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DNAzyme-Based Biosensors for the Determination of Metal Ions Using Nanomaterials

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ABSTRACT

Metal ions play significant roles in biological and environmental systems, which have thus urged scientists to develop reliable methods for the sensitive and selective detection of metal ions. The past decade has witnessed great progress in the development of metal ion sensors based on both DNAzymes (with excellent recognition selectivity towards metal ions) and nanomaterials (with unique properties to improve the detection sensitivity). This review introduces the functions and applications of nanomaterials in the DNAzymes-based metal ion sensing platforms, including gold nanoparticles (GNPs) and graphene oxides (GOs). Besides, the existing limitations and emerging trends in the area are also discussed.

INTRODUCTION

Metal ions can cause serious environmental and health problems because of their accumulativity and undegradability [1]. The emission of toxic heavy metals has posed a challenge to the environment in many countries and regions [2] The metallic pollutants also have profound effects on human health. Therefore, it is highly desired to develop efficient approaches to accurately quantify the amounts of metal ions.

Conventional instrumental analysis methods, including atomic absorption spectrometry [3] inductively coupled plasma mass spectrometry [4], inductively coupled plasma atomic emission spectroscopy [5], and reversed phase high-performance liquid chromatography [6], have been reported for reliable detection of metal ions. Despite their advantages, such as high accuracy and good sensitivity, they always rely on the application of expensive and sophisticated instruments, together with complicated and tedious sample preparation steps, which have to be executed by well-trained personnel. These problems severely prevent their wide applications in routine detection of metal ions.

To overcome the aforementioned limitations, small organic molecule-based sensing systems have gained considerable attention [7,8] because they are not only highly sensitive but also extremely simple. Although these kind of chemosensors are attractive, problems are still encountered. Most of these organic molecules possess poor water solubility. In addition, they are easily affected by other non-specific species, which shows disappointing selectivity. Sometimes, it may also suffer from other problems, such as slow response time and sophisticated synthesis of organic molecules. These drawbacks greatly restrict their use as a popular sensing scheme.

To solve the solubility and selectivity issues, DNAzymes, screened through in vitro selection, can offer an excellent solution for that, because DNAzymes are functional DNA molecules that can catalyze many chemical and biological reactions in the presence of particular metal ions with satisfactory affinity and specificity. DNAzyme-aided methods have been widely

