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A mini-review on functional nucleic acids-based heavy metal ion detection

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ABSTRACT

Recent years have witnessed great progress in developing functional nucleic acids (FNAs)-based sensors for the detection of heavy metal ion. In this review, four types of the FNAs that most widely-used in heavy metal ions detection were briefly introduced and a dozen of recently published review articles which summarized those FNAs-based sensors were introduced. Particularly, according to the degree of automation and system integration, those FNAs-based sensors which belong to the lab-on-a-chip (LOC) category were reviewed in more detail by classifying them into six types such as microfluidic LOC system, microchip, lateral flow dipstick, personal glucose meter, microfluidic paper-based analytical devices (μPADs) and disc-based analytical platform. After gave a brief description of the sensing strategies, properties, advantages or disadvantages of these FNAs-based sensors, existing problems and future perspectives were also discussed.

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1. Introduction

Functional nucleic acids (FNAs) refer to those nucleic acids whose functions are beyond the conventional genetic roles of nucleic acids (Liu et al., 2009b). As concluded in the monograph "Functional Nucleic Acids for Analytical Applications" that edited by Li and Lu (2009), the FNAs could be divided into two types: the natural ones and the artificial ones. The natural FNAs include

Abbreviations: AuNPs, gold nanoparticles; ECL, electrochemiluminescence; FNAs, functional nucleic acids; GOQD, graphene oxide quantum dot; HCG, human chorionic gonadotrophin; LFA, lateral flow assay; LFNAB, lateral flow nucleic acid biosensor; LOC, lab-on-a-chip; LOD, limit of detection; MBs, magnetic beads; MSNs, mesoporous silica nanoparticles; ODR, optical darkness ratio; PGM, personal glucose meter; SA, streptavidin; SELEX, systematic evolution of ligands by exponential enrichment; SPIA, sol particle immunoassay; ssDNA, single-stranded DNA; μPADs, microfluidic paper-based analytical devices

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ribozymes and riboswitches, and the artificial ones cover aptamers, ribozymes, and deoxyribozymes (DNAzymes) identified by *in vitro* selection. Since the discover that the nucleic acids have the ability to perform interesting functions such as catalysis and ligand binding, a great many of FNAs have been found and selected, and showed application potential in various fields including therapeutics, imaging, screening and drug development, separation, materials science, nanotechnology, organic synthesis, and sensing (Liu et al., 2009b). As Szostak claimed “perhaps the most scientifically interesting and surprising application of FNAs has been the exciting effort aimed at the development of biosensors and other analytical applications, such as bioseparations, signal amplification, and signal processing” (Li and Lu, 2009), in this review we focus on the FNAs-based biosensors and related analytical applications that been applied to a concerned research area, heavy metal ion detection.

Heavy metal refers to any metallic element that has a relatively high density and is toxic or poisonous even at low concentration (Duruibe et al., 2007). It includes lead (Pb), cadmium (Cd), zinc (Zn), mercury (Hg), silver (Ag), chromium (Cr), copper (Cu), iron (Fe) and the platinum (Pt) group elements. Arsenic (As) is also be ranged to heavy metal because of its chemical properties that analogous to heavy metals' (Wanekaya, 2011). Nowadays heavy metal ion contamination has become one of the most serious environmental problems in many countries (Wu et al., 2014a). As heavy metal ions are difficult to be degraded but easy to be enriched in the human body through the food chain (Kang et al., 2014), and most of them are not biologically essential and harmful to organisms even at very low concentration levels (Wu et al., 2014a), chronic exposure to these ions is related to various adverse health effects such as cancer and neurodegenerative diseases (Tsekenis et al., 2015). Therefore, for the sustainable evolution of environment and human health, it is imperative to develop sensitive and selective methods for heavy metal ions detection.

Traditional methods developed for heavy metal ions detection include chromatography, spectroscopy, and electrochemistry methods (Uglov et al., 2014; Zhan et al., 2014). Respectable advantages such as high accuracy and sensitivity were shown by these techniques, however, most of them need expensive sophisticated instruments, complicated sample pretreatment and well-trained personnel, failing to meet the requirement of portable and easy-to-use detection (Wei et al., 2014; Zhan et al., 2015a). Recently, novel methods based on FNAs have shown great potential in heavy metal ions detection due to their low-cost and easy to operate merits (Zhan et al., 2015b). Thus in follows some of the research efforts that have been made in this area in recent years are reviewed.

2. Common types of FNAs used in heavy metal ion detection

Though the nucleic acids that match the definition of FNAs include many types, the FNAs that applied in heavy metal ion detection mainly refer to the following four types: aptamers, metal ion-specific DNAs, DNAzymes and guanine (G)-rich oligonucleotides that can associate into G-quadruplexes.

