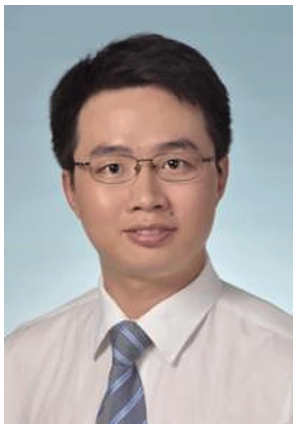
PIBB 生物化学与生物物理进展
Progress in Biochemistry and Biophysics
2018, 45(2): 237~255
www.pibb.ac.cn



陈雨，中国科学院上海硅酸盐研究所研究员，博士生导师．陈雨于2012年博士毕业于中国科学院上海硅酸盐研究所．他的研究方向是设计和合成纳米生物医用材料，用于多种疾病的诊断和治疗．研究方向涉及的材料体系有介孔氧化硅/介孔有机硅纳米颗粒，二维层状材料(石墨烯、金属氧化物、过渡金属硫化物、MXene等)和三维植入材料．这些材料用于药物输运、分子成像探针、超声治疗、声动力学治疗、心脏治疗、非病毒基因载体和原位局部肿瘤治疗等．陈雨共发表论文120余篇，论文被引用6 700余次(H因子：43)．

施剑林，中国科学院上海硅酸盐研究所研究员，博士生导师．施剑林博士毕业于中国科学院上海硅酸盐研究所．他的研究方向是设计和合成介孔材料和介孔复合材料，以及探索在催化、生物医学和光学领域中的应用．他共发表学术论文超过450篇，论文被引用24 000余次，H因子为84(2017)．施剑林主持了超过30个国家、省部级项目，并获得了多个国家和省部级的奖励．

Nanozymes in Catalytic Cancer Theranostics*

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Abstract As a special cross-discplinary research frontier, nanozyme, which is capable of accomplishing desirable enzyme-mimicking catalytic performance based on nanomaterials, has attracted great attentions from the scientific community in recent years. The research on nanozyme is becoming a rapidly emerging field since magnetic nanoparticles with intrinsic peroxidase-like activity was first reported in 2007. The unique physicochemical properties of nanozymes at nano-level endow them with excellent catalytic performance for various applications, such as cancer theranostics. In this review, we highlight the recent developments of catalytic chemistry in advancing the development of nanomedicine for diverse nanozyme-based oncological applications, and the current challenges and future developments of nanozymes are also discussed for their further clinical translations. It is highly expected that this novel nanozyme and corresponding high catalytic performance in cancer imaging and therapy would significantly promote the generation of new subdiscipline of nanomedicine by rationally integrating catalytic chemistry with clinical theranostic nanomedicine.

Key words nanozyme, cancer, theranostics, catalyse, nanomedicine
DOI: 10.16476/j.pibb.2017.0466

* This work was supported by grants from The National Key R&D Program of China (2016YFA0203700), The National Natural Science Foundation of China (51722211, 51672303) and Young Elite Scientist Sponsorship Program by CAST (2015QNRC001).
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Received: December 15, 2017 Accepted: January 9, 2018

All the life activities existing in nature is related to enzymes. Natural enzymes are unique biocatalysts which play their vital roles in the biological reactions in living systems, such as glucose oxidase (GOD). Featuring with remarkable efficiency and extraordinary specificity at mild conditions for catalysis of reactions, natural enzymes have been extensively explored by scientists for various applications beyond living systems. However, on account of intrinsic drawbacks of natural enzymes, such as ease of denaturation, laborious preparation, high cost, and difficulty of recycling, practical applications of natural enzymes still encounter difficulties, underscoring the need to re-consider proper enzymes to satisfy the stringent requirements of applications, such as industrial and biomedical uses.

Nature has provided much inspiration for scientists to achieve desirable physiochemical performances by creating interesting and useful structures [1–4]. As an important branch of biomimetic chemistry inspired by nature, artificial enzymes imitate the essential and general principles of natural enzymes using alternative materials to accomplish specific catalytic functions [5–8]. The past few decades have witnessed the establishment and development of abundant artificial enzymes as highly stable and low-cost alternatives to natural enzymes in a wide range of applications in multiple fields, such as metal complexes, antibodies, cyclodextrins, polymers, etc[9–13]. The publication of numerous excellent reviews and even several monographs on the topic, have evidenced enormous progress made in the field of artificial enzymes.

The emergence of nanotechnology has provided an unprecedented opportunity to create more reasonable fabrication methodologies for proper preparation of artificial enzymes [14–16]. Armed with the remarkable achievements made in the field of nanotechnology, varieties of functional nanomaterials, which are capable of accomplishing desirable enzyme-mimicking catalytic performance, have been discovered or synthesized extensively [17–19]. This category of functional nanomaterials was firstly termed as “nanozymes” in 2004 by Pasquato, Scrimin, and their coworkers [20] to investigate the gold nanoparticle-based transphosphorylation mimics. The unique physicochemical characteristics of nanozymes at nano-level, such as ultrasmall particle/lateral size, tunable catalytic activities, large surface area, multiple functions besides catalysis and smart response to external stimuli, have endowed them with excellent catalytic performance for various applications, such as biomedical applications to build better therapeutic platforms for pathological abnormalities. On account of the high lethality of cancer all over the world [21–22], the oncological applications of nanozymes have captured extensive attention from scientists and several types of nanozyme have successfully been exploited for cancer diagnosis and treatment, which is evidenced by the exponential number of publications in the past few years[23–33].

Nanozymes for oncological applications have gradually become a newly-emerging field which makes use of fundamental advances in nanobiotechnology to diagnose, characterize and manage cancer in a nano-catalytic way. However, a more comprehensive understanding of the interdependent relationship between different theranostic modalities, relevant biological systems and physical properties governing nanoscale interactions, which guides the rational design and fabrication of next-generation nanozymes, is supposed to be clarified to deepen the connotations of catalytic nanotherapy. In this review, we systematically summarize the recent progress on contemporarily available nanozymes (*e.g.*, Fe_3O_4, MnO_2 and Prussian Blue) for multiple biomedical applications of cancer theranostics (*e.g.*, diagnostic imaging, radiotherapy, photodynamic therapy, and chemodynamic therapy) by catalytic reactions to accomplish the desirable therapeutic outcomes(Figure 1). In the following parts, nanozymes are discussed based on the specific theranostic functions that have been discovered or developed by scientists, rather than nanomaterials or the natural enzymes which they mimic because many nanomaterials have exhibited multiple enzyme-mimicking activities. We have, for the first time, focused on combination of the enzyme-mimicking activities and catalytic mechanisms of nanozymes with their biomedical applications for catalytic cancer theranostics. In the last two parts, we discuss the biosafety and prospects of nanozyme to fulfill its great oncological potentials.

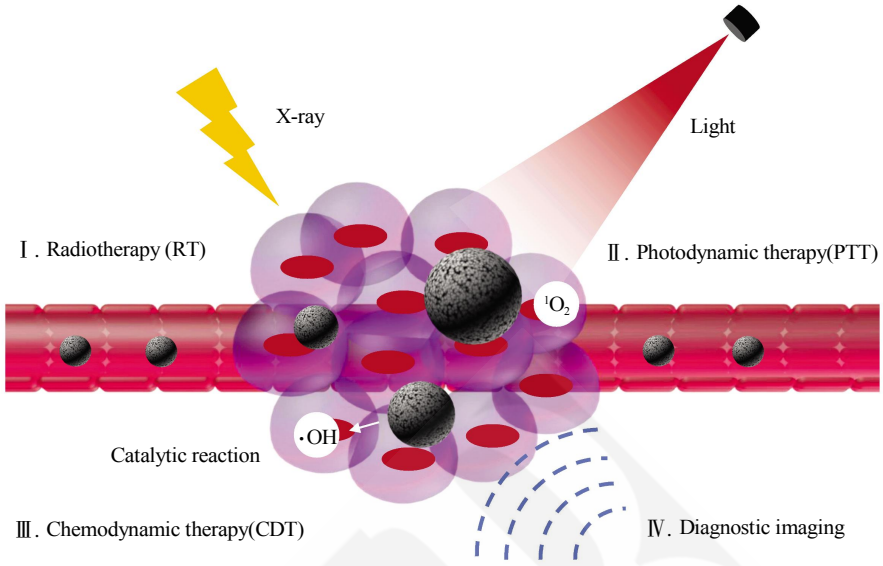

Fig. 1 Schematic illustration of multifunctional nanozyme for multiple biomedical applications of catalytic cancer theranostics

1 Nanozyme for diagnostic imaging

Recent advances in conventional diagnostic modalities provide reasonable strategies to identify certain diseases at earlier stages, or guide the therapeutic process for a more precise control of the spatiotemporal exposure of therapeutic drug and the delivery of appropriate drug ratio to the target of interest[34-45]. The research on nanozyme is becoming a rapidly emerging field since ferromagnetic nanoparticles with intrinsic peroxidase-like activity was first reported in 2007 by Prof. Yan and her co-workers[46]. They had successfully demonstrated that iron oxide nanoparticles can catalyse the oxidation of peroxidase substrates in the presence of hydrogen peroxide to produce a colour reaction similar to that of natural peroxidases. Based on the current experimental results, they discovered that, magnetoferritin (M-HFn) nanoparticles generated by encapsulating iron oxide nanoparticles inside a HFn shell, are capable of targeting TfR1 without any additional recognition ligands on their surface, and visualizing tumour tissues through the peroxidase activity of the iron oxide core (Figure 2)[47].

