Application of hairpin DNA-based biosensors with various signal amplification strategies in clinical diagnosis

Rozita Abolhasan[a,b], Amir Mehdizadeh[c], Mohammad Reza Rashidi[d], Leili Aghebati-Maleki[e,g,*], Mehdi Yousefi[f,g,*]

[a] Stem Cell Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[b] Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran
[c] Endocrine Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[d] Research Center for Pharmaceutical Nanotechnology, Tabriz University of Medical Sciences, Tabriz, Iran
[e] Immunology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[f] Aging Research Institute, Tabriz University of Medical Sciences, Tabriz, Iran
[g] Department of Immunology, Faculty of Medical Sciences, Tabriz University of Medical Sciences, Tabriz, Iran

ARTICLE INFO

ABSTRACT

Biosensors have been commonly used in biomedical diagnostic tools in recent years, because of a wide range of application, such as point-of-care monitoring of treatment and disease progression, drug discovery, commonly use food control, environmental monitoring and biomedical research. Additionally, development of DNA biosensors has been increased enormously over the past few years as confirmed by the large number of scientific publications in this field. A wide range of techniques can be used for the development of DNA biosensors, such as DNA nano-machines and various signal amplification strategies. This article selectively reviews the recent advances in DNA base biosensors with various signal amplification strategies for detection of cancer DNA and microRNA, infectious microorganisms, and toxic metal ions.

1. Introduction

Modern healthcare systems are dependent intensely on in vitro diagnostics, therefore, the number of clinical tests in life sciences have become highly demanding (Lazcka et al., 2007). On the other hand, the detection of diseases-associated nucleic acids is of great importance for on-time and precise diagnosis and therapy due to close association of nucleic acids with human diseases (Valente et al., 2016; Stratton, 2011; Esquela-Kerscher and Slack, 2006b; Jeffrey, 2008). Hence, development of sensitive, trusty, time efficient, and cheap analytical systems is needed. Usual methods, for example molecular detection methods (immunological or non-immunological) and microbial culture tests are either time consuming or need complicated and costly tools (Lazcka et al., 2007).

Biosensor technology is probably one of the most progressive ways that solves a number of problems regarding low sensitivity, time, and cost issues in clinical diagnosis. A biosensor is a device, which provides quantitative analytical information using a bio-recognition element in direct contact with a transduction element (Johnson and Mutharasan, 2014). It includes two most important components; a biological component, that reacts with a target material, and a signal-generating component, that detects the resulting products (Bhalla et al., 2016). Biosensors are employed in disease monitoring, drug discovery, and detection of pollutants, disease-causing microorganisms (Jolly et al., 2015; Sharma et al., 2015; Van Dorst et al., 2010), and markers that are indicators of a disease in bodily fluids.

Recognizing molecules are the basic elements of biosensors as the sensitivity and specificity of the sensing elements play a key role in the sensor device performance (Tothill, 2009). Different biosensors rely on different biomolecules, such as nucleic acids, antibodies or cells, which can work as both bio-receptors and signaling molecules or labels (Liebana and Drago, 2016). Nucleic acids are one of the recognizing molecules that are used in different forms, such as hairpin DNAs (hpDNAs) (Bath and Turberfield, 2007; Venkataraman et al., 2007; Green et al., 2006). In addition, over the past several decades, various techniques, as signal transducers, have been developed for precise detection of the specific nucleic acid sequences, including electrochemical (Ge et al., 2016; Liu et al., 2014; Low et al., 2017; Xiong et al., 2017b), colorimetric (Teengam et al., 2017; Duan et al., 2015), fluorescence (Yu et al., 2014; Liu et al., 2013b; He et al., 2010; Tan et al., 2015),

* Corresponding authors at: Department of Immunology, Faculty of Medical Sciences, Tabriz University of Medical Sciences, Tabriz, Iran.
E-mail addresses: Aghebatil@tbzmed.ac.ir (L. Aghebati-Maleki), Yousefime@tbzmed.ac.ir (M. Yousefi).

Electrochemiluminescence (ECL) (Freeman et al., 2011), photoelectrochemical (PEC) (Zhao et al., 2014; Zang et al., 2016; Li et al., 2015) and SPR biosensors (Zhang et al., 2012; Cao et al., 2018).

Additionally, signal amplification strategies for ultrasensitive DNA detection have attracted extra attention. Among the amplification methods that have been developed, are catalyze hairpin assembly (CHA), hybridization chain reaction (HCR), toehold-triggered strand displacement reaction (TSDR), and enzyme-assisted target recycling (Chen et al., 2016a; Wu et al., 2017; Li et al., 2015; Khodakov et al., 2013).

In this review, we will first give a brief explanation of the hpDNA structure, different signal transducers, and signal amplification strategies. Then, DNA based biosensors with various signal amplification strategies for detection of cancer DNA and microRNA (miRNA), infectious microorganisms, and toxic metal ions will be discussed.

2. DNA nano-machines

DNA can be programmed and assembled in an expectable manner owing to its perfect recognition characteristics, depending on the Watson-Crick base-pairing (Li et al., 2013). DNA has been considered as one of the most promising natural molecules in nanotechnology due to characteristics (Guo et al., 2015) , like stability of data storage and the elasticity in design (Wang and Ding, 2014; Lin et al., 2011a). The self-assembly feature of DNA makes it a unique template to be an excellently shaped and controlled matter on the nanometer scale (McLaughlin et al., 2011).

DNA has been used to develop a number of nanomechanical devices, for example nucleic acid walkers (Wang et al., 2011; Liu et al., 2013c), circuits and logic gates (Fan et al., 2015; Nie et al., 2015), tweezers (Shimron et al., 2013), catalytic amplifiers (Yin et al., 2008; Tsourkas et al., 2003), sensors (S. Liu et al., 2015; B. Liu et al., 2015; Gao et al., 2016), and other molecular devices (Li et al., 2008; Dittmer et al., 2004). These DNA nanomachines can be stimulated by different inputs, such as fuel DNA strands (Zheng et al., 2012) and metal ions (Bi et al., 2013), and have been applied for detection of targets in vitro and in vivo (Karunanayake Mudiyanselage et al., 2018; Liao et al., 2018). In the most of DNA machines, used hpDNA structure can be self-assembled into determined target structures without human intervention (Yin et al., 2008). A brief explanation of hpDNA, which is used in most DNA base biosensors, is explained below.

A hpDNA is a specifically designed single-stranded oligonucleotide with self-complementary properties that can be folded into a stem-loop structure under proper situations. Therefore, in general, it creates two main open and closed forms (Yin et al., 2008; Tsourkas et al., 2003; Bonnet et al., 1998). HpDNA has been broadly utilized as the sensing element in biosensors (Liu et al., 2008). The stem-loop hpDNA probe has high hybridization specificity and unique selectivity to the target molecules, such as DNA and small molecules (Riccelli et al., 2001; Riccelli et al., 2001).

3. Signal transduction

The fundamental role of the sensor is to create appropriate platform for the formation of the probe-target complex, causing the signal to be created for electronic readout (Bhalla et al., 2015). Therefore, one of the essential elements of each biosensor is the signal transduction, which can be coupled with the appropriate readout device. Development of hpDNA based biosensors has been carried out with various detection systems. Therefore, a electrochemical, mechanical, or optical systems is required to report DNA and target bindings (Drummond et al., 2003).

3.1. Electrochemical readout

A typical electrochemical DNA biosensor uses an electrode surface as the platform to immobilize biological sensing hpDNA, for which the analyte-binding result is monitored based on current electrochemical differences (Zhang et al., 2018c). The electrochemical method is suitable for DNA detection. Hence, electrochemical reactions directly create the electronic signals; moreover, they do not require expensive signal transduction tools. Moreover, immobilized probe sequences can be accomplished with an inexpensive electrochemical analyzer (Wang, 2005). Additionally, electrochemical systems are portable for clinical testing, with high sensitivity, low cost, low-power requirements, and high compatibility with advanced micromachining and microfabrication technologies (Ge et al., 2018; Xiong et al., 2017a).

Electrochemiluminescence (ECL) is a powerful analytical technique that has pooled the advantages of chemiluminescence and electrochemistry. ECL is a light generation-based method, in which the high-energy electron is transferred between electrogenerated species (Richter, 2004; Sun et al., 2010). ECL is attracting more attention because of its good reproducibility, low background, simplicity, and high sensitivity (Sun et al., 2010; L. Li et al., 2018; Y. Li et al., 2018; M. Li et al., 2018; Wang et al., 2018).

PEC detection is another method that is generated based on the biological interactions between the biosensing elements and their corresponding target analytes, leading to the photocurrent changes creation (Zhao et al., 2011). This method has attracted extensive attention for its benefits, such as low background signals, low cost, high sensitivity, quick response, and simplicity (Li et al., 2015; Dong et al., 2004). Consequently, in the past decade a variety of photoelectrochemical biosensors have been developed to sense biologically important species (Shi et al., 2018; L. Li et al., 2018; M. Li et al., 2018; Y. Li et al., 2018; Wang et al., 2018).

3.2. Optical readout

Optical DNA based biosensors include fluorescence-labeled (Liu et al., 2018a), enzyme-labeled, nanoparticle-labeled, or label-free detection methods, such as Surface plasmon resonance (SPR) (Li et al., 2016a). Florescence-based optical biosensors are extremely sensitive with 10^7 molecule/cm^2 detection limit; however, sophisticate and costly instruments are highly needed (Epstein et al., 2002). SPR, another optical technique, reports changes in the refractive index of a thin metal film substrate that occurs upon adsorption of the analyte and is suitable for target detection in an array-based approach that is more expensive and complicated than that of fluorescent-based techniques (McDonnell, 2001).

4. Signal amplification strategies

During the past decades, several enzyme-assisted or enzyme-free amplification strategies have commonly been employed to further increase the sensitivity and selectivity of biosensors in the biosensor's construction. Enzyme-assisted amplification includes enzyme-assisted nucleic acid amplification technologies, such as nuclease-assisted hairpin assembly (Zhang et al., 2014), enzyme catalyzed reaction (Xia et al., 2015), and enzyme-free amplification methods like catalyzed hairpin assembly (CHA) (He et al., 2016), hybridization chain reaction (HCR) (Chen et al., 2012), and toehold-triggered strand displacement reaction (TSDR) (Zhang and Seelig, 2011). Signal amplification by autonomous DNA self-assembly constructs is a simple and strong framework for target detection. Some of these strategies will be explained below.