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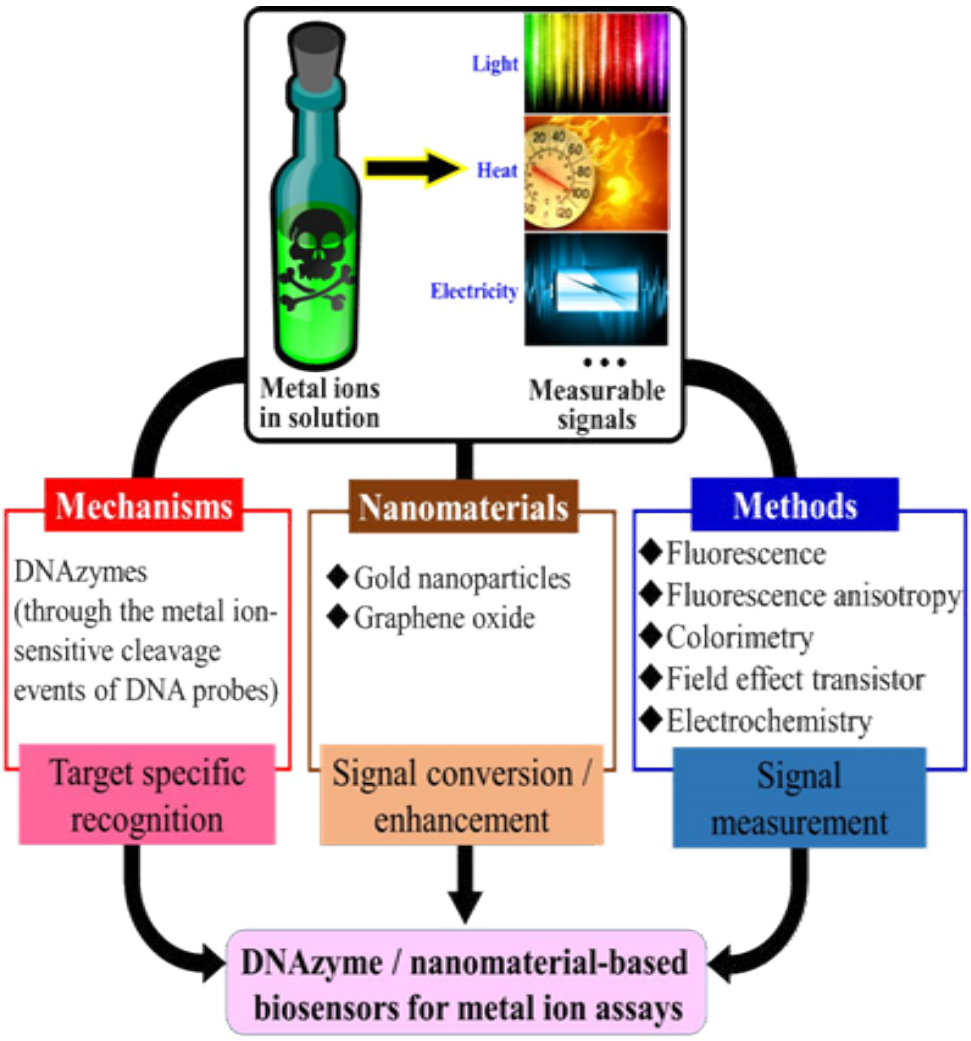
used to transduce the metal ion-dependent activity of DNAzymes into measurable signals, such as colorimetry, fluorescence, fluorescence anisotropy, surface enhanced Raman scattering, surface plasmon resonance, chemiluminescence, electrochemistry and electrochemiluminescence. This is the basic mechanism how DNAzymes are used for the quantification of specific metal ions [9]. DNAzymes can guarantee the detection selectivity for metal ion sensing, while the detection sensitivity of DNAzyme-mediated detection methods is not that appealing. But this problem can be well solved by the employment of nanomaterials.

DNAzymes possessing good recognition capability have been well integrated with nanomaterials exhibiting remarkable amplifying effects, which have injected fresh energy into the advances of DNAzyme/nanomaterial-aided biosensors for the rapid and precise quantification of metal ions [10-12]. DNAzymes can recognize their relevant targets selectively and nanomaterials are powerful tools for signal conversion and amplification, which make the integration of DNAzymes with nanomaterials perfect options for biosensor construction, as demonstrated in **Scheme 1**.

In this review, the recent progress in the metal ion sensor fabrication based on DNAzymes coupled with the employment of nanomaterials, mainly including gold nanoparticles (GNPs) and graphene oxides (GOs) is reviewed. Furthermore, existing limitations and emerging trends in the DNAzyme/nanomaterial-assisted sensitive sensing systems are pointed out as well.

Nanomaterials Performing Functions Such as Signal Transduction/Amplification

With the flourish development of nanoscience and nanotechnology, a great number of nanomaterials with exceptional properties, have received growing interest in the development of metal ion biosensors [13]. Nanomaterials possess impressive physical, chemical, electrical and mechanical properties, which can significantly enhance the performances of biosensors [14]. The roles of nanomaterials in the biosensing systems can be very different, varying from fluorescence quenchers and colorimetric indicators to efficient signal amplifier and carriers for signaling probes. The coupling use of nanomaterials and DNAzymes insures both the sensitivity and selectivity in biosensing systems for the determination of metal ions. In the following section, we will summarize the recent development of biosensors for the metal ion detection with the assistance of both DNAzymes and nanomaterials, which, in particular, include GNPs and GOs.



Scheme 1. Representative approaches of DNAzyme and nanomaterial-mediated metal ion sensing systems.