Histological staining experiments in xenograft tumors were conducted to evaluate the diagnostic performance of the M-HFn nanoparticle. FITC-conjugated HFn displayed strong fluorescence staining both in HT-29, SKOV-3 and SMMC-7721 xenograft tumours (top), evidencing the tumor binding capability of the HFn protein. For comparison, M-HFn nanoparticles showed an intensive brown peroxidase activity that visualized the tumor cells after adding DAB substrate and H_2O_2 (middle), demonstrating the excellent capability of M-HFn nanoparticle for cancer diagnostics. Moreover, the binding specificity and staining quality of M-HFn nanoparticle were also investigated by comparing with traditional immunohistochemical staining using anti-TfR1 antibodies. The intensity and the pattern of the two staining were almost the same, demonstrating the specificity and accuracy of the M-HFn nanoparticles for next-generation tumor imaging.

Selective imaging in early progression stages of tumor remains a key requirement for highly efficient cancer theranostics. As a noninvasive technique with high spatial resolution, magnetic resonance (MR) imaging plays a key role in modern clinical cancer diagnostics. Abundant MR contrast agents, such as Gd- or Mn-based nanomaterials [48-54], have been developed to enhance the MR signal in the mild acidic and reducing microenvironment of tumor. However, the MR contrast agents which based on the selective response towards reactive oxygen species (ROS) such

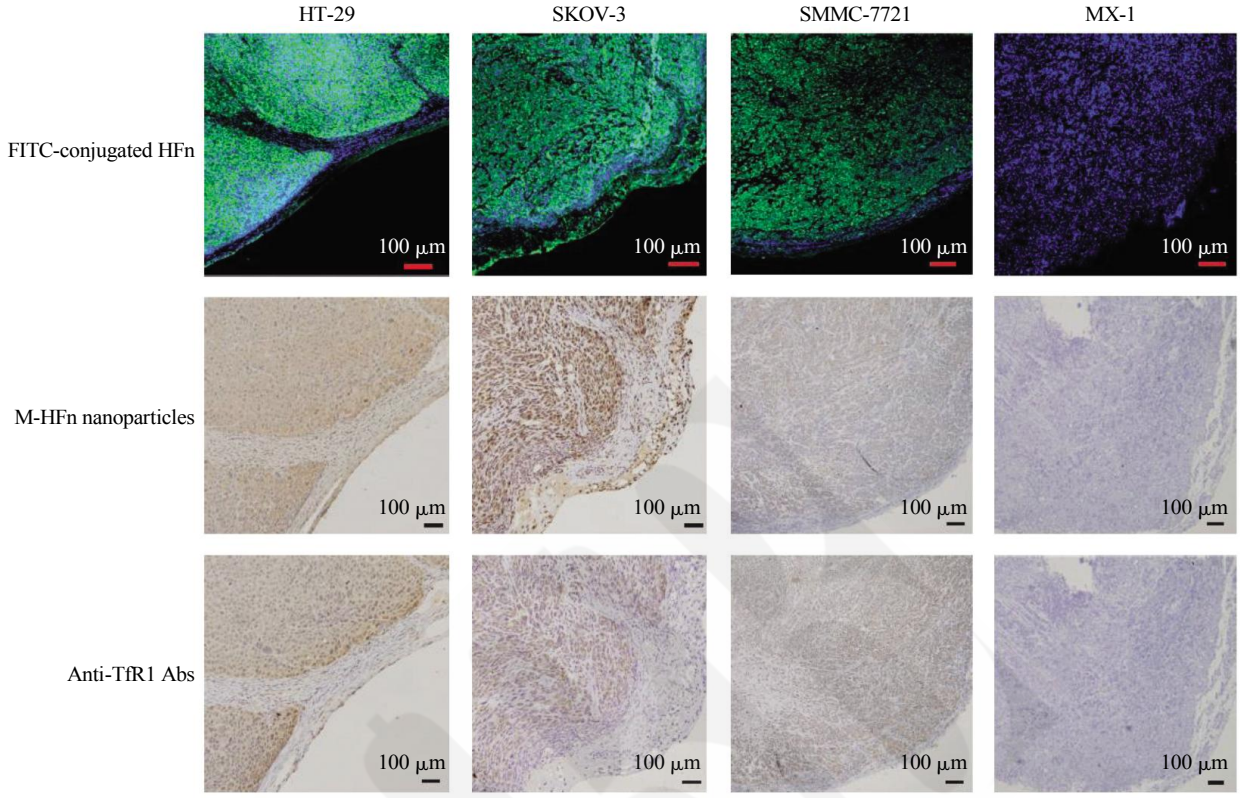

Fig. 2 Magnetoferritin nanoparticles for targeting and visualizing tumor tissues

From top to bottom, FITC-conjugated HFn-based fluorescence staining, M-HFn nanoparticle-based peroxidase staining, and anti-TfR1 Abs-based immunohistochemical staining of paraffin-embedded HT-29 colon cancer, SKOV-3 ovarian cancer, SMMC-7721 liver cancer and MX-1 breast cancer xenograft tumours. It demonstrates the the accuracy of tumour detection by the M-HFn nanoparticles[47].

as superoxide radicals, has not been reported so far. Ragg *et al* [55]. first demonstrated the intrinsic superoxide dismutase (SOD)-like activity of MnO nanoparticles is capable of enhancing the MR imaging contrast (Figure 3a). Moreover, MnO NPs can decompose H_2O_2, which is one of the SOD reaction products, in a catalase-like reaction subsequently. Therefore, the excellent dual enzymes-like activities of MnO NPs, can eliminate superoxide radical *via* a sequential catalytic reaction. The T_1 and T_2 weighted MR contrast of the MnO NPs was investigated by evaluating the specific relaxivities r_1 and r_2 of MnO NPs without/with the addition of superoxide generated by xanthine/xanthine oxidase (XO, Figure 3b, 3c). When MnO NPs were exposed to superoxide radicals, the T_1 and T_2 relaxation times increased significantly with r_1 and r_2 values of (0.06 ± 0.01) $mmol^{-1}\cdot L\cdot s^{-1}$ and (1.90 ± 0.14) $mmol^{-1}\cdot L\cdot s^{-1}$, respectively (Figure 3d), demonstrating the MnO-based nanosystem with the selective responsiveness towards superoxide radicals is capable of enhancing the MR imaging contrast by sequential catalytic reaction.

As a representative ROS in living systems, H_2O_2 is diffusible and relatively long-lived, which makes it a potential diagnostic marker for a wide range of pathological states, such as cancer[56–58]. However, some limitations of conventional H_2O_2 probes have hindered their further clinical applications, such as single modal, poor specificity, less sensitivity, and high cost for *in vivo* analysis. Therefore, it is necessary to develop multimodal probes for the detection of H_2O_2 with high spatiotemporal resolution.

Prussian Blue nanoparticles (PBNPs, $KFe^{3+}[Fe^{2+}(CN)_6]$), which are capable of catalysing the breakdown of H_2O_2 into oxygen (O_2) molecules under the neutral pH condition, have attracted great attention from the scientific community in recent years (Figure 4a) [59–60]. The O_2 molecules generated in the catalase-like activity can be used as an ultrasound contrast agent (UCA) to enhance ultrasound (US) imaging and moreover, some of the Fe^{3+} centers are accessible to water co-ordination to form paramagnetic

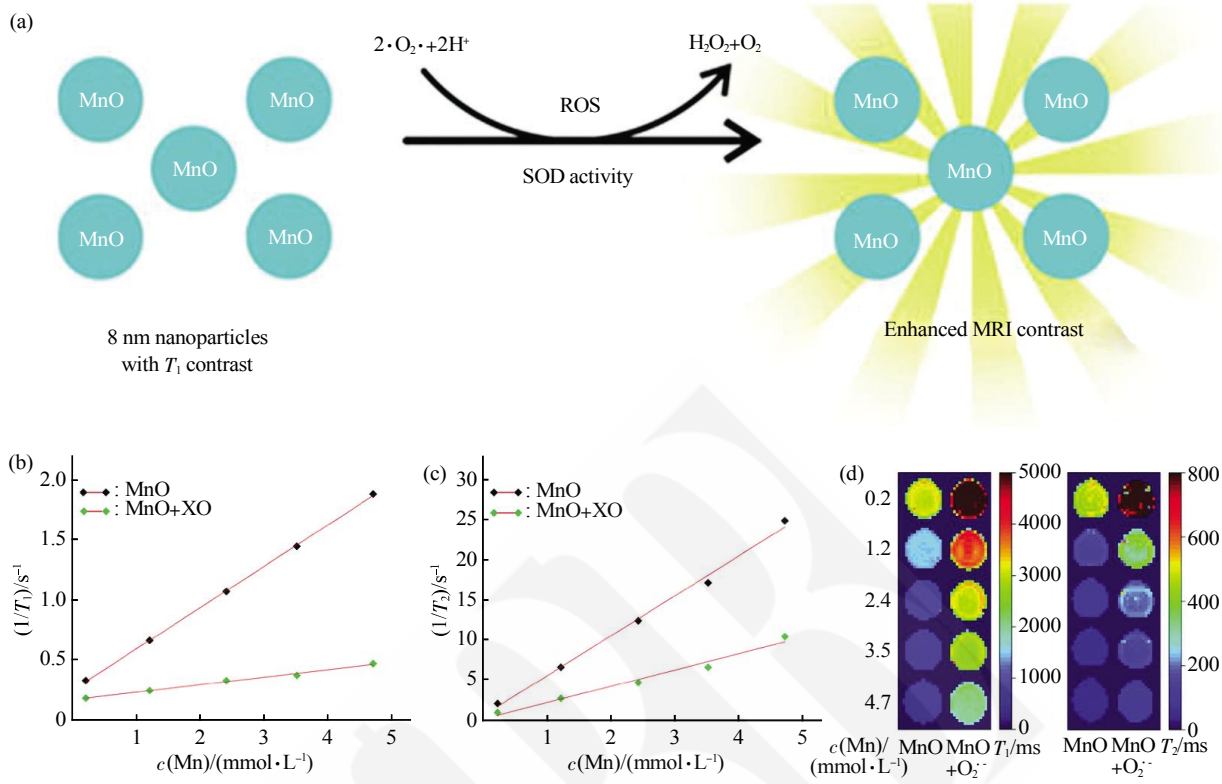

Fig. 3 Intrinsic superoxide dismutase activity of MnO nanoparticles enhances the MR imaging contrast

(a) Schematic illustration of intrinsic SOD-like activity of MnO NPs. (b) Specific relaxivity r_1 of MnO NPs without or with the addition of superoxide generated by XO. (c) Specific relaxivity r_2 of MnO NPs without or with the addition of superoxide generated by XO. (d) MR imaging of different MnO concentrations (0.2–4.7 mmol/L) showing T_1-(left) and T_2-(right) weighted images with relaxation times (T_1, T_2) measured on a standard clinical MR imaging instrument in a 96-well culture plate[55].

