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REVIEW

Nanozymes in the Treatment of Diseases Caused by Excessive Reactive Oxygen Specie

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Abstract: Excessive reactive oxygen species (ROS) may generate deleterious effects on biomolecules, such as DNA damage, protein oxidation and lipid peroxidation, causing cell and tissue damage and eventually leading to the pathogenesis of diseases, such as neurodegenerative diseases, ischemia/reperfusion ((I/R)) injury, and inflammatory diseases. Therefore, the modulation of ROS can be an efficient means to relieve the aforementioned diseases. Several studies have verified that antioxidants such as Mitoquinone (a mitochondrial-targeted coenzyme Q10 derivative) can scavenge ROS and attenuate related diseases. Nanozymes, defined as nanomaterials with intrinsic enzyme-like properties that also possess antioxidant properties, are hence expected to be promising alternatives for the treatment of ROS-related diseases. This review introduces the types of nanozymes with inherent antioxidant activities, elaborates on various strategies (eg, controlling the size or shape of nanozymes, regulating the composition of nanozymes and environmental factors) for modulating their catalytic activities, and summarizes their performances in treating ROS-induced diseases.

Keywords: nanozymes, enzyme-mimic, oxidative stress, antioxidant, ROS-related diseases

Introduction

Reactive oxygen species (ROS) contain various reactive molecules and free radicals (species with unpaired electrons) derived from molecular oxygen, such as hydrogen peroxide (H_2O_2), superoxide ($O_2^{\cdot-}$) and hydroxyl radicals ($^{\cdot}OH$).[1–3] ROS are produced by a cell converting oxygen into oxygen radicals during physiological processes in biological systems and play roles as signaling molecules in cells, including activating cell signaling cascades, inducing apoptosis, and influencing gene expression.[4–7]

However, oxidative stress occurs when ROS generation increases or antioxidant defense systems become weaker or both, which means unquenched ROS may trigger further reactions.[5,8,9] In turn, oxidative stress destroys biomacromolecules and plays a part in a series of pathologies, including neurodegeneration, inflammation, atherosclerosis, diabetes, and aging.[4,10–12] As massive ROS production and associated oxidative damage are also identified as important causative factors for diseases such as I/R, researchers speculated that scavenging excessive ROS might be a viable method for oxidative stress-related diseases in the future.[13,14]

Nanozymes are inorganic nanomaterials that mimic enzyme activities.[15] Since ferromagnetic nanoparticles (NPs) were detected to possess enzyme-like activity for the first time,[16] various nanomaterials have been developed with peroxidase-like, oxidase-like, catalase-like and superoxide dismutase (SOD)-like activities and are widely used in biomedicine fields such as biosensing, disease diagnosis and treatment.[17,18] Furthermore, as Gao and Yan et al concluded, nanozymes should be consistent with the enzyme kinetics and catalytic mechanism of natural enzymes, such as the

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Michaelis–Menten equation. As a substitute for natural enzymes, even compared to other artificial enzymes, nanozymes are more prominent in their stability to pH and temperature, low production cost, ease of synthesis in large quantities, and reusability.[19,20] In addition, the unique physicochemical properties of nanomaterials endow them with a variety of functions and provide various methods for rational design.[21] By virtue of enzyme-like activities, especially SOD-like and catalase-like activities, nanozymes are expected to eliminate intracellular ROS and have therapeutic effects in ROS-related damages or diseases.

In this review, we focus on the catalytic activity of antioxidant nanozymes and their significant research progress in the treatment of excessive ROS-caused diseases. First, nanozymes that show antioxidant activity, including carbon-based, metal-based, and metal oxide-based nanozymes, are summarized. Second, strategies for modulating nanozymes to elevate their ROS-quenching capacities are outlined. Third, the applications of nanozymes in relevant treatments are introduced. We hope that this review will provide an overview of antioxidant nanozymes in the ROS-induced disease treatment field, as well as inspiration for future clinical applications.

Antioxidant Nanozymes

Here, we introduce the representative types of antioxidant nanozymes, which have been reported as antioxidants in recent years in the following section (Table 1).

Carbon-Based Nanozymes

Carbon-based nanomaterials have outstanding physicochemical properties, such as electrical, thermal, and optical properties, which make them promising materials for biomedical applications.[22] They contain fullerene, graphene nanosheets, graphene oxide (GO), graphene quantum dots (GQDs), and carbon nanotubes (CNTs), which can be divided into zero-dimensional nanomaterials (fullerene, carbon dots, GQDs), one-dimensional nanomaterials (CNTs), two-dimensional nanomaterials (graphene), and three-dimensional nanomaterials (nanodiamonds) based on the number of dimensions exceeding the nanoscale (100 nm).[23]

Fullerenes are carbon spheres, in which C-atoms are sp^2-hybridized carbon atoms, and presently are used for various applications in nanomedicine.[24,25] The existence of abundant conjugated double bonds and low lying lowest unoccupied molecular orbital endow them the ability to scavenge radical species.[26] With the abovementioned characteristics, fullerenes show antioxidant activity in dealing with $O_2^{\cdot-}$, $^{\cdot}OH$, and H_2O_2, and are called "free radical sponges".[27–29]

Through inhibiting cellular ROS levels, fullerenes could suppress proinflammatory cytokine release in synovial inflammation-related cells in vitro, and alleviate synovitis and joint destruction significantly in vivo.[30] Fullerenol belongs to fullerene derivatives and exhibits excellent water solubility. With the intrinsic capability of eliminating ROS, fullerenol/alginate hydrogels were synthesized to protect brown adipose-derived stem cells (BADSCs) against the oxidative stress damage after myocardial infarction (MI) and improve the cardiomyogenic differentiation.[31] In MI rat model, the fullerenol/alginate hydrogel seeded with BADSCs reduced infarct size, increased wall thickness, and improved cardiac functions successfully.

CNTs, with hollow and cylindrical structure, are formed by rolled graphene sheets. Single-walled CNT consist of one graphene sheet, while multiwalled carbon nanotubes (MWCNTs) consist of multiple single graphene layers.[32] For the first time, Fubini et al reported MWCNTs exhibited a remarkable ROS scavenging capacity, including $^{\cdot}OH$ and $O_2^{\cdot-}$.[33] The excellent electron affinity of the molecular orbitals or electronic bands of the carbon atoms in the nanotube framework was conductive to the scavenging reaction.

Graphene is a flat-like layer of densely packed sp^2 carbon atoms. For graphene-based nanomaterials, Akhavan et al had summarized that the electron density, chemical composition, sp^2-hybridized carbon content and chemical properties were responsible for their ROS-scavenging abilities.[13] Just as Hurt et al reported that a series of graphene-based materials showed $^{\cdot}OH$ scavenging activities.[34] Among them, few layer graphene exhibited the best performance, followed by reduced graphene oxide (rGO) and GO. The activity order was in inverse to their total surface area. Thus, the main antioxidant activities of graphene-based materials were ascribed to pristine sp^2 carbon domains rather than oxygen-containing functional groups.

Table 1 Representative Antioxidant Nanozymes and Their Applications

Nanozymes	Activity/Mechanism	Application	Reference
Fullerenes	$^{\cdot}OH$ and $O_2^{\cdot-}$ scavenging activity	Cardiac functional recovery	[31]
		Allergic response	[165]
		Doxorubicin-induced hepatotoxicity	[166]
Graphene based NPs	$^{\cdot}OH$ and $O_2^{\cdot-}$ scavenging activity Catalase	Neuroprotection	[34]
		Cardiac repair	[36]
		Acute kidney injury	[134]
Fe_3O_4 NPs	Peroxidase Catalase	Aging	[39]
		Neurodegeneration	[39]
		Cerebral malaria	[167]
PBNPs	Peroxidase Catalase SOD	Colitis	[43]
		Acute pancreatitis	[47]
		Full-thickness skin wound	[48]
		Ischemic Stroke	[49]
CeO_2 NPs	Catalase SOD Oxidase	Ischemic stroke	[62,63]
		AD	[64–66]
		Depression	[67]
		IBD	[69]
		Acute gout	[70]
		Drug-induced liver injury	[73]
		PD	[75]
		Rheumatoid arthritis	[168]
		Traumatic brain injury	[169]
Mn_3O_4 NPs	SOD Catalase GPx	Ear inflammation	[82]
		PD	[84]
		IBD	[170]
Cu based NPs	Peroxidase SOD Catalase GPx	Acute kidney injury, acute liver injury, wound healing	[20]
		PD	[79]
Mo based NPs	SOD Catalases Peroxidases	Acute kidney injury	[162]
		Hepatic fibrosis	[171]
Pt NPs	SOD Catalases Peroxidases	Pulmonary inflammation	[172]
		Hepaticischemia/reperfusion injury	[173]

(*Continued*)

Table 1 (Continued).

