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Review

Progress and Trend on the Regulation Methods for Nanozyme Activity and Its Application

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Abstract: Natural enzymes, such as biocatalysts, are widely used in biosensors, medicine and health, the environmental field, and other fields. However, it is easy for natural enzymes to lose catalytic activity due to their intrinsic shortcomings including a high purification cost, insufficient stability, and difficulties of recycling, which limit their practical applications. The unexpected discovery of the Fe_3O_4 nanozyme in 2007 has given rise to tremendous efforts for developing natural enzyme substitutes. Nanozymes, which are nanomaterials with enzyme-mimetic catalytic activity, can serve as ideal candidates for artificial mimic enzymes. Nanozymes possess superiorities due to their low cost, high stability, and easy preparation. Although great progress has been made in the development of nanozymes, the catalytic efficiency of existing nanozymes is relatively low compared with natural enzymes. It is still a challenging task to develop nanozymes with a precise regulation of catalytic activity. This review summarizes the classification and various strategies for modulating the activity as well as research progress in the different application fields of nanozymes. Typical examples of the recent research process of nanozymes will be presented and critically discussed.

Keywords: nanozyme; activity regulation; artificial mimic enzyme

1. Introduction

All life phenomena in nature are related to enzymes. Almost all chemical reactions occurring in living cells are catalyzed and controlled by enzymes. Enzymes are a type of biomacromolecule with biocatalytic function, which can tune the metabolism of organic organisms, transmitting genetic information, sustaining life activities, and catalyzing chemical reactions. Owing to their excellent catalytic efficiency and strong substrate specificity, enzymes are widely used in biosensors, medicine and health, environmental protection, and other fields. However, due to the shortcomings of most natural enzymes, such as their poor stability, time-consuming preparation, and high preparation costs, there is great significance for practical application to design and synthesize stable and low-cost artificial mimetic enzymes to replace natural enzymes by full chemical synthesis or semi-synthetic methods [1–5].

Artificial mimetic enzymes are also known as one of the important branches of bionics; they refer to the use of artificial materials to simulate the structure and function of natural enzymes, and they were first proposed by Ronald Breslow [1,2]. In the past decades, great progress has been made in the field of mimetic enzymes [3,4]. A series of mimetic enzymes have been synthesized, such as cyclodextrins, metal complexes, porphyrins, and biological molecules, and used as substitutes for natural enzymes in various fields [5,6]. Compared with natural enzymes, these traditional mimetic

enzymes have the advantages of simple structure, low molecular weight, and high stability (especially at high temperature). However, their low catalytic activity and poor selectivity are common problems of traditional mimetic enzymes.

Scrimin and Pasquato and their coworkers found that gold nanoparticles modified by azacrown had a nuclease-like function and could catalyze the phosphodiester bonds of nucleic acids [7]. Then, they first proposed the concept of the "nanozyme" to describe this monolayer of thiol-protected gold nanoclusters with significant ribonuclease activity, which was later extended to describe nanomaterials with enzymatic activity. In 2007, the Yan group reported for the first time that magnetic iron tetroxide nanoparticles exhibited peroxidase-like properties [8]. This discovery has attracted widespread attention to the nanozyme, which has rapidly become a research hotspot. Hui Wei and Erkang Wang further defined the concept of nanozyme as "nanomaterials with enzymatic properties". As a new generation of artificial mimetic enzymes, nanozymes are more stable and economical than natural enzymes and traditional artificial enzymes. So far, a variety of nanozymes have been reported and widely used in the fields of biosensors, environmental remediation, and disease treatment [5,6].

2. Types and Classification of Nanozymes

Until now, many nanomaterials have been found to possess enzyme-mimic activity. Considering the dual characteristics of nanozymes, i.e., nanomaterials and catalysts, the nanozymes can be classified by the nanomaterial's dimensions and catalytic types. Firstly, it can be classified by the nanomaterial's dimensions. If three dimensions of a nanomaterial are in the nanoscale (usually less than 100 nm), it can be named as a zero-dimensional nanozyme [9–19]. If two dimensions of a nanomaterial are in the nanoscale, it can be named as a one-dimensional nanozyme [20–26]. In the same way, there are also two-dimensional nanozymes (one dimension in the nanoscale) [27–34] and three-dimensional nanozymes (zero dimension in the nanoscale) [35–43]. Secondly, according to the types of enzymatic reactions, we can name nanozymes according to their mimetic natural enzymes, including peroxidase nanozyme, catalase nanozyme, oxidase nanozyme, nitrate reductase nanozyme, nuclease nanozyme, and so on.

3. Regulation Strategy of Nanozyme Activity

Similar to natural enzymes, the activity of nanozymes can be regulated in different ways, including according to their material size, composition, morphology, surface modification, pH and temperature, and activators or inhibitors. This section summarizes and discusses the above-mentioned important factors for influencing the catalytic performance of nanozymes.

3.1. Size

Size is a key factor in determining many properties of nanomaterials. Generally, the catalytic activity of nanozymes can be regulated by controlling the size. In most cases, smaller nanoparticles have higher activity, which is probably due to their having a larger specific surface area. In other words, the catalytic activity of nanozymes increases with the increase of the specific surface area. Some studies have shown that the catalytic activity of one nanozyme is related to its size [44–46]. The Peng group studied the peroxidase catalytic activity of Fe_3O_4 NPs with average diameters of 11, 20, and 150 nm [47]. It was found that the peroxidase catalytic activity of Fe_3O_4 NPs increased with the decrease of the diameters of nanoparticles. Asati et al. obtained similar results when studying the oxidase activity of organic polymer-modified cerium oxide nanoparticles with different sizes of 5, 12, 14, and 100 nm [48]. Therefore, the catalytic activity of nanozymes can be achieved by tuning the size of the nanozymes.

