Sensors & Diagnostics

CRITICAL REVIEW

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Recent progress in nanozyme-based sensors for ion detection: strategies, trends, and challenges

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In situ real-time monitoring of pollution sources is one of the most effective means to control and prevent toxic ions from harming the environment and human health. To this end, it is critical to develop rapid, cost-effective, and user-friendly methods for ion detection. Nanozymes, like natural enzymes, can efficiently catalyze substrate reactions with the advantages of simple synthesis, low cost, long storage time, and excellent environmental stability. Importantly, certain ions can regulate the properties of nanozymes or affect their catalytic systems. Therefore, nanozymes have found increasing use in ion sensing. To highlight the latest advances made in this interesting area, here we focused on summarizing the progress in nanozyme-based ion assays developed mainly in the past three years. Emphatically, current trends and future challenges as well as potential solutions were discussed in detail. Our review will provide some guides to rationally design and develop nanozymes for biochemical sensing, especially for toxic ion detection and control. Also, it is expected to attract more interest in this promising field.

1. Introduction

Because of large-scale mining, industrial development and unregulated waste discharge, inorganic ions, particularly heavy metal ions, have brought severe pollution and damage to the environment and health impacts worldwide.[1] As one of

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the most effective means to control and prevent toxic ion pollution, developing efficient methods to monitor them becomes especially important. Although a few instrumental techniques (atomic emission spectrometry, atomic absorption spectrometry, atomic fluorescence spectrometry, ion chromatography, mass spectrometry, *et al.*) have been established well for ion detection in the laboratory, the requirements of sophisticated instruments and professional operators hinder their wider use in practical in-field analysis. Developing rapid, cost-effective, and user-friendly methods for ion sensing is always desired.[2]

Since magnetic Fe_3O_4 particles were discovered to exhibit intrinsic peroxidase-mimetic catalytic activity by Yan's group

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in 2007,[3] nanomaterials with enzyme-like characteristics, defined as 'nanozymes' by Wei and Wang,[4] have gradually become the most popular artificial enzymes,[5] with the superiorities of simple synthesis, low cost, long storage time, and excellent environmental stability over natural enzymes. A lot of materials, including carbon materials, noble metals, and transition metal oxides/sulfides/hydroxides, have been explored as enzyme mimics to be used in biomedicine, environmental remediation, and sensing.[6–10] In particular, in the biochemical sensing field, nanozymes can trigger chromogenic or fluorigenic reactions stably to give easy-to-read and sensitive results with catalytic signal amplification.[11,12] This attractive feature makes them intensively employed as alternatives to natural enzymes or catalytic labels in various biochemical analyses.[13–17]

As a typical example of analytical applications, various nanozymes have been explored to establish methods for toxic ion detection. Currently, there are mainly four principles developed to monitor ions based on nanozyme catalysis (Fig. 1). Ions like Ce^{4+}, Cu^{2+} and Fe^{2+} show certain catalytic activity, enabling the detection of these ions when used as nanozyme catalysts. Instead, some ions participate in nanozyme-catalyzed reactions as co-reactants, providing another important principle to sense ions. More commonly, many ions have the capacity to specifically adjust the catalytic performance of nanozymes, offering a general strategy to realize the determination of target ions *via* measuring the latter's activity change. Besides, some target ions are involved in reaction systems catalyzed by nanozymes, also enabling one to develop sensors for ion monitoring. By employing these principles, increasing experimental studies have been performed to detect toxic ions based on nanozyme catalysis.

To date, many experimental studies have been carried out to sense toxic ions with nanozymes. Several reviews have summarized this hot topic. For example, we previously presented a comprehensive overview on the applications of nanozymes as an emerging tool in environmental pollutant detection, where we systematically sorted out nanozyme-based analytical approaches for various pollutants.[18] Yan *et al.* addressed the mechanisms of the interactions between nanozyme-based colorimetric sensors and heavy metal ions from the perspective of nanozyme materials, such as metal nanoparticles, metal oxides, metal sulfides, graphene-based nanomaterials, and G-quadruplexes.[19] Recently, Huang *et al.* also summarized the strategies and mechanisms of toxic ion detection by nanozymes.[20] Although these reviews were published, no one summarized the latest nanozyme sensing trends for toxic ions. To highlight the latest advances made in this flourishing field, here we tried to make a minireview of the progress of nanozyme-based sensors for ion monitoring. Different from the previous reviews focusing on

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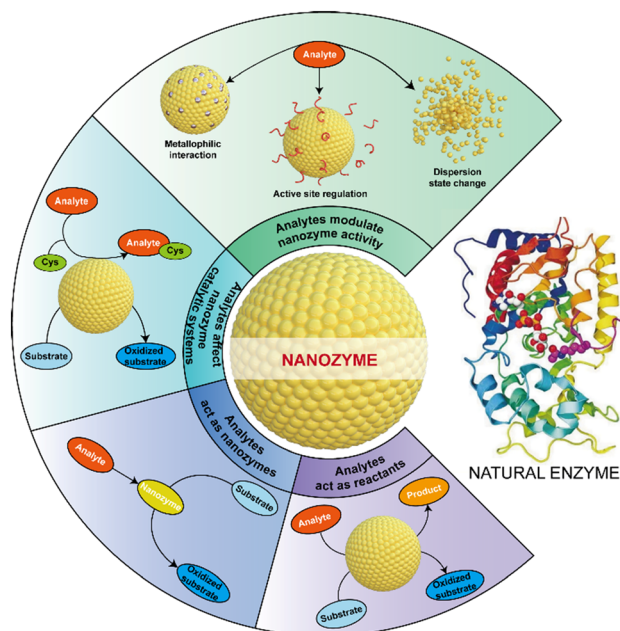
Xiangheng Niu

Fig. 1 Principles of ion detection based on nanozyme catalysis.

the mechanisms of nanozyme-based ion assays,[19,20] in the present work we summarized the latest advances of nanozyme-based sensors achieved mainly in the past three years for ion monitoring, with our focus on analyzing the development trends and current challenges of this area. Common sensing strategies were introduced first, followed by emphatically discussing current trends and future challenges as well as potential solutions in detail. Our work uncovered the mainstream of this field, revealed some doubts or controversies about detection mechanisms, and contributed to the rational development of nanozymes for ion detection. It is believed that this minireview of the latest advances can help one better understand the popular area.

