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Uses of DNA as Polyion for Cationic Sensors

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ABSTRACT : **Inorganic cations were important in a variety of chemical, biological, industrial, and environmental processes. Many DNA-based sensors were used to detect cations over the last two decades. Apart from strong genetic information, the chemical structure of DNA had been shown to be ideal for metal binding via both the phosphate backbone and nucleobases. DNA was highly stable, inexpensive, and simple to modify. For metal sensing, two types of functional DNA were used: aptamers and DNAzymes. Because metal binding aptamers were difficult to isolate, only a few had been reported. In the other side, DNAzymes were effective metal sensing tools due to their catalytic activity, there was no need for metal immobilization. Each cationic element and the known DNA sequences for its sensing was discussed in this review. We concentrated on reviewing the majority of the published researches about DNA-cationic sensors. Finally, several specific applications were discussed.**

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I. INTRODUCTION

Metal ions were linked to the evolution of the biological environment, industrial manufacturing and human existence. A large number of metal ions were released into the environment. However, because metal ions couldn't be degraded in general, continuous development of the food chain resulted in progressive serious pollution of metal ions in the environment. As a result, the qualitative and quantitative detection of metal ions is becoming increasingly important [1]. The most important metal ions were calcium and magnesium. The importance of calcium as a metal ion in the biological environment explained the extensive work in developing sensors for Ca^{2+} detection. Although many Ca^{2+} binding proteins were known, few nucleic acids could bind Ca^{2+}selectively. Because of their high stability and programmability, DNA-based biosensors were very important [2]. The determination of calcium level was critical for a diversity of applications, including industrial and household water hardness control, medical diagnosis, and food assessment [3]. Calcium was an essential mineral in the skeletal system, making up 99 % of the calcium in bones and teeth. Milk was a rich source of calcium, which might aid in the prevention of disorders such as osteoporosis [4]. Magnesium ranked eighth in abundance in the Earth's crust. It was found in large magnesite, dolomite, and mineral deposits [5]. In cells, magnesium was the fourth most prevalent metal ion (per mole). It functioned as a cofactor in over 300 enzyme systems that controlled a wide range of biochemical reactions in our bodies, such as protein synthesis, nerve and muscle function, blood glucose control, and blood pressure regulation. Energy production, oxidative phosphorylation, and glycolysis all required magnesium. It helped in bone structural development and was required for the synthesis of DNA, RNA, and antioxidants [6]. Because magnesium ions were acknowledged as one of the most valuable cations for many physiological and pathological functions, the selective and specific detection of magnesium ions with chemosensors attracted the attention of researchers and became essential in biomedical and biological studies [7]. Very sensitive and quantitative methods for the detection of metal ions were developed, including atomic absorption/emission spectroscopy (AAS) [8], X-ray fluorescence spectrometry (XRF) [9], inductively coupled plasma/atomic emission spectrometry (ICP-MS) [10] cold vapor atomic fluorescence spectrometry (CVAFS) [11] and others. However, they were restricted for in-situ usage because of the complicated sample preparation processes, the need for trained personnel, the high cost of instrumentation, and the risk of sample metamorphism during storage and handling. As a result, developing rapid, low-cost, simple, and reliable techniques for in-situ and real-time measurements of metal ions would be extremely desirable and difficult. Biosensors were widely used for metal ion detection in environmental monitoring, food inspection, and disease diagnosis as a quick and on-site testing platform [12]. DNA-based sensors were used to detect metal ions due to their high selectivity, good sensitivity, signal amplification, and nanostructured construction. DNA was a molecule that contained the instructions that an organism required to live, develop and reproduce. These instructions were placed inside each cell. It contained data used in our daily metabolism and physiological activities, and it influenced the majority of our characteristics [13]. DNA was made up of nucleotide

molecules. Each nucleotide was made up of a sugar, a phosphate, and a nitrogen base. The poly anion DNA could electrostatically attract metal cations. Hard metals could be bound by DNA phosphates, and other bases of DNA could coordinate metal cations [14]. In DNA biosensors, single-stranded DNA (ss-DNA) molecules served as the target recognition element and were referred to as probe ss-DNA. The principle was based on the probe ss-DNA hybridizing with complementary target ss-DNA or the analyte molecules disrupting the structural integrity of the probe ss-DNA. Both methods resulted in changes in mass transport, emission, light absorption, or proton concentration, resulting in the generation of a signal. The signal was then converted into a measurable response by a suitable transducer element, such as an electrochemical, optical, or thermal element, allowing the signal to be measured as current, light, or potential [15].