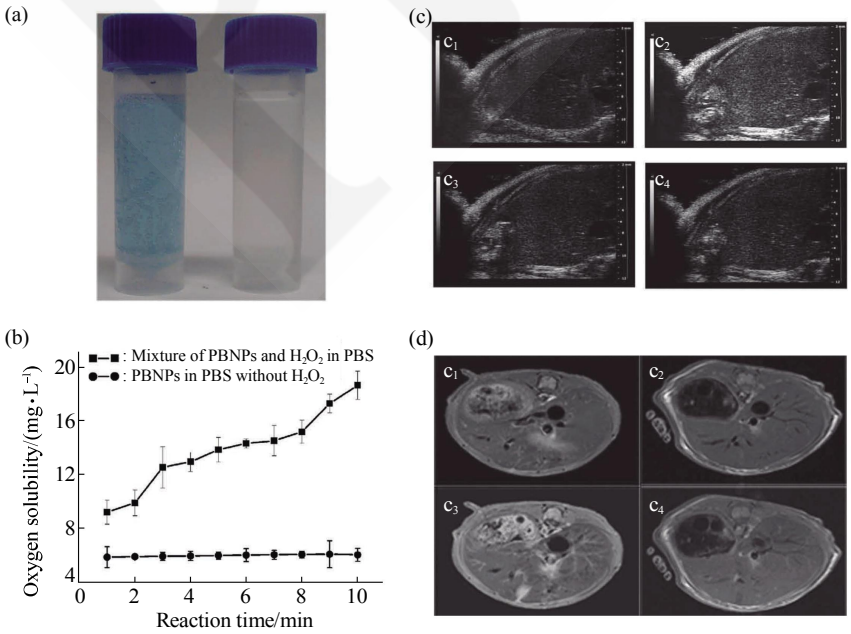

Fig. 4 Prussian Blue nanoparticles (PBNPs) possess a catalase-like activity to catalyze the breakdown of H_2O_2 into oxygen molecules for US and MR dual modality imaging

(a) The H_2O_2 solution in the PBS with (left) or without (right) the PBNPs. (b) Oxygen-solubility change with the increase of reaction time. (c) Representative US images of the mouse liver show enhanced US contrast after PBNPs injection (c_1, c_2) for 10 min. Saline injected into the LPS-treated mice was set as control (c_3, c_4). (d) Representative MRI images of the mouse liver manifest an enhanced MRI contrast after PBNPs (d_1, d_2) or saline (d_3, d_4) injected into the LPS-treated mice for 15 min[58].

oxygen bubbles, which is beneficial for shortening the T_1 relaxation time and developing nanoparticle-based T_1 MR imaging contrast agents. With the increase of the reaction time, the oxygen solubility grows rapidly, demonstrating that the generation of O_2 is much faster than gas diffusion to nucleate bubbles (Figure 4b). Both US and MR imaging show enhanced contrast after PBNPs injection, evidencing the enormous potential of PBNPs for diagnostic imaging, especially for cancer theranostics (Figure 4c, 4d).

The dual-mode diagnostic approach not only accomplishes the combination of US and MR imaging to offer complementary medical information for the diagnosis of cancer, but also provide us with much inspiration for rational design of next-generation theranostic nanozymes. On the basis of the aforementioned pioneering work of PBNPs, Wang *et al* [28] have designed a dual enzyme co-loaded multifunctional hybrid nanogel system for concurrent tumor-responsive US and T_2-weighted MR imaging. The as-designed SPIO@GCS/acryl/biotin-CAT/SOD-gel (SGC), was fabricated *via* the functionalization of the glycol chitosan monomer (GCS) followed by hydrophilic/hydrophobic interactions and electrostatic attraction between the monomer, the superparamagnetic iron oxide (SPIO) particles and dual enzymes (catalase and SOD) in the buffers (Figure 5a). The inserted catalase and SOD are capable of maintaining the redox balance of the physiological environment *via* the catalytic reaction with both the $O_2^{\cdot-}$ and H_2O_2 species to generate molecular O_2. The O_2 then gathers and forms bubbles, which could enhance the US imaging by changing the acoustic impedance of the tissue. Simultaneously, the nanogel layer around the SPIO particles can also lower the molecular diffusion coefficient of water as well as increase the transverse relaxation rate, which can facilitate in the enhancement of T_2-weighted MR imaging (Figure 5b).

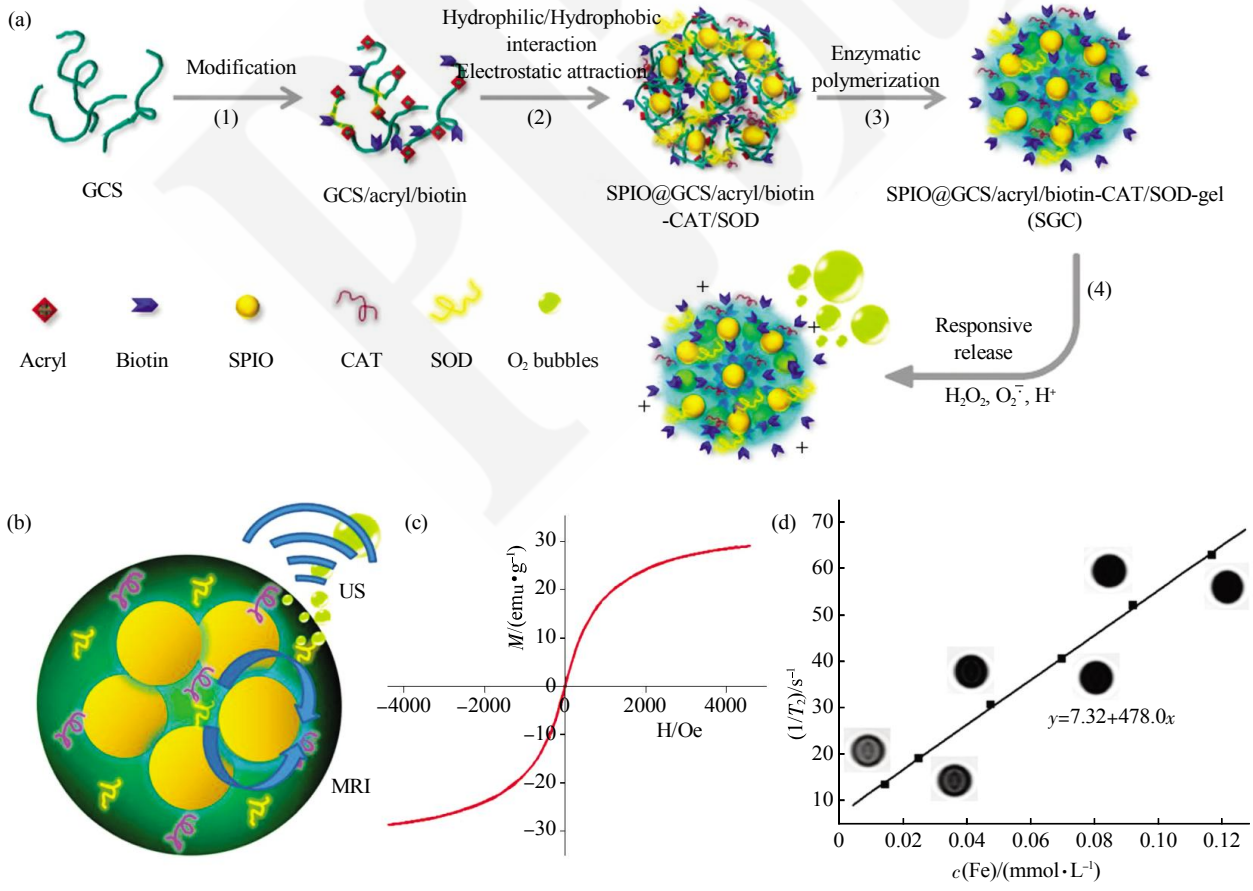

Fig. 5 Dual enzyme co-loaded multifunctional hybrid nanogel system for pathological responsive US and T_2 weighted MR imaging

(a) Schematic illustration of the fabrication process of SGC nanogel. (b) Scheme of SGC for enhanced US and MR imaging in the nanogel system. (c) Field-dependent magnetization curves (M-H) of the SGC nanoparticles at 300 K. (d) *In vitro* MR T_2 signals versus Fe concentration at pH = 7.4. The r_2 value were derived from linear fitting of the plots[28].