3.2. Morphology

The shape and morphology of nanozymes plays a key role in regulating their catalytic activity [49–52]. Tian et al. have investigated the effect of different morphologies (nanosheets, nanofibers, and nanorods) of VO_2 nanoparticles on the colorimetric assay for H_2O_2 and glucose [53].

It is found that VO_2 nanofibers exhibit the highest peroxidase-like activity, since the specific surface area of VO_2 nanofibers is much larger than that of VO_2 nanosheets and nanorods. To illuminate the morphology effects on the catalytic ability of Mn_3O_4 nanoparticles, Singh et al. studied the size, pore size, surface area, and volume of the various morphologic Mn_3O_4, including nanoflowers, cubes, polyhedron, hexagonal plates, and flakes (Figure 1) [54]. The results showed that Mn_3O_4 nanoflowers exhibited higher catalytic activity than that of other morphologic Mn_3O_4 nanomaterials due to their higher surface area and larger size as well as the bigger pore size of the Mn_3O_4 nanoflowers. Additionally, the effects of the morphology of Co_3O_4 [55], Fe_3O_4 [56], MnO_2 [57], $LaNiO_3$ [42], and $CoFe_2O_4$ [58] on their catalytic activity have also been reported.

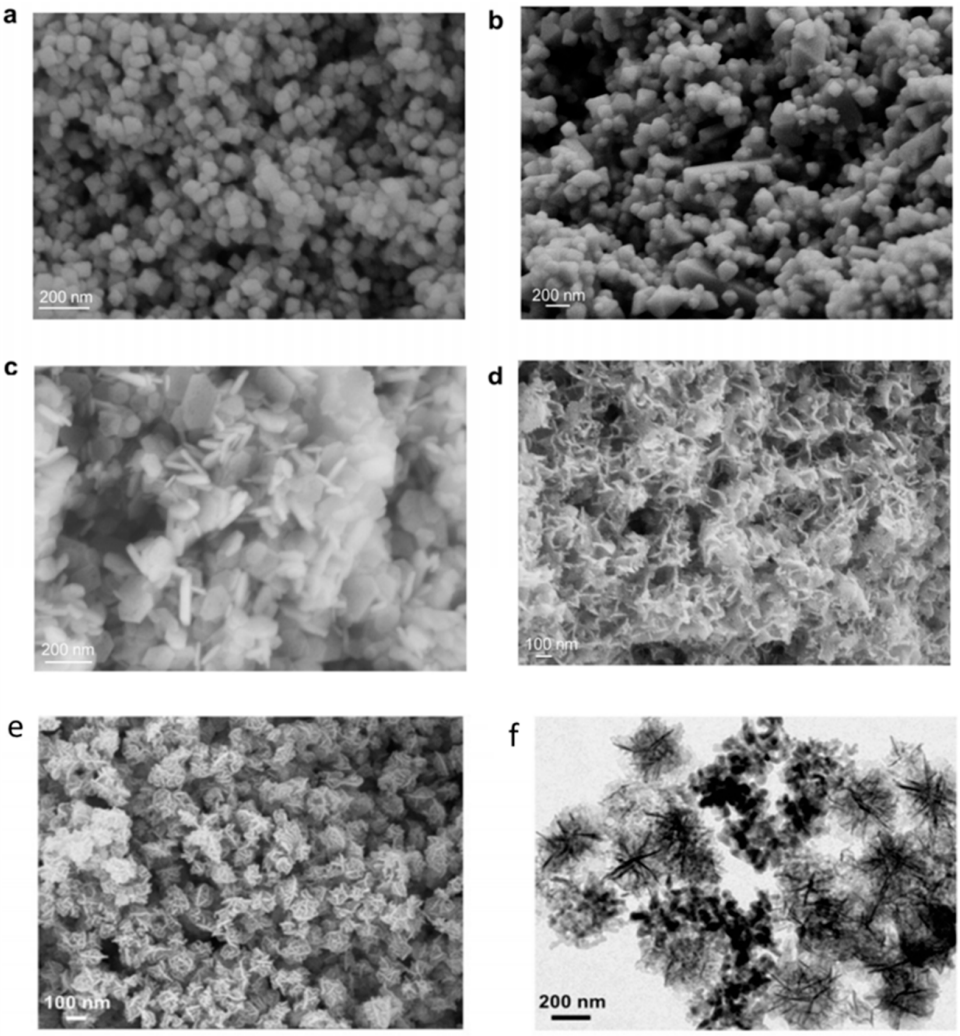

Figure 1. (**a**–**e**) SEM images of different morphologic Mn_3O_4 including the cubes, polyhedrons, hexagonal plates, flakes, and flowers, respectively. (**f**) TEM image of Mn_3O_4 nanoflowers. Reproduced from Reference [54] with permission from Wiley.

3.3. Composition

The components of nanozymes can effectively affect the catalytic activity. Doping methods and a constructing complex is often used to regulate the activity of nanozymes [59–64]. He et al. found that the simulated superoxide dismutase (SOD) activity of the CeO_2 nanozyme decreased with the doping amount of titanium, which suggested that the SOD activity was easily affected by the spheroidal nanostructure, and Ti-doping promoted a conversion from the cubic crystal phase of CeO_2 to a spheroidal nanostructure [65]. On the contrary, the oxidase-like activity of CeO_2 was somewhat enhanced by Ti doping. Two kinds of catalytic activities of Ti-doping CeO_2 were different,

because SOD activity appeared to be sensitive to the spheroidal nanostructure, while the oxidase-like activity did not. What's more, the combination of two or more similar functional nanomaterials can effectively improve the catalytic efficiency compared to the individual nanomaterial. In contrast with the individual AuNPs and Fe_3O_4 NPs, their composites exhibit higher peroxidase activity, which can be attributed to three factors: the synergistic effect [60], the polarization effect of AuNPs to Fe_3O_4 [66], and the special electronic structure interface between Fe_3O_4 and AuNPs [67]. However, the less active core could be etched for the aim of growing the higher active sites and further improving the catalytic activity of nanomaterial. Wu et al. synthesized Pt hollow nanodendrites with the more active sites and high-index facets that were derived from Pd–Pt core–frame nanodendrites, and then etched the Pd core, exhibiting the enhancement of peroxidase-like activity (Figure 2) [68].

