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Metal ion detection using functional nucleic acids and nanomaterials

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ABSTRACT

Metal ion detection is critical in a variety of areas. The past decade has witnessed great progress in the development of metal ion sensors using functional nucleic acids (FNAs) and nanomaterials. The former has good recognition selectivity toward metal ions and the latter possesses unique properties for enhancing the performance of metal ion sensors. This review offers a summary of FNA- and nanomaterial-based metal ion detection methods. FNAs mainly include DNAzymes, G-quadruplexes, and mismatched base pairs and nanomaterials cover gold nanoparticles (GNPs), quantum dots (QDs), carbon nanotubes (CNTs), and graphene oxide (GO). The roles of FNAs and nanomaterials are introduced first. Then, various methods based on the combination of different FNAs and nanomaterials are discussed. Finally, the challenges and future directions of metal ion sensors are presented.

1. Introduction

Metal ions play essential roles in biological and environmental systems (Huang et al., 2013b). Most metal ions, such as lead (Pb^{2+}), copper (Cu^{2+}), mercury (Hg^{2+}), and silver (Ag^{+}) ions, are not biodegradable and their accumulation in human bodies can cause various health problems. Inappropriate treatment of metal ions can lead to metal ion contamination, which has become a critical environmental issue in developing countries (Duong and Kim, 2010). To effectively monitor and control metal ion concentration in various sources, the detection of metal ions becomes important. The development of metal ion sensors is a hot yet challenging topic in analytical chemistry (Huang et al., 2015b). Many efforts have been devoted to developing accurate and selective approaches for metal ion detection, among which functional nucleic acid (FNA)-based methods are appealing and have great potential for practical applications (Torabi and Lu, 2014). FNAs are short but robust single-stranded DNA (ssDNA) molecules with excellent abilities for metal ion recognition. DNAzymes, G-quadruplexes, and mismatched base pair-based DNA probes (Gong et al., 2015) are representative FNAs, which exhibit unique properties for the detection of metal ions.

FNAs can ensure the selectivity of metal ion detection, while the sensitivity of FNA-based detection methods is not appealing. Fortunately, this drawback can be improved by nanomaterials, which possess superior physical, chemical, and electrical properties required in analytical chemistry. Nanomaterials, from gold nanoparticles (GNPs) and quantum dots (QDs) to carbon nanotubes (CNTs) and graphene oxide (GO), have been widely employed for sensitive and precise determination of metal ions (Cui et al., 2013b). Diverse nanomaterial-based biosensors have been constructed with different signal reporting methods, such as fluorescence, colorimetry, scattering, and electrochemistry.

There are some good review articles in the literature presenting recent advances of FNA-based sensors or nanomaterial-mediated sensing systems for metal ion detections (Cui et al., 2015; Ma et al., 2011, Zhang et al., 2011). Unfortunately, detailed reviews of the significant performance of metal ion sensors using both FNAs and nanomaterials are unavailable. In the past decade, great efforts in developing efficient and reliable sensors for metal ion detection based on the integration of FNAs and nanomaterials have been made and a detailed summary about this topic is highly demanded. Herein, the development of biosensors that take advantage of the special properties of both FNAs and nanomaterials for metal ion determination is intensively reviewed. Specifically, recent progress in the fabrication of metal ion sensors using DNAzymes, G-quadruplexes, and mismatched DNA base pairs (T-Hg^{2+}-T and C-Ag^{+}-C) is elaborated. Furthermore, the employment of nanomaterials, including GNPs, QDs, CNTs, and GO, is also discussed. Finally, the limitations and future perspectives of FNA/nanomaterial-aided metal ion sensing systems are presented.

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2. Why FNAs for metal ion detection

Traditional methods for metal ion determination include inductively coupled plasma atomic emission spectrometry (Elfering et al., 1998), atomic absorption spectroscopy (Narin and Soylak, 2003), inductively coupled plasma mass spectrometry (Moens et al., 1997), X-ray fluorescence spectroscopy (Rebocho et al., 2006), and anodic stripping voltammetry (Demetriades et al., 2004). These methods have high accuracy and sensitivity. However, they involve expensive and sophisticated instruments, which have to be performed by well-trained personnel. In addition, they usually require complex sample preparation steps. These issues severely hamper their applications in metal ion assays.

To avoid the disadvantages of the traditional methods, attempts have been made to develop new metal ion biosensors using advanced materials (Kim et al., 2012). Among them, FNAs are ideal candidates for detecting metal ions (Li et al., 2016). First, FNAs, can be theoretically selected to bind any metal ions of interest. They are superior to antibodies, which cannot target at small metal ions. Furthermore, FNAs are strictly isolated from a large DNA library that consists of 10^{14}–10^{15} different DNA molecules. This endows FNAs with ultra-high selectivity. Moreover, FNAs can be easily functionalized with desired chemical tags, which range from optical labels to electrochemical indicators, or even nanomaterials. In addition, FNAs can be denatured and renatured many times without significant loss in binding activity toward their targets. Finally, FNAs do not require deliberate design of metal-binding sites, which are indispensable for fluorophore- or genetically encoded protein-based metal ion sensors. These properties render FNAs a facile and effective candidate for metal ion sensing.