Nanozymes	Activity/Mechanism	Application	Reference
Melanin-like NPs	$^{\cdot}OH$, $O_2^{\cdot-}$, H_2O_2, NO, and $ONOO^-$ scavenging activity	Ischemic stroke	[153]
		Periodontal disease	[150]
		Osteoarthritis	[148]
		Acute peritonitis and acute lung injury	[174]
MOF based NPs	SOD Catalase	Endotoxemia	[97]
		IBD	[175]

In virtue of the antioxidant activities, graphene-based nanomaterials are used for medical treatment applications, such as neurotoxicity and cardiac repair.[35,36]

GOQDS could decompose H_2O_2 to H_2O and O_2, thus verifying their catalase-like activity.[36] Pretreatment with GOQDS in 1-methyl-4-phenyl-pyridinium ion (MPP^+) induced PC12 cells and the brains of larval zebrafish could prevent overproduction of ROS and provide neuroprotection.[35]

GOs was modified with polyethylenimine and folic acid−polyethylene glycol (PEG) to form a macrophage-targeting /polarizing GO complex (MGC).[36] The as-prepared material was verified to eliminate $^{\cdot}OH$ which invoked cardiac failure after MI. In turn, inflammatory biomarkers, such as tumor necrosis factor-α (TNF-α), were less produced during the inflammatory phase. Additionally, DNA-functionalized MGC promoted the polarization of M1 to M2 macrophages and accelerated secretion of cardiac repair-favorable cytokines. Collectively, this compound played dual roles to attenuate inflammation and improve heart function.

Metal and Metal Oxide-Based Nanozymes

Iron Based

Under different reaction conditions, iron oxide nanozymes (including Fe_3O_4 and Fe_2O_3) exhibited either peroxidase-like or catalase-like activities.[16,37,38] These activities conferred iron oxide nanozymes the abilities to scavenge ROS under appropriate conditions.

Intrigued by the discovery of the catalase-like activity of iron oxide NPs, researchers have explored how these nanoparticles dealt with oxidative stress in aging or neurodegeneration.[39] Fe_3O_4 NPs alleviated a cell model of Parkinson's disease (PD) death and reduced the levels of α-synuclein and cleaved caspase-3, which are presynaptic neuronal proteins tightly linked to PD pathogenesis and apoptosis markers, respectively. Finally, the effects of dietary Fe_3O_4 NPs on aging and the Alzheimer's disease (AD) model of Drosophila were tested, and Fe_3O_4 NPs were effective in increasing life span, antiaging, promoting locomotor activity and reducing apoptosis in these disease models.

Combining nanozymes and natural antioxidants has also been used as free radical scavengers, as shown in Figure 1A.[40] As Zhao et al designed, Fe_3O_4 NPs and the polyphenol tannic acid (TA), which is a natural antioxidant, were combined into Fe_3O_4@TAn nanoflowers (NFs), as shown in Figure 1B. The Fe_3O_4@TAn NFs could mimic peroxidase, catalase, and SOD. Through the complementary action of Fe_3O_4 and TA, the as-designed nanomaterial exhibited improved and broad-spectrum ROS eliminating activity. Additionally, the nanoflower morphology of the Fe_3O_4@TAn NFs made them fully exposed to oxidative stress conditions, thus contributing to the excellent activity. Owing to a remarkable multiple ROS scavenging activity, the Fe_3O_4@Tan NFs were employed to treat mouse endotoxemia with excellent results.

In addition, Prussian blue nanoparticles (PBNPs), as Fe-containing nanomaterials with good biosafety, were also found to possess multienzyme activities. The different redox potentials of PB, Prussian white (PW), Berlin green (BG), and Prussian yellow (PY) conferred these materials tremendous abilities to transfer electrons.[41–44] Dong et al proposed that PBNPs represented the first example of a bioinspired nanozyme.[45] They looked for the active site of PBNPs and

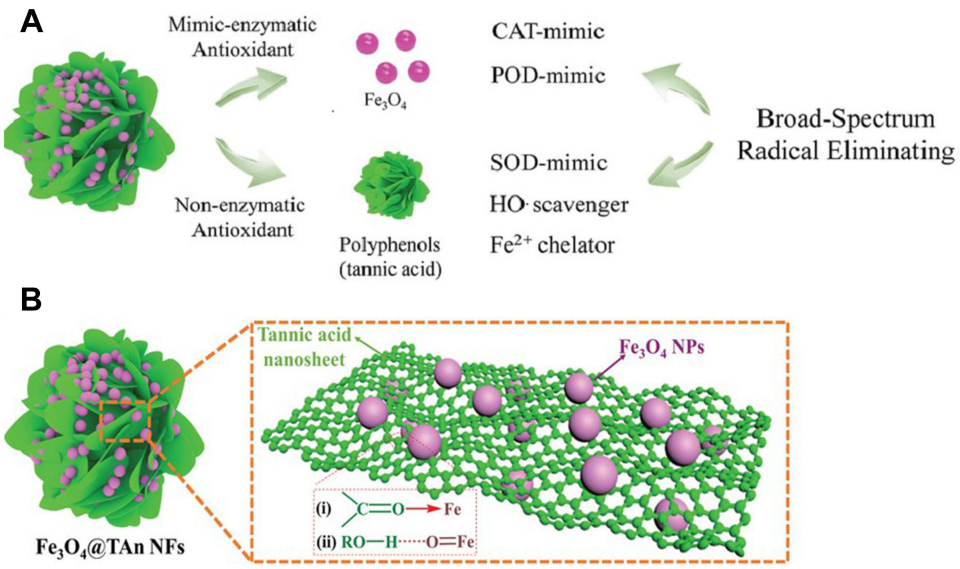

Figure 1 Iron oxide nanozyme and nonenzymatic antioxidant constructed a nanoplatform to mimic the antioxidant defense system. (**A**) The antioxidant ability of Fe_3O_4@TAn NFs. (**B**) Schematic illustration of the petal structure of Fe_3O_4@TA1.0 NFs. Reproduced with permission from Wei Z, Wang L, Tang C et al. Metal-phenolic networks nanoplatform to mimic antioxidant defense system for broad-spectrum radical eliminating and endotoxemia treatment. Adv Funct Mater. 2020;30(49). Copyright (2020) John Wiley and Sons.[40]

concluded that N-coordinated Fe units (FeN_x (x=4–6)) with intrinsic heme-like structures endowed PBNPs with peroxidase-like activity.

Thus, PBNPs could efficiently control ROS-induced cell damage and treat diseases such as mouse liver inflammation and injury, colitis, acute pancreatitis, cutaneous wound healing and ischemic stroke.[42,46–50]

Gold-Based

Au NPs were demonstrated to decompose H_2O_2 to O_2 at alkaline pH and scavenge superoxide at acidic pH.[51] The activities made Au NPs potential catalase and SOD mimetics. In addition, Guo and Lu et al showed that Au NPs played important roles in ameliorating neurologic deficits and infarction volumes and protecting the cerebra from I/R injury in rats via the regulation of inflammatory and immune responses.[52]

To eliminate the toxicity induced by ·OH produced by the catalytic action of Au nanoclusters (AuNCs), polymeric 3°-amine was added to Au NCs to simultaneously restrain the generation of ·OH and retain their catalase-like activity. The derived AuNCs-NH_2 acted as H_2O_2 scavengers, thus protecting primary mouse neurons against oxidative stress.[53]

Cerium Oxide (Ceria)-Based

As early as 2006, Schubert et al proposed that cerium oxide NPs could protect nerve cells from oxidative stress through the ability to limit the amount of ROS.[54]

As relevant studies developed, cerium oxide NPs were proven to have excellent multiple enzyme-mimicking properties due to their Ce^{3+}/Ce^{4+} oxidation state and the presence of oxygen vacancies.[55–57]

Numerous studies are performed on nanoceria and its biomedical application. CeO_2 NPs and related materials have been widely used to protect cells that are destroyed by excessive ROS, such as nerve cells, macrophages, cardiac progenitor cells, human breast cells, fibrosarcoma cells and human hepatic cells.[54,57–61] Furthermore, they may serve as a novel therapy for neurodegenerative diseases, depression, ischemic stroke, autoimmune diseases, hepatic injury, sepsis, psoriasis, inflammatory bowel disease (IBD), periodontitis, and acute gout.[62–77] Based on the excellent ROS eliminating capabilities of CeO_2, researchers have explored various kinds of targeted methods to address the aforementioned diseases.