4.1. Catalyzed hairpin assembly (CHA)

Catalyzed hairpin assembly (CHA) is a strong enzyme-free signal-amplification reaction that has a variable range of potential applications, especially in biosensing (Li et al., 2012). CHA, which was developed from DNA nanotechnology, is programmed with DNA self-
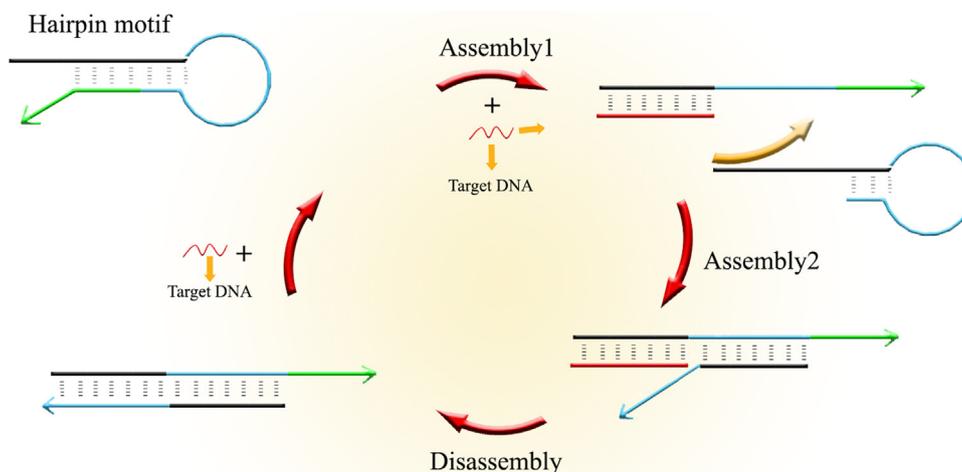
Fig. 1. Schematic diagrams of catalyzed hairpin assembly (Assembly and Disassembly reaction).

assembly and disassembly reactions (Fig. 1) (Yin et al., 2008). CHA is a naturally flexible and scalable circuit, requiring only the design of base-pairing of strands (Pan et al., 2018). Numerous CHA-based biosensors have been developed that provide low-cost and point-of-care diagnostic approaches (Tang et al., 2015; Su et al., 2017).

4.2. Hybridization chain reaction (HCR)

Hybridization chain reaction (HCR) is a complementary base paring reaction, which is triggered by an initiator (target) and circulates a chain reaction of hybridization events to produce nicked double-strand (dsDNA) to alternating copolymers, making HCR a promising enzyme-free strategy in signal amplification (Dirks and Pierce, 2004; Cao et al., 2018). This reaction gives slow background and high sensitivity in obtained results from biosensors (Chen et al., 2018; Geet al., 2018; Chen et al., 2012). These advantages make HCR as an attractive strategy in DNA sensing.

4.3. Toehold-triggered strand displacement reaction (TSDR)

Toehold-triggered strand displacement reaction (TSDR) is a method for the assembly and regulation of the DNA nanostructures and nano-machines (Zhu et al., 2014; Khodakov et al., 2013). In TSDR, through the stepwise branch migration induced by a short single-stranded do-main termed "toehold" (typically 5-8 nucleotides), one DNA strand in a pre-hybridized duplex is exchanged by another strand to make a more constant double-stranded complex (Zhang and Seelig, 2011; Jiang et al., 2018). By varying the base number of toeholds, the kinetic rate of TSDR could be quantitatively controlled over a factor of 10^6 (Zhang and Seelig, 2011). This method has displayed great benefits with respect to sensitive, portable, and rapid detection of target analytes (Zhao et al., 2018).

4.4. Difficulties encountered in the signal amplification strategies

Generally, one of the limitation of non-enzymatic amplification strategies for analytical application is that they may not be able to amplify quite small biological signals (Jung and Ellington, 2014). Be-cause of its output in placed within stem structures, CHA designing has become more difficult. On the other hand, to improve amplification well, CHA can be cascaded. Although the cascaded CHA reaction gen-erates greater amplification but causes non-specific binding and leads to background signal, as the layers of cascade increase, the time of reac-tion will be increased, making it less useful for diagnostic applications. To overcome these problems, CHA can be brought along with enzymes (Jung and Ellington, 2014; Jiang et al., 2014).

Another signal amplification strategy is HCR, which is not typically used in complex circuits due to lack of a specific sequence output. Although HCR reaction continues until the substrates are exhausted, it is difficult to quantify the targets (Jung and Ellington, 2014; Chen et al., 2017). In our opinion, some difficulties might be related to loading or bio-conjugation of signaling probe on the modified electrode and some others might be attributed to site specific binding of capture and target probes. It seems that in the future, in situ controlling of hybridization of capture and target probes via high resolution imaging techniques, and consequently, the specificity of the developed system will be highly improved. Furthermore, hybridization temperature and time will be controlled via mentioned techniques that might have significant effect on the sensitivity of the designed biosensors.

5. Application of hpDNA base biosensor in clinical diagnosis

Beyond all these features, the applications of DNA base biosensors as bio-components have offered extraordinary prospects in diagnostic assays. Here we will briefly define some applications of DNA-based biosensors with various signal amplification strategies for detection of cancer-related microRNAs (miRNAs) and DNA, infectious micro-organism, and toxic metal ions.

5.1. Application of hpDNA based biosensors for detection of cancer miRNA

MiRNAs are a class of small (21–24nt), endogenous, and non-coding RNA molecules (Wen et al., 2012) that can regulate gene expression and play essential roles in a range of biological processes (Rossi, 2009; Ventura and Jacks, 2009). Cancer, diabetes, and neurological diseases can be resulted from the unusual expression of miRNAs (Lujambio and Lowe, 2012; Deng et al., 2014; Eacker et al., 2009). Because of the crucial role of miRNAs in the development and progression of cancer, it can be considered as one of the biomarkers for early diagnosis of var-ious cancers (Shah et al., 2014). Therefore, quantitative analysis of miRNAs is important for better understanding of their roles in cancers. Many traditional methods, such as bioluminescence assays, quantitative Real-time PCR, and Northern blotting are broadly used to detect miRNAs (Cissell et al., 2008; Valoczi et al., 2004; Ruby et al., 2006). However, these methods are inappropriate in clinical analysis due to low sensitivity, consuming time, complexity, and high cost. Alter-natively, the DNA-based biosensors with high sensitivity is developed in recent studies. A list of instances of the accessible reports of DNA based biosensors with various signal amplification strategies for detection of different cancer-related miRNA is provided in Tables 1, 2. In addition, typical examples of DNA based biosensors for recognition of miR-21 are argued in the following part.

Table 1

A list of examples of the available reports of DNA base biosensors with various signal amplification strategies for cancer miR-21.

Signal amplification strategies	Signal transduction	Limit of detection(LOD)	Reference
WO₃-Gr coupling with CHA target recycling and SA-ALP as a signal indicators	Electrochemical	0.05 fM	(Shuai et al., 2016)
Dual target-recycling amplification based on (DSN) and CHA	Fluorescence and ECL	5.4 fM	(Hao et al., 2015)
GNP modified hairpin ssDNA	SPR	Low as 3 nM	(Hu et al., 2015)
CHA amplification coupling with streptavidin aptamer	SPR	1 pM	(Li et al., 2016a)
Two-stage signal amplification BBA consist of MNP-DNA and AuNP-DNA along with CHA	Fluorescence	Low as 97.9 zM	(Tang et al., 2018)
Strand displacement amplification(SDA) and CHA with DNAzyme formation	Colorimetry	Low as 1.7 fM	(Yan et al., 2015)
GMNP-labeled CHA-3WJ	Colorimetry	Low as 1 aM	(Hosseinzadeh et al., 2018)
Enzyme-free target recycling amplification labled with ferrocene hairpin DNA 2D	Electrochemical	0.31 fM	(Zhang et al., 2018a)
CHA amplifier and lighting up AgNCs system	Fluorescence	38 pM	(Pan et al., 2018)
End blocked DNAzyme-CHA	Chemiluminescence	0.02 fM	(Deng et al., 2018)

Abbreviations: WO₃-Gr, tungsten oxide-graphene composites; CHA, catalyzed hairpin DNA; SA-ALP, streptavidin-conjugated-alkaline phosphatase; DSN, duplex-specific nuclease; GNP, gold nanoparticle; BBA, bio-barcode assay; MNP-DNA, magnetic nanoparticles functionalized with DNA probe; AuNP, Au nanoparticle; SDA, strand displacement amplification; GMNP, gold decorated magnetic nanoparticle; 3WJ, 3 way junction.

MiR-21 is one of the most common oncomiRs and is overexpressed in most human cancers (Esquela-Kerscher and Slack, 2006a). Recent studies have reported the survival and proliferation of tumor cells upon over expression of miR-21 (Medina et al., 2010).

In a study, an ultrasensitive platform was designed with multilayer signal amplification strategy for identification of miR-21. In this study, the gold decorated magnetic nanoparticle (GMNP)-labeled hpDNA provided a foundation for multilayer G-quadruplex DNAzyme formation and brought along with CHA (Catalyzed hairpin assembly) reaction for signal amplification. In the presence of miRNA biomarker, DNAzyme, which is A DNA sequence with catalytic activity, produces a colored complex, which is measured by the colorimetric method. This biosensor has the ability to detect less than 1 aM of miR-21 and has high specificity compared to other methods. Additionally, due to its special design, it can easily separate the single mismatches (Hosseinzadeh et al., 2018).