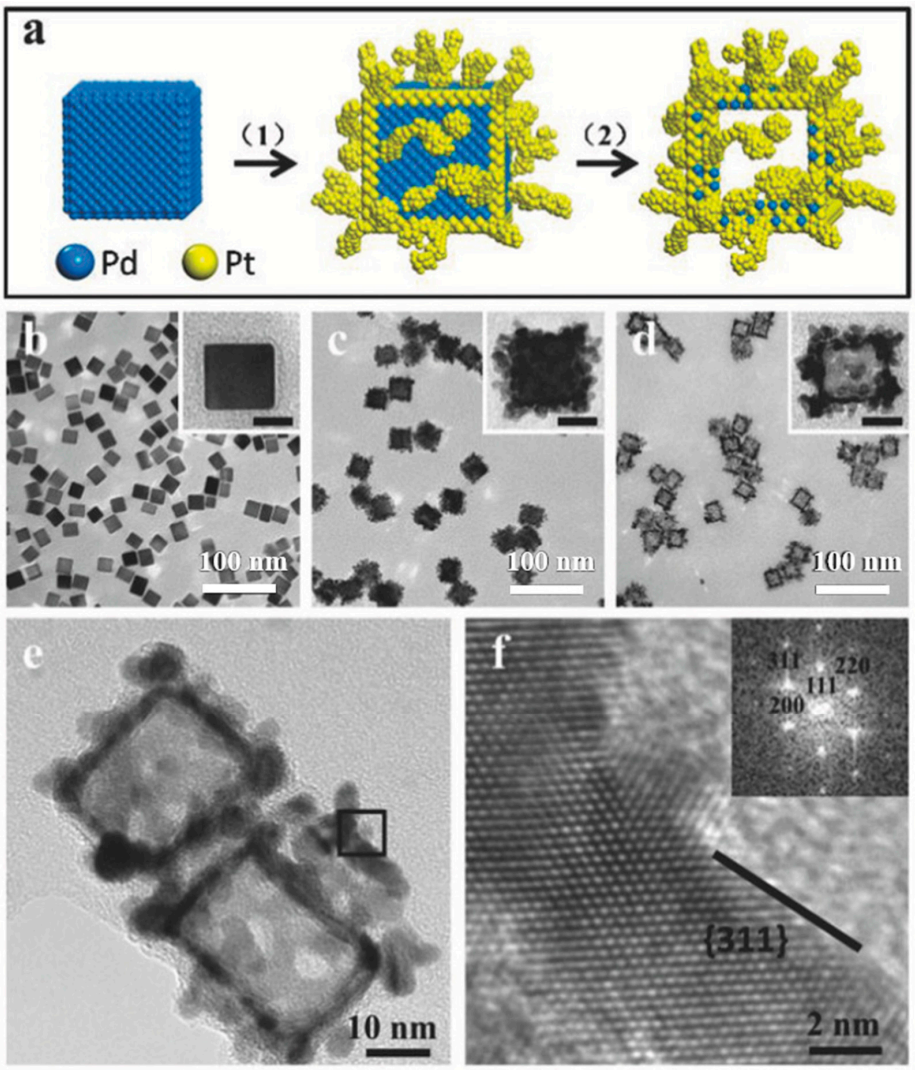

Figure 2. (**a**) The formation of Pt hollow nanodendrites including the (**1**) deposition process of Pt atoms for the generation of Pd@Pt core–frame nanodendrites and the (**2**) etching process of Pd cores using $FeBr_3$. (**b**–**d**) TEM images of Pd nanocubes, Pd@Pt core–frame nanodendrites, and Pt hollow nanodendrites, respectively. (**e**) TEM image of Pt hollow nanodendrites with hollow interiors and abundant branches. (**f**) HRTEM image taken from the corner region of a Pt hollow nanodendrite. The corresponding FT pattern is shown in the inset. Reproduced from Reference [68] with permission from Wiley.

3.4. Surface Modification

The surface modification can be achieved by covalently immobilizing functional groups and electrostatic adsorption. After surface modification, nanozymes possessed different catalytic abilities and delivered the required performances for further biological coupling [8]. Generally, if the number of active sites that can bind with the substrate is reduced by the surface modification method, it will decrease the catalytic activity of a nanozyme. Gao et al. studied the Fe_3O_4 NPs coated with 3-aminopropyltriethoxysilane, polyethylene glycol, dextran, and silica [8]. It was found that the peroxidase activity of these coated Fe_3O_4 NPs was generally lower than that of unmodified Fe_3O_4 NPs. However, some coatings can also improve the catalytic activity of nanozymes. Zhang et al. found that the peroxidase-like activity of Prussian blue-coated γ-Fe_2O_3 NPs increased significantly [69]. They attributed the reason to two points: the surface charge of the coated γ-Fe_2O_3 NPs was changed from positive charge to negative charge and the substrate-binding was enhanced by electrostatic interaction; in addition, more ferrous active centers were introduced by Prussian blue. However, it is noteworthy that Prussian blue itself has peroxidase activity. Qu's group studied the effect of surface functional groups on peroxidase activity in graphene quantum dots (GQD) (Figure 3) [14]. Carbonyl, hydroxyl, and carboxyl groups on the surface of GQD were selectively modified by benzoic anhydride (BA), phenylhydrazine (PH), and 2-bromo-1-phenylethyl ketone (BrPE), respectively. Compared with unmodified GQD, the peroxidase activity of GQDs-BA and GQDs-BrPE was increased, while the peroxidase activity of GQDs-PH was inhibited. Using terephthalic acid, they found that the carbonyl group on GQD was the active site, the carboxyl group was the substrate-binding site, and the hydroxyl group inhibited the activity of the enzyme. This discovery explains the mechanism of carbon materials as peroxidase mimetic enzymes, providing a solid theoretical basis for the design and synthesis of carbon materials in the future. Therefore, surface modification acts as one of the effective methods to regulate the catalytic efficiency of nanozymes.