During the treatment of ROS-related diseases, CeO_2 also plays roles in downregulating proinflammatory cytokine levels, upregulating anti-inflammatory cytokine levels, inhibiting the ROS–NFκB pathway, etc.[69,73,77]

Copper Based

Cu-based nanozymes have been widely used to eliminate ROS and improve ROS-related diseases, including PD, acute liver injury, acute kidney injury, and wound healing.[20,78,79]

Deng's group considered that large surface-to-volume ratios would confer high catalytic activity, so they made ultrasmall $Cu_{5.4}O$ NPs ($Cu_{5.4}O$ USNPs), the average hydrodynamic diameter of which was as small as 4.5 nm.[20] The as-designed nanoparticles were verified to have multiple enzyme-mimicking activities, including catalase, glutathione peroxidase (GPx), SOD and excellent broad-spectrum ROS scavenging ability. The reason for the name "$Cu_{5.4}O$ USNPs" was because the materials were a mixture of Cu and Cu_2O NPs.

Manganese-Based

Lv et al first discovered that manganese dioxide (MnO_2) nanoparticles possessed enzyme-mimicking activities, which was further demonstrated in another study in 2017.[80,81]

Recently, Mn_3O_4 nanozymes were also confirmed to possess antioxidant enzyme-like properties, and when compared with the most widely used CeO_2, researchers found that Mn_3O_4 nanozymes were more effective in terms of ROS elimination.[82,83] The mixed valance states of Mn^{2+}/Mn^{3+}, tolerance to oxidation, large surface area and extremely large pore size of Mn_3O_4 nanozymes contributed to their outstanding multienzyme activity.[82]

Mn_3O_4 nanozymes could provide efficient cytoprotection in SHSY-5Y, which is a human cell line model for the PD phenotype, and protect mice from phorbol 12-myristate 13-acetate (PMA)-induced ear inflammation.[82,84] Furthermore, Mn_3O_4 nanozymes were proven to protect cells suffering from oxidative stress.[83] The related expression of various stress markers and antioxidant enzymes in the presence of Mn_3O_4 nanozymes was also detected. Conclusively, Mn_3O_4 nanozymes complemented the antioxidant machinery and rescued the cells under oxidative stress independent of the endogenous antioxidant machinery.

Other Metal-Based Nanozymes

Qu and his cooperators synthesized GO-Se nanocomposites and Se@PDA (polydopamine) nanozymes, which both showed GPx-like properties.[85,86] Se@PDA nanocomposites showed excellent antioxidant activity, which was ascribed to the enzyme-like effect of the Se component and the nonenzymatic antioxidant ability of pDA.[86] By decomposing excessive intracellular H_2O_2, the nanocomposites successfully alleviated neumonia in the mouse model. To achieve higher GPx-like activity, mesoporous selenium NPs (MSeNPs) with a high specific surface were synthesized.[87] Then, hyaluronic acid (HA), which could specifically attach to CD44 on the surface of macrophages, was assembled on the MSe NPs to facilitate the accumulation of the as-designed nanozyme at the site of inflammation. Taken together, treatment with MSe-HANPs successfully relieved local inflammation and sepsis.

Metal Organic Frameworks (MOFs) Based

MOFs are a class of supramolecular coordination complexes with metal ions/clusters bridged with organic linkers by coordination bonds.[88,89] They also have natural enzyme-mimicking properties. For example, MOF-derived copper nanoparticle@carbon nanocomposites, iron(III)-based MOFs (MIL-68 and MIL-100) (MIL=Material Institute of Lavoisier), PA-Tb-Cu MOF, Cu^{2+} ion-modified UiO-type MOF NPs (UiO = University of Oslo), MOF-808 and zirconium-ferriporphyrin (Zr-FeP) MOF were verified to possess peroxidase-like activities.[90–95]

Tb^{3+} as a metal ion and a boronic acid ligand as a linker constituted a luminescent Tb-MOF.[96] The boronic acid groups of Tb-MOF reacted with ROS through the rapid nucleophilic addition reaction, which endowed the MOF with ROS quenching capability. Further investigation proved that Tb-MOF effectively scavenges exogenous or endogenous ROS in living cells, including HeLa cells and RAW 264.7 cells.

According to the size and active sites of natural SOD, Qu and Ren et al designed ultrasmall and bioinspire Cu-TCPP MOF nanodots (CTMDs), the average size of which was less than 5 nm.[97] The Cu active sites of CTMDs showed a similar coordination of N and O atoms to that of SOD, while the ordered channels were similar to substrate channels that could accumulate superoxide, thus contributing to the potent SOD-like activities of CTMDS. Additionally, CTMDs could catalyze H_2O_2 into H_2O with glutathione (GSH), which mimicked the activity of GPx. Combining SOD-like and

GPx-like activity, CTMDs could effectively destroy $O_2^{\cdot-}$ and H_2O_2. As demonstrated in vivo, CTMDs could alleviate endotoxemia efficiently by eliminating ROS and reducing systemic inflammation.

Others

Melanin and Its Derivatives

Nanomaterials derived from natural organisms have been used in biological and medical applications due to their biocompatibility and biodegradability. As a natural biopolymer, melanin is distributed in the human body, such as skin, eye, brain, and hair.[98,99] It showed scavenging activity toward ROS and protected skin from UV damage.[100] In addition, PDA NPs, as the most typical synthetic melanin, are produced by the oxidative polymerization of dopamine. The reductive functional groups of PDA NPs, including catechol and imine, endow them with robust potential in scavenging ROS.[98,101,102]

Ultrasmall Mn^{2+}-chelated melanin NPs (MMPPs) were also verified to exhibit multiple ROS scavenging activities and used to treat murine acute kidney injury.[103] Considering the characteristics of targeted disease, MMPPs were designed with an ultrasmall hydrodynamic size, good physiological stability, and stable radiolabeling performance. Thus, they could preferentially concentrate in the kidney and show a robust antioxidative protection response with few side effects.

Single Atom Nanozymes (SAzymes)

SAzymes contain single metal atoms on various supports, which can maximize the utilization of metal atoms, thus achieving high activity and selectivity and shrinking the difference between nanozymes and natural enzymes.[104–106]

To obtain an efficient antioxidant therapy for sepsis, Qu and Ren et al synthesized a SAzyme, Co/PMCS, characterized by atomically dispersed coordinatively unsaturated active Co porphyrin centers. The SAzymes could mimic SOD, catalase and GPx, thus obliterating multiple RONS.[107] In another experiment, the researchers tried to develop a clinically applicable bandage based on a single-atom Pt/CeO_2 nanozyme for brain trauma (Figure 2). [108] The nanozyme had high and persistent catalytic activity, which could fight against oxidative stress, decrease neuroinflammation and improve neurotrauma. The high catalytic activity was ascribed to the 2% lattice expansion induced by Pt single atoms dispersed on the CeO_2 (111) matrix, thus decreasing the binding energy of the chemical reactions. Moreover, Pt/CeO_2 avoided obvious decay due to continuous exposure to oxygen and maintained catalytic activity for up to 30 days, which was ascribed to its sustained electron-donating ability via the Mars–van Krevelen reaction.

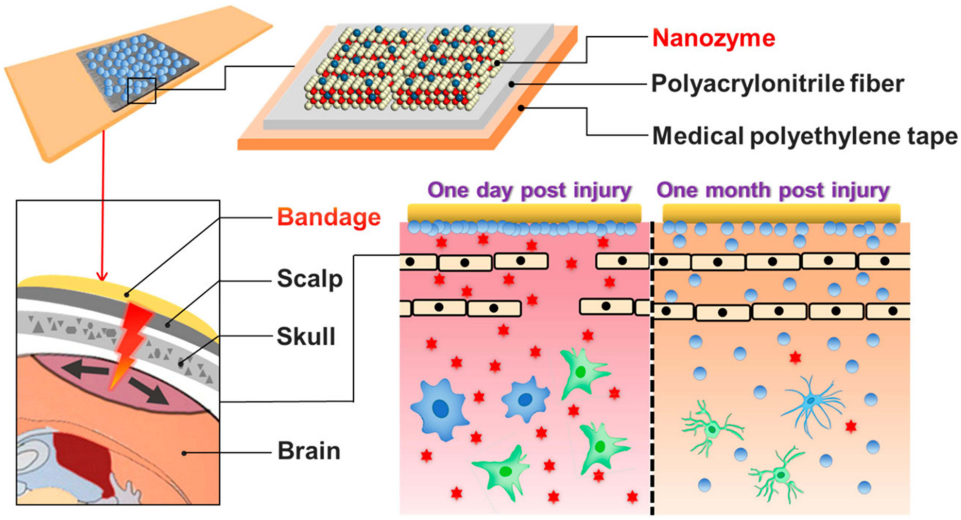

Figure 2 Schematic diagram of the nanozyme-based bandage to treat brain trauma. Reprinted with permission from Yan R, Sun S, Yang J et al. Nanozyme-based bandage with single-atom catalysis for brain trauma. *ACS nano*. 2019;13(10):11,552–11,560. Copyright (2019) American Chemical Society.[108]

Regulatory Factors for Nanozyme Activity

Elevating the catalytic properties of nanozymes is a topic of common concern. Studies focused on activity regulation have been performed in the past few years. The following are several important factors that influence the antioxidant activity of nanozymes.