In another study, an enzyme-free electrochemical biosensor was developed for sensitive detection of miR-21. This biosensor is designed based on two ferrocene-labeled DNA nanoprobe (DNP) and targeted recycling amplification. In the presence of miR-21 and a hpDNA strand, two ferrocene-labeled DNA strand and the target miRNA are released from electrode surface and dramatically decrease the electrochemical signal through the toehold-mediated strand displacement reaction (TSDRs). Detection limitation of this biosensor for miR-21 is 0.31 fM. The suggested biosensor showed high sensitivity, stability, and specificity for the biomarkers analysis (Zhang et al., 2018a).

Recently a label-free and enzyme-free isothermal biosensor was designed based on fluorescence method for assaying the nucleic acid.

This study used CHA reaction with high signal amplification ability and DNA-template silver cluster (AgNCs) lighting up strategy for more reliable and efficient biosensing. MiR-21, as a target, started the CHA reaction and caused fluorescence enhancer and AgNCs in close proximity, leading to the fluorescence enhancement that could be easily visualized. This simple system is able to detect vital clinical analytes like miRNAs without necessity to complex processes or special instrumentations (Pan et al., 2018).

Meanwhile, hpDNA biosensors can be utilized for recognition of targets with several working principles, Hong et al. have presented an electrochemical biosensor for miRNA detection that is based on tungsten oxide-graphene (WO3-Gr) composites combination with CHA target recycling and enzyme signal amplification that allow the detection of miRNA with high sensitivity and selectivity. Sensing platform formed by coupling with WO3-Gr composites and gold nanoparticles (AuNPs) was used for the immobilization of captured hairpin probe (H1). H1 hairpin structure is opened when hybridization with target miR-21 occurs, then target miRNA is displaced with another biotinylated hpDNA (H2) and released for starting next cycle. Therefore, a large amount of H1-H2 duplex is produced and a large number of signal indicator streptavidin-conjugated alkaline phosphatase (SA-ALP) is conjugated to avidin-biotin on the surface of electrode. Finally, a large amount of the enzymatic product of ALP and ascorbic acid produce a strongly electrochemical response with electrochemical-chemical-chemical (ECC) redox cycling induction in the presence of ferrocene methanol (FcM) and tris (2-carboxyethyl) phosphine (TCEP). Combining of these will ultimately lead to a very low detection limitation for target miR-21 down to 0.05 fM (Fig. 2) (Shuai et al., 2016).

Table 2

A list of examples of the available reports of DNA base biosensors with various signal amplification strategies for different cancer microRNAs.

Target microRNA	Signal amplification strategies	Signal transduction	Limit of detection (LOD)	Reference
miR-15a	Distance-dependent ERET system between QDs and AuNCs	Electrochemiluminescence	At fM	(Cheng et al., 2014)
miR-16	Hairpin-structured DNA with MB in 5ʹ terminal and thiol group in 3ʹ terminal immobilized on the gold electrode	Electrochemical	0.14 nM	(Gao et al., 2018a)
miR-122	Target-CHA and iron based metal-organic frame works mediated nonenzymatic co-reaction	Electrochemical	0.003 fM	(M. Li et al., 2018; Y. Li et al., 2018; L. Li et al., 2018)
	CHA base biosensor by using 2-AP and ThT	Fluorescence	72 pM	(Liu et al., 2017b)
miR-106a	CHA with CNNS	Fluorescence	0.10 pM	(Liao et al., 2018)
miR-141	Combining of two enzyme free amplifications strategies HCR and CHA	Fluorescence	0.3 fM	(Wei et al., 2016)
miR-155	CHA and cascade electrocatalysis (Cyt c and Alcohol oxidase)	Electrochemical	0.35 fM	(Wu et al., 2015)
Let7a microRNA	CHA coupled with HCR	Colorimetry	7.4 fM	(Wu et al., 2016)
miR-17 and miR-222	SDA and CHA with DNAzyme formation	Colorimetry	Low as 1.7 fM	(Yan et al., 2015)
miR-221	Combination of the target-CHA and supersandwich amplification strategies with HRP-DNA as signal tags	Electrochemical	Low as 0.6 pM	(Zhang et al., 2017)

Abbreviations: ERET, electrochemiluminescence resonance energy transfer; QDs, quantum dots; AuNCs, Au nanocluster; MB, methylene blue; CHA, catalyzed hairpin DNA; 2AP, 2-amino purine; ThT, thioflavin T; CNNS, carbon nitride nanosheets; HCR, hybridization chain reaction; Cyt c, cytochrome c; SDA, strand displacement amplification; HRP, horseradish peroxidase.
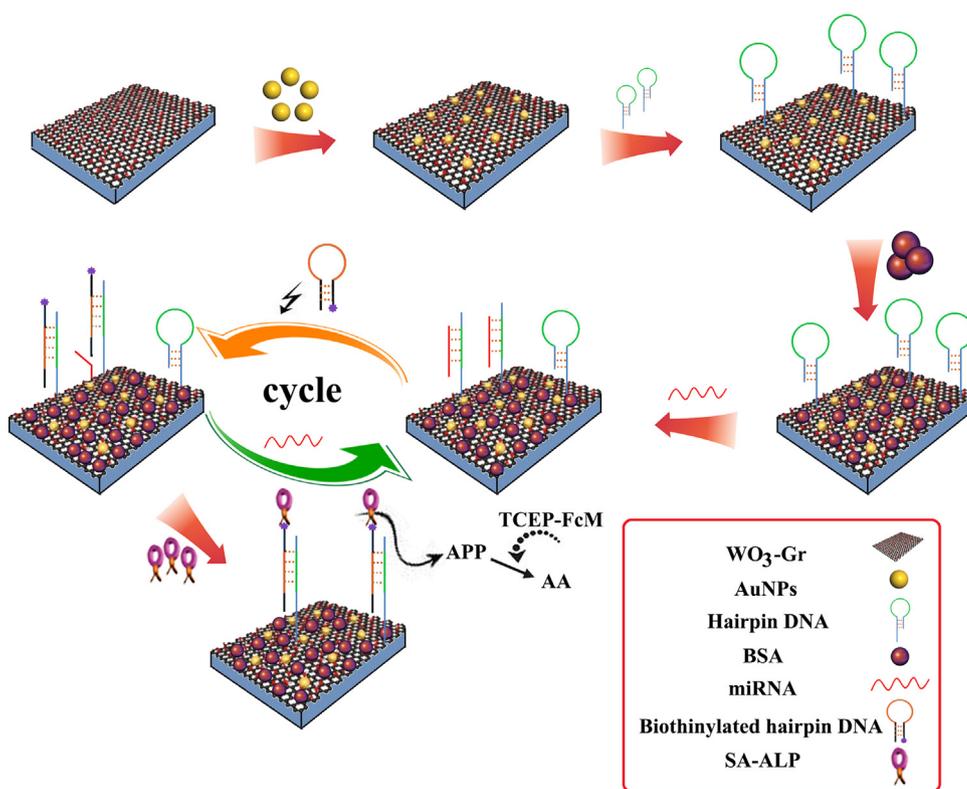
Fig. 2. Schematic diagram of preparation of the electrochemical biosensor based on CHA and enzyme signal amplification for detection of miR-21(Abbreviations: WO3-Gr, tungsten oxide-graphene composites; AuNP, Au nanoparticle; BSA, bovine serum albumin; SA-ALP, streptavidin-conjugated alkalin phosphatase; TCEP, tris (carboxyethyl) phosphin; FcM, ferrocen methanol; APP, ascorbyle poly phosphate; AA, ascorbic acid).

5.2. Application of hpDNA base biosensors for detection of nucleic acids

In the past decades, the development of amplified nucleic acid biosensors have been considered for sensitive and selective detection of DNA sequences for genetic therapy, cancer screening, molecular diagnosis, and environmental monitoring (Das et al., 2015; Wang et al., 2014; Meng et al., 2016; Rodriguez-Mozaz et al., 2006). Until now, various biosensors have been designed with different amplification strategies and signal transducers. In these amplification strategies, DNA based nanomaterials such as hpDNAs have mostly been used. Here is a typical example of these biosensors discussed which is developed for DNA detection. Additionally, Table 3 lists instances of DNA base biosensors for recognition of various cancer DNAs.

Recently, a simple enzyme-free electrochemical biosensor was designed for nucleic acid detection with 0.3 pM detection limit. In this study beneficial properties of TSDR and host-guest interaction of β-cyclodextrin (β-CD) are used. This was due to elevation of Fe3O4@SiO2@β-CD nanocomposites detection sensitivity as the capture probe and ferrocene-labeled hpDNA as the electrochemical probe. In the presence of target DNA, TSDR process induced the conformation change of hpDNA (H1) and subsequent assembly stimulation of assistant probes with H1 along with the release of target DNA and initiated the next TSDR recycling. This reaction causes production of many open H1 substrates. In the next step, the separation of these hpDNAs was done with a magnet, which resulted in a clear current peak decrease. This biosensor showed low detection limitation and excellent selectivity for nucleic acid sensing (Jiang et al., 2018).

5.3. Application of hpDNA based biosensors for detection of infectious microorganisms

The detection of pathogenic microorganisms is crucial for prevention and identification of health and safety-related problems (Lazcka et al., 2007). We need to obtain analytical results in the shortest time. That is while, the traditional detection approaches of microorganism are clearly insufficient and, therefore, developments of rapid and

sensitive methods are needed. Biosensors are promising approaches and several biosensors with hpDNA probe have been developed to identify microorganisms and viral DNAs (Velusamy et al., 2010; Gu et al., 2006). Two typical examples of hpDNA biosensor developed for detection of viruses will are argued in the next part. In addition, Table 4 lists instances of hpDNA for recognition of microorganisms and viruses.

Recently, an ultrasensitive PEC biosensor with cascade signal amplification was designed for Human T-lymphotropic virus-1 (HTLV-1) DNA detection. This system benefits combination of λ-exonuclease assisted target recycling, hybridization chain reaction (HCR), and enzyme catalysis for signal amplification. In the presence of HTLV-1 DNA (target DNA), the hpDNA (H1) hybridizes with target DNA, and then, this structure will be recognized by λ-Exo and cleaving. λ-Exo helps to target DNA recycling. This enzymatic reaction leads to release of the target DNA and output DNA. Afterwards, output DNA binds to capture DNA and many biotin-labeled hpDNAs with HCR loaded on the photoelectrode. Finally, biotin-labeled hpDNAs interact with avidin-labeled alkaline phosphatase (avidin-ALP) and catalyze dephosphorylation of Phospho Ascorbic Acid (AAP) to Ascorbic Acid (AA), resulting in increasing the photo current signal. The designed PEC displayed a sensitive and specific detection of HTLV-1 DNA down to 11.3 aM, therefore, this strategy provides an effective assessment for diseases early diagnosis (Shi et al., 2018).