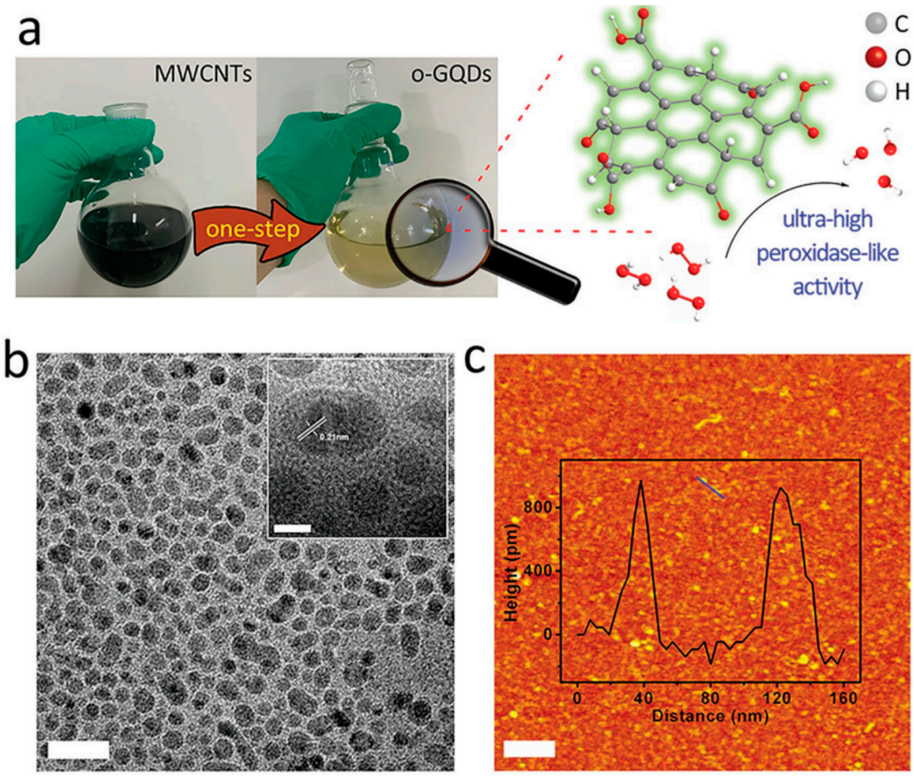

Figure 3. (**a**) Schematic representation of the preparation of graphene quantum dots (GQDs). (**b**) TEM image of GQDs. The scale bar is 20 nm. (**c**) Atomic force microscope image of GQDs. Reproduced from Reference [14] with permission from Wiley.

3.5. pH and Temperature

The pH factor plays an important role in the reactions catalyzed by nanozymes. It was found that some nanozymes exhibited different enzyme activities at different pH values [70–73]; for example, if the pH of α-ZrO_2 is lower than 5.3, it shows the catalytic activity of peroxidase, and when the pH is higher than 5.3, it shows the catalytic activity of catalase [71]. Additionally, the temperature factor can also regulate the catalytic efficiency of nanozymes. Qu's group designed bovine serum albumin (BSA) as the model protein to construct the BSA–Cu_3 $(PO_4)_2 \cdot 3H_2O$ hybrid nanoflower. In the temperature range from 15 to 65 °C, the nanoflowers showed high-temperature catalytical activity compared with the natural horseradish peroxidase (HRP) under the same condition [74]. More interestingly, the catalytic activity of the nanoflower was improved with the increment of temperature. Additionally, Qu's group performed an interesting study on pH and temperature modulation [75]. A dual photoresponsive system for the photoregulation of chemical reactions based on the combination of ultraviolet (UV) and near-infrared (NIR) light-sensitive materials were developed. The achievement of regulatory effect was via the modulation of reaction temperature and pH. The hybrids of the photobase reagent malachite green carbinol base (MGGB) and graphene oxide were used for the photoregulation of pH and temperature. Under the stimulation of ultraviolet and near-infrared light, high temperature from graphene oxide and OH^- from MGCB were produced, respectively. Accordingly, the change of pH and temperature were tuned under irradiation, resulting in the modulation of the catalytic activities of nanozyme. By using nanozyme and enzyme-mediated chemical reactions as models, they verified the feasibility and high performance of this method (Figure 4) [75].