No hysteresis loop is visualized from the magnetization curve collected at room temperature, further demonstrating the super paramagnetic nature of SGC (Figure 5c). Moreover, the SGC solutions are observed to become darker in T_2-weighted MR images accompanied by the increasement of Fe concentration, evidencing excellent MR imaging capability of SGC solution (Figure 5d). This hybrid nanogel has the potential to be used as a new dual-modality contrast agent for concurrent US and T_2-weighted MR imaging, paving the way to accelerate the development of cancer theranostics by designing proper nanozymes with desirable catalytic performance.

2 Nanozyme for enhancing the radiotherapy efficiency

Radiation therapy (RT), a conventional commonly applied treatment modality which employs ionizing radiation to kill malignant cells, has been widely used for clinical cancer treatment [61–67]. However, the RT efficacies are limited by different mechanisms, such as the tumor hypoxia-associated radiation resistance. It is an essential task to enhance radiation-induced DNA damages by regulating hypoxia and elevating the concentration of intratumoral oxygen. With the rapid development of nanobiotechnology, abundant strategies to enhance radiation responses of tumors have been implemented by proper design of nanomaterials, and nanozymes are also engineered to accomplish the desired RT therapeutic outcome by catalyzing the generation of O_2, such as MnO_2 nanoparticles serving as catalase to attenuate hypoxia and enhance radiation response[68–69].

Wu *et al* have engineered multifunctional and colloidally stable bioinorganic nanoparticles composed of albumin complex and MnO_2 nanoparticles (A-MnO_2 NPs) based on the reactivity of MnO_2 toward peroxides for regulation of the tumor microenvironment (TME) with simultaneous oxygen generation and pH increase (Figure 6). MnO_2 NPs are able to generate O_2 *in situ* for a prolonged time by reacting with undesirable and abundantly available tumor metabolites (H_2O_2 and H^+) based on the intrinsic breaking-up capability under either mild acidic or reducing microenvironment. MnO_2 NPs were endowed with dual functions as both catalyst and reactant, which avoid the *in vivo* accumulation of the metal oxide. It is the first demonstration that MnO_2 NPs are capable of simultaneous modulation of hypoxia and acidosis of the TME to enhance ionizing radiation-induced tumor cell cytotoxicity in a murine breast tumor animal model. Moreover, this as-designed A-MnO_2 NPs can promote downregulation of crucial tumor progression-related factors, such as HIF-1R and VEGF by intratumoral injection approach. These experimental results obtained in the work encourage continuing efforts for the optimization and application of MnO_2 NPs in combination with other cancer treatments such as photodynamic therapy (PDT) and chemotherapy.

Liu *et al.* developed gold@manganese dioxide (Au@MnO_2) core-shell nanoparticles with a polyethylene glycol (PEG) coating as a novel radiosensitizing agent to improve RT efficacy for better therapeutic outcome (Figure 7). The Au core is a well-known RT sensitizer that interacts with X-rays to produce charged particles for improved cancer treatment under RT, while the MnO_2 shell is capable of triggering the decomposition of endogenous H_2O_2 in the tumor microenvironment as catalase to generate oxygen and finally overcome hypoxia-associated RT resistance.

The Au@MnO_2 nanoparticles were first synthesized by growing a MnO_2 nanoshell around Au nanoparticles, followed by PEG modification in a layer-by-layer approach, then yielded Au@MnO_2-PEG nanoparticles with high stability in different physiological environment (Figure 7a). Transmission electron microscope (TEM) image of Au@MnO_2 nanoparticles revealed that the Au core was well-coated by a MnO_2 shell with an average particle size of about 50 nm (Figure 7b). Energy-dispersive X-ray spectroscopy (EDS) mapping of Au@MnO_2 nanoparticles further evidenced the Au core/MnO_2 shell structure in the Au@MnO_2 nanoparticles (Figure 7c). By combining Au nanoparticles core with MnO_2 shells that promote O_2 elevation in pathological sites, Au@MnO_2-PEG core-shell nanoparticles displayed remarkable tumor therapeutic efficiency compared with efficiencies of either Au-PEG or MnO_2-PEG *in vitro* and *in vivo*. Moreover, Au@MnO_2-PEG nanoparticles induced no obvious toxicity to treated mice at 4 times of the therapeutic dose as determined by routine blood examination and blood biochemistry assays, demonstrating the desirable biocompatibility of these nanomedicine as synthesized.

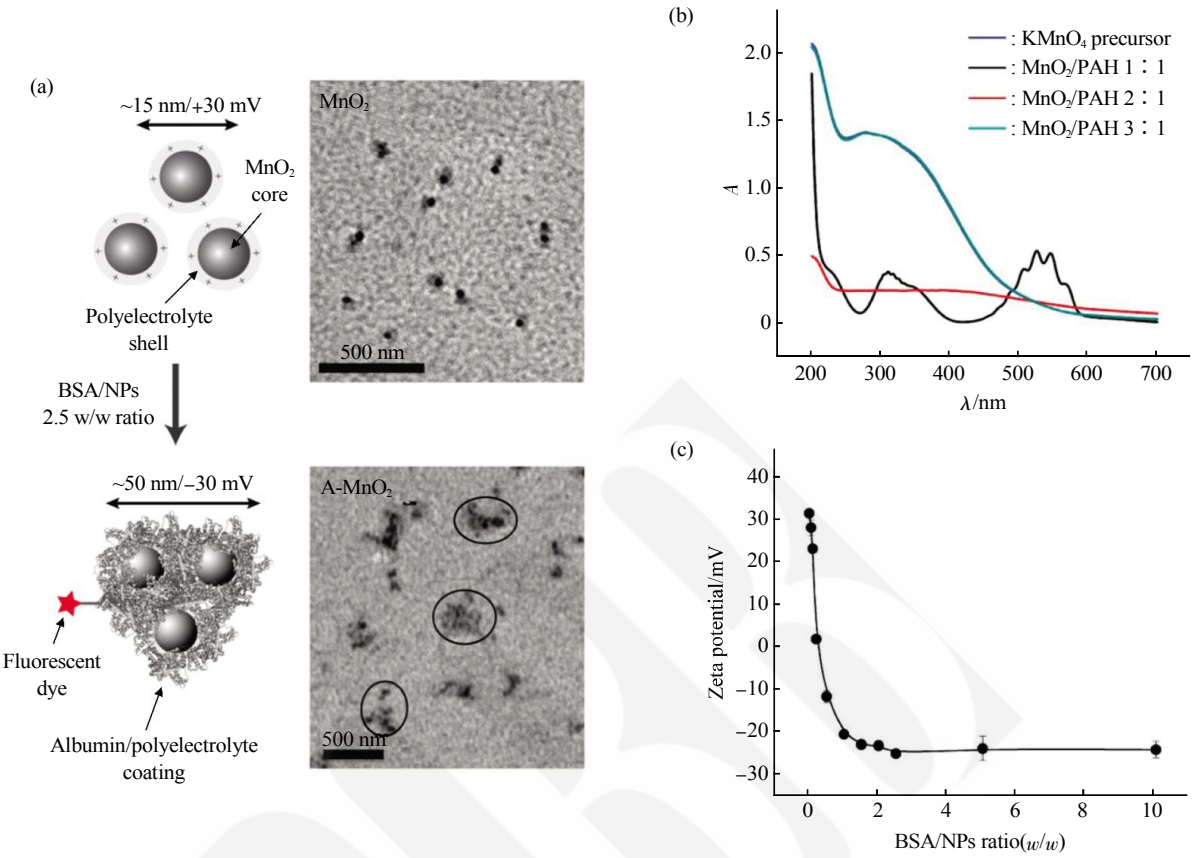

Fig. 6　Multifunctional albumin-MnO_2 nanoparticles serve as catalase to attenuate hypoxia and enhance radiation response

(a) Diagram and corresponding TEM images of MnO_2 and A-MnO_2 NPs. (b) UV-vis absorption of $KMnO_4$ precursor and MnO_2 NPs prepared at various molar ratios between PAH and MnO_2. (c) Zeta potential of MnO_2 NPs with BSA for various BSA/NPs ratios[68].