Moreover, another study employed a rapid and cost effective optical biosensor based on Thioflavin T (ThT)-induced G-quadruplexes for Human immunodeficiency virus (HIV) DNA detection. This system uses two hpDNA structure (HP1 and HP2) and Thioflavin T (ThT) as a fluorescent probe for G-quadruplex in target DNA assay. In the presence of HIV DNA, HP1 is open and releases complementary region for HP2, hence, HP2 hybridizes with HP1, leading to exposing of the G-rich sequence. Finally, Thioflavin T (ThT) is added and bound to G-quadruplex, leading fluorescence intensity enhancement. The biosensor exhibited high sensitivity with detection limit of 2.4 nM (Zhang et al., 2018b).

Table 3
Lists of examples of DNA base biosensors for detection of various cancer DNAs.

Target DNA	Signal amplification strategies	Signal transduction	Limit of detection (LOD)	Reference
tDNA	For enzyme-free sensing strategy used $Fe_3O_4@SiO_2@\beta$-CD nanocomposites as the capture probe and ferrocene-labeled hairpin DNA as a electrochemical probe	Electrochemical	0.3 pM	(Jiang et al., 2018)
	Combining of three divers dynamic DNA assembly strategies include DNA-fueled target recycling, CHA and HCR	Electrochemical	50 aM	(Liu et al., 2017a)
	Conformation change of G-quadruplex hairpin DNA	Fluorescence	Down to 40 pM	(Liu et al., 2018b)
CML, Type b3a2 DNA sequence	CdTe/TCPP nanocomposites labeled probe DNA, λ-Exoassisted target recycling, hairpin DNA immobilized with ZnO/CdS hetero nanostructure	Photoelectrochemical	25.6 aM	(Shi et al., 2016)
tDNA	Autonomous cascade DNA replication strategy and enzyme/gold nanoparticle post amplification strategy_ hairpin DNA probe with recognition site for tDNA and nicking endonuclease	Electrochemical	0.065 fM	(Liu et al., 2016)
K-ras gene	Hairpin DNA probe labeled with MB and FC immobilized on the gold electrode and Exo III-assisted target recycling amplification	Electrochemical	4.16 fM	(Xiong et al., 2015b)
tDNA	CHA and FeTMPyP-mediated chemiluminescence	Photoelectrochemical	2.2 fM	(Zang et al., 2015)
	CdSe QD modified GCE act as the coreactant of $Ru(bpy)_3^{2+}$ ECL/ $Ru(bpy)_3^{2+}$ intercalated into the loop of hairpin DNA probe	Electrochemiluminescence	1.9×10^{-16}	(Dong et al., 2015)
	Thiolated shared-stem hairpin DNA tagged with $Ru(bpy)_3^{2+}$ on the surface of GO/AuNPs modified GCE	Electrochemiluminescence	65 aM	(Huang et al., 2015)
	CHA combined with nanocatalyst label-based redox cycling reaction	Electrochemical	0.3 aM	(Hun et al., 2015)
	Exo III-assisted cascade target recycling combined with DNAzyme	Fluorescence	20 fM	(B. Liu et al., 2015; S. Liu et al., 2015)
K-ras gene	Used biotin labeled hairpin DNA probe/HRP-streptavidin capped AuNPs	Electrochemical	0.035 fM	(Fang et al., 2014)
tDNA	Hairpin DNA probe functionalized MNPs and Exo III-induced two-stage autocatalytic recycling amplification strategy mediated by ZnPPIX/G-quadruplex as a fluorescent nanotag	Fluorescence	0.75 fM	(Xue et al., 2014)
P53 mutation gene	LC biosensor based on formation of DNA dendrimers from hairpin DNA probes by HCR	Optical	Low as 0.08 nM	(Tan et al., 2014)
tDNA	Multi-functional dual-hairpin DNA labeled with MB	Electrochemical	50 nM	(He et al., 2013)
Cytochrome P450 2D6	NASDP as a signal amplification and biotinylated hairpin DNA with NEase recognition site as a probe	Lateral-flow biosensor	100 aM	(Liu et al., 2013a)
tDNA	Enzyme-free biosensor based on the combination of CHA and HCR	Electrochemical	0.1 fM	(Liu et al., 2013a)

Abbreviations: β-CD, β-cyclodxtrin; CHA, catalyzed hairpin DNA; HCR, hybridization chain reaction; CML, chronic myelogenous leukemia; TCPP, meso-tetra(4-carboxyphenyl) porphine; Exo, exonuclease; MB, methylene blue; Fc, ferrocene; FeTMPyP, iron(III) meso-tetrakis(N-methylpyridinium-4-yl) porphyrin; QD, quantum dot; GCE, glassy carbon electrode; $Ru(bpy)_3^{2+}$, 2,2'-bipyridine-ruthenium; ECL, electrochemiluminescence; GO/AuNP, graphene oxide/Au nanoparticle; HRP, horseradish peroxidase; MNPs, magnetic nanoparticles; ZnPPIX, zinc(II)-protoporphyrin IX; LC, liquid crystal; NASDP, NEase-assisted strand-displacement polymerization; NEase, nicking endonuclease.

Table 4
Examples of DNA base biosensor for detection of microorganisms and viruses.

Target microorganism	Signal amplification strategies	Signal transduction	Limit of detection (LOD)	Reference
HTLV-1	λ-Exoassisted target recycling with HCR and enzyme catalysis	Photoelectrochemical	11.3 aM	(Shi et al., 2018)
HIV	Thioflavin T-induced G-quadruplexes based biosensor	Fluorescence	2.4 nM	(Zhang et al., 2018b)
HIV-1	Exo-1 hydrolysis assisted hairpin DNA to reduce background signal	Electrochemical	150 fM	(Gao et al., 2018b)
HTLV-II DNA	Three stage cascade signal amplification strategy include CHA, HCR and ALP-triggered in-situ generation of AA	Photoelectrochemical	0.052 fM	(Xiong et al., 2018)
HIV gene	Autocatalytic and Exo III-assisted cascade signal amplification strategy and hairpin DNA	Electrochemical	4.83 fM	(Xiong et al., 2017b)
HIV-1	Biosensor based on electrochemical signal strategy and triple-helix molecular switch with a hairpin DNA probe labeled with MB immobilized on gold electrode and ssDNA modified with two FC	Electrochemical	0.12 pM	(Xiong et al., 2017a)
HIV-1, HIV-2	Label-free multi-electrode array with thiolated hairpin DNA probe	Electrochemical	0.1 nM	(Zhang et al., 2010)
Aflatoxin B of Aspergillus	Cascaded signal amplification with enzyme-free catalytic DNA circuit and using gold nanoparticle	Colorimetry	2 pM	(Chen et al., 2016b)
Lyt A gene of S.pneumoniae and whole cell of Salmonella Typhimurium	Combining the signal transducer and CHA based signal amplification	Colorimetry	32 pM	(Chen et al., 2015)
Vibrio parahaemolyticus	Used hairpin DNA aptamer conjugated with TEX 615 (Fluorescent dye)	Chemiluminescence	2230 cells/ml	(Kwun et al., 2014)
Legionella Pneumophila	Label-free detection with hairpin DNA-ferrocene probes on gold electrode	Electrochemical	2.3×10^{-14}	(Rai et al., 2012)
E.coli DNA ligase	Conformation change of the hairpin DNA probe	SPR	0.6 nM	(Luan et al., 2010)

Abbreviations: HTLV, human T-cell lymphotropic virus; Exo, exonuclease; HCR, hybridization chain reaction; HIV, human immunodeficiency virus; CHA, catalyzed hairpin DNA assembly; ALP, alkaline phosphates; AA, ascorbic acid; MB, methylene blue; Fc. ferrocene.

5.4. Application of hpDNA based biosensors for detection of toxic metal ions

Metals heavier than threshold limit are toxic to human and there are several health risks related with them (Jaishankar et al., 2014). Delayed detection and assessment of these metal toxins in solutions has been reported as the reason of numerous health problems in human (Priyadarshini and Pradhan, 2017). Therefore, there is a massive need to measure the toxic metal content in drinking water resources. To this aim, on time and accurate analysis of toxic metal ions in aqueous samples is the main challenge today. Very sophisticated equipment like inductively coupled plasma mass spectrometry (ICP-MS), Atomic absorption spectrometry (AAS), ICP-AES and etc. have been used for monitoring and detecting metal ions in solutions (Parham et al., 2009; D'Ilio et al., 2008). However, these methods have several disadvantages, including highly cost instrumentation, complicated sample preparation, and the need for well-trained operators (Kim et al., 2008). Hence, investigation of a feasible, rapid, and cost effective method for metal ion detection is a major prerequisite today.

Nanotechnology has presented a major advance in this regard, with the development of numerous nanoprobes for detection of metal ions. In this part, two typical examples of biosensors that combine hpDNA probe and DNA species are developed for detection of lead and mercury will be argued in the next part. Additionally, Table 5 lists instances of biosensors with various signal amplification strategies for detection of metal ions.

In the past several decades, ECL has attracted much attention because of its sensitive and simplified set up and low background signal (Richter, 2004). Lin Cheng et al. in 2017, constructed ECL biosensor for mercury (Hg) (II) detection. This system used ferrocene-labeled hpDNA probe as a recognition molecule and modified Ruthenium (II) tris-(bipyridine) (Ru (bpy)$_3^{2+}$)/ Cyclodextrins-Au nanoparticles (CD-AuNps)/ Nafion on the glass carbon electrode (GCE). In the presence of Hg(II), the probe tends to form T_Hg (II)_Tcomplex and leads to palpable recovery of ECL of Ru (bpy)$_3^{2+}$, which provides a simple, rapid, and selective sensing platform for mercury identification with 0.1 nM detection limit (Cheng et al., 2017).