2. Nanozyme strategies to detect ions

2.1. Analytes act as reactants

One of the most crucial aspects of environmental evaluation is to detect target ions selectively and sensitively. Given that the biological toxicity of multivalent ions varies with their forms, detecting these unstable species becomes more important and difficult. The rapid conversion, hydrolysis, and coordination between different forms render them unsuitable for conventional measurement methods that require long-term storage or long-distance transfer of samples. Visualization methods based on nanozyme catalysis have recently been discovered to allow rapid sensing of multivalent ions *in situ*. Taking advantage of the redox property of multivalent ions, metal species like Cr^{6+} and Fe^{2+} can act as co-reactants to trigger nanozyme-catalyzed reactions,[21–24] thus supplying the basis to identify these multivalent ions. Typically, Lu's group explored Au@Hg as an oxidoreductase mimic and employed it to catalyze the redox

reaction between Cr^{6+} and 3,3′,5,5′-tetramethylbenzidine (TMB), thus establishing a colorimetric method for Cr^{6+} analysis.[23] In the presence of a small quantity of oxidoreductase-like Au@Hg, Cr^{6+} replaced H_2O_2 and directly oxidized the colorless reactant TMB to blue oxTMB (Fig. 2). The color of the solution changed dramatically from colorless to blue as the Cr^{6+} concentration increased. This finding provided a new foundation to detect Cr^{6+} with high sensitivity, rapid response, and excellent selectivity against coexisting ions.

2.2. Analytes act as nanozymes

Certain ions like Ce^{4+},[25] Cu^{2+} (ref. 26) and UO_2^{2+} (ref. 27) exhibit unexpected enzyme-like activity through hydrolysis, oxidation or the formation of intermediates, which can catalyze some reaction systems to allow the establishment of analytical methods for target ions. For example, considering that Ce^{4+} was easily hydrolyzed and difficult to detect, Liu's group proposed an ingenious detection idea by using the hydrolyzate of Ce^{4+} as a nanozyme, whose catalytic activity could further be enhanced with the help of F^-.[25] Similarly, the same group found that the enzyme-like activity of Cu^{2+} was effectively improved after the addition of nucleotides or bases to generate coordination polymers, on the basis of which a colorimetric detection strategy for Cu^{2+} was implemented.[26] Jiang *et al.* found that UO_2^{2+} exhibited efficient artificial peroxidase activity to catalyze the oxidation of 2,2′-azino-bis-(3-ethylbenzthiazoline-6-sulphonate) (ABTS) by H_2O_2, whereas other common substrates were not oxidized.[27] Based on this finding, they developed a simple, cost-effective, and stable colorimetric method to detect UO_2^{2+}.

2.3. Analytes modulate nanozyme activity

Since the catalytic sites of nanozymes are often exposed on the external surface, their activity is susceptible to the influence of outside substances. The modulation of
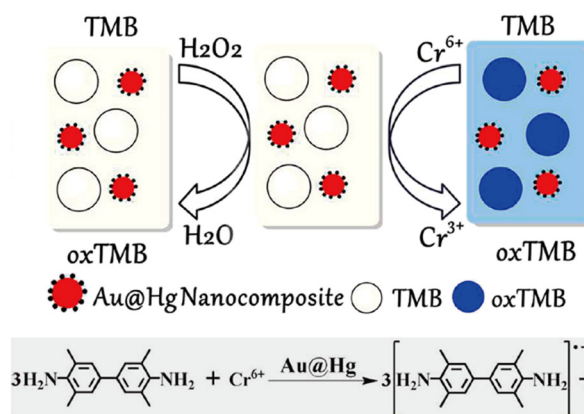

Fig. 2 Cr^{6+} acted as a co-reactant to induce the oxidation of TMB with Au@Hg as an oxidoreductase mimic (reproduced from ref. 23 with permission from the American Chemical Society, copyright 2018).
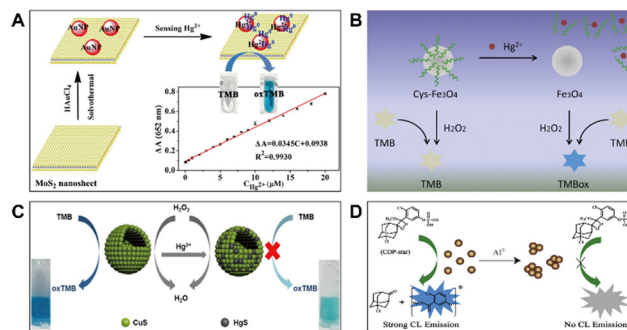
nanozyme catalytic activity by toxic ions leads to a main principle to detect these targets. In detail, certain metal ions can be reduced *in situ* and deposited onto the surface of nanozymes through metallophilic interactions; also, target ions can strengthen or decrease the catalytic activity of nanozymes *via* interacting with the modifiers on the latter's surface; besides, some ions can change the dispersion state of nanozymes, which also affects the catalytic activity of the latter. As a result, these interactions result in a few strategies for detecting target ions based on nanozyme activity change.