1.1. Electrochemical biosensors

A sensor was an apparatus which responded to a physical stimulus, such as light, heat, pressure, or magnetism, and transferred an electrical signal which represented the measured change of any fundamental property of the component material. The word "sensor" in English was derived from the Latin word sentire that means to feel. Chemical sensors that used an electrode as a transducer when an analyte was present were known as electrochemical sensors [16]. They translated chemical reactions of the target species on electrodes into electrical signals which exhibited alterations in potential, current, and conductivity. The advantage of the electrochemical methods was that they presented high selectivity, very low detection limits, and needed a very small volume of sample to produce signals. Electrochemical devices composed of a system of either two or three electrodes. An ideal three-electrode cell composed of working electrode which made of gold, platinum, and/or carbon, a reference electrode which was usually a silver-silver chloride electrode (Ag/AgCl), and a platinum wire which used as a counter/auxiliary electrode [17]. There were three major types of electrochemical sensors: amperometric, potentiometric and conductometric. When using a potentiometric sensor, a local equilibrium was created at the sensor's interface, where the membrane potential or electrode potential was measured. The potential difference between two electrodes could be utilized to determine the sample composition. Amperometric sensors used the applied potential between a reference and a working electrode to stimulate the oxidation or reduction of an electroactive species and then measured the resulting current. Conductometric sensors, on the other hand, relied on the measurement of conductivity at a sequence of frequencies [18]. Electrochemical biosensors, a type of chemical sensors, exhibited high sensitivity, low detection limits and the high specificity of biological recognition processes. These devices comprised a biological recognition element (proteins, enzymes, nucleic acids, antibodies, tissues, cells) which selectively reacted with the target analyte and created an electrical signal which was related to the analyte concentration. Electrochemical biosensors were classified into two types based on the biological recognition process's nature: biocatalytic devices and affinity sensors. Enzymes, cells, or tissue slices were used in biocatalytic devices to identify the target analyte and generate electroactive species. Affinity sensors relied on a specific binding interaction between the analyte and a biological component like an antibody, nucleic acid or receptor [19]. A general scheme for the electrochemical biosensors was shown in Figure 1.

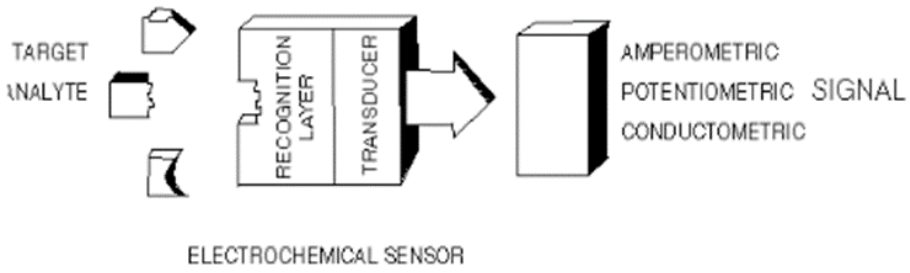

Figure 1. Electrochemical biosensors: biorecognition and signal transduction

1.2. Development of DNA-electrochemical biosensors

DNA was the genetic information's carrier and played a big part in regulating lots of biological processes. Moreover, DNA proved to be an excellent building block for the creation of new devices in biosensor technology [20]. The main idea of most DNA biosensors based on the hybridization of a precise DNA-base sequence with its complementary strand [21]. Moreover, functional DNAs comprising DNA aptamers and DNAzymes could also be used for the establishment of DNA biosensors achieving high selectivity [22]. DNA aptamers were single-stranded nucleic acids or peptide molecules that were selected through in vitro systematic ligand evolution via exponential enrichment (SELEX). The DNA aptamer could particularly bind a definite target with high selectivity and affinity,

which were embraced as the bio-recognition elements in the construction of DNA biosensors [23]. The other type of functional DNAs was DNAzymes, which were DNA-based enzymatic molecules selected by SELEX and were able to catalyze the chemical and biological reactions. DNAzymes were more stable than nature enzymes, that could be denatured and renatured more than one time without any significant lose in their catalytic activities toward substrates. G-quadruplex/hemin DNAzyme [24] and metal ion-dependent DNAzymes [25] were the most major types of DNAzymes which were extensively used as signal amplifiers or catalytic units for enzyme-free detection of biomolecules with high sensitivity. Currently, the rising demand for effective and biomedical tests generated new challenges to conventional DNA-based electrochemical biosensors. Therefore, label-free strategy introduces smart alternatives in establishing DNA-based electrochemical biosensors [26]. The development of DNA-based label-free electrochemical biosensors depended on either the electroactivity of target nucleic acid molecules, or the detection of changes in electrochemical signal related to the hybridization reaction [27, 28]. In the beginning of development of DNA-based electrochemical biosensors, label-free strategies were mostly depended on the intrinsic redox-active properties of DNA bases, particularly using guanine electrochemical oxidation signal [29-32]. The purines guanine (G) and adenine (A) was proved to be oxidized at positive potentials lower than pyrimidines thymine (T) and cytosine (C) [33]. For example, Paleček utilized the direct oxidation of guanine on the mercury drop electrode for earliest DNA detection [34]. Afterward, a series of research efforts were accomplished by the same group that put down the basis for the development of DNA-based label-free electrochemical biosensors [35-37]. Additionally, Wang et al developed various label-free electrochemical advances relied on redox activity of the target guanine for DNA hybridization detection [38-40]. The electrodes were frequently improved by using high-performance functional materials to achieve high sensitivity, which had distinctive properties, like large surface area, good adsorption ability, excellent biocompatibility and great conductivity. So far, a series of research studies were dedicated for the preparation of modified electrodes for label-free electrochemical detection [41, 42]. Gooding et al developed self-assembled monolayer (SAM) technology for the adjustment of electrodes, which offered a molecular control of the interfaces [43]. A DNA-electrochemical biosensor composed of an electrode which represented the electrochemical transducer with a DNA probe immobilized on its surface that represents the biological recognition element and was utilized to detect DNA-binding molecules which represented the analyte that interacted and caused alterations in DNA structure and electrochemical properties that were further converted into an electrical signal [44]. With rapid detection, great selectivity, high sensitivity, and much lower price than the conventional nucleic-acid assays [45], the electrochemical DNA biosensor possessed great importance and value in gene-expression researches, pharmacogenomics, genotyping, , pathogen categorization, drug detection, and molecular diagnostics [46-47]. These classes of sensor connected nucleic-acid layers with electrochemical transducers to create the biosensors [48]. The dynamics of nucleic acid hybridization determined how the electrochemical DNA biosensor was designed. Electrochemical detection of DNA hybridization frequently included monitoring of a current response, under controlled potential conditions, based on a complementary matching recognition event, [49-51]. The probe-modified electrode was generally immersed in the solution that included the target DNA. A hybrid duplex DNA was developed at the electrode's surface when the sequence of the target DNA matched that of the immobilized oligonucleotide-probe DNA (Fig. 2). This type of hybridization event was detected by changes in the current signals of specific electroactive indicators (which bind to the DNA duplex), which were associated to the usage of enzyme labels or redox labels. The design of useful DNA-modified electrodes and the selectivity of electrochemical probes were of great significance in developing electrochemical DNA biosensors [52].