In another study, electrochemical biosensor amplified determination of lead ions (Pb^{2+}) and was designed based on a specific DNAzymes for selective detection and immobilization of these DNAzymes, which utilizes reduced grapheme oxide-tetra-ethylenepentamine-gold nanoparticles (rGO-TEPA-Au). Also, as the signal tag, hpDNA labeled with Palladium-Platinum nanoparticles was used as modified Fe metallo-organic frameworks (Fe-MOFs/PdPt NPs). In the presence of Pb^{2+} substrate, strand of DNAzyme conformation changed to single strand DNA and caused to hybridize with the labeled hpDNA and catalyze H$_2$O$_2$ with Fe-MOFs/PdPt NPs to increase the sensitivity of the biosensor (Yu et al., 2018).

6. Conclusion

In summary, in this review, we tried to summarize the DNA based biosensors with various signal amplification strategies for detection of cancer DNA and miRNA, infections microorganisms, and toxic metal ions. The applications of DNA based biosensors as bio-components have presented strong views in diagnostic tests and DNA nanotechnology has a lot of applications in this area. Additionally, in order to increase the sensitivity of the biosensor-based methods, they use a variety of signal amplification strategies, such as CHA, HCR and enzyme-assisted target recycling, which show high sensitivity and specificity and can be easily programmed and modified to different requests. We believe that it is possible that in the future, signal amplifiers can reconstruct the diagnostic device or lead to new treatment options. DNA base biosensors in comparison to other methods of DNA identification confer advantages, such as high sensitivity, specificity, selectivity, and cost effectiveness. As a consequence, DNA based biosensors may give great assistance to improve the accuracy and specificity for clinical diagnosis such as point

Table 5
Examples of biosensors with various signal amplification strategies for detection of metal ions.

Target ion	Signal amplification strategies	Signal transduction	Limit of detection (LOD)	Reference
Hg^{2+}	Used Ru(bpy)$_3$$^{2+}$/CD-AuNPs/Nafion on the surface of GCE and Fc labeled hairpin DNA as a probe	Electrochemiluminescence	0.1 nM	(Cheng et al., 2017)
	Metallo-toehold-triggerd/CHA formation of three-way DNAzyme junctions containing hairpin DNA	Fluorescence	Down to 4.5 pM	(Li et al., 2017)
	Sandwich-type/HCR coupled with (+)Ag@Au CSNPs as a detection probe/two Fc labeled hairpin DNA as a capture probe	Electrochemical	3.6 pM	(Li et al., 2016b)
	Tymine(T)-rich hairpin DNA probe labeled with MB and Fc	Electrochemical	0.08 nM	(Xiong et al., 2015a)
	Used GNPs on the surface of GCE/Fc labeled hairpin DNA	Electrochemiluminescence	0.1 nM	(Gao et al., 2013)
Pb^{2+}	Pb^{2+}-specific DNAzyme/CHA/Ds DNA labeled on Pt@Pdnanocages	Electrochemical	0.033 pM	(Zhao et al., 2017)
	Pb^{2+}-specific DNAzyme/Fe-MOFs/PdPtNPs/hairpin DNA as signal tag	Electrochemical	2 pM	(Yu et al., 2018)
	Pb^{2+}-specific DNAzyme as a probe bind to Magnetic besds/Fc labeled hairpin DNA/HCR	Electrochemical	37 pM	(Zhuang et al., 2013)
	Conformational switch of G-rich hairpin DNA to G-quadruplex	Electrochemical	0.5 nM	(Lin et al., 2011b)

Abbreviations: Ru(bpy)$_3$$^{2+}$, 2,2'-bipyridine-ruthenium, CD-AuNps, Cyclodextrins-Au nanoparticles; GCE, glassy carbon electrode; Fc, ferrocene; CHA, catalyzed hairpin DNA assembly; HCR, hybridization chain reaction; (+)Ag@Au CSNPs, positively charge Ag@Au core-shell nanoparticles; MB, methylene blue; GNP, gold nanoparticle; Ds DNA, dendritic structure DNA; Fe-MOFs, Fe-metal organic frameworks.

of care monitoring of disease, environmental monitoring, food control and biomedical research in the future.

Acknowledgements

Disclosure of conflict of interests

None of the authors has any conflict of interest to declare.

References

Bath, J., Turberfield, A.J., 2007. DNA nanomachines. Nat. Nanotechnol. 2 (5), 275.

Bhalla, N., Jolly, P., Formisano, N., Estrela, P., 2016. Introduction to biosensors. Essays Biochem. 60 (1), 1–8.

Bi, S., Ji, B., Zhang, Z., Zhu, J.-J., 2013. Metal ions triggered ligase activity for rolling circle amplification and its application in molecular logic gate operations. Chem. Sci. 4 (4), 1858–1863.

Bonnet, G., Krichevsky, O., Libchaber, A., 1998. Kinetics of conformational fluctuations in DNA hairpin-loops. Proc. Natl. Acad. Sci. USA 95 (15), 8602–8606.

Cao, W., Gao, W., Liu, Z., Hao, W., Li, X., Sun, Y., Tang, B., 2018. Visualizing miR-155 to monitor breast tumorigenesis and response to chemotherapeutic drugs by a self-assembled photoacoustic nanoprobe. Anal. Chem. 90 (15), 9125–9131.

Chen, C., Li, N., Lan, J., Ji, X., He, Z., 2016a. A label-free colorimetric platform for DNA via target-catalyzed hairpin assembly and the peroxidase-like catalytic of graphene/Au-NPs hybrids. Anal. Chim. Acta 902, 154–159.

Chen, J., Wen, J., Zhuang, L., Zhou, S., 2016b. An enzyme-free catalytic DNA circuit for amplified detection of aflatoxin B1 using gold nanoparticles as colorimetric indicators. Nanoscale 8 (18), 9791–9797. https://doi.org/10.1039/c6nr01381c.

Chen, J., Tang, L., Chu, X., Jiang, J., 2017. Enzyme-free, signal-amplified nucleic acid circuits for biosensing and bioimaging analysis. Analyst 142 (17), 3048–3061.

Chen, W., Yan, Y., Zhang, Y., Zhang, X., Yin, Y., Ding, S., 2015. DNA transducer-triggered signal switch for visual colorimetric bioanalysis. Sci. Rep. 5, 11190. https://doi.org/10.1038/srep11190.

Chen, Y.X., Huang, K.J., He, L.L., Wang, Y.H., 2018. Tetrahedral DNA probe coupling with hybridization chain reaction for competitive thrombin aptasensor. Biosens. Bioelectron. 100, 274–281.

Chen, Y., Xu, J., Su, J., Xiang, Y., Yuan, R., Chai, Y., 2012. In situ hybridization chain reaction amplification for universal and highly sensitive electrochemiluminescent detection of DNA. Anal. Chem. 84 (18), 7750–7755. https://doi.org/10.1021/ac3012285.

Cheng, L., Wei, B., He, L.L., Mao, L., Zhang, J., Ceng, J., Fan, H., 2017. "Off-On" switching electrochemiluminescence biosensor for mercury(II) detection based on molecular recognition technology. Anal. Biochem. 518, 46–52. https://doi.org/10.1016/j.ab.2016.09.018.

Cheng, Y., Lei, J., Chen, Y., Ju, H., 2014. Highly selective detection of microRNA based on distance-dependent electrochemiluminescence resonance energy transfer between CdTe nanocrystals and Au nanoclusters. Biosens. Bioelectron. 51, 431–436. https://doi.org/10.1016/j.bios.2013.08.014.

Cissell, K.A., Rahimi, Y., Shrestha, S., Hunt, E.A., Deo, S.K., 2008. Bioluminescence-based detection of microRNA, miR21 in breast cancer cells. Anal. Chem. 80 (7), 2319–2325. https://doi.org/10.1021/ac702577a.

D'Ilio, S., Petrucci, F., D'Amato, M., Di Gregorio, M., Senofonte, O., Violante, N., 2008. Method validation for determination of arsenic, cadmium, chromium and lead in milk by means of dynamic reaction cell inductively coupled plasma mass spectrometry. Anal. Chim. Acta 624 (1), 59–67. https://doi.org/10.1016/j.aca.2008.06.024.

Das, J., Ivanov, I., Montermini, L., Rak, J., Sargent, E.H., Kelley, S.O., 2015. An electrochemical clamp assay for direct, rapid analysis of circulating nucleic acids in serum. Nat. Chem. 7 (7), 569–575. https://doi.org/10.1038/nchem.2270.

Deng, L., Wu, Y., Xu, S., Tang, Y., Zhang, X., Wu, P., 2018. Improving the signal-to-background ratio during catalytic hairpin assembly through both-end-blocked DNAzyme. ACS Sens. 3 (6), 1190–1195. https://doi.org/10.1021/acssensors.8b00243.

Deng, R., Tang, L., Tian, Q., Wang, Y., Lin, L., Li, J., 2014. Toehold-initiated rolling circle amplification for visualizing individual microRNAs in situ in single cells. Angew. Chem. Int. Ed. Engl. 53 (9), 2389–2393. https://doi.org/10.1002/anie.201309388.

Dirks, R.M., Pierce, N.A., 2004. Triggered amplification by hybridization chain reaction. Proc. Natl. Acad. Sci. USA 101 (43), 15275–15278. https://doi.org/10.1073/pnas.0407024101.

Dittmer, W.U., Reuter, A., Simmel, F.C., 2004. A DNA-based machine that can cyclically bind and release thrombin. Angew. Chem. Int. Ed. Engl. 43 (27), 3550–3553. https://doi.org/10.1002/anie.200353537.

Dong, D., Zheng, D., Wang, F.Q., Yang, X.Q., Wang, N., Li, Y.G., Cheng, J., 2004. Quantitative photoelectrochemical detection of biological affinity reaction: biotin-avidin interaction. Anal. Chem. 76 (2), 499–501. https://doi.org/10.1021/ac035184p.