Aptamers are artificial short single-stranded DNA (ssDNA), RNA sequences or peptide molecules that selected through the systematic evolution of ligands by exponential enrichment (SELEX) approach (Iliuk et al., 2011; Yuce et al., 2015) and can fold into specific secondary and tertiary structures on binding to certain targets with extremely high specificity (Mascini et al., 2012; Song et al., 2012a). It should be noticed that although the acronym SELEX was often be applied to describe all selection experiments, strictly speaking it applies only to the selections of aptamers but not to that of nucleic acid enzymes (RNAzymes and DNAzymes) (Li and Lu, 2009). Though the SELEX method has been reported since 1990 (Ellington and Szostak 1990; Tuerk and Gold, 1990) and claimed able to selected aptamer for almost every desired target (Famulok et al., 2007), until now only four heavy metal ions, such as Zn^{2+} (Rajendran and Ellington, 2008), Cd^{2+} (Wang et al., 2016; Wu et al., 2014b), Pd^{2+} (Cho et al., 2015) and As (Kim et al., 2009) have obtained their aptamers through SELEX. The actually binding mechanism of aptamer to its target remains indistinct, but it is widely believed that hydrogen bonds (Fig. 1), Van der Waals force or base-stacking interactions play a significant role in enabling and stabilizing those bindings (Hermann and Patel, 2000; Macaya et al., 1993; Song et al., 2012b; Wu et al., 2012; Zhang et al., 2014a).

Metal ion-specific DNAs are those specific nucleic acid sequences of which certain DNA bases can selectively bind with metal ions to form strong metal-base complexes. Two of the most impressive DNAs of this type are thymine (T)-rich DNA that selectively binds Hg^{2+} to form T-Hg^{2+}-T mismatch (Miyake et al., 2006; Wu et al., 2011) and cytosine (C)-rich DNA that selectively binds Ag^{+} to form C-Ag^{+}-C mismatch (Ono et al., 2008; Zhan et al., 2012). Both of these two mismatches are belong to coordination bonds, and previous studies show that the T-Hg^{2+}-T mismatches are more stable than the natural adenine-thymine (A-T) base pair with a binding constant close to $10^6\ M^{-1}$ (Torigoe et al., 2010). Miyake et al. (2006) studied the formation of T-Hg^{2+}-T with ^1H NMR spectra and found that the formation was attributed to the replacement of imino proton of T residues by Hg^{2+} (Fig. 2 left). Much similar to the T-Hg^{2+}-T formation, Ag^{+} replaced the imino proton of C residues and leaded to C-Ag^{+}-C formation (Fig. 2 right) with a binding constant in the range of $10^5\ M^{-1}$ (Torigoe et al., 2011). Besides these Hg^{2+}/Ag^{+}-specific DNAs, other heavy metal ions' specific DNAs have also been reported in recent years, for example, Liang et al. (2013) designed a G-/T-rich oligonucleotides that selectively recognize Arsenite (As(III)), Zhan et al. (2015c) discovered a Cu^{2+}-specific ssDNA and Cai et al. (2015) modified the streptavidin (SA) aptamer sequence and made it selective to Pt^{2+}.

DNAzymes (also called catalytic DNAs) refer to these artificial

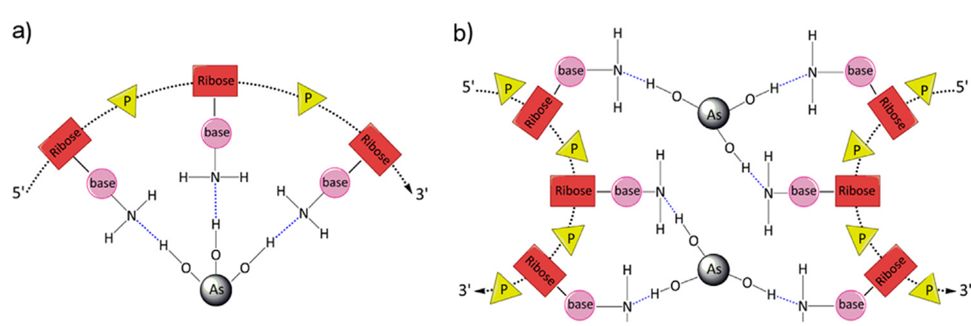

Fig. 1. Supposed principles of the interactions between As(III) and its aptamer. (a) intramolecular hydrogen bonds between As(III) and the bases of DNAs, (b) intermolecular hydrogen bonds between As(III) and the bases of DNAs. Adapted from Wu et al. (2012) by permission of The Royal Society of Chemistry.