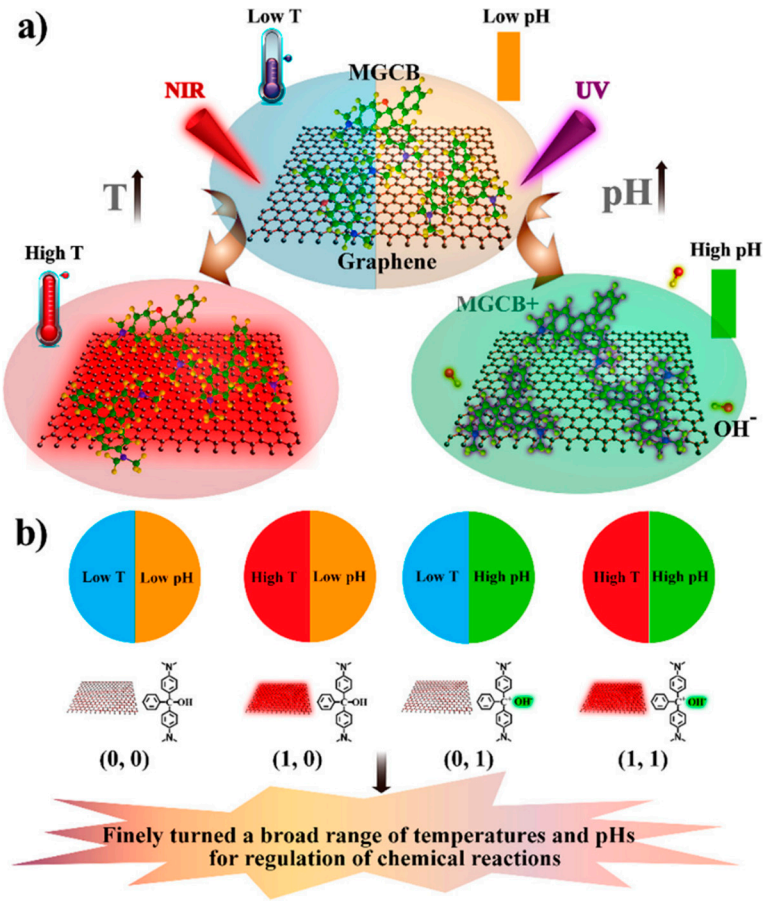

Figure 4. (**a**) Photothermal effect of graphene and light-induced pH changing the effect of malachite green carbinol base (MGCB). (**b**) Finely tuned a broad range of temperatures and pHs for the regulation of chemical reactions. Reproduced from Reference [75] with permission from The American Chemical Society.

3.6. Activators and Inhibitors

Apart from the above factors, activators and inhibitors also affected the catalytic performance of nanozymes [76–79]. For natural enzymes, activators can increase the activity of enzymes, while inhibitors can decrease the activity of enzymes. Inspired by this, researchers are also trying to find activators and inhibitors to regulate the catalytic activity of nanozymes. In some cases, certain ions and other molecules could react with the nanozymes to affect the catalytic activity of nanozymes. Singh's studies have shown that phosphate ions can keep Ce in the +3 valence state, increasing the catalase-like activity of nano-cerium dioxide [59]. Liu et al. carried out a series of screening experiments to select the optimum condition to inhibit the activity of Au@Pt nanorod oxidase [80]. It found that Fe^{2+} was an irreversible inhibitor, while Cu^{2+} and NaN_3 were reversible inhibitors. Additionally, it was found that Hg^{2+} was an effective inhibitor, and a method for detecting Hg^{2+} inhibition was established.

Herein, some regulation strategies of typical nanomaterials and their applications were summarized in Table 1.

Table 1. The regulation strategy of typical nanomaterials and their applications. BSA: bovine serum albumin.

Types of Nanozymes	Nanomaterial	Regulation Strategy	Application	Reference
zero dimension	CeO_{2-X}	size (4.5 nm, 7.8 nm, 23 nm, and 28 nm); composition (surface area concentration of Ce^{3+})	decomposition of H_2O_2	44
	Fe_3O_4 NPs	size (11 nm, 20 nm, 150 nm)	catalyze the oxidation of the substrate TMB by H_2O_2	47
	dextran-coated nanoceria	size (5 nm, 12 nm, 14 nm, 100 nm)	enzyme-linked immunosorbent assay	48
	Au-Fe_3O_4 NPs	composition (complex)	detection of H_2O_2	60
	Ti-doped CeO_2	composition (doping)	biological applications	65
	Pt hollow nanodendrites	composition (etching)	antibacteria	68
	Fe_3O_4	surface modification (3-aminopropyltriethoxysilane, polyethylene glycol, dextran, and SiO_2)	immunoassay	8
	graphene quantum dots	surface modification (phenylhydrazine, benzoic anhydride, and 2-bromo-1-phenylethyl ketone)	glucose detection	14
	γ-Fe_2O_3 NPs	surface modification (Prussian blue)	immunoassay	69
	Ag	activator (mercury (II))	colorimetric assays for mercury (II)	76
	Pt	inhibitor (mercury (II))	colorimetric assays for mercury (II)	77
	Au_xPt_y -DNA	inhibitor (biothiol)	colorimetric assay of biothiols	78
	Pt–apoferritin	inhibitor of catalase activity (NaN_3), inhibitor of catalase and superoxide dismutase activities (3-amino-1,2,4-triazole)	engineering targeting enzyme mimetics	79
	CeO_2	inhibitor (phosphate)	catalyst	59
	Prussian Blue	pH	multienzyme mimetics and reactive oxygen species scavengers	71
	$CoFe_2O_4$	pH, surface modification	chemiluminescence without the need for H_2O_2	73
one dimension	VO_2	morphology (nanofibers, nanosheets, and nanorods)	detection of H_2O_2 and glucose	53
	Mn_3O_4 nanoflower	morphology (nanoflowers, cubes, polyhedron, hexagonal plates, and flakes)	preventing the cells from oxidative damage	54
	Co_3O_4 nanoplates	morphology (nanoplates, nanorods, and nanocubes)	determination of calcium ion	55
	Au@Pt nanorods	inhibitor (Fe^{2+}, Cu^{2+}, and NaN_3)	screening of inhibitors for oxidase mimics	80
two dimension	graphene oxide	pH, temperature	programmable wound healing	75
	WS_2	temperature	glucose detection	31
three dimension	ZrO_2 gel	pH	nonredox system construction	70
	BSA–$Cu_3(PO_4)\cdot 3H_2O$	temperature	decompose organic pollutants	74