Physicochemical Properties

Size

Generally, smaller nanozymes show better catalytic activity than larger nanozymes. As the size decreases, nanozymes obtain a higher surface-to-volume ratio, expose more active sites, and have a larger surface energy.[21,109] However, there are some special cases; for example, the catalytic performance of Pd-Ir NPs increased with increasing size.[110] To exclude other physicochemical factors, the researchers synthesized nanomaterials with the same morphologies and surface structures except for size. Catalytic activity parameters, such as K_{cat} (catalytic rate constant) and K_{cat}/S (area-specific K_{cat}), were compared. As the size of the Pd-Ir NPs increased, K_{cat} continuously increased by nearly 12-fold. However, the K_{cat}/S values for different sizes of Pd-Ir NPs were similar. Combining the results, the conclusion was that the catalytic activity of the NPs was mainly ascribed to the catalytic surface areas, which could promote the interaction of individual nanoparticles and more substrates.

Shape and Morphology

The catalytic activity of nanomaterials also depends on shape and morphology.[111] For instance, Ge et al speculated that antioxidant activity was structure-dependent for the carbon nanomaterial family.[29] They evaluated the radical scavenging activities of buckyball-shaped fullerene derivatives and sheet-shaped GQDs by electron spin resonance (ESR) measurements. After comparison, the activities were in the order C70>C60>GQD. By theoretical calculations of the Gibbs free energies of reactions (*G*r), the *G*r's of C60 and C70 were much lower than that of GQD, suggesting that larger radical scavenging activity depends on the lower *G*r values.

More deeply, scientists revealed the prominent effect of surface facets in determining the enzyme-like activity of Pd nanocrystals.[112] They discovered that Pd octahedrons enclosed by 111 facets had greater enzyme-mimic activity than Pd nanocubes enclosed by 100 facets through ESR experiments (Figure 3A). Taking advantage of theoretical simulations, the ROS clearance that reacted on Pd 111 and 100 facets was calculated. The reaction energy (*E*r) of the rate-limiting step could be used as the descriptor of the enzyme activity of the metal. As shown in Figure 3B, the *E*r values of H_2O_2 and $O_2^{\cdot-}$ on the 111 facet were both stronger than those on the 100 facet, which indicated greater H_2O_2 and $O_2^{\cdot-}$ scavenging activities.

Interestingly, Kuang et al prepared a complex of CuO and Cu_2O nanoparticle clusters (Cu_xO NCs) by selecting L-phenylalanine (L-Phe) as the structure-directing agent.[79] The Phe ligand was confirmed to take part in determining the Cu_xO NC structure, which had a uniform diameter and morphology, a larger volume of pores and a larger pore size than those of other materials, such as Cu_xO-aspartic acid (Asp) (Figure 3C), thus endowing the Cu_xO NCs with higher catalytic performance.

Composition

Tailoring the composition of nanomaterials, such as doping other elements or forming bimetallic or multimetallic nanocomposites, poses another way to tune the activity of nanozymes.[113–118]

Hyeon and Lee et al introduced Zr^{4+} into ceria nanoparticles to increase the Ce^{3+}/Ce^{4+} ratio and convert Ce^{4+} to Ce^{3+} since Ce^{3+} targets $O_2^{\cdot-}$ and $^{\cdot}OH$.[72] Through investigation, the $Ce_{0.7}Zr_{0.3}O_2$ (7CZ) NPs showed the best ROS-scavenging performance. Additionally, in vivo tests also demonstrated that 7CZ NPs effectively reduced mortality and systemic inflammation in sepsis. By Li doping, the catalytic activities of $ZnMn_2O_4$ nanozyme developed from single antioxidant activity to multiple activities, including SOD-like, catalase-like and GPx-like activities, with enhanced performance.[119] Through XPS analysis, the molar ratio of Mn^{4+}/Mn^{3+} increased from 0.56 to 2.29 along with gradual Li doping.

Another doping strategy was adopted to improve the catalytic activity of Prussian blue analog (PBA)-based nanozymes (Figure 3D and E).[120] In this study, Ni-Fe bimetal PBA-based nanocages doped by molybdenum-polysulfide (Nanocages)

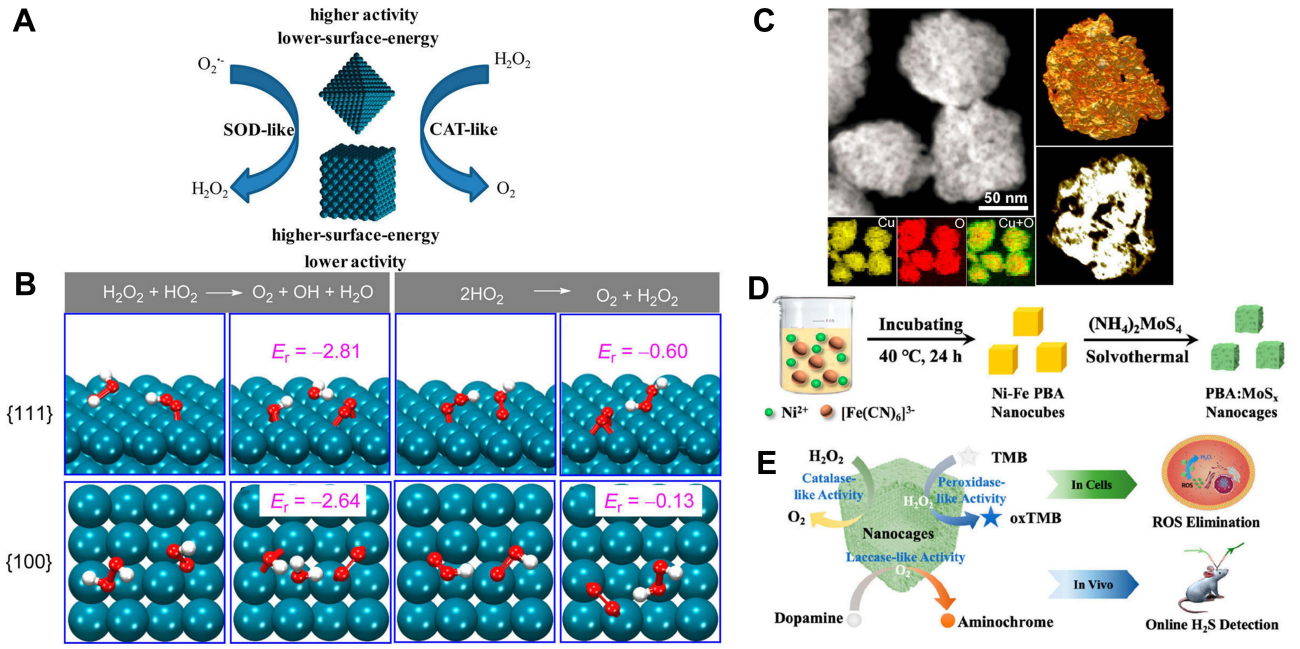

Figure 3 The regulation of nanozyme activity based on physicochemical properties. (**A**) Lower surface energy {111}-faceted Pd octahedrons and higher surface energy {100}-faceted Pd nanocubes. (**B**) Lowest-energy adsorption structures and reaction energies (in eV) for the reactions on structures having either Pd 111 or 100 facets. Reprinted with permission from Ge C, Fang G, Shen X et al. Facet energy versus enzyme-like activities: the unexpected protection of palladium nanocrystals against oxidative damage. *ACS Nano*. 2016;10(11):10,436–10,445. Copyright (2016) American Chemical Society.[112] (**C**) STEM, energy dispersive X-ray spectroscopy (EDS) mapping and electron tomographic reconstruction of Cu_xO NCs. Reprinted with permission from Hao C, Qu A, Xu L et al. Chiral molecule-mediated porous CuxO nanoparticle clusters with antioxidation activity for ameliorating Parkinson's disease. *J Am Chem Soc*. 2019;141(2):1091–1099. Copyright (2019) American Chemical Society.[79] Synthetic process (**D**) and catalytic performance (**E**) of the Nanocage. Reprinted with permission from Wang C, Ren G, Yuan B et al. Enhancing enzyme-like activities of Prussian blue analog nanocages by molybdenum doping: toward cytoprotecting and online optical hydrogen sulfide monitoring. *Anal Chem*. 2020;92(11):7822–7830. Copyright (2020) American Chemical Society.[120]

were prepared and were proved to have multiple enzyme-like activities. Doping molybdenum into PBA successfully regulated the size (decreased), shape (from solid to hollow), composition, and electronic structure of the nanocage, thus bringing in more catalytic sites and binding sites.