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GNPs used in the DNAzyme-Based Metal Ion Sensing Systems

An inherent advantage of using GNPs as biosensing tools is their distinct absorption properties for single-stranded DNA (ssDNA) and double-stranded DNA (dsDNA), as well as their flexible signal transduction mechanisms. ssDNA probes can tightly wrap on GNP surfaces and form stable complexes via the strong interactions between the nitrogen atoms of the DNA bases and gold atoms. But for dsDNA, the binding affinity with GNPs is significantly weaker. This is because dsDNA structures are much more rigid with nitrogen-containing bases buried inside yet the negatively charged phosphate backbones exposed outside, which results in strong repulsions between dsDNA and negatively charged GNPs. The distinct interaction affinities towards ssDNA and dsDNA are the basic working mechanisms how DNAzyme/GNP-based biosensors are designed.

The poor fluorescence quantum yields of GNPs make them unsuitable to serve as fluorescence indicators. However, the unique electronic properties endow GNPs with fantastic quenching efficiency. GNPs provide promising opportunities to revolutionize fluorescence resonance energy transfer (FRET) assays due to the fact that the quenching effect of GNPs is several orders of magnitude higher than that of commonly used fluorophores that functions as quenchers. GNPs can also be regarded as universal quenchers for almost all dyes. All these merits make GNPs a powerful tool for the construction of FRET-based biosensors that can allow the effective and precise analysis of metal ions [15].

GNPs have made meaningful significance in the development of metal ion biosensors, especially in the colorimetric approaches. Generally, dispersed GNPs with diameter of about 13 nm appear red in color, because they exhibit a strong optical absorption around 520 nm due to the presence of surface plasmon resonance. As GNPs aggregate, their size increase significantly, this brings about a red shift in the absorbance wavelength of GNPs, associated with a color change from red to blue. This can be easily visualized by the naked eyes. The assembly and disassembly of GNPs can be programmably achieved by modulating the recognition principles coupled with the configurational change of the DNA probes involved. The colorimetric biosensors based on GNPs and DNAzymes provide an elegant platform for metal ion detection, which does not require any costly or complicated equipment yet can be utilized for on-site analysis.

Based on the crucial roles that GNPs play in the DNAzyme-mediated sensors, the design principles of DNAzyme/GNPs biosensing systems can be categorized into several types: fluorescence quenchers, colorimetric indicators and signal enhancers [16-18].

GO Applied in the Construction of DNAzyme-Based Metal Ion Sensors

Since its discovery in 2004, graphene has significantly accelerated the advances of two-dimensional nanotechnology [19]. As an amazing two-dimensional nanomaterial, graphene consists of a single layer form of carbon atoms. Plenty of research effort has been made to the investigation and application of graphene and its derivatives due to their fascinating properties, such as outstanding mechanical strength, high elasticity, good thermal conductivity, controllable optical properties. As one of promising graphene derivatives, GOs are of particular interest due to its excellent water solubility and convenient functionalization, which is attributed to the existence of many oxygen-containing functional chemical groups. With a wide absorption band from about 200 nm to 800 nm, GO can offers flexible options for donor-acceptor pairs in FRET. GO can act as a universal fluorescence quencher without stringent requirement of spectral overlap between GO and the fluorescence energy donors. GO exhibits a superior quenching capability with an effective quenching distance as long as 30 nm via a long range fluorescence energy transfer processes. This distance is much longer than that of the typical distance for the traditional FRET pairs, which is reported to be about 10 nm. All these properties allow GOs to actively take part in the development of fluorescence sensors with applications in the fields of biomedical diagnosis and environmental inspection [20].

The special absorption affinity between GO and DNA probes have received considerable attention in biosensor construction since they can help to realize the essential goals in biosensing: target recognition, signal transduction and enhancement. Compared with dsDNA probes, ssDNA probes exhibit preferential binding affinity onto the GO surfaces, which is mainly due to the π-π stacking between the aromatic rings of nucleobases in DNA and the hexagonal cells in GO. However, the absorption affinity between GO and dsDNA, in which the nucleobases are buried inside the helical structure, becomes much weaker [21].