(1) Metallophilic interactions between analytes and nanozymes. Many studies have demonstrated that some ions can be rapidly adsorbed, reduced, and deposited onto the surface of noble metal nanozymes (Pt, Au, Ag, *etc.*) *via* metallophilic interactions to form alloys, thereby modulating the catalytic activity of the nanozymes.[28,32–42] Typically, Hg^{2+} can be reduced by nanosized noble metal atoms or by interaction with modifiers on the surface of the nanozyme. As a result, the catalytic activity of these noble metals is stimulated or inhibited by the presence of Hg^{2+}. For instance, Wu *et al.* created platinum nanoparticles (Pt NPs) using sodium borohydride and trisodium citrate as reducing and stabilizing agents, respectively, where the citrate species covering the surface of the Pt NPs could chemically reduce Hg^{2+} into Hg^0, and the formation of the PtHg amalgam inhibited the peroxidase-like activity of Pt NPs significantly.[32] Based on such a principle, a colorimetric sensor with high specificity and good sensitivity for Hg^{2+} was developed. In this experiment, a suitable reducing agent is usually desired to transform Hg^{2+} totally to Hg^0. The type and content of the reducing agent used can greatly affect the assay's accuracy. Instead of using any reducing agent, Hg^{2+} can also be directly reduced on the Pt surface due to the difference in the standard potentials of Pt^{4+}/Pt and Hg^{2+}/Hg.[34,43] The findings demonstrate that Pt^0 stimulates Hg^{2+} reduction in Pt NPs and produces PtHg alloy on its surface, which drastically suppresses the nanozyme's catalytic activity. Apart from Pt nanoparticles, Au-based nanomaterials can also interact with Hg^{2+} to form amalgams.[28,39] Typically, Ma *et al.* synthesized a MoS_2–Au composite with peroxidase activity *via* a microwave-assisted solvothermal method, where MoS_2 nanosheets provided a large surface area and synergized with Au to endow the composite with excellent catalytic activity.[28] The addition of Hg^{2+} could further stimulate its peroxidase-like activity, which was used to determine Hg^{2+} through employing the chromogenic system of H_2O_2 and TMB (Fig. 3A).

(2) Analyte-induced active site regulation of nanozymes. Because the catalytic reaction takes place primarily at the catalyst's interface, the exposure or masking of active sites becomes one of the most important factors influencing nanozyme catalytic activity. With this consideration, our group suggested a new method based on the peroxidase-mimicking activity of cysteine-modified ferromagnetic particles (Cys–Fe_3O_4) for the ultrasensitive and selective measurement of Hg^{2+}.[29] Due to the coordination interaction

Fig. 3 (A) Schematic diagram for the colorimetric determination of Hg^{2+} based on the excitation of MoS_2–Au peroxidase activity (reproduced from ref. 28 with permission from Elsevier, copyright 2019). (B) Principle of Hg^{2+} detection based on the target-triggered peroxidase activity of Cys–Fe_3O_4 (reproduced from ref. 29 with permission from Elsevier, copyright 2019). (C) Addition of Hg^{2+} led to the production of HgS on the CuS surface and decreased the enzymatic activity of the latter (reproduced from ref. 30 with permission from the American Chemical Society, copyright 2020). (D) Al^{3+}-induced aggregation effect of ceria nanoparticles led to a decrease in their phosphatase mimetic activity (reproduced from ref. 31 with permission from Elsevier, copyright 2020).

between Cys and Fe_3O_4, Cys wrapped around the outer surface of Fe_3O_4 and blocked its active sites. Therefore, the prepared Cys–Fe_3O_4 showed almost no peroxidase activity (Fig. 3B). When Hg^{2+} was present, the stronger coordination between Hg^{2+} and Cys (Cys–Hg^{2+}–Cys) caused Cys to slip off the surface of Fe_3O_4, resulting in the re-exposure of the Fe_3O_4 active site and the restoration of the catalytic substrate color development ability. Because of the strong interaction between Cys and Hg^{2+}, the developed sensor has improved selectivity and can detect Hg^{2+} without external interference. A similar strategy was also applied to the sensing of Ag^+ when using histidine-modified palladium nanoparticles as a nanozyme.[44]

Another strategy for analyte-induced modulation of enzyme activity is based on the high affinity of Hg^{2+} toward S-containing nanozymes. Hg^{2+} can generate stable HgS *via* strong chelation with the S^{2-} component in nanozymes, and the formed HgS inhibits the nanozymes' activity *via* replacing their active components and blocking reaction sites.[30,45–48] Thus, Hg^{2+} can effectively modulate the catalytic activity of nanozymes. For example, Fang *et al.* found that CuS nanoparticles with peroxidase-like activity exhibited excellent selectivity and adsorption capacity for Hg^{2+} (Fig. 3C).[30] By utilizing the analyte-triggered peroxidase activity inhibition *via* forming an inert HgS layer onto the CuS surface, an extremely sensitive Hg^{2+} nanosensor was verified, demonstrating its great promise in environmental and food analyses.