In addition, the peroxidase-like, catalase-like and SOD-like activity of PtCu nanoalloys was related to the atomic ratio of Pt/Cu.[121] At the same time, by changing the atomic ratio of Pt/Cu, the particle size, alloy composition and crystal structure of PtCu nanoalloys were controlled correspondingly.

Surface Coating and Modification

Controlling surface chemistry by surface coating and modification is also an advantageous way to improve catalytic performance because chemical reactions take place mainly on the surface of catalysts.[122] Ions (fluoride), small molecules such as amino acids, citrate, Prussian blue, amino acids, and polymers (protein, dextran, DNA) can act as materials for modification.[123–128]

Yan and Gao et al modified Fe_3O_4 NPs with histidine (His) residues to mimic the active site of horseradish peroxidase (HRP) and expected hydrogen bond formation between the distal imidazole group and H_2O_2.[129] The bionic design effectively altered the catalytic properties of the Fe_3O_4 nanozyme.

Specifically, abundant efforts have been made to improve the specificity of nanozymes for chiral substrates. By virtue of the surface coating of amino acids and DNA with chiral structures on nanozymes as chiral ligands, nanozymes can be designed with chiral selectivity.[130–133]

Natural phenolic antioxidants gave Qu and Ren et al inspiration; they used $NaBH_4$ as the reductant to convert C=O on classical GQDs (c-GQDs) to C–OH and formed GQDs (h-GQDs) with phenol-like groups.[134] Through comparison, the antioxidant activity of h-GQDs was at least 5 times that of c-GQDs under the same conditions. By means of experimental research and theoretical calculations, the researchers discovered step by step that phenol-like groups played an important

role in the catalytic performance of h-GQDs. In addition, carbonyl groups, which suppress the H-donating ability of the phenol-like group, were removed from h-GQDs, which also promoted the antioxidative activity of h-GQDs.

Form Complex or Hybrid Nanozymes

The construction of different nanozymes may improve their catalytic performance and result in synergistic effects and even multistep cascade reaction activity, thus attracting many intentions in recent years.[135–139]

A multinanozyme cooperative platform was assembled in which V_2O_5 nanowires acted as GP_X mimics, while MnO_2 nanoparticles mimicked SOD and catalase (Figure 4A). [140] V_2O_5@pDA@MnO_2 exhibited excellent ROS depletion performance that could mimic a natural antioxidant enzyme system (Figure 4B). Compared with Se NPs, GO-Se nanocomposites exhibited much higher GPx-like activity.[85] The reason might be that GO endows the GO-Se hybrid with a greater surface area and rapid electron transfer capacity.

Zeolitic imidazolate framework-8 (ZIF-8) was used to encapsulate CeO_2 NPs to form CeO_2@ZIF-8 and overcame some limitations of CeO_2.[141] According to the design, ZIF-8 mimicked peroxidase to maintain antioxidant activity and controlled the size, morphology, and surface potential of CeO_2, which was beneficial for biological applications.

Environmental Factor

The antioxidant performance of nanozymes is also sensitive to the surrounding environment, such as pH, temperature, and light. The catalytic activity of nanozymes is greatly influenced by pH. As Wei concluded, under acidic conditions, nanozymes showed peroxidase-mimicking activities, while under neutral and alkaline conditions, they exhibited SOD-like and catalase-like properties.[21]

Application of Nanozymes in Excessive ROS-Induced Diseases Treatment

In this section, we introduce the application of nanozymes in excessive ROS-induced diseases, including neurodegenerative diseases, inflammatory diseases, and stroke et al.

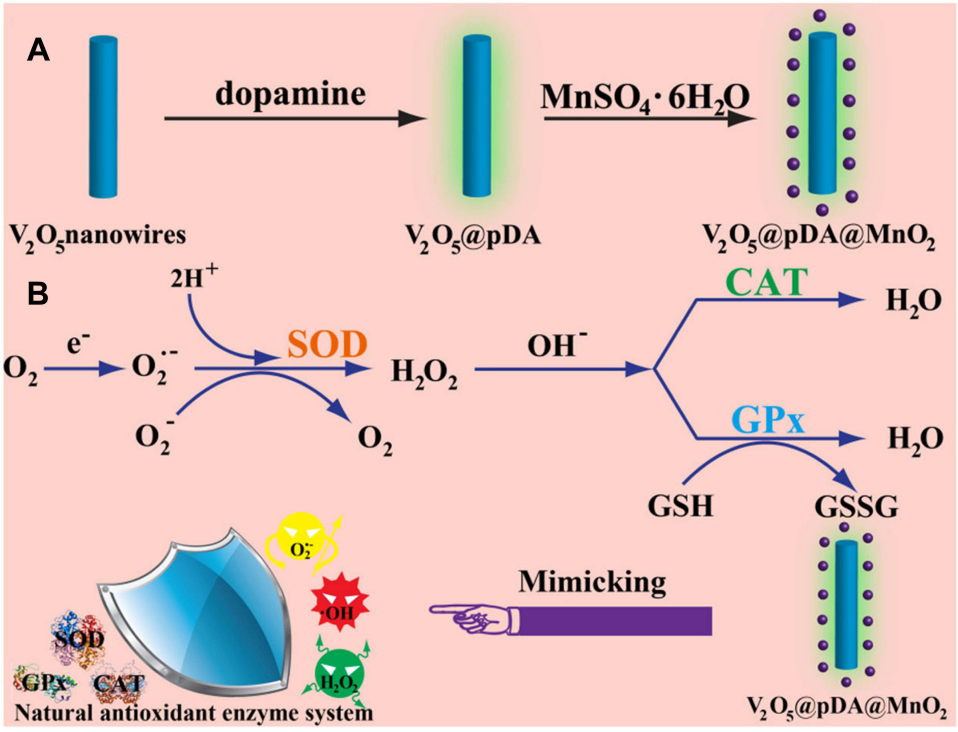

Figure 4 A multinanozyme cooperative platform to efficiently reduce ROS levels. (**A**) The synthesis process of V_2O_5@pDA@MnO_2 nanocomposites. (**B**) The multinanozyme system mimics the intracellular antioxidant enzyme-based defense system. Reprinted with permission from Huang Y, Ren J, Qu X. Nanozymes: classification, catalytic mechanisms, activity regulation, and applications. *Chem. Rev.* 2019, 119, 6: 4357–4412. Copyright (2019) American Chemical Society.[176]

Treatment of Inflammatory Diseases

The accumulation of ROS may be one of the signaling pathways connecting the UPR (unfolded-protein response) and inflammation, thus initiating an inflammatory response.[12,142] Excessive inflammation can cause chronic or systemic inflammatory diseases, including cardiovascular disease, atherosclerosis, asthma, cystic fibrosis, and rheumatoid arthritis.[143,144]

IBD, as a troublesome colorectal inflammatory disease, is also closely related to excessive ROS.[145] Current treatment for IBD mainly relies on antibiotics, which will induce problems such as antibiotic resistance. Prussian blue, which has been approved as an antidote by the US Food and Drug Administration (FDA) and with good biosafety, can also act as an artificial nanozyme, effectively scavenging ROS.[146] To improve the solubility of PB NPs, PPB NPs were prepared with the help of poly(vinylpyrrolidone) via a one-pot strategy.[43] The in vivo experiments showed that through intravenous administration, PPBs targeted the inflamed sites and alleviated colitis in mice; in addition, proinflammatory cytokines were inhibited significantly. Furthermore, to realize oral administration, it was an ingenious design to combine clinically approved montmorillonite (MMT) and CeO_2 in targeting the inflamed colon.[69] MTT, with negative charges and high tolerance to pH, endowed CeO_2@MMT with stability to pH and specific adsorption onto the inflamed colon, which was positively charged based on electrostatic interactions. Thus, the nanozyme could be efficiently delivered through the digestive tract, which made it suitable for oral administration. MMT could simultaneously decrease the systemic absorption of CeO_2, thus reducing potential toxicity. Budesonide, a promising drug for IBD, and MnO_2 nanozyme, a nanocarrier, when taken together, became more effective and could be taken orally, as Tong et al demonstrated in mouse models.[147] The main reasons for selecting hollow MnO_2 NPs were as follows: first, they possessed intrinsic enzyme-like properties, which could scavenge ROS; second, they had an adjustable hollow structure, which was conducive to the loading of drugs; and thirdly, they could be modified with dextran sulfate sodium (DSS), which could target activated macrophages. In addition, hollow MnO_2 NPs were influenced by the inflammatory microenvironment and were prone to release budesonide, thus fulfilling their role as nanocarriers. Compared with free budesonide, the nanocarrier system exhibited fewer side effects and had a better curative effect on IBD.