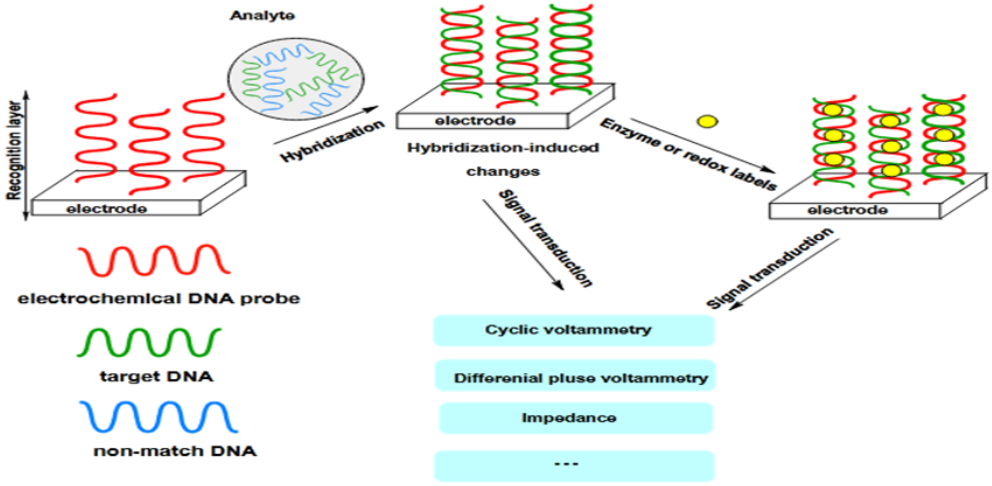

Figure 2. General design of DNA biosensor.

.II. Metal cation sensing by DNA

Natural DNA was a duplex with nucleobases protected by a phosphate backbone. As a result, linking such DNA to precise metal recognition was difficult. The bases in single-stranded oligonucleotides could also participate in metal coordination by forming 3D binding pockets. Many DNA sequences with significant metal binding affinity and specificity were reported over the last two decades [53]. By using pure electrostatic interactions, metal ions were treated as point charges that diffused around DNA polyanions. Metal binding to the phosphate backbone stabilises the DNA duplex (for example, by increasing the melting temperature of the DNA, Tm). This pure electrostatic picture, however, ignored the chemical nature of metal ions and DNA. Group 1A and 2A metals, for instance, mostly interacted with DNA phosphate and duplex DNA stability was maintained even with 1 M Na+ or Mg2+ [54] However, both phosphate and bases interacted with the first row of transition metals, including Cd2+, Pb2+ and trivalent lanthanides. They started to destabilize duplex DNA beyond a few μM since they could coordinate with DNA bases, therefore internucleobase hydrogen bonds disruption [55].

2.1. Alkali Metal Ions

The alkali metals included Li+, Na+, K+, Rb+, and Cs+ that could directly affect their interaction with DNA. These cations were utilized as common buffer salts for a long time to screen charge repulsion in DNA. A few methods were utilized to quantitatively study their binding to DNA, such as molecular dynamics simulation [56] nuclear magnetic resonance NMR [57,58] atomic force microscopy (AFM) [59] electrochemistry [60], and crystallogra-phy [61]. However, the general trend of interaction among them was quite incompatible in different reports, which was most likely because of various experimental systems and characterization techniques [62]. Among the alkali ions, Li+, Na +, and K+ were the most vital in biology. Rb+ had almost no reported biological functions, and Cs+ was slightly toxic. Up to now, DNA-based sensors were established for Na+, K +, and Cs+. Lu and co- workers had successfully isolated a DNAzyme called NaA43 (Figure 3) with a rate of 0.1 min−1 in 400 mM Na+ alone, whereas other mono, di, and trivalent metals were inactive [63]. Na+ could also stabilize G4 structures, but it was usually less effective than K+ for this function [64]. Even so, Tang et al [65] reported that G4 structures with Na+ specificity were used for Na+ sensing. They utilized a G4 sequence named p25, producing a hybrid-type conformation with K+ but an antiparallel one with Na+.