(3) Analyte-induced dispersion state change of nanozymes. Recent research has indicated that the target-induced dispersion state change can be utilized to modulate nanozyme activity.[31,49,50] The aggregation state of nanozymes has a significant impact on their catalytic activity; thus, the

resulting target-induced changes in the dispersion state of nanozymes will have a significant impact on the catalytic system. Tian *et al.* described a highly sensitive chemiluminescence strategy for Al^{3+} sensing based on ceria's phosphatase mimetic activity.[31] As a result of the coordination between Al^{3+} and ceria, the nanozyme aggregated and lost its catalytic activity for substrate hydrolysis (Fig. 3D). Similarly, our group applied the nanozyme dispersion state change strategy to detect arsenite. Arsenite could cause the aggregation of citrate-stabilized gold nanoparticles to exhibit enhanced oxidase-like activity, providing a new colorimetric pathway for arsenite determination.[51]

2.4. Analytes affect nanozyme catalytic systems

Some nanozyme catalytic systems can be modulated indirectly by the stronger interactions between target ions and foreign reagents like cysteine (Cys),[52,53] glutathione (GSH),[54,55] mercaptopropionic acid[56] and 8-hydroxyquinoline.[57] Typically, Christus *et al.* discovered that the Fe_3O_4@ZIF-67 hybrid showed peroxidase activity to catalyze the conversion of colorless TMB to blue TMBox in the presence of H_2O_2.[54] After the addition of GSH to the solution, the blue color disappeared due to its strong antioxidant ability against reactive oxygen species (Fig. 4A). When Hg^{2+} was further introduced into the Fe_3O_4@ZIF-67/TMB/GSH system, the solution color returned to blue because

of the generation of mercury–thiol complexes. Using this mechanism, the authors created a high-selectivity Hg^{2+} colorimetric sensor. The strategy assisted by foreign molecules can also be extended to detect other toxic cations and anions, including Cr^{6+},[57] Cu^{2+} (ref. 56) and phosphate ions.[58]

Another sensing strategy affecting nanozyme catalytic systems is based on the chromogenic substrates' competitive interaction with target ions, which alters the color of the solution. For example, C-dots/Mn_3O_4 acting as an oxidase mimic facilitates the transformation of Fe^{2+} into Fe^{3+} (Fig. 4B). Meanwhile, this oxidation reaction had a significant impact on the nanozyme-catalyzed TMB oxidation.[59] Due to the competitive interaction between TMB and Fe^{2+}, a colorimetric method for Fe^{2+} detection could be proposed. Furthermore, S^{2-} can be detected in a similar manner, but the potential mechanism involves not only the competitive oxidation of S^{2-} and TMB but also the re-reduction of TMBox to colorless TMB by S^{2-}.[60]

3. Recent progress in detecting ions using nanozymes

With the rapid development of nanozymes for toxic ion detection, a large number of studies have emerged in the last few years. To summarize the cutting-edge advances in this flourishing area, the mainstream ideas and research hotspots would be analyzed and discussed in this part, mainly including improvement of nanozyme catalytic activity, expansion of enzyme-like activity types, design of multifunctional nanozymes, and diversification of detection modes (Fig. 5).

3.1. Improvement of nanozyme catalytic activity

Improvement of nanozyme catalytic activity is critical to ion sensing because the activity of the nanozyme used directly decides detection sensitivity. For most of the nanomaterials with enzyme mimetic properties, their catalytic activities still have a certain gap compared with natural enzymes. As a result, one of the most important topics in this field is how to improve their catalytic activity. To date, several strategies have been proposed to efficiently improve nanozyme catalytic activity, such as size control, morphology screening, element doping, and crystal plane regulation. Here we would like to introduce the material compositing strategy and the active area increasing method to boost the activity of nanozymes,
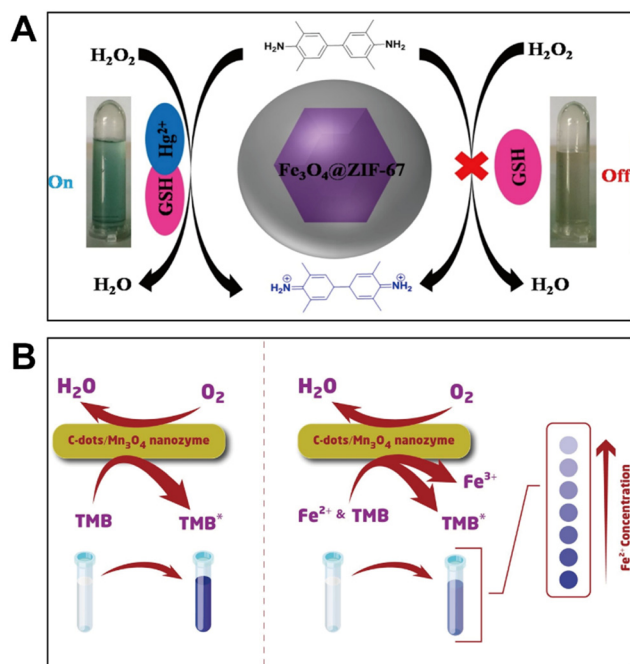