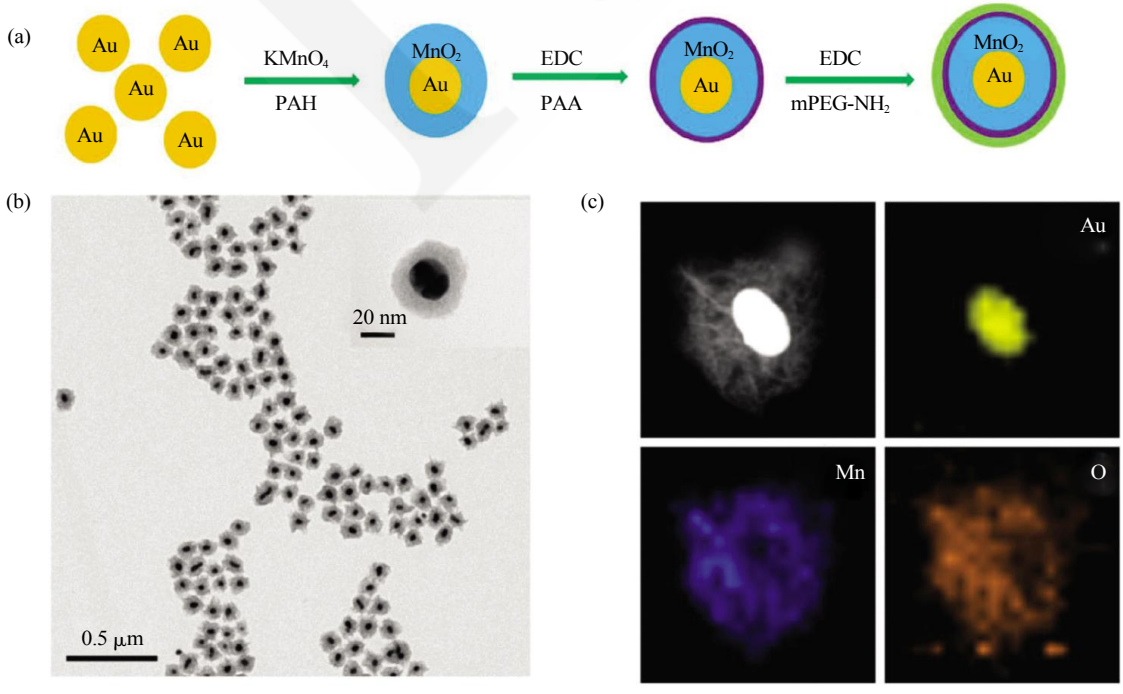

Fig. 7　Core-shell Au@MnO_2 nanoparticles for enhanced radiotherapy via improving the tumor oxygenation

Synthetic procedures (a), TEM images (b) and EDS elemental mapping (c) of Au@MnO_2 nanoparticles[69].

3 Nanozyme for enhancing the photodynamic therapy efficiency

As an emerging noninvasive therapeutic modality with great spatiotemporal selectivity for oncology, PDT has received extensive attentions in recent years[70–75]. PDT usually consists of three components: a photosensitizer (PS), light, and tissue oxygen. The light-activated photosensitizer (PS) is capable of transferring its excited-state energy to the surrounding oxygen for the generation of ROS, which cause cancerous cells to perish directly or indirectly. Various nanosystems with novel nanostructures have been discovered or fabricated to investigate their photodynamic performance [76–85]. However, obstacles are presently in the way of further clinical translation of PDT. Conventional PDT typically involves significant O_2 consumption, presenting strong oxygen dependence. This leads to drastically decreased antitumor therapeutic efficacy during continuing treatment, especially for the inherent hypoxic tumor tissue. It is necessary to develop a new therapeutic platform with desirable capability for the generation of ROS as well as the elevation of intratumoral oxygen.

Inspired by the nanozymes engineered to accomplish the desired RT therapeutic outcome by catalyzing the generation of O_2 as catalase to attenuate hypoxia and enhance radiation response, the therapeutic efficacy of PDT can also be enhanced by the integration of photosensitizer with nanozyme to regulate the tumor microenvironment for combinational therapy. Liu *et al* [86]. have fabricated multifunctional chlorine e6 (Ce6)-loaded MnO_2 nanoparticles with surface polyethylene glycol (PEG) modification (Ce6@MnO_2-PEG) to achieve enhanced tumor-specific PDT (Figure 8a)[87]. Benefited from the catalytic reaction between MnO_2 and H_2O_2, the *in vitro* and *in vivo* studies indicate that Ce6@MnO_2-PEG nanoparticles could effectively enhance the efficacy of light-induced PDT (Figure 8b). This work also highlights the application prospect of modulating unfavorable tumor microenvironment by taking advantage of nanobiotechnology to overcome current limitations of cancer therapies.

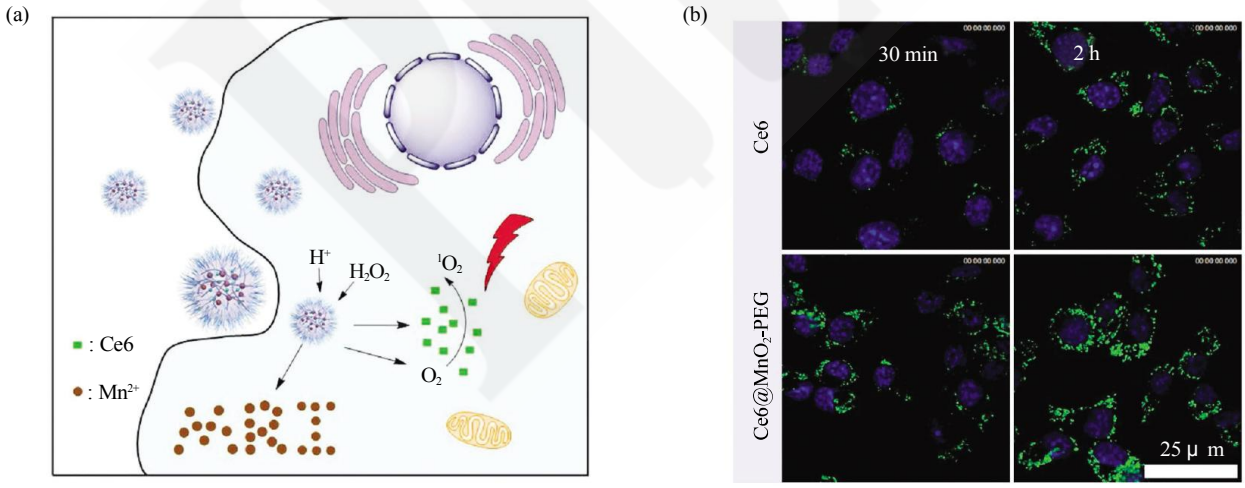

Fig. 8 MnO_2 nanoparticles modulate hypoxia in solid tumor microenvironment for better photodynamic therapy

(a) Scheme illustration of cellular uptake of Ce6@MnO_2-PEG nanoparticles and generation of O_2. (b) Confocal images of 4T1 cells incubated with Ce6 or Ce6@MnO_2-PEG taken at different times points[87].

Hence, it is here conceived that, if the therapeutic outcomes of PDT and RT, which are both strongly dependent on the concentrations of oxygen in pathological sites, could be enhanced concurrently by regulating the TME and elevating the intratumoral O_2. This strategy, if applicable, is capable of trigger the synergetic therapeutic process within tumorous tissues *via* single intravenous injection of the as-designed nanoparticles, hopefully resulting in the concurrent desirable therapeutic outcome and negligible damages to normal tissues. Shi *et al* have successfully developed intelligent 2D theranostic nanosystems based on the MnO_2 nanosheets integrated with upconversion nanoprobes (UCSMs) for

pH-/H_2O_2-responsive high-resolution upconversion luminescent (UCL) imaging and oxygen-elevated synergetic radio/photodynamic therapy (Figure 9)[88].

Based on the catalase-like activity of MnO_2 toward H_2O_2, the *in situ* oxygen generation and upconversion luminescent imaging can be achieved simultaneously, which is capable of accomplishing the desirable cancer theranostics *via* the oxygen-elevated synergetic radio/photodynamic therapy under the guidance of high-resolution UCL imaging. The experimental results *in vitro* and *in vivo* demonstrate remarkable tumor cells' apoptosis/necrosis and significant tumor growth inhibition, as well as the modulation of hypoxia in solid tumor microenvironment and circumvention of tumor angiogenesis/metastasis *via* the down-regulation of HIF-1α and VEGF, manifesting the feasibility of "one catalyst, two therapeutic modals" approach.

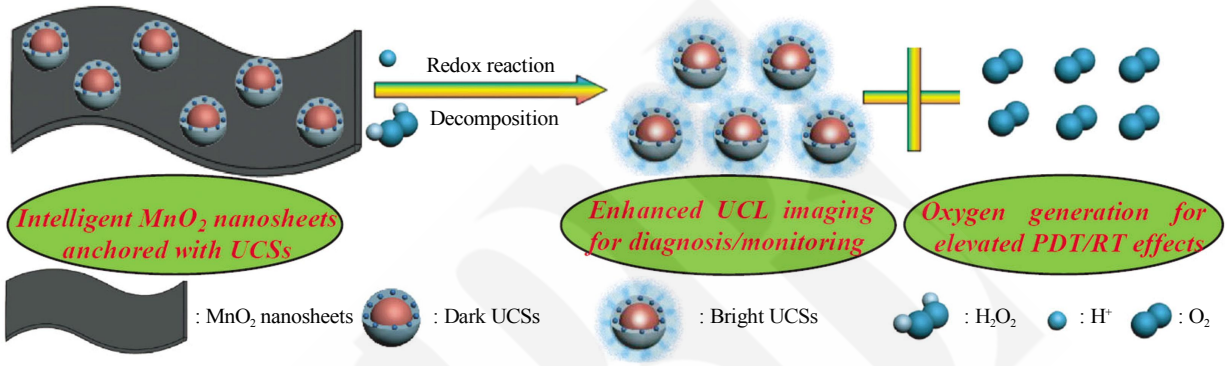

Fig. 9 Enhanced UCL imaging for diagnosis/monitoring as well as the massive oxygen generation by the decomposition of MnO_2 nanosheets of UCSMs for synergetic PDT/RT effects[88]