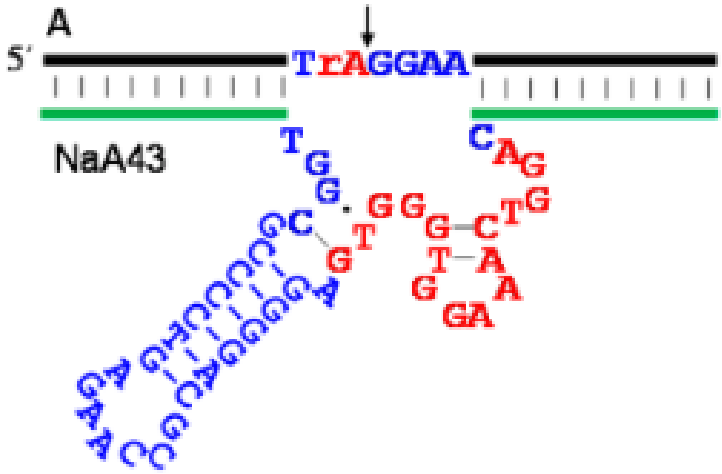

Figure 3. Secondary structures of the NaA43.

The utilization of DNA for K+ detection based mainly on G4 DNA. G4 was a non-canonical nucleic acid structure with diffused guanine tetrads gathered by Hoogsteen hydrogen bonding, where the O6 of guanines coordinate with K+ [66.67]. Two or more such G-tetrads stacked together to form a G4 structure. Each two sequential stacked G-tetrads have eight O6 groups that could coordinate with K+ (fig 4). Chaires and co-workers studied the kinetics of K+ and Na+ induced G4 folding using three model human telomeric oligonucleotides [68]. The results showed that the folding was a process carried out by more than one step and a fast formation of intermediate cation oligonucleotide complexes accompanied by slower isomerizing steps. For K+- induced folding, a single isomerization was noticed with a relaxation time τ of 20−60 ms depended on the sequence. Na+ driven folding, on the other hand, composed of three exponentials with the τ-values of 40−85 ms, 250−950 ms,

and 1.5−10.5 ms, respectively, demonstrating three isomerization steps. It was noticed that the folding pathway in the presence of K+ was easier than that in Na+.

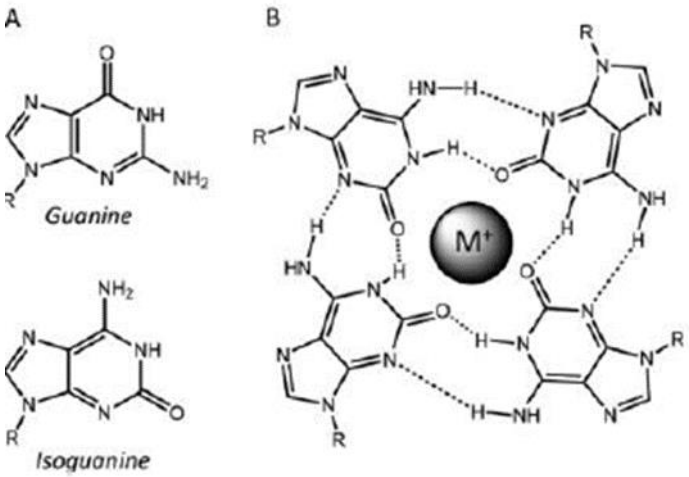

Figure 4. (A) Structures of guanine and isoguanine. (B) A tetraplex stabilized by monovalent cations.

To recognize its biological applications, lots of studies were reported to increase selectivity. A few studies demonstrated nanomolar K+ sensitivity with 104-fold selectivity over Na+. With these studies, utilizing G4 DNA for K+ detection in serum and urine was accomplished [69.72]. However, because G4 could respond to several other metals, new DNA sequences that could better distinguish K+ from Na+ and other ions were developed.

2.2. Alkaline Earth Metal Ions

Group 2A called alkaline earth metals which included Be2+, Mg2+, Ca2+, Sr2+, Ba2+, and Ra2+. Among them, Mg2+ and Ca2+ were the most important cations in biology, whilst Be2+ was toxic [73], Ba2+ was utilized to facilitate X-ray imaging, and Ra2+ was radioactive. The phosphate backbone of DNA was the major binding site for these metals [74,75]. Zheng et al. examined the Mg2+-binding architectures in RNA by utilizing RNA crystals in the Protein Data Bank (PDB) [76]. The inner-sphere binding of Mg2+ to imine N1/N3/N7 atoms in RNA, DNA, and purine containing metabolites was re-examined by Leonarski et al, also deduced that the inner-sphere binding to those atoms were much less common than formerly presented [77]. Few DNAzymes were active with Ca2+, including the 8-17 and 10-23 DNAzymes. Famulok et al separated a variant of the 8-17 DNAzyme named Mg5 which is about 10-fold more active with Ca2+ than with Mg2+ [78,79]. Sugimoto et al. concluded that the 10-23 could be progressed to a Ca2+-specific DNAzyme through rational truncations. Because Sr2+ and Ba2+ didn't have significant biological functions, their sensing function was rarely studied except for utilizing G4 DNA. Kankia and Marky [80] utilized a mixture of calorimetry, spectroscopy, density, and ultrasound techniques to determine the spectral properties, thermodynamics, and hydration effects for the development of G-quadruplexes with Sr2+ and Ba+2. Qu et al [81] used thiazole orange (TO) as a signal reporter to develop a simple Sr2+ detection attempt depended on Sr2+ induced human telomeric DNA. Leung et al [82] created a highly selective G-quadruplex-based luminescent switch-on probe for nanomolar strontium (ii) ions detection in sea water.