Fig. 4 (A) Colorimetric detection of Hg^{2+} using Fe_3O_4@ZIF-67 to catalyze the oxidation of TMB affected by GSH (reproduced from ref. 54 with permission from Elsevier, copyright 2018). (B) Colorimetric sensing of Fe^{2+} based on its competitive effect on the TMB + O_2 system catalyzed by C-dots/Mn_3O_4 (reproduced from ref. 59 with permission from Springer Nature, copyright 2020).
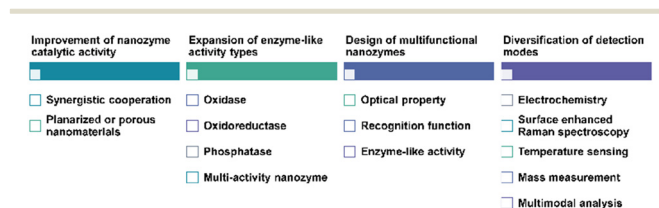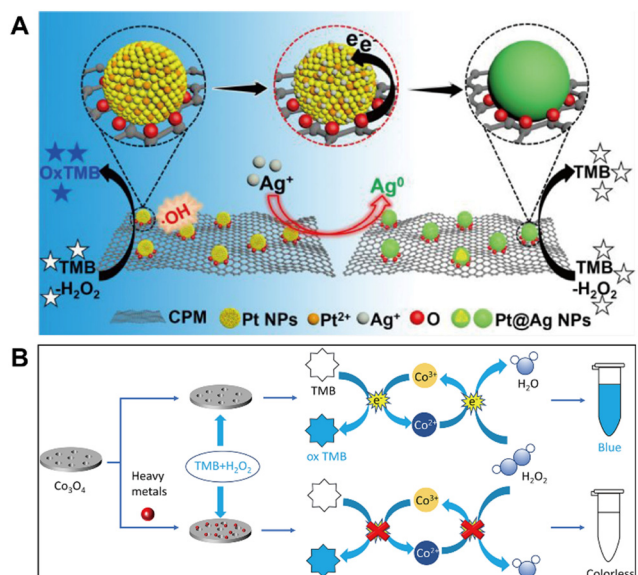

Fig. 5 Recent progress in detecting ions using nanozymes.

both of which have been verified to be effective in improving the analytical performance of toxic ions.

In recent years, the synergistic cooperation of different property compounds that can confer new or enhanced properties to nanozymes has attracted a great deal of research interest. Typically, Guo and coworkers successfully prepared 5,10,15,20-tetrakis(4-carboxyphenyl)porphyrin (H_2-TCPP)-modified bimetallic sulfide ZnS/CoS core–shell nanospheres with significantly enhanced peroxidase activity.[61] It was demonstrated that the increased catalytic activity of H_2TCPP/ZnS/CoS is due to the high number of active sites produced by metal cations on the surface of the nanozyme and the synergistic interaction between the various components. The synergistic interaction between porphyrin molecules and ZnS/CoS not only improves the catalytic activity of the nanozyme but also unexpectedly contributes to the selectivity of the nanozyme analysis. For example, Dai *et al.* achieved ultrasensitive colorimetric detection of Ag^+ by synergistic interaction between different components as well as active site modulation (Fig. 6A).[62] In this work, natural peat moss (PM) leaves were selected as a carbon source, enabling the *in situ* reduction and stabilization of Pt NPs on the formed support (carbonized peat moss, CPM). The porous structure and large surface area of CPM allowed more Pt NPs to be uniformly loaded, and the abundant active sites give the material good peroxidase activity and boost the detection performance. The analyte Ag^+ could interact with Pt NPs *via* metallophilic interactions as well as the component synergistic effect to generate Ag atoms, thus modulating the enzyme-like activity of the hybrid and enabling the rapid detection of ultratrace Ag^+ with satisfactory selectivity.

Since the catalytic ability of nanozymes is closely related to their surface properties, designing planarized or porous nanomaterials is one of the simplest and most effective ways to increase the specific surface area, expose the active site, and thus improve the catalytic activity of nanozymes. Recently, Zou and coworkers obtained porous Co_3O_4 nanodisks with significantly enhanced peroxidase mimetic activity.[63] With a soft template method, the obtained porous Co_3O_4 could show significantly improved peroxidase-mimicking activity compared to the counterpart without pores. This was because the porous Co_3O_4 nanodisks offered a larger area, thus exposing more active sites for catalyzing reactions. The peroxidase-like activity of porous Co_3O_4 nanodisks is severely inhibited by many heavy metals, including Cd(ɪɪ), Hg(ɪɪ), Pb(ɪɪ), and arsenic. As a result, the authors constructed an ultrasensitive colorimetric sensing platform for the detection of these four heavy metals (Fig. 6B). Thanks to the nanozyme's enhanced enzyme-like activity, the colorimetric sensor could detect these metal ions with high sensitivity and reliability.

3.2. Expansion of enzyme-like activity types

The nanozyme-based sensing approach now relies mostly on peroxidase-like activity. In fact, the peroxidase-like activity has some deficiencies. Typically, high-concentration H_2O_2 is often required to fabricate reaction systems, while the H_2O_2 species itself is a potentially harmful chemical to the environment and human health. On the other hand, H_2O_2 is a redox agent, and the use of high-concentration H_2O_2 may change the form of analytes in original samples. Instead, a few studies have explored the use of oxidases,[64,65] oxidoreductases,[21,22] phosphatase mimics[31,66] or multi-activity nanozymes[24,67,68] for toxic ion detection. For instance, using ascorbic acid-coated platinum nanoparticles (AA-PtNPs) with catalase properties to catalyze the
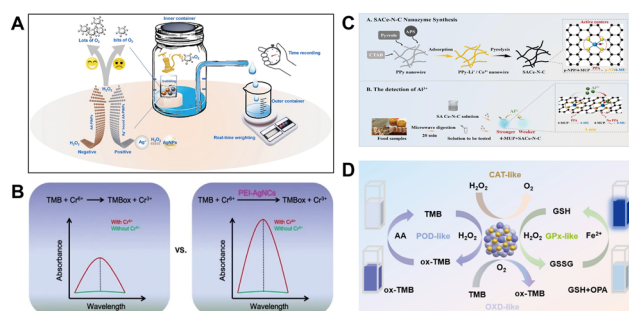

Fig. 6 (A) Ag^+ colorimetric assay based on the enhanced peroxidase activity of CPM-Pt NPs (reproduced from ref. 62 with permission from the American Chemical Society, copyright 2022). (B) Multi-heavy metal colorimetric detection based on target suppressed peroxidase activity of porous Co_3O_4 nanodisks (reproduced from ref. 63 with permission from Elsevier, copyright 2021).