Dong, Y.P., Gao, T.T., Zhou, Y., Jiang, L.P., Zhu, J.J., 2015. Anodic electrogenerated chemiluminescence of Ru(bpy)3(2+) with CdSe quantum dots as coreactant and its

application in quantitative detection of DNA. Sci. Rep. 5, 15392. https://doi.org/10.1038/srep15392.

Drummond, T.G., Hill, M.G., Barton, J.K., 2003. Electrochemical DNA sensors. Nat. Biotechnol. 21 (10), 1192–1199. https://doi.org/10.1038/nbt873.

Duan, R., Wang, B., Hong, F., Zhang, T., Jia, Y., Huang, J., Xia, F., 2015. Real-time monitoring of enzyme-free strand displacement cascades by colorimetric assays. Nanoscale 7 (13), 5719–5725.

Eacker, S.M., Dawson, T.M., Dawson, V.L., 2009. Understanding microRNAs in neuro-degeneration. Nat. Rev. Neurosci. 10 (12), 837–841. https://doi.org/10.1038/nrn2726.

Epstein, J.R., Biran, I., Walt, D.R., 2002. Fluorescence-based nucleic acid detection and microarrays. Anal. Chim. Acta 469 (1), 3–36.

Esquela-Kerscher, A., Slack, F.J., 2006a. Oncomirs—microRNAs with a role in cancer. Nat. Rev. Cancer 6 (4), 259.

Esquela-Kerscher, A., Slack, F.J., 2006b. Oncomirs - microRNAs with a role in cancer. Nat. Rev. Cancer 6 (4), 259–269. https://doi.org/10.1038/nrc1840.

Fan, D., Wang, K., Zhu, J., Xia, Y., Han, Y., Liu, Y., Wang, E., 2015. DNA-based visual majority logic gate with one-vote veto function. Chem. Sci. 6 (3), 1973–1978. https://doi.org/10.1039/c4sc03495c.

Fang, X., Bai, L., Han, X., Wang, J., Shi, A., Zhang, Y., 2014. Ultra-sensitive biosensor for K-ras gene detection using enzyme capped gold nanoparticles conjugates for signal amplification. Anal. Biochem. 460, 47–53. https://doi.org/10.1016/j.ab.2014.05.019.

Freeman, R., Liu, X., Willner, I., 2011. Chemiluminescent and chemiluminescence re-sonance energy transfer (CRET) detection of DNA, metal ions, and aptamer–substrate complexes using hemin/G-quadruplexes and CdSe/ZnS quantum dots. J. Am. Chem. Soc. 133 (30), 11597–11604.

Gao, T., Zhi, J., Mu, C., Gu, S., Xiao, J., Yang, J., Xiang, Y., 2018a. One-step detection for two serological biomarker species to improve the diagnostic accuracy of hepatocel-lular carcinoma. Talanta 178, 89–93. https://doi.org/10.1016/j.talanta.2017.09.011.

Gao, W., Wei, X., Wang, X., Cui, G., Liu, Z., Tang, B., 2016. A competitive coordination-based CeO 2 nanowire–DNA nanosensor: fast and selective detection of hydrogen peroxide in living cells and in vivo. Chem. Commun. 52 (18), 3643–3646.

Gao, W., Zhang, A., Chen, Y., Chen, Z., Chen, Y., Lu, F., Chen, Z., 2013. A novel probe density controllable electrochemiluminescence biosensor for ultra-sensitive detection of Hg2+ on DNA hybridization optimization with gold nanoparticles array patterned self-assembly platform. Biosens. Bioelectron. 49, 139–145. https://doi.org/10.1016/j.bios.2013.05.013.

Gao, X., Wang, X., Li, Y., He, J., Yu, H.Z., 2018b. Exonuclease I-hydrolysis assisted electrochemical quantitation of Surface-immobilized DNA hairpins and improved HIV-1 gene detection. Anal. Chem. 90 (13), 8147–8153. https://doi.org/10.1021/acs.analchem.8b01445.

Ge, L., Wang, W., Sun, X., Hou, T., Li, F., 2016. Versatile and programmable DNA logic gates on universal and label-free Homogeneous electrochemical platform. Anal. Chem. 88 (19), 9691–9698.

Ge, S., Zhao, J., Wang, S., Lan, F., Yan, M., Yu, J., 2018. Ultrasensitive electro-chemiluminescence assay of tumor cells and evaluation of H2O2 on a paper-based closed-bipolar electrode by in-situ hybridization chain reaction amplification. Biosens. Bioelectron. 102, 411–417.

Green, S.J., Lubrich, D., Turberfield, A.J., 2006. DNA hairpins: fuel for autonomous DNA devices. Biophys. J. 91 (8), 2966–2975.

Gu, H., Xu, K., Xu, C., Xu, B., 2006. Biofunctional magnetic nanoparticles for protein separation and pathogen detection. Chem. Commun. 9, 941–949. https://doi.org/10.1039/b514130c.

Guo, Y., Wu, J., Ju, H., 2015. Target-driven DNA association to initiate cyclic assembly of hairpins for biosensing and logic gate operation. Chem. Sci. 6 (7), 4318–4323. https://doi.org/10.1039/c5sc01215e.

Hao, N., Dai, P.P., Yu, T., Xu, J.J., Chen, H.Y., 2015. A dual target-recycling amplification strategy for sensitive detection of microRNAs based on duplex-specific nuclease and catalytic hairpin assembly. Chem. Commun. 51 (70), 13504–13507. https://doi.org/10.1039/c5cc05350a.

He, H., Dai, J., Duan, Z., Zheng, B., Meng, Y., Guo, Y., Dan, X., 2016. Unusual sequence length-dependent gold nanoparticles aggregation of the ssDNA sticky end and its application for enzyme-free and signal amplified colorimetric DNA detection. Sci. Rep. 6, 30878. https://doi.org/10.1038/srep30878.

He, S., Song, B., Li, D., Zhu, C., Qi, W., Wen, Y., Fan, C., 2010. A graphene nanoprobe for rapid, sensitive, and multicolor fluorescent DNA analysis. Adv. Funct. Mater. 20 (3), 453–459.

He, X., Wang, G., Xu, G., Zhu, Y., Chen, L., Zhang, X., 2013. A simple, fast, and sensitive assay for the detection of DNA, thrombin, and adenosine triphosphate based on Dual-hairpin DNA structure. Langmuir 29 (46), 14328–14334. https://doi.org/10.1021/la403192p.

Hosseinzadeh, E., Ravan, H., Mohammadi, A., Mohammad-Rezaei, R., Norouzi, A., Hosseinzadeh, H., 2018. Target-triggered three-way junction in conjugation with catalytic concatemers-functionalized nanocomposites provides a highly sensitive colorimetric method for miR-21 detection. Biosens. Bioelectron. 117, 567–574. https://doi.org/10.1016/j.bios.2018.06.051.

Hu, Y., Zhang, L., Zhang, Y., Wang, B., Wang, Y., Fan, Q., Wang, L., 2015. Plasmonic nanobiosensor based on hairpin DNA for detection of trace oligonucleotides bio-marker in cancers. ACS Appl. Mater. Interfaces 7 (4), 2459–2466. https://doi.org/10.1021/am507218g.

Huang, H., Bai, W., Dong, C., Guo, R., Liu, Z., 2015. Quenching of the electrochemiluminescence of RU-complex tagged shared-stem hairpin probes by graphene oxide and its application to quantitative turn-on detection of DNA. Biosens. Bioelectron. 70, 441–446. https://doi.org/10.1016/j.bios.2015.03.072.

Hun, X., Xie, G., Luo, X., 2015. Scaling up an electrochemical signal with a catalytic hairpin assembly coupling nanocatalyst label for DNA detection. Chem. Commun. 51 (33), 7100–7103. https://doi.org/10.1039/c5cc00680e.

Jaishankar, M., Tseten, T., Anbalagan, N., Mathew, B.B., Beeregowda, K.N., 2014. Toxicity, mechanism and health effects of some heavy metals. Interdiscip. Toxicol. 7 (2), 60–72. https://doi.org/10.2478/intox-2014-0009.

Jeffrey, S.S., 2008. Cancer biomarker profiling with microRNAs. Nat. Biotechnol. 26 (4), 400.

Jiang, J., Lin, X., Ding, D., Diao, G., 2018. Enzyme-free homogeneous electrochemical biosensor for DNA assay using toehold-triggered strand displacement reaction cou-pled with host-guest recognition of Fe3O4@SiO2@beta-CD nanocomposites. Biosens. Bioelectron. 114, 37–43. https://doi.org/10.1016/j.bios.2018.04.035.

Jiang, Y.S., Bhadra, S., Li, B., Ellington, A.D., 2014. Mismatches improve the performance of strand-displacement nucleic acid circuits. Angew. Chem. 126 (7), 1876–1879.

Johnson, B.N., Mutharasan, R., 2014. Biosensor-based microRNA detection: techniques, design, performance, and challenges. Analyst 139 (7), 1576–1588.

Jolly, P., Formisano, N., Estrela, P., 2015. DNA aptamer-based detection of prostate cancer. Chem. Pap. 69 (1), 77–89.

Jung, C., Ellington, A.D., 2014. Diagnostic applications of nucleic acid circuits. Acc. Chem. Res. 47 (6), 1825–1835.

Karunanayake Mudiyanselage, A., Yu, Q., Leon-Duque, M.A., Zhao, B., Wu, R., You, M., 2018. Genetically encoded catalytic hairpin assembly for sensitive RNA imaging in live cells. J. Am. Chem. Soc. 140 (28), 8739–8745. https://doi.org/10.1021/jacs.8b03956.

Khodakov, D.A., Khodakova, A.S., Linacre, A., Ellis, A.V., 2013. Toehold-mediated nonenzymatic DNA strand displacement as a platform for DNA genotyping. J. Am. Chem. Soc. 135 (15), 5612–5619. https://doi.org/10.1021/ja310991r.

Kim, T.H., Kim, S.H., Tan le, V., Dong, Y., Kim, H., Kim, J.S., 2008. Diazo-coupled calix[4] arenes for qualitative analytical screening of metal ions. Talanta 74 (5), 1654–1658. https://doi.org/10.1016/j.talanta.2007.10.033.