2.3. Transition Metals

Most of transition metals could easily lose their bound water molecules because of inner-sphere coordination, leading to a high DNA binding affinity metals desire DNA bases to the phosphate backbone with binding affinity as follow Hg2+ > Cu 2+ > Cd 2+ > Zn2+ > Mn 2+ > Ni 2+, Co 2+ > Fe+2 [83]. Comparison of the coordination strength of several metal ions with DNA (Cu2+, Zn 2+, Mn 2+, Ca 2+, and Mg2+) was reported by Hackl et al [84]. This study demonstrated that Cu2+ was the most effective ions to compact DNA, because of its strong coordination with DNA bases. Cuenoud and Szostak picked out a DNA-ligating DNAzyme in the presence of Cu2+ [85], Carmi and co-workers isolated a few DNA-cleaving DNAzymes using Cu2+ and ascorbate [86, 87]. Wang et al. proposed a G-rich chain which forms a G4 structure stabilized by Cu2+, which could catalyze the enantioselective Friedel−Crafts reaction [88]. Zhan et al. introduced a ssDNA named Cu100 which went through specific folding in the presence of Cu2+ permitting a turn-off sensing of Cu2+ by SYBR Green I (SGI) [89]. Breaker and co-workers preferred DNA-cleaving DNAzymes with only Zn2+ through circular library. A tiny DNAzyme called I-R3 was developed with a rate of 1 min−1 in the presence of 2 mM Zn2+. This DNAzyme was then utilized in the construction of a biosensor which reported a detection limit of 1 nM Zn2+ [90]. The Yarus group first discovered RNA aptamers via immobilizing Zn2+ on a column. The isolated sequences had a Kd of 100−400 μM Zn2+ [91]. In 2000, Sugimoto and coworkers mentioned a few

Zn2+- dependent RNA aptamers which could combine with the HIV-1 Tat protein [92]. Ditzler and co-workers presented two parallel ribozyme selections via Mg2+ and Fe2+, respectively. Self-cleaving ribozymes were isolated in each case, proving that Fe2+ was definitely as good as Mg2+ for RNA catalysis [93]. Wrzesinski et al. choosed RNA aptamers for Co2+ by immobilizing Co2+ on a resin. Two RNA aptamers were isolated with a binding affinity of low mM Co2+ [94].

2.4. Noble Metals

Silver, gold, platinum, and palladium were all examples of noble metals. These noble metals didn't participate in fundamental biological processes and weren't endogenous metals in living things. Furthermore, such metals were resistant to oxidation, and they might be used to create stable metal nanoparticles for DNA adsorption [95,96]. Cytosine-rich DNAs were usually utilized for Ag+ detection [97]. Lee et al. reported that poly-C templated AgNCs could create a dimer by the addition of free Ag+ ion. This dimerization of AgNCs changed the fluorescence from red to green, leading to Ag+ quantification [98]. Kang et al. developed a label-free i-motif DNA sensor for the detection of Ag+ via thiazole orange as a fluorescent stain [99]. Tan et al. designed AMP/Tb3+ coordination polymers that initially emitted a very weak luminescence. On the other hand, in the presence of Ag+, the same sample turned out to be strongly luminescent because of the enhanced transfer of energy from adenine to Tb3+ [100]. Au3+ could form coordination polymers with nucleobases, nucleotides, and nucleosides. For instance, Wei and Wang generated nanoparticles via mixing adenine and Au3+, and they proposed a coordination mode on adenine as shown in (fig 5). The nanoparticles were made of aggregated small 2−3 nanoclusters.

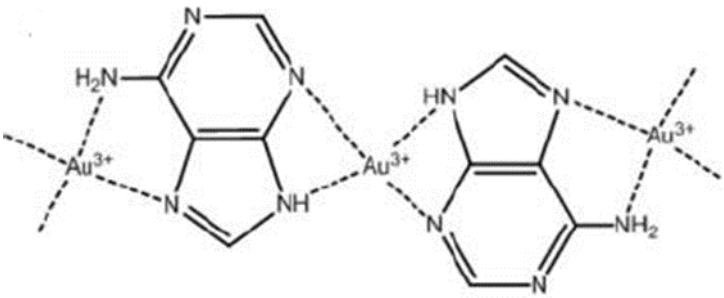

Figure 5. Scheme of coordination between Au3+ and adenine.

2.5. Electrochemical DNAzyme Biosensors for Metal Ions

Because of their amazing characteristics, like high sensitivity, low production cost, simple instrumentation, and good response speed, electrochemical methods were developed to establish DNAzyme-based biosensors used for metal ions detection. Plaxco and coworkers [101] established a DNAzyme-based electrochemical biosensor for Pb2+ detection (Figure 6a). A redox-active compound methylene blue was utilized with a DNAzyme strand and sticked on a gold electrode through a thiol-gold interaction. The DNAzyme was then hybridized to its substrate strand that banned any contact between methylene blue and the electrode. In the presence of Pb2+, the substrate was cut and released. Due to this release, the enzyme strand became more flexible and enhanced the electrochemical communication between the redox label and the electrode, generating an electrochemical signal related to the concentration of the present Pb2+. The biosensor possessed a detection limit of 300 nM and was effectively employed to detect Pb2+ in soil samples. Shao and coworkers [102] utilized reporter DNA functionalized with AuNPs to enhance the sensitivity and to intensify the electrochemical signal of a DNAzyme biosensor, resulting in a detection limit of 1 nM (Figure 6b).