GOs can not only be used as excellent fluorescence quenchers, but can also serve as amazing signal amplifiers, especially for the biosensing systems where fluorescence anisotropy values are measured. The fluorescence anisotropy value is highly sensitive to changes in the rotational motion of fluorescently labeled molecules, which in turn depends upon various parameters, including molecular mass, temperature, and solution viscosity. Among them, molecular mass is one of the crucial factors that can significantly influence the measurement of fluorescence anisotropy. GOs, with large molecular masses, can provide a good opportunity for signal enhancement in the biosensing platforms.

Critical advantages that graphene possesses over other materials, such as silicon, is the ultrahigh carrier mobility and monatomic thickness [22], which make it promising in the applications of FET sensors. It has been predicted that graphene can even have a mobility as high as 200,000 $cm^2 V^{-1} s^{-1}$ at room temperature [23]. Moreover, the monatomic thickness warrants ballistic transport across the base, which thus results in a high gain and low base resistance. More importantly, graphene possesses amazing mechanical strength and flexibility, and the uniformly fabrication is also easily achieved. Good carrier mobility and signal gain, low electrical noise, as well as monatomic thickness and mechanical properties collectively represent the most favorable

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features that can make it possible for graphene to significantly improve the performances of FETs [24]. GO has found its way into a great number of biosensing strategies, coupling with various signal transduction modes, such as fluorescence, colorimetric and electrochemistry.

Figure 1 illustrates two typical cases where GNPs **(Figure 1A and 1B)** and GO **(Figure 1C and 1D)** serve as fluorescence quenchers [25,26]. Coupled with DNAzymes, GNPs and GO are designed for the determination of UO_2^{2+} and Pb^{2+}, respectively. As shown in **Figure 1A**, first, DNAzyme (designated as 39E) was linked to GNPs (designated as AuNP) to form DNAzyme-GNP complexes (39E-AuNP). This is followed by the hybridization between the DNAzyme and its corresponding substrate, 39S, which was labeled with a fluorophore and a quencher at the ends. Then the complex of GNP/DNAzyme/substrate is formed (designated as 39ES-AuNP) [27-31]. The close distance between the fluorophore and the GNPs significantly quenched the fluorescence and weakened the background signal after the hybridization. The introduction of UO_2^{2+} then triggered the enzymatic cleavage and separated the fluorescent DNA fragments from the GNPs and the quenchers. The remarkable fluorescence enhancement was thus used to report the presence of UO_2^{2+} in a quantitative manner, as indicated in **Figure 1B**. The inset in **Figure 1B** is the result to show the detection selectivity of the method. This was the first report that DNAzyme was used for metal ion sensing in living cells. It should be noted that GNPs are desirable for cellular studies due to their stability in serum and resistance to enzymatic degradation [32-40].