4 Nanozyme for chemodynamic therapy

Chemodynamic therapy (CDT) is a newly-emerging therapeutic modality that takes advantage of endogenous chemical energy to generate ROS, which is capable of inducing cell death without the need for external energy input by laser irradiation, and circumventing the limitations of conventional therapeutic modalities, such as the penetration of light through tissues[89]. Abundant nanozymes with unique physicochemical properties are applied to participate in the catalytic reaction to generate ROS for cancer treatment[90–91]. As a representative nanozyme for oncological applications, ferromagnetic nanoparticles have captured great attentions from scientific community due to the dual enzyme-like activity both *in vitro* and *in vivo* in a pH-dependent manner[92–98]. Gu *et al* systematically investigated the capabilities of iron oxide nanoparticles (IONPs) to produce hydroxyl radicals (•OH) in neutral or acidic condition and their toxic potential as Fenton reaction catalyst(Figure 10)[99]. IONPs are capable of catalytically decomposing H_2O_2 into non-toxic H_2O and O_2 under neutral pH condition, presenting catalase-like activity. More importantly, they could disproportionate H_2O_2 into highly toxi •OH, displaying peroxidase-like activity under acidic condition, as first reported in 2007 by Prof. Yan and her coworkers. This unique dual enzyme-like activity

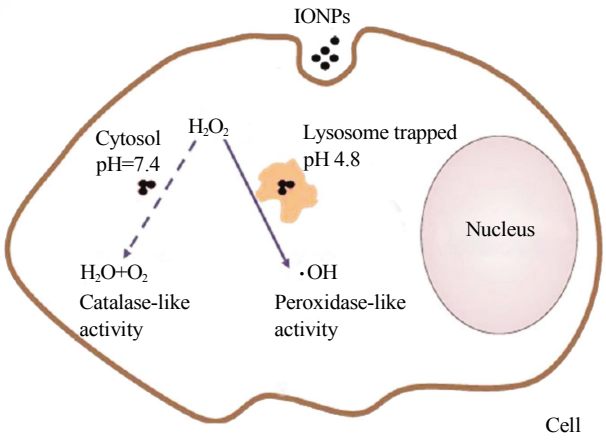

Fig. 10 Dual enzyme-like activities of iron oxide nanoparticles (IONPs)

IONPs are mostly located in acidic lysosomes after being internalized into cells, so they are capable of catalyzing H_2O_2 to produce hydroxyl radicals, presenting peroxidase-like activity; however, in neutral cytosol, IONPs would decompose H_2O_2 through catalase-like activity[99].

of IONPs, which can generate highly toxic ROS to kill cancer cells based on the specific microenvironment, endows them with great potential for next-generation oncological applications.

Ferrous ion-based therapeutic platforms, which have been developed for a long time, has remained highly attractive due to their desirable capability to liberate Fe^{2+}/Fe^{3+} ions in solution as Fenton's reagent to catalyze the disproportionation of hydrogen peroxide and the generation of highly toxic •OH. However, the non-specificity during the circulation process in the blood stream has hindered their further oncological applications. Resulting from the relatively low potential of the Fe^{3+}/Fe^{2+} redox couple (0.77 V), the ferrous ion-based nanoparticles may suffer from premature bio-oxidation processes, which will lead to the unsatisfied therapeutic outcome and even cause serious side effects in noncancerous regions with H_2O_2 overproduction[100].

Zhang *et al*[89]. have first synthesized amorphous iron nanoparticles (AFeNPs) and systematically investigated their superior physicochemical properties by comparing to their crystalline counterpart, iron nanocrystals (FeNCs, Figure 11). The AFeNPs can be used for cancer theranostics by taking advantage of the mild acidity and the up-regulated H_2O_2 in a tumor microenvironment to induce a Fenton reaction. The interaction with environmental acidic tumor tissue enables on-demand ferrous ion release based on the ionization of the AFeNPs, and subsequent H_2O_2 disproportionation leads to efficient •OH generation in the Fenton reaction. Therefore, by combining the two

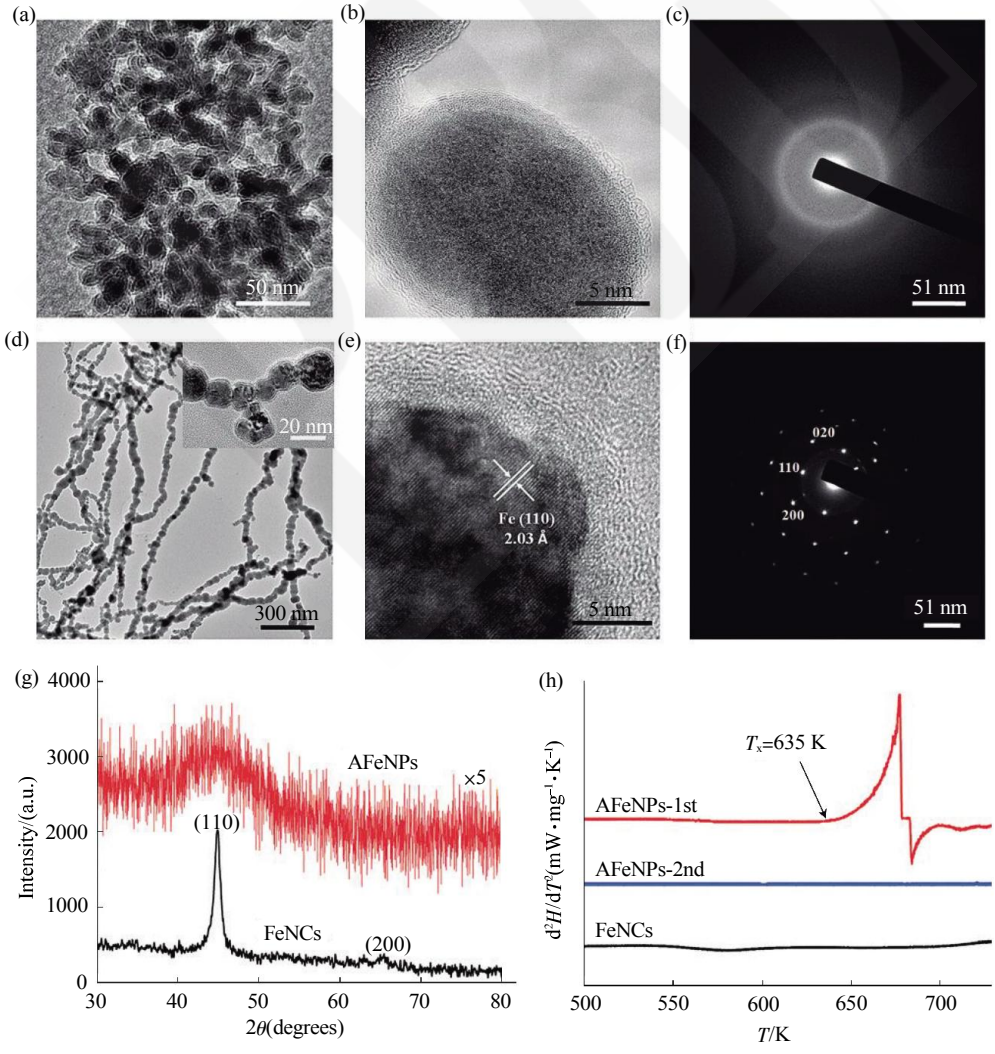

Fig. 11 Synthesis of iron nanometallic glasses and their oncological application by a localized Fenton reaction

(a-f) Low (a, d)- and high (b, e)-resolution TEM images of AFeNPs (a, b) and FeNCs (d, e), and their corresponding SAED patterns (c and f, respectively). (g) XRD patterns of the AFeNPs and FeNCs. (h) DSC analyses of the FeNCs and AFeNPs (first measurement: red line, second measurement: blue line)[89].

emerging fields (metallic glasses and cancer theranostics), which seems to be irrelevant to each other, this as-designed bioresponsive •OH generation by AFeNPs provides a highly specific cancer therapeutic approach to accelerate the development of ferrous ion-based nanozymes.

A catalytic nanomedical therapeutic concept was first proposed and established by Shi *et al*. to accomplish higher selectivity and efficiency for tumor therapeutics (Figure 12) [101]. The as-designed biocompatible and multifunctional GOD-Fe_3O_4@DMSNs nanocatalysts (GFD NCs), which are fabricated by integrating glucose oxidase (GOD) and synthetic ultrasmall Fe_3O_4 nanoparticles into the large mesopores of dendritic mesoporous silica nanoparticles (DMSNs), can *in situ* catalyze the generation of toxic ROS in response to the specific TME. Firstly, serving as the starting enzyme catalyst, GOD is capable of catalyzing the glucose into abundant H_2O_2 in tumor region. Then the elevated H_2O_2 is catalyzed by the downstream Fe_3O_4 NPs *via* Fenton-like reactions to release highly toxic hydroxyl radicals, which could further induce cancer cell death and tumor apoptosis. In this sequential catalytic reaction, the Michaelis-Menten steady-state kinetics have been determined as $V_{max} = 4.22 \times 10^{-8}$ mol•L^{-1}•s^{-1} and K_M = 10.93 mmol/L, which displayed the high catalytic performance of GFD NCs. Moreover, this elaborately designed sequential nanocatalysts with high biodegradability and biocompatibility exhibit highly desired tumor-suppression effect towards 4T1 breast tumor xenografts both intravenously (79.81%) and intratumorally (85.60%), concurrently with high therapeutic biosafety, further demonstrating the feasibility that Fe_3O_4 nanoparticles serve as highly efficient nanozyme for desirable chemodynamic therapy by combining with nature enzyme to construct an ingenious sequential catalytic reaction.