The researchers noticed some problems in the therapy of osteoarthritis, such as antioxidants, melatonin and N-acetylcysteine (NAC), were too small to stay long enough in the joint.[148] Therefore, they designed appropriately sized dopamine-melanin (DM) NPs, which were 112.5 nm in size, and made the nanomaterials suitable for retention in the joint for a long time. In a rat osteoarthritis model, DM NPs were found to combat damage caused by inflammation and protect chondro by scavenging intracellular RONS and activating antioxidant enzymes by autophagy. Sharma et al chose cartilage that suffered irreversible damage under oxidative stress as the therapeutic target.[149] PEG-MnO_2 NPs were designed with a size of less than 20 nm and positive surface charge. Due to the small size and zeta potential, the nanoparticles enabled cartilage penetration and chondrocyte uptake in vitro and in vivo. After one week, 75% of the initial signal remained in the joint space, which might be connected with the electrostatic interactions between nanoparticles and anionic cartilage tissue. Combined with the intrinsic ROS scavenging capability of MnO_2 NPs, the materials improved chondrocyte viability and extracellular matrix preservation by reducing inflammation-induced oxidative stress in cartilage.

Yang et al pointed out that in periodontal disease suffering from oxidative stress, PDA NPs with strong ROS removal capacity successfully decreased local periodontal inflammation.[150] PDA NPs that could satisfy the following conditions, such as robust antioxidative activity, degradability and low toxicity, might act as intelligent treatments for clinical application.

Treatment of Ischemic Stroke

Ischemic stroke, caused by artery thrombi in blood vessels, in turn leads to excessive ROS production and the resulting damaged neurons during the I/R process.[151,152]

Bioinspired melanin NPs (Me NPs) were employed as a novel antioxidant to treat ischemic stroke disease, as shown in Figure 5. The infarction area of the brain in a murine model was greatly reduced compared to that in the control.[153]

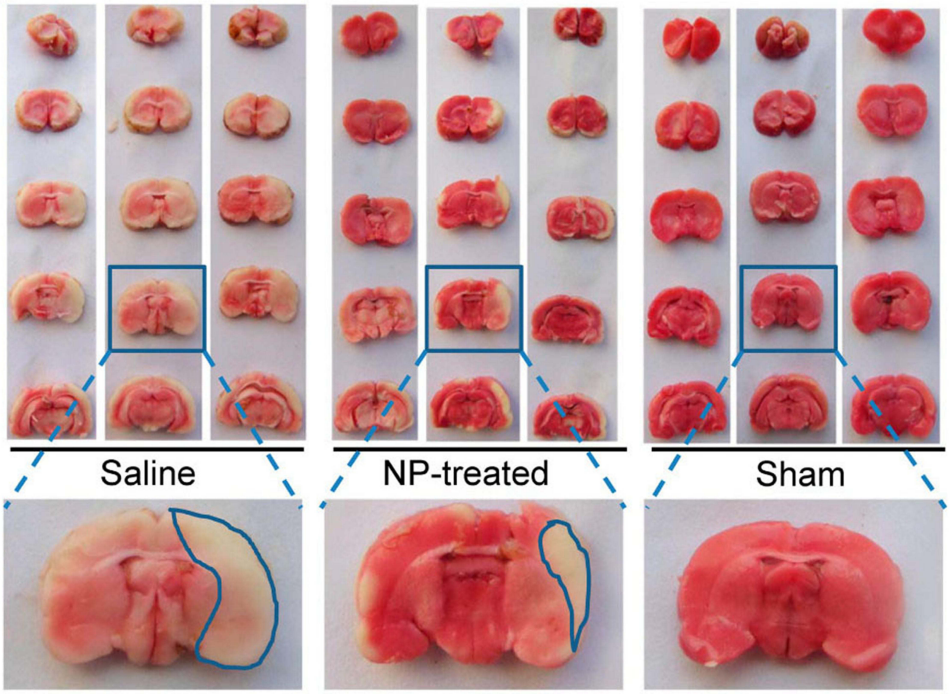

Figure 5 Comparison of the infarction area of 2,3,5-triphenyltetrazolium chloride-stained brain slices from different groups. Reprinted with permission from Liu Y, Ai K, Ji X et al. Comprehensive insights into the multi-antioxidative mechanisms of melanin nanoparticles and their application to protect brain from injury in ischemic stroke. *J Am Chem Soc*. 2017;139(2):856–862. Copyright (2017) American Chemical Society.[153]

The melanin NPs not only scavenged ROS, including $O_2^{\cdot-}$, H_2O_2, and $^{\cdot}OH$, but also reduced inflammatory responses by inhibiting the expression of inflammatory mediators and cytokines.

A stable composite formed by human serum albumin (HSA) bound to the Mn_3O_4 nanozyme was used to alleviate nervous system injury caused by ischemic stroke reperfusion.[154] Owing to HSA, the as-designed nanozyme showed excellent stability, which was important for high bioavailability and prolonged blood circulation time. Moreover, Mn ions were released from HSA-Mn_3O_4 into bodily circulation and thus promoted SOD2 expression. PEG- and angiopep-2 (ANG)-modified CeO_2 nanozyme was loaded with edaravone for the treatment of ischemic stroke.[62] PEGylation endowed CeO_2 nanozyme with superior characteristics of uniformity, small size, and prolonged blood circulation, while ANG led to effective cross blood–brain barrier (BBB) (through receptor-mediated transcytosis), which solved the problem of maintaining BBB integrity and the high accumulation need of nanozyme in damaged areas (Figure 6). The loaded edaravone and CeO_2 core both contributed to the removal of ROS, thus providing an efficient strategy for treating strokes. To solve the problems that exist in nanozyme treatment, such as less nanozyme accumulation in the ischemic brain site, a neutrophil-like cell membrane-coated mesoporous Prussian blue nanozyme (MPBzyme@NCM) was prepared.[50] The preparation of the nanomaterials translocated the entire cell membrane to the surface of the nanozyme and realized interaction between inflamed brain microvascular endothelial cells and neutrophils. The operation could help to promote nanozyme to access damaged brain and realize a noninvasive active-targeting therapy for ischemic stroke. PBNPs also polarized microglia from M1 to M2, decreased the accumulation of neutrophils, reduced neuronal apoptosis, and upregulated neurogenesis. This work proposed a new way to treat brain diseases by combining biomembranes and nanozymes.

Treatment of Neurological Diseases

The common feature of neurodegenerative diseases, such as AD and PD, is a gradual loss of neuron function. More deeply, the deposition of the peptide amyloid-β (Aβ) for plaques and the deposition of the protein tau for neurofibrillary tangles comprise the histopathological hallmarks of AD.[155–157] Studies have confirmed that abnormal ROS affect the

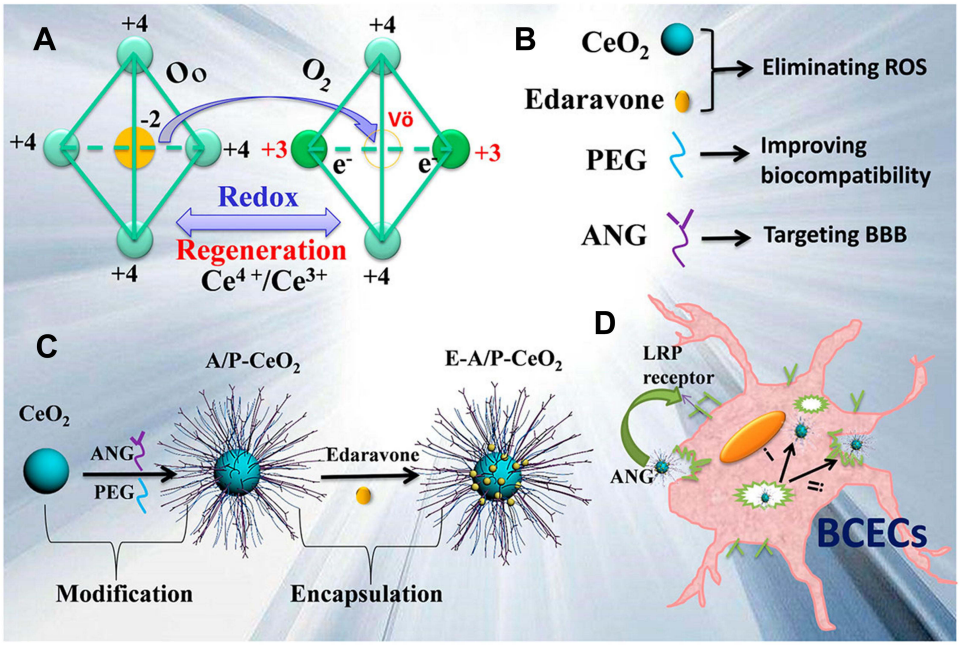

Figure 6 TPP-CeO_2 NPs acted as antioxidants for AD. (**A**) Formations of oxygen vacancies, cerium(III) and cerium(IV) species in CeO_2 NPs. (**B**) Main roles of components on edaravone-carried and PEG/ANG-conjugated CeO_2 NPs (E-A/P-CeO_2). (**C**) Synthetic process for E-A/P-CeO_2. (**D**) ANG-LRP endocytosis of E-A/P-CeO_2. Reprinted with permission from Bao Q, Hu P, Xu Y et al. Simultaneous blood-brain barrier crossing and protection for stroke treatment based on edaravone-loaded ceria nanoparticles. *ACS Nano.* 2018;12(7):6794–6805. Copyright (2018) American Chemical Society.[62]

production and aggregation of Aβ peptides and metal ion homeostasis and cause mitochondrial dysfunction in AD.[158] ROS can also contribute to the degeneration of dopamine cells in PD.[159]