Kwun, J., Yun, S., Park, L., Lee, J.H., 2014. Development of 1,1'-oxalyldiimidazole che-miluminescent biosensor using the combination of graphene oxide and hairpin ap-tamer and its application. Talanta 119, 262–267. https://doi.org/10.1016/j.talanta.2013.10.067.

Lazzka, O., Del Campo, F.J., Munoz, F.X., 2007. Pathogen detection: a perspective of traditional methods and biosensors. Biosens. Bioelectron. 22 (7), 1205–1217.

Li, B., Jiang, Y., Chen, X., Ellington, A.D., 2012. Probing spatial organization of DNA strands using enzyme-free hairpin assembly circuits. J. Am. Chem. Soc. 134 (34), 13918–13921. https://doi.org/10.1021/ja300984b.

Li, C., Wang, H., Shen, J., Tang, B., 2015. Cyclometalated iridium complex-based label-free photoelectrochemical biosensor for DNA detection by hybridization chain re-action amplification. Anal. Chem. 87 (8), 4283–4291.

Li, D., Wieckowska, A., Willner, I., 2008. Optical analysis of Hg2+ ions by oligonu-cleotide-gold-nanoparticle hybrids and DNA-based machines. Angew. Chem. Int. Ed. Engl. 47 (21), 3927–3931. https://doi.org/10.1002/anie.200705991.

Li, J., Lei, P., Ding, S., Zhang, Y., Yang, J., Cheng, Q., Yan, Y., 2016a. An enzyme-free surface plasmon resonance biosensor for real-time detecting microRNA based on allosteric effect of mismatched catalytic hairpin assembly. Biosens. Bioelectron. 77, 435–441. https://doi.org/10.1016/j.bios.2015.09.069.

Li, L., Niu, C., Li, T., Wan, Y., Zhou, Y., Wang, H., Liao, P., 2018. Ultrasensitive elec-trochemiluminescence biosensor for detection of laminin based on DNA dendrimer-carried luminophore and DNA nanomachine-mediated target recycling amplification. Biosens. Bioelectron. 101, 206–212.

Li, M., Xiong, C., Zheng, Y.N., Liang, W.B., Yuan, R., Chai, Y., 2018. Ultrasensitive pho-toelectrochemical biosensor ased on DNA tetrahedron as nanocarrier for efficient immobilization of CdTe QDs-methylene blue as signal probe with near-zero back-ground noise. Anal. Chem

Li, W., Yang, Y., Yan, H., Liu, Y., 2013. Three-input majority logic gate and multiple input logic circuit based on DNA strand displacement. Nano Lett. 13 (6), 2980–2988. https://doi.org/10.1021/nl4016107.

Li, X., Xie, J., Jiang, B., Yuan, R., Xiang, Y., 2017. Metallo-toehold-activated catalytic hairpin assembly formation of three-way DNAzyme junctions for amplified fluor-escent detection of Hg(2). ACS Appl. Mater. Interfaces 9 (7), 5733–5738. https://doi.org/10.1021/acsami.6b13717.

Li, Y., Yu, C., Yang, B., Liu, Z., Xia, P., Wang, Q., 2018. Target-catalyzed hairpin assembly and metal-organic frameworks mediated nonenzymatic co-reaction for multiple signal amplification detection of miR-122 in human serum. Biosens. Bioelectron. 102, 307–315. https://doi.org/10.1016/j.bios.2017.11.047.

Li, Z., Miao, X., Xing, K., Peng, X., Zhu, A., Ling, L., 2016b. Ultrasensitive electrochemical sensor for Hg2+ by using hybridization chain reaction coupled with Ag@ Au core–shell nanoparticles. Biosens. Bioelectron. 80, 339–343.

Liao, X., Li, L., Pan, J., Peng, T., Ge, B., Tang, Q., 2018. In situ biosensor for detection miRNA in living cells based on carbon nitride nanosheets with catalytic hairpin as-sembly amplification. Luminescence 33 (1), 190–195. https://doi.org/10.1002/bio.3392.

Liebana, S., Drago, G.A., 2016. Bioconjugation and stabilisation of biomolecules in bio-sensors. Essays Biochem. 60 (1), 59–68.

Lin, Y., Tao, Y., Pu, F., Ren, J., Qu, X., 2011a. Combination of graphene oxide and thiol-activated DNA metallization for sensitive fluorescence turn-on detection of cy-steine and their use for ogic gate operations. Adv. Funct. Mater. 21 (23), 4565–4572.

Lin, Z., Chen, Y., Li, X., Fang, W., 2011b. Pb2+ induced DNA conformational switch from hairpin to G-quadruplex: electrochemical detection of Pb2+. Analyst 136 (11), 2367–2372. https://doi.org/10.1039/c1an15080d.

Liu, B., Sun, Z., Huang, P.J.J., Liu, J., 2015. Hydrogen peroxide displacing DNA from nanoceria: mechanism and detection of glucose in serum. J. Am. Chem. Soc. 137 (3), 1290–1295.

Liu, G., Wan, Y., Gau, V., Zhang, J., Wang, L., Song, S., Fan, C., 2008. An enzyme-based E-DNA sensor for sequence-specific detection of femtomolar DNA targets. J. Am. Chem. Soc. 130 (21), 6820–6825. https://doi.org/10.1021/ja800554t.

Liu, J., Chen, L., Lie, P., Dun, B., Zeng, L., 2013a. A universal biosensor for multiplex DNA detection based on hairpin probe assisted cascade signal amplification. Chem. Commun. 49 (45), 5165–5167. https://doi.org/10.1039/c3cc41941j.

Liu, J., Zhang, Y., Zhao, Q., Situ, B., Zhao, J., Luo, S., Zheng, L., 2018a. Bifunctional aptamer-mediated catalytic hairpin assembly for the sensitive and homogenous detection of rare cancer cells. Anal. Chim. Acta 1029, 58–64. https://doi.org/10.1016/j.aca.2018.04.068.

Liu, S., Cheng, C., Liu, T., Wang, L., Gong, H., Li, F., 2015. Highly sensitive fluorescence detection of target DNA by coupling exonuclease-assisted cascade target recycling and DNAzyme amplification. Biosens. Bioelectron. 63, 99–104. https://doi.org/10.1016/j.bios.2014.07.023.

Liu, S., Fang, L., Wang, Y., Wang, L., 2017a. Universal dynamic DNA assembly-programmed surface hybridization effect for single-step, reusable, and amplified electrochemical nucleic acid biosensing. Anal. Chem. 89 (5), 3108–3115. https://doi.org/10.1021/acs.analchem.6b04871.

Liu, S., Lin, Y., Wang, L., Liu, T., Cheng, C., Wei, W., Tang, B., 2014. Exonuclease III-aided autocatalytic DNA biosensing platform for immobilization-free and ultrasensitive electrochemical detection of nucleic acid and protein. Anal. Chem. 86 (8), 4008–4015.

Liu, S., Wang, Y., Ming, J., Lin, Y., Cheng, C., Li, F., 2013a. Enzyme-free and ultrasensitive electrochemical detection of nucleic acids by target catalyzed hairpin assembly followed with hybridization chain reaction. Biosens. Bioelectron. 49, 472–477. https://doi.org/10.1016/j.bios.2013.05.037.

Liu, S., Wei, W., Wang, Y., Fang, L., Wang, L., Li, F., 2016. Ultrasensitive electrochemical detection of nucleic acid by coupling an autonomous cascade target replication and enzyme/gold nanoparticle-based post-amplification. Biosens. Bioelectron. 80, 208–214. https://doi.org/10.1016/j.bios.2016.01.067.

Liu, S., Zhang, C., Ming, J., Wang, C., Liu, T., Li, F., 2013b. Amplified detection of DNA by an analyte-induced Y-shaped junction probe assembly followed with a nicking endonuclease-mediated autocatalytic recycling process. Chem. Commun. 49 (72), 7947–7949.

Liu, X., Niazov-Elkan, A., Wang, F., Willner, I., 2013c. Switching photonic and electrochemical functions of a DNAzyme by DNA machines. Nano Lett. 13 (1), 219–225. https://doi.org/10.1021/nl303894h.

Liu, Y., Liao, R., Wang, H., Gong, H., Chen, C., Chen, X., Cai, C., 2018b. Accurate and sensitive fluorescence detection of DNA based on G-quadruplex hairpin DNA. Talanta 176, 422–427. https://doi.org/10.1016/j.talanta.2017.08.003.

Liu, Y., Shen, T., Li, J., Gong, H., Chen, C., Chen, X., Cai, C., 2017b. Ratiometric fluorescence sensor for the microRNA determination by catalyzed hairpin assembly. ACS Sens 2 (10), 1430–1434. https://doi.org/10.1021/acssensors.7b00313.

Low, K.-F., Zain, Z.M., Yean, C.Y., 2017. A signal-amplified electrochemical DNA biosensor incorporated with a colorimetric internal control for Vibrio cholerae detection using shelf-ready reagents. Biosens. Bioelectron. 87, 256–263.

Luan, Q., Xue, Y., Yao, X., Lu, W., 2010. Hairpin DNA probe based surface plasmon resonance biosensor used for the activity assay of E. coli DNA ligase. Analyst 135 (2), 414–418. https://doi.org/10.1039/b920228e.

Lujambio, A., Lowe, S.W., 2012. The microcosmos of cancer. Nature 482 (7385), 347–355. https://doi.org/10.1038/nature10888.

McDonnell, J.M., 2001. Surface plasmon resonance: towards an understanding of the mechanisms of biological molecular recognition. Curr. Opin. Chem. Biol. 5 (5), 572–577.

McLaughlin, C.K., Hamblin, G.D., Sleiman, H.F., 2011. Supramolecular DNA assembly. Chem. Soc. Rev. 40 (12), 5647–5656. https://doi.org/10.1039/c1cs15253j.

Medina, P.P., Nolde, M., Slack, F.J., 2010. OncomiR addiction in an in vivo model of microRNA-21-induced pre-B-cell lymphoma. Nature 467 (7311), 86–90. https://doi.org/10.1038/nature09284.