Fig. 7 (A) Schematic diagram of a catalase-based weight method for the detection of Ag^+ and AgNPs (reproduced from ref. 69 with permission from Elsevier, copyright 2021). (B) Colorimetric determination of Cr^{6+} using PEI-AgNCs as oxidoreductase mimics (reproduced from ref. 21 with permission from Springer Nature, copyright 2020). (C) Synthesis of the phosphatase-like SA Ce–N–C enzymes and detection of Al^{3+} (reproduced from ref. 70 with permission from Elsevier, copyright 2022). (D) Multi-target assay based on multiple enzyme activities (AA and Fe^{2+}) (reproduced from ref. 67 with permission from the American Chemical Society, copyright 2021).

decomposition of H_2O_2 to produce hydrogen gas, the produced gas can expel water from the device, leading to a reduction in the weight of the device,[69] and because Ag^+ can inhibit the AA-PtNPs' catalytic activity and reduce gas production, it is possible to measure the Ag^+ content by observing changes in the device's weight (Fig. 7A). The device can accurately measure Ag^+ and AgNPs without relying on advanced instruments with minimum detection limits of 2.0 nM and 3.8 pM, respectively.

As mentioned above, some materials have been discovered to exhibit oxidoreductase-like activity capable of catalyzing the redox reaction between Cr^{6+} and TMB.[23] In this regard, our group proposed an environmentally friendly and inexpensive colorimetric method for Cr^{6+} detection using polyethyleneimine-stabilized silver nanoclusters (PEI-AgNCs) (Fig. 7B). It was demonstrated that the PEI-AgNCs acted as neither an oxidant nor an oxidase mimic. Instead, they function as an oxidoreductase mimic, catalyzing the oxidation process between TMB and Cr^{6+}, where electrons tended to flow from TMB to the PEI-AgNCs and then are delivered to Cr^{6+}. As a result, the PEI-AgNCs could be regarded as an electron mediator in accelerating the redox process. Compared to the use of Au@Hg as an oxidoreductase,[23] the PEI-AgNCs seem to be more attractive in terms of reduced material cost and secondary pollution risk to the environment. Instead of using any noble metal, Alula and co-workers found that magnetic Fe_3O_4 nanoparticles also possessed the oxidoreductase-like activity to realize the determination of Cr^{6+}.[22]

Recently, some nanomaterial-based phosphatase mimics to facilitate the hydrolysis of phosphate esters have emerged for ion analysis.[31,66,70] For instance, Song et al. demonstrated that single-atom Ce–N–C has good phosphatase activity,[70] which could catalyze the dephosphorylation of organophosphates. Simultaneously, they discovered that Al^{3+} could specifically attach to the O atom in the nanozyme, inhibiting its phosphatase-like activity. Based on this principle, they constructed a facile, portable, and highly efficient fluorescent sensor to detect Al^{3+} in food matrices (Fig. 7C).

In natural living systems, two or more enzymes are often used to form cascade reactions that are involved in catalyzing metabolism. Researchers are developing nanozymes that can display numerous activities simultaneously under similar conditions in an effort to more closely replicate these systems. Consequently, several materials with multiple enzyme-like activities have been developed for ion determination.[24,67,68] For example, Xu et al. proposed polymetallic oxide (POM)-decorated copper oxide nanoparticles (CuO NPs) with four-in-one enzyme-like activities for multi-target detection (Fig. 7D).[67] Based on the fact that ascorbic acid (AA) could hinder the peroxidase-like activity of CuO NP–POM and Fe^{2+} could boost its glutathione peroxidase-like activity, highly sensitive colorimetric and fluorescence platforms were constructed for AA and Fe^{2+} sensing, respectively. In a different study, a self-cascade

catalytic system was created using the nanozyme's dual-mimetic activity.[68] The CuO NPs are capable of catalyzing the oxidation of glutathione to generate glutathiol (GSSG) and H_2O_2, exhibiting glutathione oxidase and peroxidase activities. Also, p-phenylene dicarboxylic acid (TA) can be further oxidized by the released H_2O_2 to provide the intensely fluorescent product TAOH. On the basis of multi-enzymatic activity, a self-cascade reaction system was developed. When Ag^+ was added to the catalytic system, Ag^+ ions could quench the fluorescence of the catalytic system, based on which the authors established a fluorescence method for the detection of GSH and Ag^+. The use of nanozymes with multiple activities has greatly benefited the sensing field. Despite the success of developing multi-activity nanozymes in the field of analytical sensing, there are still many issues to be addressed. Because different classes of enzyme activities can be expressed simultaneously under similar conditions, it is difficult to select the appropriate enzyme activity for the test, potentially causing the assay results to be influenced. For one aspect, in multi-activity catalytic reactions, the same substrates may be involved and consumed, as well as the same intermediates produced, which can result in potentially competing reactions that will inevitably affect the test's accuracy. For example, both peroxidase- and oxidase-like mimics generate signal output by oxidizing chromogenic substrates, and oxidases can directly catalyze chromogenic reactions under oxygen conditions, which will unavoidably affect peroxidase nanozyme-based detection assays. As for another aspect, multi-active nanozymes may be more susceptible to environmental factors than single-active materials. In particular, in cascade catalytically involved sensing systems, an external element that influences the activity of the nanozyme might have a significant effect on the entire process. As a result, more variables that could have an impact on the sensing system need to be investigated, and a more stable and dependable nanozyme sensing system has to be developed.[14]

3.3. Design of multifunctional nanozymes

Thanks to the designability of nanomaterials, multifunctional nanozymes for analytical applications have gradually become a research hotspot in recent years. One can integrate some optical properties with enzyme-like activity into the same material.[71–73] Also, both the target recognition function and the loading function can be introduced to nanozymes.[74,75] As a result, the integrated multifunctional nanozymes enable not only the enhancement of detection performance but also the expansion of application scenarios.