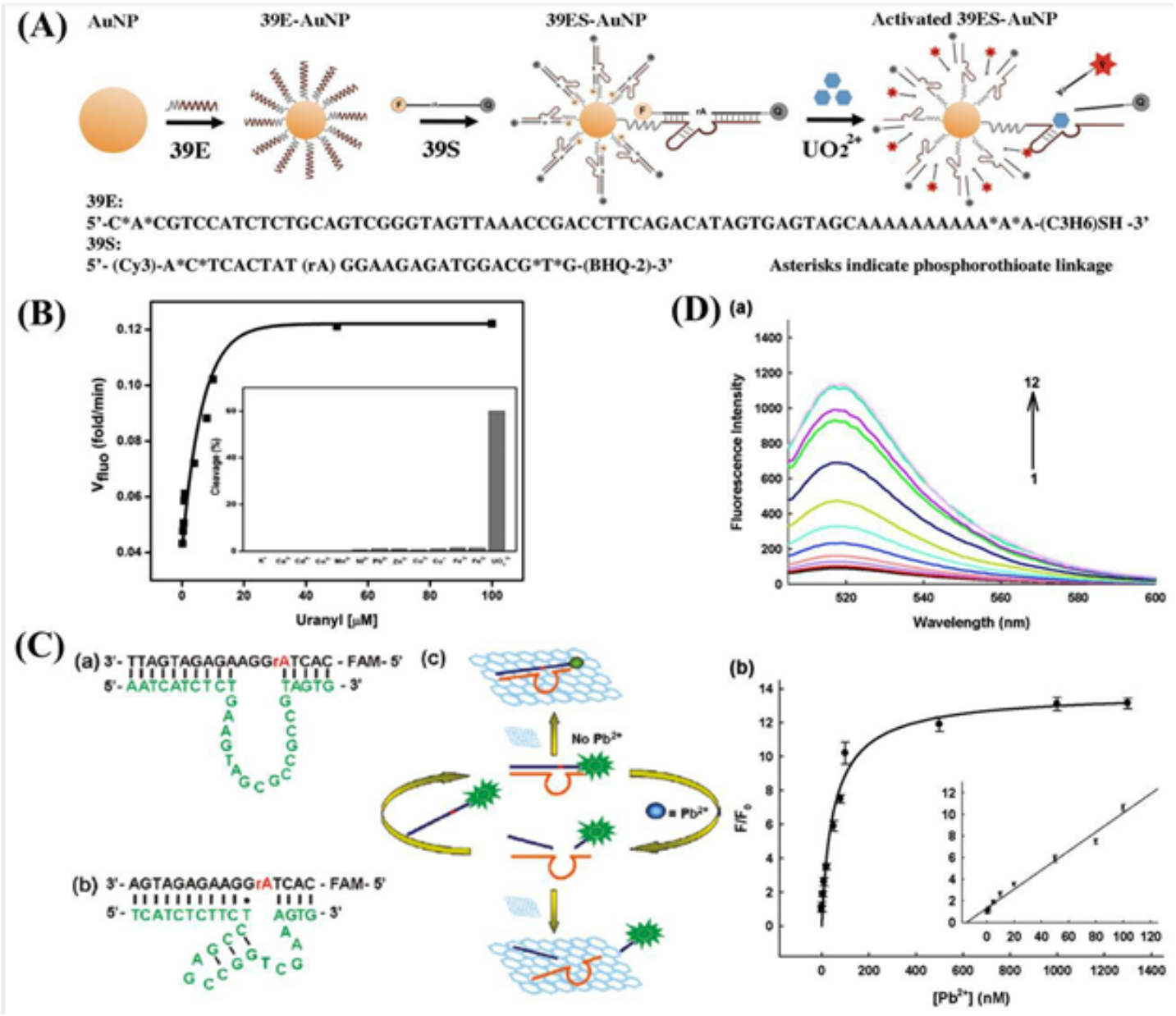

Figure 1. The working principle of DNAzyme-based methods for the detection of UO_2 based on GNPs (A and B) and GO ((C and D). (A and B) Adapted with permission from Wu et al. Copyright 2013 American Chemical Society, (C and D) Adapted with permission from Zhao et al. Copyright 2011 American Chemical Society).

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Figure 1C demonstrates a turn-on fluorescence sensing strategy, where the signal enhancement was related to the concentration of Pb2+ [40-45]. In this method, a unique DNAzyme with large ssDNA loop was chosen, which ensures the strong interaction between the DNAzyme and GO. In the absence of Pb2+, a complex containing both Pb2+-dependent DNAzyme and its substrate labeled with FAM was attracted and quenched by GO, thereby resulting in a greatly suppressed signal. Upon the introduction of Pb2+, substrate strands were cleaved and many short ssDNA segments were generated, among which FAM-tagged ssDNA products were only 5 nucleotides in length. These short FAM-ssDNA probes exhibited very weak affinity with GO and their fluorescence was well maintained. The relationship between the fluorescence signal change and the concentration of target (Pb2+) is depicted in **Figure 1D** [46-69].