For the treatment of AD, researchers synthesized small and positively charged triphenylphosphonium-conjugated CeO_2 NPs (TPP-CeO_2 NPs), which could enter mitochondria and destroy ROS to relieve oxidative stress in a 5XFAD transgenic AD mouse model.[64] Concretely, the derived nanoparticles mitigated reactive gliosis and maintained mitochondrial morphology. The TPP orientation verified the feasibility of mitochondrial therapeutics against neuroinflammation. Another strategy aimed at the accumulation of Aβ is shown in Figure 7.[65] Aβ antibody-conjugated magnetite/CeO_2 nanoparticle assemblies (MCNAs) with core/shell structures were synthesized to remove Aβ peptides from blood. When applying an external magnetic field, MCNAs isolated the captured Aβ peptides through magnetic force, while CeO_2 NPs in MCNAs scavenged ROS overproduced by the immune response. Collectively, the assemblies reduced the levels of blood Aβ and brain Aβ in 5XFAD transgenic mice and prevented spatial working memory deficits.

Ling and Tian et al exploited a new approach aimed at the tau pathway to deal with AD, involving tau hyperphosphorylation and aggregation of hyperphosphorylated tau.[66] As Figure 8 shows, the nanocomposite CeNC/IONC/MSN was formed by modifying CeO_2 and iron oxide nanocrystals on mesoporous silica NPs (MSN). Then, T807, which can bind tau protein, was immobilized on its surface; while methylene blue (MB), which can inhibit tau aggregation, was adsorbed into the pores of MSNs. CeO_2 scavenged ROS and suppressed tau hyperphosphorylation, while MB inhibited hyperphosphorylated tau aggregation. Through the cooperation of components, the as-nanocomposite successfully protected neuronal survival and ameliorated learning and memory impairments developed in AD.

PD is characterized by the accumulation of misfolded α-synuclein (a prion-like protein) into Lewy bodies, which plays a central role in the pathogenesis of PD.[160] A concept of proof that used nanozymes to fight against α-synuclein spreading was provided by Mao's group.[121] PtCu nanoalloys (NAs) were prepared and possessed three enzyme-like activities, including peroxidase-like, catalase-like and SOD-like activities. The application of PtCu NAs in vitro or in vivo significantly inhibited α-synuclein preformed fibril (PFF)-induced α-synuclein pathology, cell death, and neuron-to-neuron transmission by scavenging ROS. Moreover, the PtCu NAs strongly inhibited α-synuclein spreading in the PD brain. Zheng and Cai et al considered that inflammasome-mediated pyroptosis may be a therapeutic target

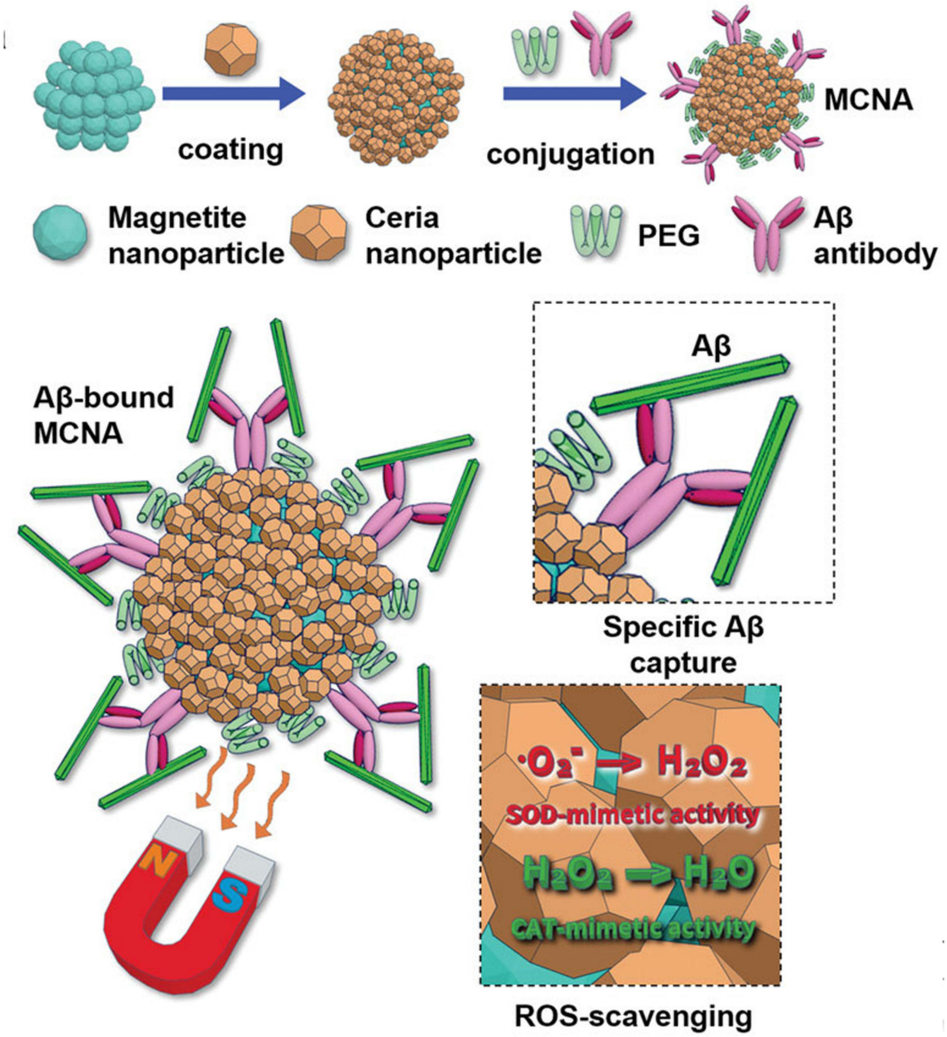

Figure 7 Schematic illustration of MCNA synthesis and mechanism. Reprinted with permission from Kim D, Kwon HJ, Hyeon T. Magnetite/ceria nanoparticle assemblies for extracorporeal cleansing of amyloid-beta in Alzheimer's disease. *Adv Mater.* 2019;31(19):e1807965. Copyright (2019) John Wiley and Sons.[65]

for PD and discovered PB NPs as a pyroptosis inhibitor.[161] Due to their potent ROS-scavenging activity, PB NPs inhibited the activation of the nucleotide-binding domain and leucine-rich repeat family pyrin domain containing 3 (NLRP3) inflammasome and caspase-1, reduced the cleavage of gasdermin D and the production of inflammatory factors, and effectively suppressed the pyroptosis of microglia in PD cell and mouse models. Although the study reveals a good effect of PB NPs on the treatment of PD, the deeper mechanism in vivo is currently unclear. The pharmacokinetics and long-term toxicity of PB NPs remain an issue of concern.