As a typical nanozyme material widely used in biochemical analysis, metal–organic frameworks (MOFs) can play multiple roles in fabricating sensors.[16] Typically, MOFs are preferred materials for encapsulating natural enzymes due to their ordered channels, stable structures and abundant functional groups. The integration of nanozymes or natural enzymes into MOFs can simplify the assay process, improve the
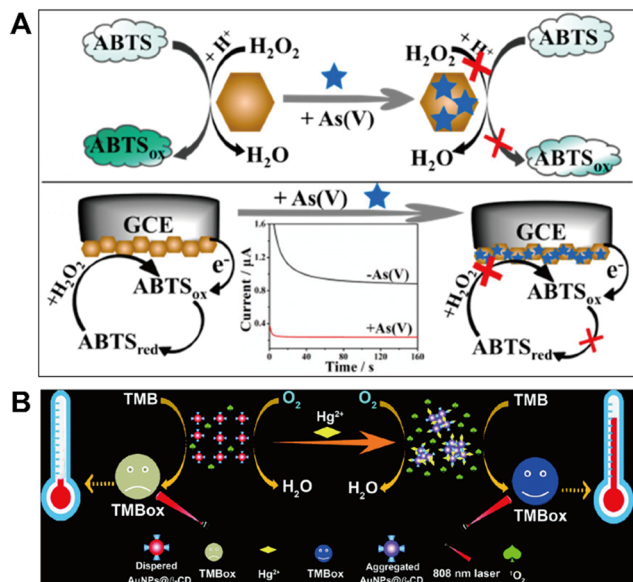
Fig. 9 (A) Colorimetric/electrochemical dual-mode arsenate determination based on the peroxidase activity of CoOOH nanoflakes (reproduced from ref. 79 with permission from the American Chemical Society, copyright 2019). (B) A platform for Hg^{2+} temperature analysis based on the altered aggregation state of AuNPs@β-CD (reproduced from ref. 50 with permission from the Royal Society of Chemistry, copyright 2020).

electrochemical method for the detection of trace As(v) can be developed with significantly improved sensitivity and detection limits.

Interestingly, Xue's team has recently developed a photothermometric system for home use, utilizing the photothermal effect of the TMBox to convert mercury detection into temperature monitoring in an innovative manner.[50] As illustrated in Fig. 9B, under 808 nm laser irradiation, cyclodextrin-capped Au nanoparticles (AuNPs@β-CD) hardly oxidized the substrate TMB to TMBox with no significant temperature change. When a small amount of Hg^{2+} was added, AuNPs@β-CD agglomerated, resulting in a significant increase in the material's catalytic activity and the rapid formation of a blue TMBox. The material also displayed a photothermal effect, significantly raising the temperature in response to laser irradiation. Therefore, changes in the temperature of the reaction system can be recorded with an ordinary thermometer, and the quantitative determination of trace amounts of Hg^{2+} can be achieved.

4. Challenges and potential solutions

It is undeniable that nanozymes have become one of the most attractive materials for applications in many areas. In particular, for ion detection, nanozymes offer several potential principles for the development of sensing methods and devices. Driven by these principles, great success has been achieved in nanozyme-based ion assays. Even so, there is still plenty of room to promote the application area, including understanding the sensing mechanisms better,

achieving high-selectivity detection, expanding target ions, exploring low-cost and environmentally friendly nanozymes for sensing, and developing portable detection technologies and devices.

(1) Better understanding of sensing mechanisms

Although effective detection of many toxic ions has been achieved using nanozyme catalysis, some of the detection mechanisms are ambiguous due to the complexity of nanozyme-involved processes. For example, in the redox process of substrates catalyzed by nanozymes, one often employs the electron paramagnetic resonance (EPR) technique or chemical reagents to identify the reactive radicals generated during reactions, and thus proposes that the oxidation of substrates is caused by the radicals produced from nanozyme-catalyzed H_2O_2 or O_2, while in some cases nanozymes catalyze reactions through electron transfer. Even in the same system, the two mechanisms may coexist. In terms of regulating nanozyme activity *via* foreign substances, our group found that phosphate ions could promote the oxidase-like activity of oxidized UiO-66(Ce/Zr) when TMB was used as the substrate, while an inhibiting effect was found when ABTS was employed.[83] The zeta potential characterization revealed that this phenomenon was closely related to the change of the electrical charge on the nanozyme surface. As a result, the substrates with different charges responded to it differently. Additionally, many studies demonstrated that Hg^{2+} could be reduced *in situ* and deposited on the surface of noble metals (Au, Ag, Pt, *etc.*) to form amalgams, but the generated AuHg alloy typically promoted the catalytic activity of Au-based nanozymes,[84,85] while the PtHg alloy often exerted an inhibiting effect oppositely.[86] The detailed reason for the different impacts has not been revealed well. Even in the same category of materials, *e.g.*, Au-based peroxidase mimics, different activity regulation effects made by Hg^{2+} were observed.[38,87] To better understand the above phenomena and results, advanced characterization techniques and theoretical calculations may help one uncover the underlying mechanisms.