4. Applications of Nanozymes

4.1. Nanozymes in Antibacteria for Topical Application

Up to now, the usage of nanozymes in combatting multi-drug resistant bacteria and biofilms has become an attractive field. Metal oxide-based and sulfide metal-based nanozymes, carbon-based enzymes, and nanocomposites show good biocompatibility and antibacterial activities, which have been applied for killing bacteria [3]. However, most related works about nanozyme antibacterial agents were applied for topical applications such as mouse skin, since they would release reactive oxygen species (ROS) in an aspecific manner. Therefore, nanozymes for antibacterial applications cannot be systemically administered until now. Although the antibacterial and antibiofilm mechanism of nanozymes are largely unknown, three aspects are mainly summarized as following [3]: (1) nanozymes trigger the generation of reactive oxygen species (ROS) such as hydroxyl radical (•OH) and superoxide anion ($O_2^{\bullet-}$), which can attack bacteria and biofilms because of the high oxidation capability of ROS [81], and unselectively defunctionalize many important substances such as lipids, proteins, and nucleic acids, thus causing the lysis of the bacterial cytoplasmic membrane, protein deactivation, and DNA damage. (2) Deoxyribonuclease mimics, as a kind of hydrolytic nanozymes, can catalytically cleave the extracellular DNA for inhibiting the formation of biofilms and dispersing the integrity of the biofilm [82]. (3) Haloperoxidase mimics that can reduce autoinducers have exhibited a successful inhibition of biofilm growth and the destruction of biofilms [83]. However, most of the existing antibacterial mechanism was focused on the above first one. Karim et al. reported that CuO nanorods could serve as high-efficiency antibacterial agents under light illumination, which causes a 20 times enhancement of the •OH production rate compared with the dark condition [84]. Yan's group first demonstrated a zinc-based zeolitic-imidazolate-framework (ZIF-8) derived Zn–N–C single-atom nanozyme (SAzyme) that is considered as a high therapeutic effect single-atom catalyst for wound antibacterial application (Figure 5) [85]. The high catalytic activity of the SAzyme was due to the coordinatively unsaturated Zn-N_4 active site, leading to the dissociation of H_2O_2 and the generation of •OH. The formation of high oxidative •OH could trigger the oxidation of cellular components and then result in the bacteria apoptosis. The result showed that the inhibition rate of the SAzyme on bacteria was 99.87%. Moreover, the SAzyme significantly promoted wound healing with low toxicity to the organism.

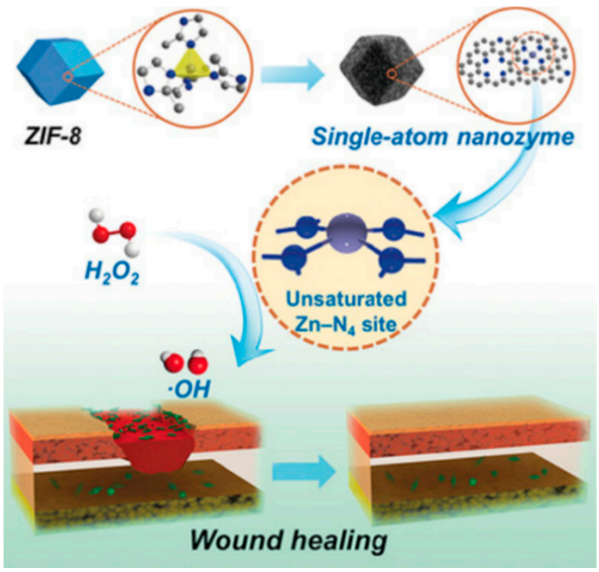

Figure 5. Schematic representation of zinc-based zeolitic-imidazolate-framework (ZIF-8) derived Zn–N–C single-atom nanozyme for wound antibacterial application. Reproduced from Reference [85] with permission from Wiley.

4.2. Nanozymes in Hazardous Degradation

Organic pollutants, especially those with high toxicity, have shown serious effects on the eco-environment system and human health [86]. The degradation of organic pollutants for decreasing environmental pollution has been a focus of attention of the international community. Until now, a variety of methods have been proposed to decompose organic pollutants, including chemical oxidation, physical adsorption, and biological degradation. Among them, physical adsorption is not an ideal method, since it lacks the efficiency in the process and needs abundant adsorbing materials [87]. For chemical oxidation, it needs a Fenton reagent including Fe^{3+}, Fe^{2+}, and H_2O_2. However, chemical oxidation usually produces iron ions and sludge, which were easily discharged into the environment, resulting in secondary pollution [88,89]. Biological degradation has the properties of being highly efficient and environmentally friendly. Nevertheless, the natural enzyme which is applied for biological degradation is expensive and unstable. Thus, it is urgent to explore new materials and methods to decompose organic pollutants. The nanozyme is an ideal degradation agent. So far, the reported organic molecules of nanozyme degradation include phenol, bisphenol A, methyl blue, sulfamethoxine, 4-chlorophenol, norfloxacin, xylenol orange, sulfathiazole, rhodamine B, methylene blue, and congo red. Wang et al. prepared a novel CH–Cu nanozyme based on the coordination of Cu^{+}/Cu^{2+} with a Cys-His dipeptide for the degradation of chlorophenols and bisphenols (Figure 6) [90]. The CH–Cu nanozymes can mimic the laccase activity and exhibit an excellent catalytic activity, recyclability, and substrate universality comparable with laccase. Employing key peptides as metal ligands for the metal ions complexing reaction is a novel concept and method for the design and synthesis of new nanozymes, which could mimic the structure of the active site of a natural enzyme. Despite this process, an enormous challenge is the immobilization of nanozymes, since attaching ligands to nanozymes may block active sites and affect their catalytic activity [91]. To solve this problem, the idea of growing a layer of nanozymes on magnetic nanoparticles is proposed, which could be a benefit for separation and recycling as well as the maintaining of catalytic activity. Zhang et al. reported a novel magnetic laccase-like nanozyme (Fe_3O_4@Cu/guanosine 5′-monophosphate (GMP)), which could oxidize harmful o-phenylenediamine and remove phenolic compounds [92]. Based on the complexed Cu^{2+} and GMP, which possessed the laccase-like activity and were modified on the outside of Fe_3O_4 nanoparticles, the catalytic performance of Fe_3O_4@Cu/GMP was achieved. The application of magnetic nanoparticle as a magnetic core is conducive to further separation and recycling. Besides, the photocatalytic degradation of organic pollutants generally takes place in a stepwise fashion [93]. Photocatalytic degradation can occur under ultraviolet (UV) or visible light irradiation, causing the degradation of organic pollutants. Fan et al. reported an efficient titanate nanomaterials (NTs) photocatalyst modified with H_2O_2 (HTNM), exhibiting an enhanced photoresponse to visible light with high photocatalytic activity for the degradation of naproxen [94]. These above reports show that nanozymes can potentially be a substitution for natural enzymes in hazardous degradation and environmental remediation.