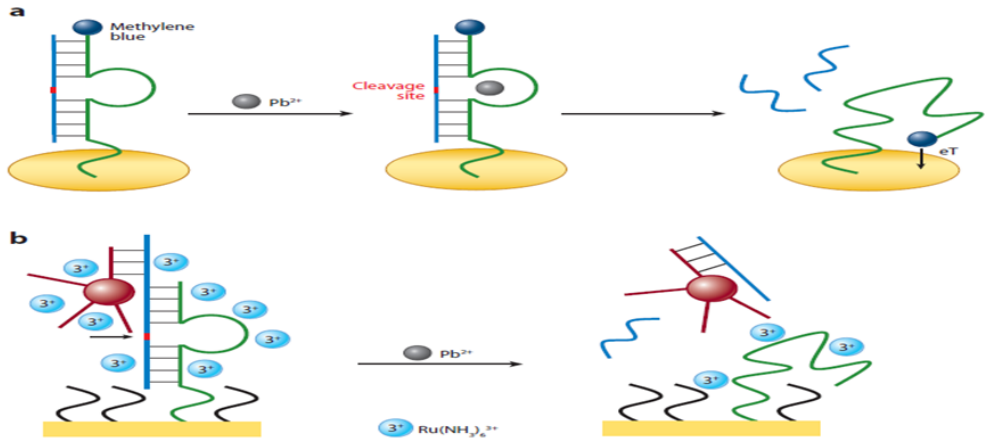

Figure 6. (a) Schematic of an electrochemical Pb2+ sensor based on the conformational change of a DNAzyme, (b) Schematic of a label-free electrochemical Pb2+ sensor with gold nanoparticle–functionalized reporter DNA as a signal amplifier.

Hg2+ and Ag+ could selectively bind certain DNA bases to develop strong metal base complexes. These complexes could, in turn, stabilize DNA mismatches in the DNA duplex [103, 104]. Based on this phenomenon, different signal transduction mechanisms, such as colorimetry, fluorescence and electrochemistry, were applied to establish DNA mismatch–based biosensors for Hg2+ and Ag+. Guanine-rich fragments of DNA could blend into four-stranded structures called G-quadruplexes that were distinguished by stacked arrays of four guanine bases. Besides, hydrogen-bonding forces, metal ions such as K+ and Pb2+ could stabilize G-quadruplexes [105, 106].

2.6. Electrochemical sensor for calcium estimation

Many methods like molecular fluorescent chelators were developed by Tsien and co-workers [107], flame atomic absorption spectroscopy (FAAS) [108] and nuclear magnetic resonance (NMR) analysis [109] had been established to estimate Ca2+. Heidari's group invented a paper based microfluidic device for colorimetric assay of Ca2+ and Mg2+ based on sticker templates with specific designs and a highly controllable waterproof eye pencil [110]. Javey's group designed a wearable electrochemical platform for nonstop monitoring of Ca2+ with an elastic printed circuit board [111]. Wu et al. extended the palette of genetically encoded fluorescent Ca2+ indicators based on protein engineering [112]. However, the limit of detection was relatively high with current electrochemical, colorimetric, or fluorescent techniques, which might also require intense handling [113]. Although accurate results provided by these methods, they were not suitable for analysis of large number of ecological samples. In addition, it could be informed that the forementioned methods required proficiency and virtuous infrastructure. But, when there are many samples, ion sensors are very valuable for the monitoring of heavy metals, because they are suitable, rapid, easy to operate, no sample pre–treatment required, appropriate for online monitoring and low cost. Many ion-selective electrodes were made for the determination of calcium. Vijayalakshmi and Thamaraiselvi [114] established an effective calcium ion selective electrode using ionophore based on surface modified Zeolite. The electrode showed typical response for Ca (II) ion with a working range of 1.0 × 10-4 M to 1.0 M. The proposed sensor exhibited relatively good selectivity and high sensitivity for Ca (II) over mono–valent cations. It could be used within the pH range of 5.57 to 6.24. The effect of medium and the selectivity coefficient values were assessed using fixed interference method found to give an improved response. It was also effectively used in the analysis of calcium ion concentration in several real samples. Alizadeh et al [3] developed Ca+2 plastic membrane electrode, using nano-sized Ca2+ imprinted polymers as ionophore. The electrode exhibited response time of 10 seconds, Nernstian slope of 30.3 (±0.4) mV decade-1, a dynamic linear range of 1×10-6–1×10-1 M and DL of 7.5×10-7 M was obtained for the electrode. Yang et al [115] developed a composite mediator layer of reduced graphene oxide (RGO)-coated black phosphorus (BP). A perfect Nernstian response was obtained with a linear range 1.0×10-6–1.0×10-1 M, a response slope of 28.3 mV/decade, and detection limit of 7.2 × 10-6 M. Vijayalakshmi and Thamaraiselvi [116] developed a new, effective calcium ion selective electrode using ionophore based on Schiff base. The lifetime of the proposed electrode was 3 months with good reproducibility of E.M.F values. The thermodynamic parameter value ΔG, ΔH and ΔS of the electrode had effectively determined. Van Dat et al [117] developed a fine tip Ca2+ selective electrode. The LOD was 3.16×10-8 mole L-1 and the slope was close to 30 mV.