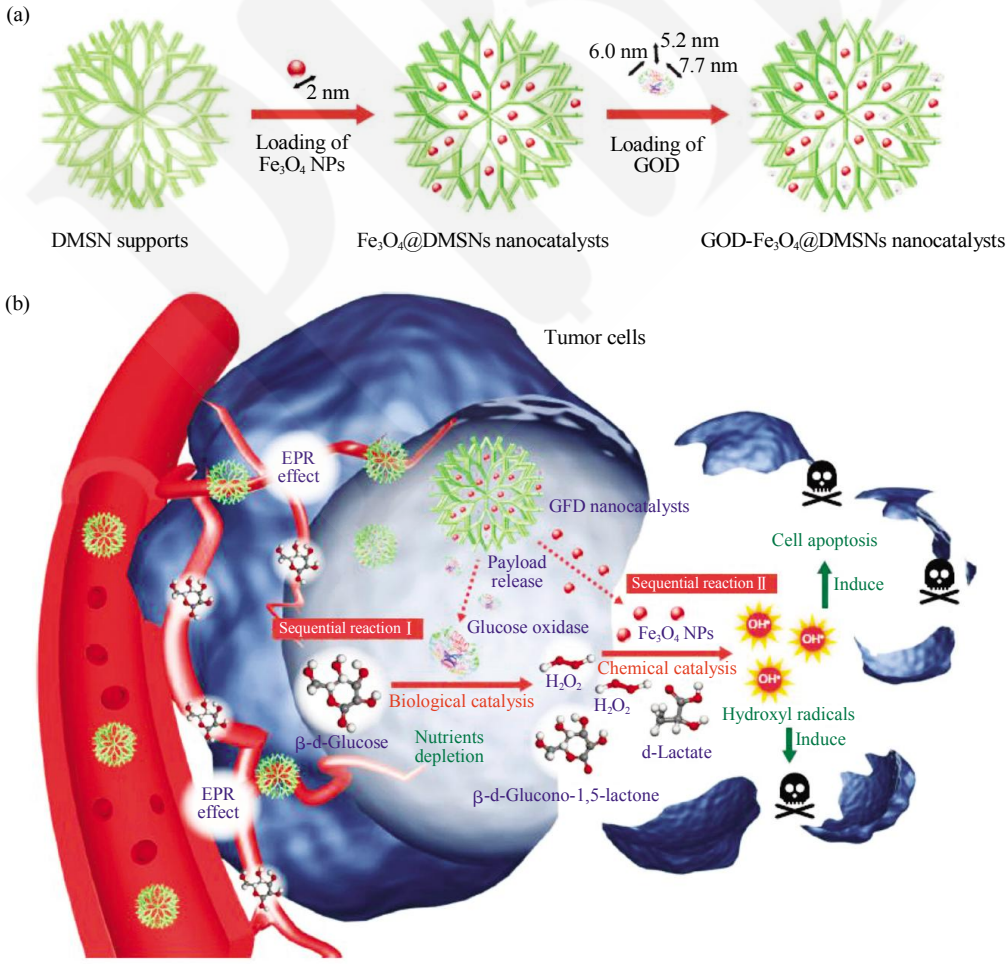

Fig. 12　Schematic illustrations of fabrication process and catalytic-therapeutic methodologies of sequential GFD NCs

(a) Synthetic procedure for Fe_3O_4@DMSNs and GOD-Fe_3O_4@DMSNs nanocatalysts. (b) Sequential catalytic-therapeutic mechanism of GFD NCs to generate hydroxyl radicals for cancer therapy[101].

5 Organic nanozymes for cancer theranostics

“Smart” bioresponsive materials, which are sensitive to biological signals or to pathological abnormalities, has been a growing interest in recent years, especially for the rational design of controlled drug delivery system [102−108]. Numerous synthesis strategies of nanozymes, such as encapsulating organic enzymes into nanoparticles to fabricate new types of nanozymes, have attracted broad attention owing to the superior catalytic performance by combine the advantages of both nature/artificial organic enzymes and outer nanoparticles. For example, we can endow nanozymes with bioresponsibility based on the unique physicochemical property of the outer nanoparticles to accomplish enhanced therapeutic specificity and treatment simplicity.

Chen *et al*[109] reported a nanocarrier system which is capable of synergistically releasing both drug molecules and O_2 when triggered by a biologically relevant concentration of H_2O_2. This as-designed nanozyme was fabricated by incorporating organic catalase and platinum anticancer agents into the aqueous core of poly (lactic-co-glycolic acid) (PLGA) nanoparticles (Figure 13). The PLGA nanoparticles were chosen as a drug carrier, and the inner catalase served as an O_2-generating agent to catalyze the decomposition of intracellular H_2O_2, which results in the shell rupture of nanoparticles owing to the increased pressure by the generation of O_2. Therefore, the nanoparticles could selectively liberate the encapsulated platinum anticancer drugs responsive to the high concentrations of H_2O_2 in cancer cells. Moreover, the O_2 generated *in situ* can be favorable for overcoming hypoxia-induced multi-drug resistance and enhancing the efficiency of chemotherapy subsequently. This is the first demonstration that chemotherapy and oxygen-elevation approach can be integrated synergistically to accomplish desirable therapeutic outcome.

Liu *et al*. designed a new type of bio-nanoreactors by encapsulating catalase into tantalum oxide (TaOx) nanoshells [110]. After the encapsulation process *via* a simple and mild one-step method, the obtained TaOx@Catalase nanoparticles are functionalized with polyethylene glycol (PEG) to improve the solubility. The mesoporous TaOx shell, which served as

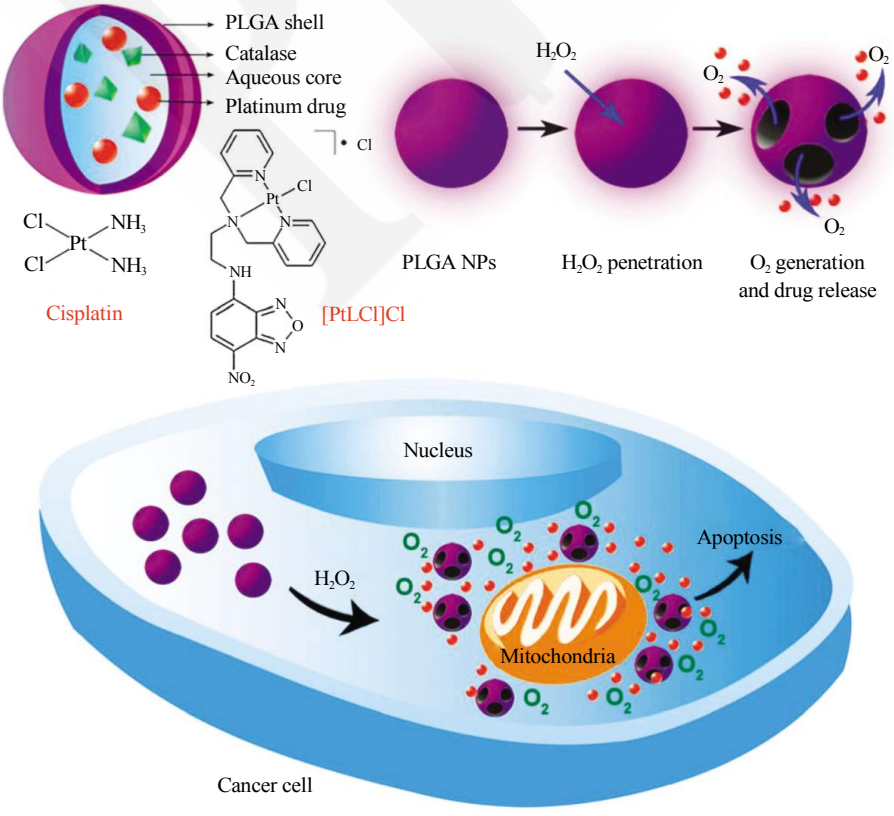

Fig. 13 Schematic illustration of the H_2O_2-responsive nanocarrier for dual-release of platinum anticancer drugs and O_2[109]

radiosensitizer in the nanosystem, can enhance the efficiency of radiotherapy by concentrating the radiation energy into tumor. Moreover, it can enable the free exchange of substrate H_2O_2 and product O_2 and keep high catalytic activity/stability of catalase to overcome tumor hypoxia and enhance the therapeutic efficiency synergistically. This strategy can be extended to the design of other types of nanozymes with intriguing applications in biomedical therapy and imaging.

6 Biosafety of nanozyme

Standing on the intersection of two different fields (catalytic chemistry and biomedicine), the further clinical application of nanozymes strongly depends on their biocompatibility and therapeutic biosafety. Both the dynamic and final fates of nanozymes should be systematically investigated at different therapeutic stages to address the potential toxicity concerns. For example, in consideration of the potential neurotoxicity of Mn^{2+}[111−113], it is necessary to maintain the concentration of MnO_2 at a lower level and reduce its needless addition when the MnO_2 nanoparticles/nanosheets are utilized to regulate the TME. Therefore, it will be a hard but significant work to keep a good balance between low concentration of MnO_2 component and desirable therapeutic outcome by catalyze the generation of O_2 to enhance the RT/PDT efficacy.

For a comprehensive view of biosafety of nanozyme, pharmacokinetics (PK), absorption, distribution, metabolism, duration of therapeutic effect, excretion, and toxicity of nanozyme should be taken into consideration [105]. Biodistribution studies suggested that the nanozymes without targeting molecules would accumulate mainly in liver, spleen, and lung. It is necessary to endow nanozymes with targeting ability by surface modification for enhanced therapeutic efficacy and mitigatory cytotoxicity[26].

To develop a nanozyme as a therapeutic agent for further clinical application, it must meet the strict safety and efficacy requirements of the regulatory agencies (such as the US Food and Drug Administration). Encouragingly, several studies showed that a few regulatory agencies approved that nanomaterials (such as Resovist) present catalytic activity and have been used as nanozymes [114]. However, for most of the currently available nanozymes, both their acute and long-term biosafety should be evaluated systematically before they could be applied in clinical treatment. Recent studies focusing on nanozymes only evidence the biocompatibilities of them by presenting the hematoxylin and eosin (H&E) staining images of dissected major organs (Figure 14). However, more systematical investigations should be taken into consideration while evaluating the biosafety of one nanozyme.