4.3. Nanozymes in Sensing

Nanozymes have been extensively explored for the sensing of various important targets in the fields of food safety analysis, environmental monitoring, disease diagnosis, and pharmaceutical analysis, ranging from food and environmental pollutants, bioactive small molecules, metal ions, nucleic acids, biomarkers, and cancer cells. Nevertheless, the simultaneous analysis of multiple targets by using one single nanozyme is still a challenge. To solve this problem, the Qu group established a multiplex readout method for the pattern recognition of different proteins by using graphitic carbon nitride (g-C_3N_4) nanosheets as a single sensing receptor with peroxidase-like activity (Figure 7) [95]. It is surprising that the catalytic activity of g-C_3N_4 nanosheets can be regulated into different degrees because of the different interactions between g-C_3N_4 and proteins. The advantage of this platform is no need for numerous sensing receptors and sophisticated instruments, resulting in lower cost and time consumption, providing a new pathway for the construction of convenient, feasible, and flexibly nanozyme-based sensing arrays. The g-C_3N_4-based nanozyme is not only used for the construction

of colorimetric sensors, but it can also be used for fluorescent sensors. However, the fluorescence performances at a single emission wavelength are easily affected by environmental factors, such as exciting and emitting light efficiency, and fluorescence probe concentration [96]. The ratio of double emission wavelengths is obtained as a response signal that improves the accuracy of the results by the self-calibration of two different emission wavelengths. The Wei group designed the ratiometric sensing systems by using three kinds of fluorescent C_3N_4-based nanozymes such as C_3N_4-Ru, C_3N_4-Cu, and C_3N_4-hemins, which possessed excellent peroxidase mimic catalytic activities [97]. The fluorescent intensity at 438 and 564 nm as the signal output was used to construct ratiometric sensor assays for the determination and discrimination of five phosphates, providing more reliable and robust sensing performance.

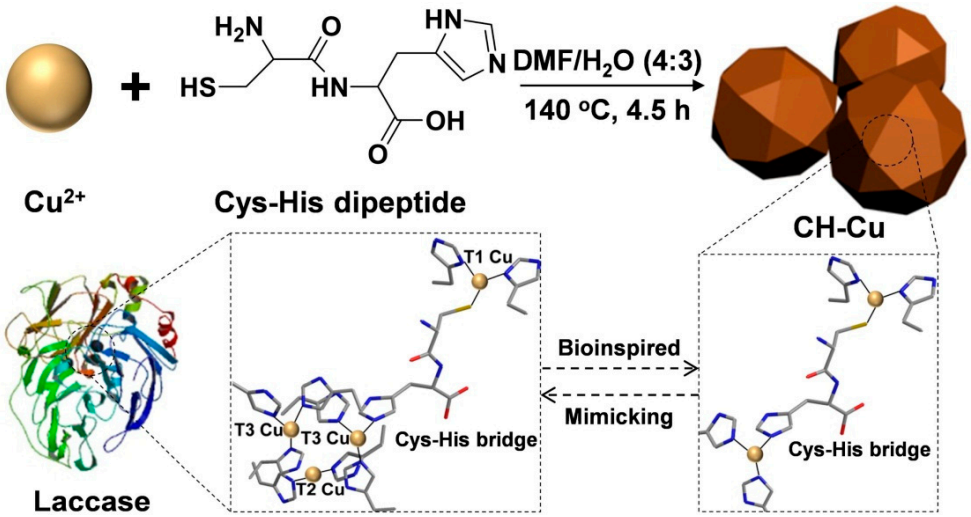

Figure 6. Schematic representation of a new CH–Cu nanozyme via the coordination of Cu^+/Cu^{2+} with a Cys-His dipeptide for the degradation of chlorophenols and bisphenols. Reproduced from Reference [90] with permission from Elsevier.

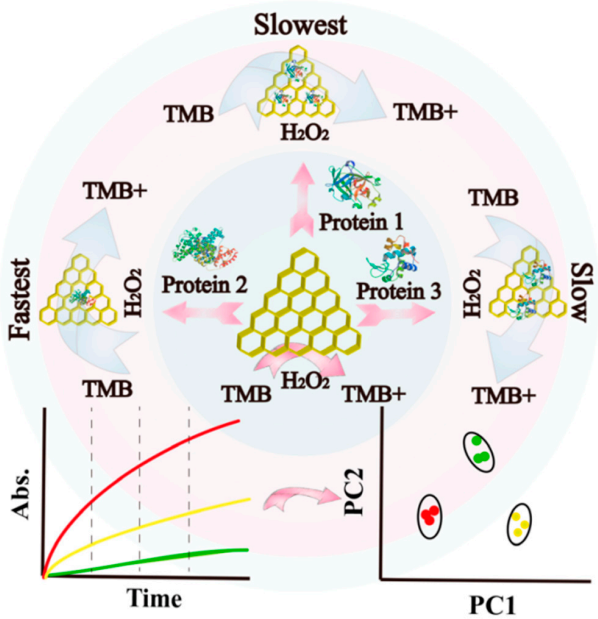

Figure 7. Schematic representation of one kind of multiple readout system based on g-C_3N_4 nanosheets for the recognition of different proteins. Reproduced from Reference [95] with permission from The American Chemical Society.

