, and further accelerates the generation of O_2. In a word, rMGB utilizes the mutual promotion of nanozymes and natural enzymes to realize self-supplying H^+ and O_2 generation, alleviates tumor hypoxia, and exhibits great antitumor effects *in vitro* and *in vivo*. Thanks to the erythrocyte membrane coating, rMGB exhibits long blood circulation and excellent biodiversity. This biomimetic hybrid nanozymes may be a potential oxygen donor for hypoxic tumor therapy and provides an innovative design guide for developing catalytic nanomedicines for cancer therapy (Figure 12d−f).

3. SUMMARY AND OUTLOOK

Nanozymes combine the advantages of nanomaterials and natural enzymes, such as simple preparation, high catalytic efficiency, and good stability, and are considered as a potential method for cancer treatment. Furthermore, the specific ability of nanomaterials to respond to endogenous or exogenous physical and chemical stimulation improves the therapeutic efficiency and decreases side effects.

During the development of nanocatalytic medicine, ROS are one of the key factors in nanomedicine therapy. Nanomaterials are utilized to catalyze intracellular oxygen or oxygen molecules to generate excessive ROS to induce cells apoptosis. At present, the applications of nanozymes in biomedicine mainly focus on the simulation of catalase, peroxidase, and oxidase. A variety of nanocatalytic drugs that have unique responses to endogenous or exogenous physical stimuli, such as sensitizers, photosensitizers, and photothermal agents, are applied to activate or assist the generation of ROS for a high level of activity.

Despite the great progress nanozymes have made in cancer treatments, deficiencies still urgently need to be resolved, such as biocompatibility and toxicity. First, while the catalytic impact of nanozymes has been shown to improve tumor treatment efficacy, several difficulties remain, such as the potential toxicity of nanomaterials and their ease of clearance by the immune system, resulting in poor tumor targeting. As a result, cell membranes can be used as natural biomaterials with unique biological characteristics, such as good biocompatibility, strong targeting ability, ability to evade immune surveillance, and high drug loading capacity, thus improving the targeting ability of nanozymes and further enhancing the therapeutic effect of tumors.[74] Second, it is crucial to address issues related to biocompatibility and potential toxicity associated with *in vivo* use. Understanding the long-term effects of nanozyme exposure on healthy tissues and organs is beneficial for successful clinical translation. Finally, as most of the nanozymes are inorganic materials, the degradation of materials should be considered. Furthermore, the kinds of nanozymes are plain, with most utilizing the activity of catalase, and the design of nanozyme systems with other catalytic activities holds great potential. In addition, most of the current treatments depend on oxygen, so the development of nanomedicines will move a new direction for the treatment of hypoxic tumors.

https://doi.org/10.1021/acsomega.4c00258
ACS Omega 2024, 9, 15753−15767

Although significant progress has been made in the research of nanozymes, there is still great room for advancement in future research. Breakthroughs in nanozyme technology can be made from the following aspects, bringing about a new wave of widespread applications for new biocatalysts.

(1) Imaging and diagnosis: Nanoenzymes can serve as imaging agents for detecting cancer and monitoring treatment responses. Studying their potential in diagnostic applications such as tumor imaging and biomarker detection can significantly broaden their application in the field of oncology.[75]
(2) Collaborative therapy: Exploring the synergistic effects of combining nanozyme-based therapies with traditional therapies such as chemotherapy, immunotherapy, or targeted therapy can reveal new therapeutic strategies to improve efficacy and reduce side effects.[76]
(3) Clinical translation: Although preclinical studies have demonstrated the potential of nanozymes in cancer treatment, bringing these discoveries into clinical practice presents significant obstacles. Addressing regulatory and safety concerns, as well as streamlining manufacturing processes, is critical to accelerating clinical translation. The pursuit of this objective mandates a thorough and comprehensive research endeavor.

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Funding

This work was supported by the National Natural ScienceFoundation of China (no. 82003305) and the National Natural Science Foundation Youth Cultivation Project of Nanjing Drum Tower Hospital (2022-JCYJ-QP-73).

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank the Jiangsu Chia Tai Fenghai Pharmaceutical Co. Ltd.

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https://doi.org/10.1021/acsomega.4c00258
ACS Omega 2024, 9, 15753−15767