7 Conclusions and perspectives

Recent advances in nanotechnology have been deepening the understanding of nanoparticle-tumor interactions, and creating tailor-designed nanomedicines for individualized tumor treatment [37]. Such a rapidly evolving field of nanozymes at the front line in the war on diseases will pave a new way to solve the critical issue of currently unsatisfactory therapeutic efficacy. By taking the advantages of catalytic chemistry, nanomedicine, biotechnology and oncology, nanozymes will play a vital role in combating the tumor.

As has been demonstrated in the preceding parts of the review, great research interests have been focused on the field of nanozymes owing to their unique physicochemical characteristics. However, despite the remarkable progress has been made, most contemporary available nanozymes were investigated for their catalytic performance, the nanozyme research for oncological applications is still in its infancy (Figure 15). Therefore, to increase the possibility of clinical translation of nanozymes, several unsolved critical issues need to be addressed:

(1) There have been abundant types of natural enzymes and organic catalysts capable of catalyzing almost all the important reactions. However, the currently developed nanozymes for oncological applications are mainly to mimic redox enzymes, *i.e.* peroxidase and catalase. Given the fact that there are six major types of natural enzymes, more efforts in the future should be focused on how to design novel nanozymes rationally that may mimic their diversified catalytic and other functionalities for more potential clinical applications. Currently, these nanozymes for cancer theranostics are mainly limited to several inorganic catalysts (Fe_3O_4, MnO_2, *etc.*), more categories of nanozymes are expected to be discovered or developed.

(2) Nature enzymes' activities are highly

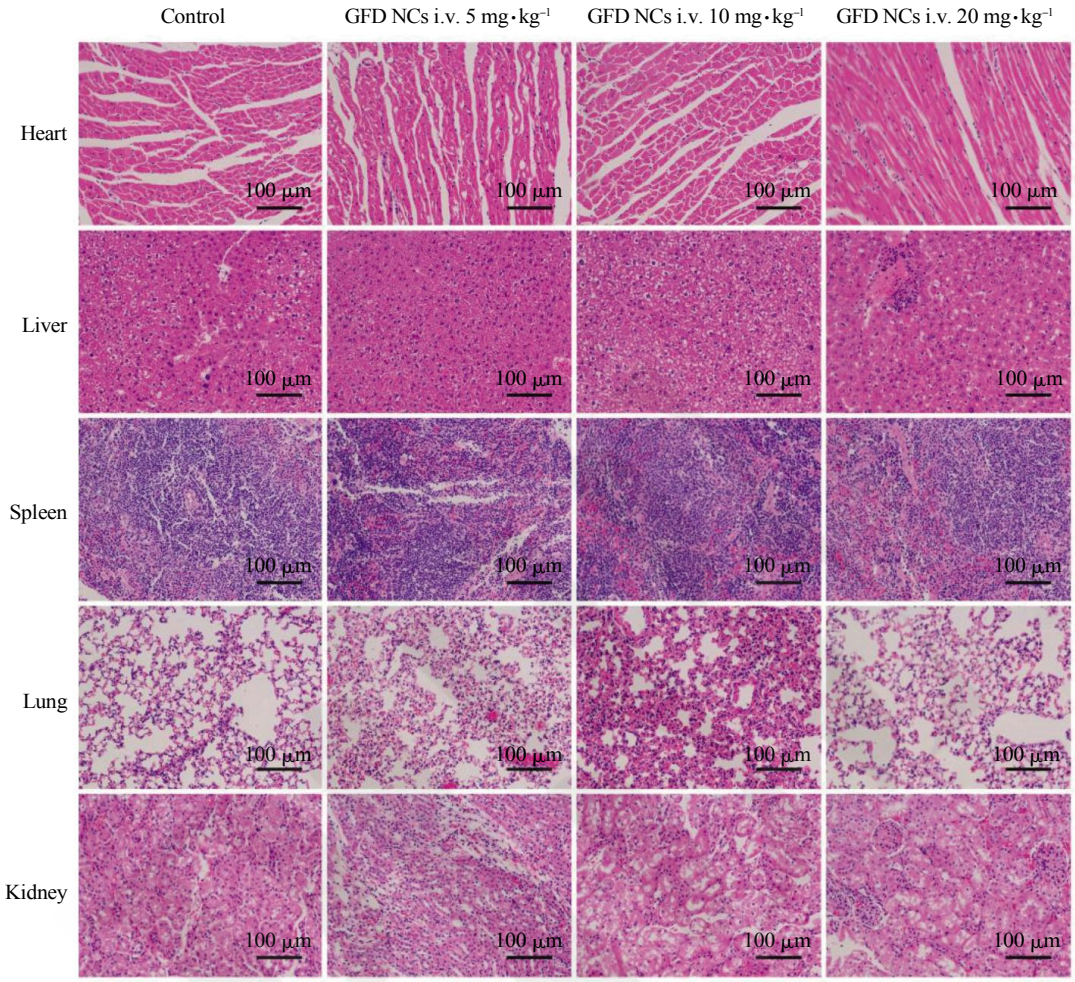

Fig. 14 Histopathology images of dissected major organs (heart, liver, spleen, lung and kidney) stained with H&E of control and all experiment groups for in vivo biosafety evaluation of the GFD NCs in Figure 12

It demonstrates the desirable biocompatibility of the nanocatalyst for clinical translation[101].

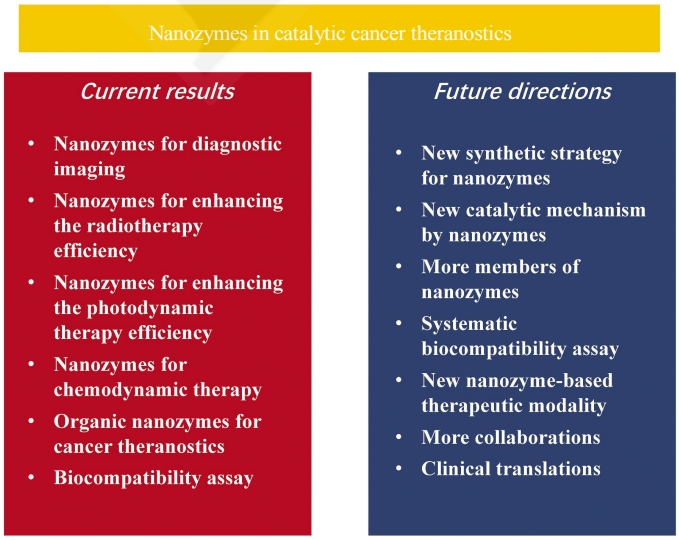

Fig. 15 Summary of the status of nanozyme-based catalytic cancer theranostics and future research directions for the development of the next-generation nanozymes

regulated in biological systems, which has provided much inspiration for us to develop various strategies to tune the nanozymes' activities for optimized therapeutic outcomes. The nanozymes' catalytic activities are supposed to be regulated by controlling its surrounding environment and its interaction with specific ligands, *i.e.*, to be bioresponsive as nature enzymes do. Responding to specific biological triggers either for interacting with biological targets or for stimulating the release of therapeutic agents, such as highly toxic hydroxyl radicals, can endow nanozymes with ever-greater application potentials for desirable cancer theranostics.

(3) Aiming to accomplish higher catalytic performance for tumor imaging and therapy, the catalytic activities from both the core and the surface coating should be more comprehensively investigated. For some nanozymes with catalytically active core, additional surface coating and bioconjugation may shield their activities and decrease the activity dramatically. Therefore, how to adopt suitable coatings will be a significant task to achieve the perfect balance between desirable targeting ability and high catalytic activity.

The intrinsic limitations of conventional cancer therapeutic modalities have accelerated the emergence and development of various nanozymes for more effective and biosafe cancer treatment. This review highlights the recent progresses in the field of nanozymes for catalytic cancer diagnosis and therapeutics. As elucidated above, researches in this frontier area of biomedical nanozymes is highly active, as evidenced by the rapidly growing number of publications. Like most other significant scientific advances that have revolutionized medicine over the past decades, nanozymes are believed to play a vital role in the battle against cancer in near future.

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纳米酶在肿瘤催化诊疗方面的应用 *

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摘要 作为一个特殊的交叉学科前沿，纳米酶在近几年来引起了科学界的广泛关注．自 2007 年首次发现四氧化三铁纳米材料具有类似辣根过氧化物酶的催化特性以来，纳米酶的研究迅速兴起．纳米酶在纳米尺度的特殊理化性质赋予它们优越的催化性能，以应用于各方面，例如癌症的诊断和治疗．本文重点介绍近年来催化化学的发展所促进的纳米医学在肿瘤诊疗方面的应用，以及纳米酶的研究现状和未来的展望．通过合理地将催化化学与临床纳米诊疗医学相结合，这些新型的纳米酶及其在肿瘤成像和治疗方面优越的催化性能，将会极大地促进纳米医学新子学科的产生．

关键词 纳米酶，癌症，诊疗，催化，纳米医学

学科分类号 Q814，R730 **DOI**: 10.16476/j.pibb.2017.0466

* 国家重点研发计划 (2016YFA0203700)，国家自然科学基金(51722211，51672303)和中国科协青年人才托举工程(2015QNRC001)资助项目.

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收稿日期：2017-12-15，接受日期：2018-01-09