4.4. Nanozymes in Cancer Therapy

In cancer diagnosis and therapy, nanozymes have received great attention. Nanozymes can be remotely controlled by different stimuli such as magnetic field, light, ultrasound, and heat [98]. These above stimuli factors can be applied for improving the diagnostic and therapeutic efficacies of different diseases in biomedical applications. For example, Li et al. developed a PtFe@Fe_3O_4 nanozyme with two kinds of enzyme-like catalytical activities for tumor therapy [99]. In the tumor microenvironment, the PtFe@Fe_3O_4 nanozymes exhibited a photothermal effect with photo-enhanced catalase-like and peroxidase-like activities. The current systems are mainly based on oxygen status and/or external stimuli to produce ROS, which can cause the apoptosis of tumor cells and act as a promising treatment strategy for malignant neoplasms. However, for hypoxic tumors, the therapeutic efficacy is limited, because the generation of ROS highly relied on oxygen status and external stimuli. A self-assembly of MnO_2@PtCo nanoflowers-based nanozymes that catalyzed a cascade of intracellular reactions to generate ROS in both normoxic and hypoxic conditions which were dispensed with external stimuli were rationally designed and synthesized by the Qu group [100] (Figure 8). PtCo and MnO_2 served as an oxidase mimic and catalase mimic, respectively. The MnO_2@PtCo nanoflowers can relieve hypoxic conditions as well as induce the apoptosis of tumor cells based on the ROS-mediated mechanism, thus causing a remarkable and specific inhibition of neoplasm growth. In contrast with traditional ROS-mediated systems, this platform possesses many advantages; for example, no external stimuli were needed. By combining the oxidative activity of PtCo with the supplement ability of O_2 from MnO_2, remarkable therapeutic efficacies for hypoxic tumors were achieved. The MnO_2@PtCo nanoflowers could preferentially cause the apoptosis of tumors, since the oxidative ability of nanoflowers depends on the acidic pH.

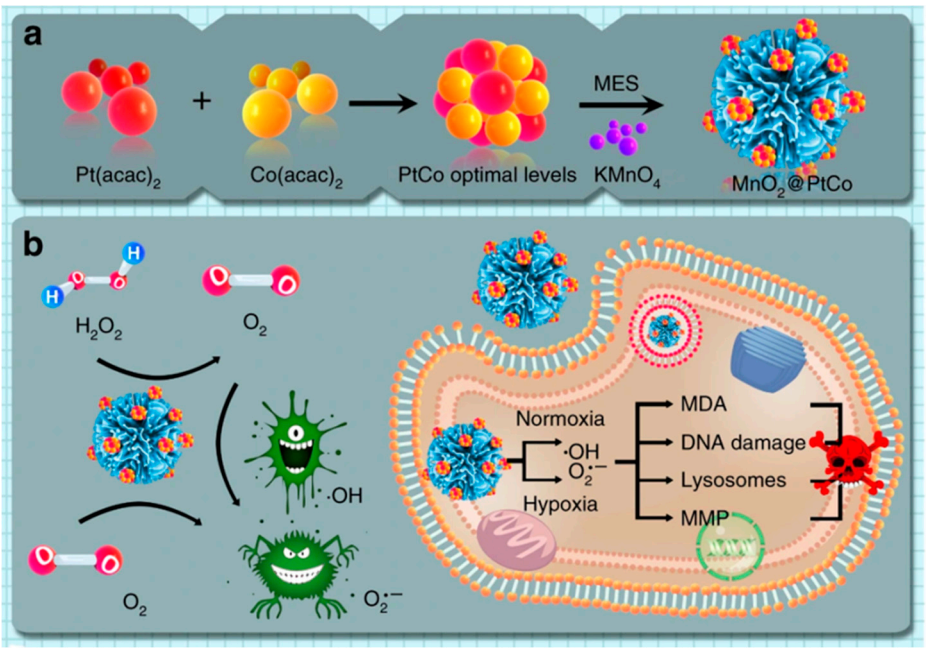

Figure 8. Schematic representation of (**a**) the synthesis of MnO_2@PtCo nanoflowers and (**b**) the generation mechanism of reactive oxygen species (ROS) and cytotoxicity by MnO_2@PtCo nanoflowers under different oxygen tensions. Reproduced from Reference [100] with permission from The Nature Publishing Group.

5. Summary and Outlook

The emergence of nanozymes not only changes the traditional concept that nanomaterials are biological inert substances, but also provides a new perspective for the study of the biological effects of nanomaterials. Nanozymes enrich the research content of enzyme mimics, making it expand

from organic compounds to inorganic nanomaterials, expanding the application of nanomaterials. Although tremendous progress has been achieved in the field of nanozymes, this field still faces great challenges. Firstly, the catalytic mechanism of different kinds of nanozymes should be thoroughly investigated. Generally, the nanozymes exhibit multiple enzyme-mimicking catalytical properties due to the diversity of substrates. Therefore, the catalytic specificity and substrate selectivity of the nanozyme should be regulated and explored for designing different applications. With the development of nanotechnology, numerous and new discoveries of nanozymes should be explored, expanding the scope of enzyme categories. Future designs will be focused on reversibly turning ON/OFF the catalytic activity of nanozymes by changing the environmental condition. Nanozymes possess dual-functional characteristics as nanomaterials with catalytic properties. It is possible, by means of combining the dual functional characteristics of nanozymes, to create more nanozymes with unique functions and reveal their mechanisms of action that can be applied to human health, environmental protection, and bioenergy in the future.

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