Summarized from a rapidly growing literature, the details of the biosensing methods employing both DNAzymes and nanomaterials are listed in **Table 1**.

Table 1. Comparison of DNAzyme/nanomaterial-aided methods for the determination of metal ions.

DNA	Nanomaterials	Target ions	Signal	Detection limit	Ref.
DNAzymes	GNPs	Pb^{2+}	Colorimetry	-	[44]
				0.4 μM	[44]
			Electrochemistry	3 nM	[60]
				20 pM	[66]
				1 nM	[54]
				12 pM	[67]
				0.8 pM	[68]
				0.34 pM	[71]
		Cu^{2+}	Colorimetry	20 μM	[45]
				290 nM	[59]
		UO_2^{2+}	Fluorescence	-	[62]
			Colorimetry	50 nM	[16]
		Zn^{2+} and Cu^{2+}	Fluorescence	37 nM	[35]
				0.47 nM and 0.45 nM	[41]
	GOs	Pb^{2+}	Fluorescence	0.5 nM	[61]
			Fluorescence	0.3 nM	[70]
			FET	0.18 nM	[58]
			Electrochemistry	34 fM	[63]
			Fluorescence	2 nM	[46]
		$_{Cu}2+$		365 pM	[47]
			Fluorescence anisotropy	~1 nM	[65]
		$_{Hg}2+$	FET	0.5 fM	[32]
			FET	0.5 nM	[57]

CONCLUSIONS AND OUTLOOK

Metal ions have posed severe accumulativity and undegradability threats to environment and human health because of their it is thus of considerable importance to establish effective dreliable strategies for metal ion determination. To avoid the drawbacks of the conventional methods and the organic molecule-involved schemes, approaches based on the employment of advanced materials have been proposed. Among them, sensing methods based on the involvement of both DNAzemes and nanomaterials (such as GNPs and GO) have been developed for the detection of metal ions, such as Pb^{2+}, Cu^{2+}, Hg^{2+}, Pb^{2+} and so on. DNAzymes are attractive DNA probes that guarantee the recognition selectivity towards numerous metal ions and allow flexible signal transduction mechanisms to indicate the presence of targets. Additionally, nanomaterials with amazing properties can always ensure sensitivity improvement because they can significantly amplify the response signals, including fluorescence, colormetrics, electrochemistry and so on.

Fluorescence biosensors make it possible for real-time and noninvasive monitoring of metal ions in a rapid and reproducible manner. However, they easily suffer from some limitations, such as irreversible photobleaching and costly laboratory facilities. Colorimetric approaches offer alternative opportunities to realize the on-site detection of metal ions. They are usually much more cost-effective because they do not rely on any sophisticated instruments and the results can be visualized by naked eye. But there are still some drawbacks, including insufficient color change and poor sensitivity. Electrochemical measurements also attract substantial interest due to their low cost and simplicity. Unfortunately, problems still exist, such as poor reproducibility and unsatisfactory stability. All these sensing methods have their own strengths and weaknesses.

The employment of both DNAzymes and nanomaterials has permitted the reliable and robust determination of metal ions in environmental monitoring and medical diagnosis. Although there is significant progress in the fileds, many problems still

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exist. First, it is a challenge to develop strategies to realize the multiplexing determination of several metal ions in a single test. Additionally, DNAzymes currently available are usually targeted to Pb^{2+}, Cu^{2+}, UO_2^{2+}, Zn^{2+}, and Mg^{2+}, while DNAzymes that are related to other crucial metal ions, such as Sr^{2+} and Cr^{3+}, are still unavailable. To solve these problems, it is highly demanded to isolate more DNAzymes and prepare advanced nanomaterials with superior signaling and sensing capability.

With the great progress achieved in the development of nanotechnology and biosensing, we believe that DNAzyme/nanomaterial-mediated metal ion sensors will show promising potentials in practical applications in the future.

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