2.7. Electrochemical sensor for magnesium estimation

HUA LU et al [118] presented an innovative PVC membrane electrochemical biosensor for Mg2+ ions using chlorophyll a as bio electro active membrane carrier, The sensor exhibited a Nernstian slope of 30.41 mV decade−1 for Mg+2 concentration range from 1×10-5 M to 1×10 -1 M. Also, the response time and selectivity

for Mg+2 compared to certain other cations have been studied. Vinod K Gupta et al [119] made-up magnesium (II)-selective sensors from poly (vinyl chloride) (PVC) matrix membranes comprising neutral carrier, benzo-15-crown-5 (I) as ionophore. The membrane having a composition crown:PVC:sodium tetraphenyl borate (NaTPB):dioctyl phthalate (DOP) in the ratio 10:150:3:150 had the best performance. This membrane functioned very well over a wide concentration range 1.0×10−5 to 1.0×10−1 M of Mg2+ with a perfect Nernstian slope of 31.0±1.0 mV decade−1. The response time was 15 seconds and the membrane could be used over a long period of 4 months with good reproducibility. The electrode worked well in a wide pH range 2.2–9.8 with good selectivity over a number of mono-, di-, and trivalent cations. Sulekh et al [120] fabricated a PVC-membrane-based Mg (II) selective electrode by using methyl phenyl semicarbazone (MPS) as a neutral carrier. The sensor exhibited a Nernstian response of 28.4mV decade−1 for Mg (II) ion over a wide concentration range 1.0×10−8 to 1.0×10−1 M, and detection limit 1.7×10−9 M with a fast response time (<10s for concentration ≥1.0×10−3 and < 15s for concentration of ≥ 1.0×10−6 M) and could be used over a long period of 8 months without significant divergence in potentials. The proposed sensor presented good selectivity and high sensitivity for Mg (II) over a mono-, di-, and trivalent cations and could be used in a wide pH range of 1.0–9.5. Neda hajizadeh [121] made a coated graphite electrode for determination of Mg2+ in pharmaceutical supplements. The constructed sensor showed an ideal Nernstian slope (30.1 mV Decade-1) over a wide concentration range (1×10-6- 1×10-1 Mol L-1). The response time and life span of the suggested electrode were 20 seconds and 2 months respectively. S. Khalil et al [122] generated an optimum composition for magnesium liquid membrane sensor depended on the reaction of magnesium ions with the macro cyclic reagent 1,4,7 - triazacyclononane - 1,4,7 - tris – methylene methylphosphinic acid. The created sensor exhibited a perfect Nernstian slope (30.5 mV), limit of detection (6.2 x 10-7 M), response time (15 s) and long lifetime (180 days), the pH effect on the sensor potential and the main analytical parameters were studied. The sensor was successfully used to estimate the concentration of magnesium ions in some pharmaceutical preparations. Huifang zhang et al [123] designed an innovative “off-on” fluorescent probe depended on 1, 8-naphthalimide derivative for the detection of Mg2+ in ethanol solution, the probe exhibited a fast detection process (45 s), high fluorescence enhancement (up to 15-fold), a good binding constant (6.17×105 M-1) and low detection limit of (5.01×10-8 M). Chunwei Yu et al [124] produced a novel Mg2+-selective fluorescent probe P With optimum conditions, the suggested probe P exhibited a wide linear range of 5.0 × 10−7 – 6 × 10-6 M and a detection limit of 1.7 × 10−7 M Mg2+ in ethanol-water solution (9:1, v/v, 20 mM HEPES, pH = 10.0). Guangwen Men et al [125] established a fluorescent sensor specific to Mg2+ used for quantitative determination of magnesium in drinking water, The sensor exhibited high sensitivity and selectivity with a wide detection range (0-40 μM), a low detection limit (2.89×10-7 mol/L) and fast response time (< 0.5 s).

III. Developing Applications

Metal ion measurement was important for a variety of applications. Such DNA-based metal sensors were intended to gradually replace conventional analytical instruments for initial on-site monitoring. Sensors with high sensitivity and selectivity could achieve this.

3.1. Environmental Monitoring

Metal monitoring in the environment was a common analytical task. Heavy metal outbreaks were frequently reported in the media. Therefore, both government agencies and home users required dependable and affordable metal sensors. The US EPA established maximum contamination concentrations of some metal ions in drinking water and the majority of these concentrations could be detected by DNA-based sensors, demonstrating the potential environmental impact of such sensors [126,127]. Environmental water samples were less complicated than biological samples because there were no concentrated proteins in the matrix. Other samples involved dust, soil and paint were examples of environmental solid samples, A standard method used to extract metals from these solid samples for analysis. The performance of DNA-based sensors for real sample detection might be affected by ionic strength and temperature. While the majority of research in academic laboratories was only for proof-of-concept purposes, there were examples of commercialized DNAzyme-based sensors. ANDalyze Inc., based in Champaign, IL (USA), created a portable fluorometer to read the kinetics of DNAzyme-based sensor signals, thereby avoiding the calibration issue associated with fluorescence intensity measurements. Sensors for a few common heavy metals had received EPA certification and were commercially available.