(2) How to achieve high-selectivity detection

Despite the rapid development of nanozymes in ion sensing, their biggest weakness is the far less selectivity compared to natural enzymes, particularly when multivalent or interconvertible ions are to be measured. In many cases, the nanozyme sensing technology cannot detect target ions specifically. Therefore, there is an urgent need to explore effective methods to improve detection selectivity.[10] One of the most effective strategies at present is to introduce recognition elements into nanozyme catalytic systems to possess special interactions with target ions.[64,65,88–90] For instance, doping S^{2-} or Se^{2-} into nanozymes enables the highly selective detection of Hg^{2+} by taking advantage of the strong precipitation between Hg^{2+} and S^{2-} or Se^{2-}. Another appealing strategy is the use of the molecular imprinting

technique, where analytes are imprinted onto the surface of nanozymes as template molecules or ions.[91,92] After the template molecules or ions are eluted off, recognition sites perfectly matching the size and shape of the analytes are obtained for measurement. Finally, some efforts have been made on the differentiation and simultaneous detection of analogues by constructing nanozyme sensor arrays.[93–95] Such a strategy can effectively solve the interference problem of coexisting substances.

(3) Expansion of target ions

Although many sensor systems based on nanozyme catalysis have been successfully manufactured to detect certain analytes, the type of target ions that nanozymes can selectively detect is quite limited (mainly limited to Hg^{2+}, Pb^{2+}, Cr^{6+}, Ag^+ and F^-). This is because the type of analytes interacting with nanozymes directly or indirectly is still very limited. It is quite necessary to systematically study the influences of different analytes on the catalytic behavior of nanozymes. Encouragingly, several recent studies have expanded the detectable targets to rare earth elements.[27,96] In addition to inorganic ions, some organic forms are more harmful to living organisms. Recently, detection of methylmercury has been achieved by combining nanozyme catalysis with SERS sensing.[80] Future exploration should be encouraged to develop potential principles and methods for the detection of more targets.

(4) Developing low-cost and environmentally friendly nanozymes for sensing

Compared to natural enzymes, one of the most significant advantages of nanozymes is their low cost. To further reduce the cost, non-precious metal or metal-free materials are attracting increasing attention to replace noble metal-based nanozymes. Furthermore, when nanozymes are used in environmental analysis, their own toxicity cannot be overlooked. Because most of the nanozymes used in currently available sensing systems cannot be recycled and reused and some materials may have adverse effects on the environment and human health, the toxicity of nanozymes is of great concern to the academia and the public. Exploring low-cost, environmentally friendly nanozymes for toxic ion detection should be a continuing goal for the field.[77,89,97]

(5) Development of portable detection technologies and devices

In order to obtain mobile devices suitable for *in situ* analysis, integrating sensors with portable tools, such as smartphones, is an effective and easy-to-prepare strategy. Similarly, there is growing interest in combining nanozyme-based assays with low-cost test strips to create inexpensive, portable assays.[64,98,99] The development of intelligent devices and test strips can help detect analytes quickly in remote areas. Currently, smartphone-based optical sensors with catalytic signal amplification are very popular in quick analysis, but

this paradigm highly depends on the color change of test strips with a complicated matrix background. In some of these sensors, the detection sensitivity obtained is still low even with the help of color extraction software. It is necessary to develop sensitive and stable portable devices with the assistance of other high-sensitivity paradigms like electrochemical measurement.

5. Conclusions

To sum up, the fascinating advantages of low cost, excellent stability and easy-to-adjust performance have endowed nanozymes with extensive applications in the past few years. In particular, in the ion sensing field, several detection strategies have been explored and verified to monitor toxic heavy metals. More excitingly, increasing efforts are being paid to push forward this area by developing high-activity and multifunctional nanozymes as well as establishing new detection methods and modes. In this review, we have briefly introduced common principles for the determination of toxic ions based on nanozyme catalysis, summarized the latest developments in this area, and discussed current problems and potential solutions for toxic ion monitoring. It is believed that the work will provide guides to rationally design and develop nanozymes for biochemical sensing, especially for toxic ion analysis and control. Also, we hope that the review can attract more attention to this promising field.

List of abbreviations

1,4-BDC-NH$_2$	2-Aminoterephthalic acid
AA	Ascorbic acid
AA-PtNPs	Ascorbic acid-coated platinum nanoparticles
ABTS	2,2′-Azino-bis-(3-ethylbenzthiazoline-6-sulphonate)
ACP/hemin@Zn-MOF	Zn-based metal–organic framework nanosheets loaded with acid phosphatase and hemin
AuNPs@β-CD	Cyclodextrin-capped Au nanoparticles
CPM	Carbonized peat moss
CS	Chitosan
CuO NPs	Copper oxide nanoparticles
Cys	Cysteine
Cys–Fe$_3$O$_4$	Cysteine-modified ferromagnetic particles
EPR	Electron paramagnetic resonance
GSH	Glutathione
GSSG	Glutathiol
H$_2$TCPP	5,10,15,20-Tetrakis(4-carboxyphenyl)porphyrin
IFE	Internal filtration effect
MOFs	Metal–organic frameworks
OPD	*o*-Phenylenediamine
PEI-AgNCs	Polyethyleneimine-stabilized silver nanoclusters
PM	Peat moss

POM	Polymetallic oxide
Pt NPs	Platinum nanoparticles
SERS	Surface-enhanced Raman spectroscopy
TA	p-Phenylene dicarboxylic acid
TMB	3,3′,5,5′-Tetramethylbenzidine
UiO-66(Fe/Zr)–NH$_2$	Fe/Zr bimetal–organic frameworks

Author contributions

Supervision: Xiangheng Niu; writing – original draft: Xin Li and Jinjin Liu; writing – review & editing: Jia Chen, Hongdeng Qiu and Xiangheng Niu.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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