Treatment of Acute Liver/Kidney Injury

The researchers used $Cu_{5.4}O$ USNPs to treat acute kidney injury and acute liver injury, and verified that $Cu_{5.4}O$ USNPs functioned as antioxidants to eliminate ROS and induced remission of the diseases.[20] In the meantime, the ultrafine size of the nanoparticles accelerated renal clearance and conferred high biocompatibility. The therapeutic mechanism involved in acute kidney injury was uncovered in a further study. GSH metabolism, the MAPK signaling pathway, and the TNF signaling pathway, which exacerbated renal injury, were inhibited by $Cu_{5.4}O$ USNPs. The nanoparticles also maintained the expression of antioxidant genes, inhibited excessive proinflammatory factors such as TNF-α and interleukin-1β (IL-1β), and promoted the expression of kidney-associated genes. The $Cu_{5.4}O$ USNPs were reused three

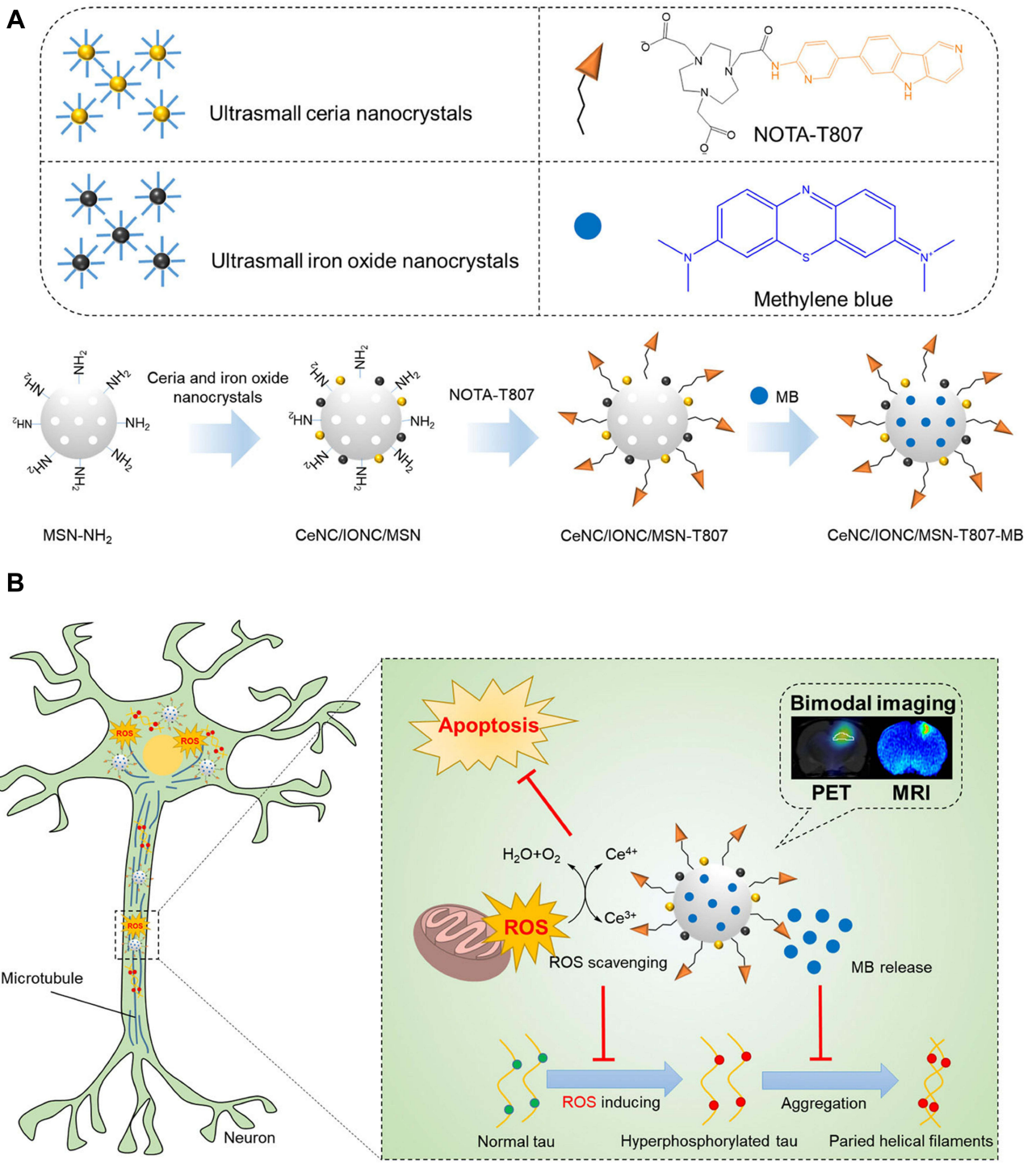

Figure 8 CeNC/IONC/MSN-T807-MB and its tau-targeted synergistic treatment for AD. (**A**) Schematic illustration of the progressive fabrication of CeNC/IONC/MSN-T807-MB. (**B**) Treatment mechanism of the nanocomposite. Reprinted with permission from Chen Q, Du Y, Zhang K et al. Tau-targeted multifunctional nanocomposite for combinational therapy of Alzheimer's disease. *ACS Nano*. 2018;12(2):1321–1338. Copyright (2018) American Chemical Society.[66]

times to decompose H_2O_2. The results showed that the nanomaterials could maintain almost the same catalytic activity as the original solution, indicating that they had good stability and recyclability.

Mo-based polyoxometalate (POM) nanoclusters were synthesized with potent ROS-scavenging activity owing to the dual oxidation states of Mo^{5+}/Mo^{6+}.[162] Furthermore, POM nanoclusters acted as new antioxidants for ameliorating acute kidney injury in a murine model. By positron emission tomography (PET) imaging, radionuclide ^{89}Zr-labeled POM nanoclusters

were observed to be more likely to accumulate in the injured kidneys due to their ultrasmall hydrodynamic diameter. The treatment effect demonstrated that POM improved the renal function of acute kidney injury mice with excellent safety.

The therapeutic mechanisms of PBNPs were probed in anthracycline-induced liver injury.[46] PBNPs activated the Nrf2/ARE pathway to upregulate antioxidative genes, thus reducing oxidative stress in response to liver injury. They also attenuated inflammatory reactions by decreasing the expression levels of myeloperoxidase and F4/80 (a specific indicator for macrophages) in the liver.

Others

The main pathological features of depression, a serious mental disease, are oxidative stress and excessive ROS. Thus, Zheng and Zhang et al considered using CeO_2 nanozyme as a novel drug to treat depression.[67] To overcome the disadvantage of CeO_2, such as its large size, bovine serum albumin (BSA) served as a space constraint to avoid nanoparticle aggregation. The as-designed CeO_2@BSA nanoclusters were endowed with an ultrasmall size as small as 2 nm, potent ROS scavenging activity and BBB penetration ability. When used in a depressive model induced by chronic restraint stress, CeO_2@BSA decreased depression-like behaviors, relieved neuroinflammation and provided neuroprotection with few side effects.

Conclusion and Future Perspective

An imbalance of ROS leads to oxidative stress and is linked to various diseases, including diabetes, neurodegeneration, and aging.[4] Nanozymes with intrinsic antioxidant ability are widely employed to treat ROS-involved diseases.

In this review, we mainly introduce considerable experimental studies that showed satisfactory performances of nanozymes in disease models such as inflammation, neurodegenerative diseases and stroke. In addition, we summarize the enzyme-mimicking traits of nanozymes and show the rational design of nanozymes to improve antioxidant enzyme-like activities. For example, shapes, surface areas, surface facets, particle morphologies, porous structures, pore sizes and volumes, metal doping, and combinations of different functional enzymes may lead to the different catalytic abilities of nanozymes. Although abundant efforts have been made on nanozymes in ROS-involved diseases, there are still shortcomings and deficiencies that need further improvement.

1. The low catalytic activity and poor substrate selectivity of nanozymes are still big problems, which will be a huge stumbling block for their practical application in the future. According to the above summary, doping, control of shape and morphology, forming complex nanozymes, single atom technology, etc., are effective measures to improve the activity of nanozymes. A biomimetic strategy that simulates the active sites of natural enzymes may help to enhance the efficiency of nanozymes.
2. It is well known that living organisms are complex systems. When nanozymes are used in vivo, their pharmacokinetics, ie, the absorption, distribution, biochemical conversion and excretion of nanozymes in the body, need a detailed examination, and based on this information, the application prospects of nanozymes can be overall assessed. In addition, the lack of detailed evaluation of the biosafety and biocompatibility of nanozymes is another problem. Fears have been raised about the potential toxicity of nanozymes on biological systems. The problem in the usage of nanozymes in the central nervous system also includes BBB permeability. It is worth noting that the compatibility of nanozymes can be improved by the loading of natural proteins, which may be a feasible strategy.[163,164]
3. At present, the use of nanozymes for ROS-related diseases involves AD, PD, colitis, acute kidney injury and acute liver injury, which are serious and incurable; however, the treatment should expand to diseases that are not life threatening but also bring pain to patients, such as oral ulcers caused by radiation therapy and difficult-to-heal wounds.

With respect to the problems above, further refinement for high-performance, excellent biosafety, and detailed research in diverse animal models, nanozymes, which are easy to synthesize and low-cost, may be further developed and hold promise as a new therapeutic strategy for ROS-related diseases in clinics.

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Disclosure

The authors report no conflicts of interest in this work.

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