Therefore, compared with the traditional methods, FNA-enabled biosensor platforms for metal ions detections exhibit better performance in terms of generality, selectivity, versatility, stability, and operation convenience. The exceptional specificity of FNAs ensures good recognition abilities. It can also be integrated with the superb sensitivity of nanomaterials, which have opened great opportunities for advancing FNA-based biosensors to realize rapid and precise quantification of metal ions. FNAs can recognize their relevant targets selectively and nanomaterials can significantly enhance the sensitivity through signal conversion and amplification, as illustrated in Fig. 1. Hence, the combination of FNAs and nanomaterials offers a perfect option for biosensor construction.

3. FNAs as recognition probes

FNAs can be mainly categorized into three groups: DNAzymes, G-quadruplexes related to guanine (G)-rich DNA probes, and mismatched DNA base pairs, as shown in Fig. 2. Their applications in metal ion detection are discussed in the following sub-sections.

3.1. DNAzyme-based sensing strategies

DNAzymes, screened through in vitro selections, have been frequently used as highly specific sensing elements for a variety of cofactors, including Pb^{2+}, Cu^{2+}, $UO_2{}^{2+}$, Zn^{2+}, Ca^{2+}, Mg^{2+}, Mn^{2+}, Co^{2+}, and Hg^{2+}. Figs. 2a and 2b show the main function of DNAzymes that are highly specific to metal ions. They can bind with substrates associated with certain ions (Pb^{2+} and Cu^{2+} in Figs. 2a and 2b, respectively). Upon the addition of relevant target ions, the activities of DNAzymes are activated and the substrates are cut into two pieces from the specific positions indicated by the triangles in Figs. 2a and 2b. Then the DNA duplex dissociates from each other and generates several short ssDNA fragments. DNAzymes have exceptional recognition abilities and efficient catalytic activities, which are strongly dependent on the metal ions being detected. DNAzymes have been extensively employed in optical and electrochemical sensors for the determination of metal ions in a rapid and reliable fashion.

Inspired by the design of molecular beacons, Tan and co-workers (Wang et al., 2009) designed an innovative ssDNA probe (Fig. 3a) conjugated with a fluorophore and a quencher at the ends. The ssDNA probe was unique because it integrated the Pb^{2+}-dependent DNAzyme with the substrate in the same DNA molecule and the fluorescence resonance energy transfer (FRET) pair (the fluorophore and quencher) were brought close to each other, which remarkably suppressed the background signal. Upon the addition of Pb^{2+}, DNAzyme would initiate the cleavage of the substrate strands and result in the separation of the fluorophore and the quencher, liberating the fluorescence emission.

Based on a similar design principle, Tan and co-workers created another elegant ssDNA probe, within which a Cu^{2+}-specific DNAzyme and the corresponding substrate strand were incorporated into one molecule (Yin et al., 2009), as shown in Fig. 3b. When Cu^{2+} appeared, the digestion reaction of the substrates was triggered, thereby leading to the detachment of short ssDNA fragments from the DNAzyme-substrate complexes. Different from the FRET used for fluorescence signal generation in Fig. 3a, horseradish peroxidase (HRP)-mimicking enzyme sequences were incorporated into the liberated ssDNA fragments, which, aided by the hemin molecules, produced a strong colorimetric signal to quantitatively reveal the concentration of Cu^{2+}. Without the presence of Cu^{2+}, the catalytic activity of the HRP-mimicking sequences were inhibited because they were effectively caged inside the stable hairpin structures.

3.2. G-quadruplex-enabled detection platforms

G-quadruplexes, in which four guanines form a square planar tetrad, have drawn considerable attention recently. Since metal ions are essential in the formation of G-quadruplexes, as shown in Fig. 2c, G-quadruplexes have been widely employed for the detection of a great number of metal ions, such as K^+ and Na^+. G-quadruplexes have an interesting property that their structures can switch from single strand states to quadruplex structures, which makes them compatible with diverse reporting mechanisms. Fig. 4 shows typical cases illustrating how G-quadruplexes enable selective detections of metal ions. In Fig. 4a, a special ssDNA probe was prepared with the two ends modified with a fluorophore and a quencher (Ueyama et al., 2002). It adopted a random coil structure and maintained its fluorescence signal very well. However, upon the addition of K^+, it rearranged its configuration and assumed a G-quadruplex structure, which brought the fluorophore and quencher close to each other, thereby permitting FRET. The fluorescence decrease could reveal the presence of K^+ accurately and selectively.

Different from the dual-labeled ssDNA probe in Fig. 4a, Fig. 4b shows a new and label-free ssDNA probe (Xu et al., 2015b), which allows the determination of K^+ in a cost-effective and straightforward manner. The presence of K^+ urged the ssDNA probe to change its initial random coil structure to a G-quadruplex conformation. The formation of G-quadruplex could accommodate Riboflavin, a special ligand that can emit fluorescence signal upon binding with G-quadruplexes, and generate a strong response signal.

3.3. Mismatched DNA base pair-mediated assays

It has been reported that, Hg^{2+}, can link two thymine (T) bases to form stable T-Hg^{2+}-T structures. As shown in Fig. 2d, the imino proton of T residues can be replaced by Hg^{2+} to form T-Hg^{2+}-T structure, which is even more stable than a natural A-T base pair. Therefore, mismatched T-T base pairs can be used for Hg^{2+} detections. Likewise, hybridization events between cytosine (C) bases can be selectively induced to form C-C base pairs with the aid of Ag^+, as illustrated in Fig. 2e. Great efforts have been devoted to developing techniques for reliable and effective determination of Hg^{2+} and Ag^+, which make good use of metal ion-assisted mismatched base pairs: T-Hg^{2+}-T and C-Ag^+-C.