3.2. Intracellular Sensing and Imaging

Intracellular metal concentration measurement was critical for understanding bioinorganic chemistry, physiology and metal poisoning. DNA usage for intracellular sensing was an interesting but difficult concept. First, because DNA was a polyanion, it couldn't cross the cell membrane on its own, necessitating the use of a delivery vehicle. These delivery vehicles were frequently made of cationic polymers or lipids, which made them cytotoxic. After entering cells, DNA must escape from endosomes/lysosomes in order to reach the intended

measurement site (e.g., cytoplasm). Microinjection or engineering lipid-based vehicles which could directly fuse with the cell membrane could improve delivery. DNA-based nanomaterials for intracellular sensing and imaging were also emerged [128,130]. For instance, Spherical nucleic acids, for instance (a nanoparticle with densely grafted DNA) could go through cells without the use of a transfection agent [131-133]. DNA dendrimers created by self-assembly had also been shown to enter cells efficiently [134]. These nanostructures, however, must still deal with the endosome/lysosome escape issue. Another factor to consider for intracellular sensing was metal binding affinity. K^+ (>100 mM), Na^+ (10 mM), and Mg^{2+} (1 mM free Mg^{2+}) were the most abundant metals in a cell, while Ca^{2+} was only present in trace amounts. Most transition metal ions, such as Zn^{2+}, Cu^{2+} and Fe^{3+}, had very low free metal concentrations due to binding by proteins and other biomolecules like GSH [135]. Most DNA, on the other hand, bound transition metals with low micromolar affinities. As a result, measuring transition metals in physiological conditions was difficult for DNA. The majority of recent research concentrated on cell cultures. DNA probes must work in animal models via tail vain injection to have a real clinical impact. Some difficulties in using aptamers for in vivo targeted drug delivery were observed, most likely due to the high negative charges on nucleic acids, which cause nonspecific protein adsorption and rapid systematic clearance [136]. Despite these obstacles, it's believed that developing DNA-based sensors for intracellular metal detection was a viable option. The Lu group had already made significant advancements. They first attached uranyl-specific 39E DNAzyme to the surface of AuNPs, which served as both a carrier for intracellular DNAzyme delivery and a fluorescence quencher [137]. Tan and colleagues used the L-DNAzyme instead of natural D-DNA to detect metal ions in serum and living cells to improve DNA stability during transfection and resistance to nuclease degradation [138]. Ca^{2+} and Mg^{2+} metal concentrations in serum were measured using DNAzymes [139,140]. DNAzymes were found to be stable in serum for hours, which was sufficient for standard measurements [141]. G4 DNA was used to analyse K^+ levels in serum [142]. Urine, in addition to blood, was a common biological sample for metal analysis. G4 DNAs were also used to detect K^+ in urine [143]. Aptamers had also been investigated for their use in metal detection in other biological fluids such as saliva [144,145].

3.3. DNA Nanotechnology

Metal-specific DNAzymes and aptamers were also useful for research in DNA nanotechnology. DNAzyme catalyzed chemical reactions; for instance, provided chemical energies for the motion of DNA nanodevices. Mao and colleagues built an autonomous tweezers-like nanomachine that contained the 10-23 DNAzyme and used the cleavage reaction to activate the tweezers [146]. They also created a "DNA walker," in which a DNAzyme (the walker) walked along a DNA track that was powered by a DNAzyme cleavage reaction as well as a strand-displacement process [147]. Following that, various DNA machines, such as "stepper" [148] and "rotor" [149], were reported to use metal-activated DNAzymes or aptamers as a critical component. While these devices were a long way from being useful, they could be combined with biosensors for analytical applications to achieve signal amplification and simultaneous detection of multiple metal ions. Recently, DNA nanotechnology had facilitated intracellular sensing applications of DNAzymes and aptamers, as demonstrated by the above-mentioned construction of DNA dendrimers and DNA tetrahedrons.

3.4. Metal Speciation

Understanding environmental chemistry and biology required knowledge of metal speciation. For instance, Cr^{3+} was less toxic than Cr (VI). Hg^{2+} and organomercury were both toxic in different ways. Metal ions associated with dissolved organic matter (DOM) had a lower bioavailability and could thus be detoxified [150]. Other important species information in biology included Fe^{2+}/Fe^{3+} and Cu^{2+}/Cu^{+}. Because Fe^{2+} and Cu^{+} were unstable at room temperature, they were only important in biological systems. Most instrumentation methods, however, only measured total metal concentration without specifying oxidation state. Biosensors might be more useful in this regard because they could provide such information.

3.5. Pharmaceutical and theranostic applications

DNAzyme diagnostic and therapeutic applications were also reported [151]. Min and colleagues, for instance, adsorbed a fluorophore labelled DNAzyme on grapheme oxide (GO) [152]. The recognition of mRNA desorbed the DNAzyme from GO, resulted in an increase in fluorescence. Simultaneously, the DNAzyme was activated to cleave the target mRNA. Furthermore, DNAzymes were used as a regulator for stimuli-responsive drug release using metal ions. The Willner group demonstrated this by trapping fluorophores and anticancer drugs in the pores of mesoporous silicananoparticles. After that, the pores were sealed with either DNAzymes or metal binding aptamers [153-154] The capped DNA was cleaved (for DNAzymes) or folded (for aptamers) in the presence of target metals, resulting in content release.

IV. Conclusion

Metal ion measurement was important for a variety of applications. Such DNA-based metal sensors were intended to gradually replace conventional analytical instruments. Besides being the genetic information's carrier, DNA proved to be an excellent building block for the creation of new devices in biosensor technology. This paper presented an overview of DNA-electrochemical biosensors and different metal cations sensed by DNA-electrochemical biosensors. Finally several developed applications were mentioned.

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