Meng, H.M., Liu, H., Kuai, H., Peng, R., Mo, L., Zhang, X.B., 2016. Aptamer-integrated DNA nanostructures for biosensing, bioimaging and cancer therapy. Chem. Soc. Rev. 45 (9), 2583–2602. https://doi.org/10.1039/c5cs00645g.

Nie, J., Zhao, M.Z., Xie, W.J., Cai, L.Y., Zhou, Y.L., Zhang, X.X., 2015. DNA cross-triggered cascading self-amplification artificial biochemical circuit. Chem. Sci. 6 (2), 1225–1229. https://doi.org/10.1039/c4sc03225j.

Pan, M., Liang, M., Sun, J., Liu, X., Wang, F., 2018. Lighting up fluorescent silver clusters via target-catalyzed hairpin assembly for amplified biosensing. Langmuir. https://doi.org/10.1021/acs.langmuir.8b01576.

Parham, H., Pourreza, N., Rahbar, N., 2009. Solid phase extraction of lead and cadmium using solid sulfur as a new metal extractor prior to determination by flame atomic absorption spectrometry. J. Hazard Mater. 163 (2–3), 588–592. https://doi.org/10.1016/j.jhazmat.2008.07.007.

Priyadarshini, E., Pradhan, N., 2017. Gold nanoparticles as efficient sensors in colorimetric detection of toxic metal ions: a review. Sens. Actuators B: Chem. 238, 888–902.

Rai, V., Nyine, Y.T., Hapuarachchi, H.C., Yap, H.M., Ng, L.C., Toh, C.S., 2012. Electrochemically amplified molecular beacon biosensor for ultrasensitive DNA sequence-specific detection of Legionella sp. Biosens. Bioelectron. 32 (1), 133–140. https://doi.org/10.1016/j.bios.2011.11.046.

Riccelli, P.V., Merante, F., Leung, K.T., Bortolin, S., Zastawny, R.L., Janeczko, R., Benight, A.S., 2001. Hybridization of single-stranded DNA targets to immobilized complementary DNA probes: comparison of hairpin versus linear capture probes. Nucleic Acids Res. 29 (4), 996–1004.

Richter, M.M., 2004. Electrochemiluminescence (ECL). Chem. Rev. 104 (6), 3003–3036. https://doi.org/10.1021/cr020373d.

Rodriguez-Mozaz, S., Lopez de Alda, M.J., Barcelo, D., 2006. Biosensors as useful tools for environmental analysis and monitoring. Anal. Bioanal. Chem. 386 (4), 1025–1041. https://doi.org/10.1007/s00216-006-0574-3.

Rossi, J.J., 2009. New hope for a microRNA therapy for liver cancer. Cell 137 (6), 990–992. https://doi.org/10.1016/j.cell.2009.05.038.

Ruby, J.G., Jan, C., Player, C., Axtell, M.J., Lee, W., Nusbaum, C., Bartel, D.P., 2006. Large-scale sequencing reveals 21U-RNAs and additional microRNAs and endogenous siRNAs in C. elegans. Cell 127 (6), 1193–1207. https://doi.org/10.1016/j.cell.2006.10.040.

Shah, P., Thulstrup, P.W., Cho, S.K., Bhang, Y.J., Ahn, J.C., Choi, S.W., Yang, S.W., 2014. In-solution multiplex miRNA detection using DNA-templated silver nanocluster probes. Analyst 139 (9), 2158–2166. https://doi.org/10.1039/c3an02150e.

Sharma, T.K., Ramanathan, R., Rakwal, R., Agrawal, G.K., Bansal, V., 2015. Moving forward in plant food safety and security through NanoBioSensors: adopt or adapt biomedical technologies? Proteomics 15 (10), 1680–1692.

Shi, X.M., Fan, G.C., Shen, Q., Zhu, J.J., 2016. Photoelectrochemical DNA biosensor based on dual-signal amplification strategy integrating inorganic-organic nanocomposites sensitization with lambda-exonuclease-assisted target recycling. ACS Appl. Mater. Interfaces 8 (51), 35091–35098. https://doi.org/10.1021/acsami.6b14466.

Shi, X.M., Fan, G.C., Tang, X., Shen, Q., Zhu, J.J., 2018. Ultrasensitive photoelectrochemical biosensor for the detection of HTLV-I DNA: a cascade signal amplification strategy integrating lambda-exonuclease aided target recycling with hybridization chain reaction and enzyme catalysis. Biosens. Bioelectron. 109, 190–196. https://doi.org/10.1016/j.bios.2018.03.023.

Shimron, S., Cecconello, A., Lu, C.H., Willner, I., 2013. Metal nanoparticle-functionalized DNA tweezers: from mechanically programmed nanostructures to switchable fluorescence properties. Nano Lett. 13 (8), 3791–3795. https://doi.org/10.1021/nl4017539.

Shuai, H.L., Huang, K.J., Xing, L.L., Chen, Y.X., 2016. Ultrasensitive electrochemical sensing platform for microRNA based on tungsten oxide-graphene composites coupling with catalyzed hairpin assembly target recycling and enzyme signal amplification. Biosens. Bioelectron. 86, 337–345. https://doi.org/10.1016/j.bios.2016.06.057.

Stratton, M.R., 2011. Exploring the genomes of cancer cells: progress and promise. Science 331 (6024), 1553–1558.

Su, F.X., Yang, C.X., Yan, X.P., 2017. Intracellular messenger RNA triggered catalytic hairpin assembly for fluorescence imaging guided photothermal therapy. Anal. Chem. 89 (14), 7277–7281. https://doi.org/10.1021/acs.analchem.7b01348.

Sun, B., Qi, H., Ma, F., Gao, Q., Zhang, C., Miao, W., 2010. Double covalent coupling method for the fabrication of highly sensitive and reusable electrogenerated chemiluminescence sensors. Anal. Chem. 82 (12), 5046–5052. https://doi.org/10.1021/ac9029289.

Tan, C., Yu, P., Hu, Y., Chen, J., Huang, Y., Cai, Y., Wang, L., 2015. High-yield exfoliation of ultrathin two-dimensional ternary chalcogenide nanosheets for highly sensitive and selective fluorescence DNA sensors. J. Am. Chem. Soc. 137 (32), 10430–10436.

Tan, H., Li, X., Liao, S., Yu, R., Wu, Z., 2014. Highly-sensitive liquid crystal biosensor based on DNA dendrimers-mediated optical reorientation. Biosens. Bioelectron. 62, 84–89. https://doi.org/10.1016/j.bios.2014.06.029.

Tang, S., Gu, Y., Lu, H., Dong, H., Zhang, K., Dai, W., Zhang, X., 2018. Highly-sensitive microRNA detection based on bio-bar-code assay and catalytic hairpin assembly two-stage amplification. Anal. Chim. Acta 1004, 1–9. https://doi.org/10.1016/j.aca.2017.12.004.

Tang, Y., Lin, Y., Yang, X., Wang, Z., Le, X.C., Li, F., 2015. Universal strategy to engineer catalytic DNA hairpin assemblies for protein analysis. Anal. Chem. 87 (16), 8063–8066. https://doi.org/10.1021/acs.analchem.5b02504.

Teengam, P., Siangproh, W., Tuantranont, A., Vilaivan, T., Chailapakul, O., Henry, C.S., 2017. Multiplex paper-based colorimetric DNA sensor using pyrrolidinyl peptide nucleic acid-induced AgNPs aggregation for detecting MERS-CoV, MTB, and HPV oligonucleotides. Anal. Chem. 89 (10), 5428–5435.

Tothill, I.E., 2009. Biosensors for cancer markers diagnosis. Paper presented at the Seminars in cell & developmental biology.

Tsourkas, A., Behlke, M.A., Rose, S.D., Bao, G., 2003. Hybridization kinetics and thermodynamics of molecular beacons. Nucleic Acids Res. 31 (4), 1319–1330.

Valente, W.J., Ericson, N.G., Long, A.S., White, P.A., Marchetti, F., Bielas, J.H., 2016. Mitochondrial DNA exhibits resistance to induced point and deletion mutations. Nucleic Acids Res. 44 (18), 8513–8524.

Valoczi, A., Hornyik, C., Varga, N., Burgyan, J., Kauppinen, S., Havelda, Z., 2004. Sensitive and specific detection of microRNAs by northern blot analysis using LNA-modified oligonucleotide probes. Nucleic Acids Res. 32 (22), e175. https://doi.org/10.1093/nar/gnh171.

Van Dorst, B., Mehta, J., Bekaert, K., Rouah-Martin, E., De Coen, W., Dubruel, P., Robbens, J., 2010. Recent advances in recognition elements of food and environmental biosensors: a review. Biosens. Bioelectron. 26 (4), 1178–1194.

Velusamy, V., Arshak, K., Korostynska, O., Oliwa, K., Adley, C., 2010. An overview of foodborne pathogen detection: in the perspective of biosensors. Biotechnol. Adv. 28 (2), 232–254. https://doi.org/10.1016/j.biotechadv.2009.12.004.

Venkataraman, S., Dirks, R.M., Rothemund, P.W., Winfree, E., Pierce, N.A., 2007. An autonomous polymerization motor powered by DNA hybridization. Nat. Nanotechnol. 2 (8), 490.

Ventura, A., Jacks, T., 2009. MicroRNAs and cancer: short RNAs go a long way. Cell 136 (4), 586–591. https://doi.org/10.1016/j.cell.2009.02.005.

Wang, F., Lu, C.H., Willner, I., 2014. From cascaded catalytic nucleic acids to enzyme-DNA nanostructures: controlling reactivity, sensing, logic operations, and assembly of complex structures. Chem. Rev. 114 (5), 2881–2941. https://doi.org/10.1021/cr400354z.

Wang, H., Zhu, L., Duan, J., Wang, M., Yin, H., Wang, P., Ai, S., 2018. Photoelectrochemical biosensor for HEN1 RNA methyltransferase detection using

peroxidase mimics PtCu NFs and poly (U) polymerase-mediated RNA extension. Biosens. Bioelectron. 103, 32–38.

Wang, J., 2005. Electrochemical Nucleic Acid Biosensors Perspectives in Bioanalysis. Elsevier, pp. 175–194.

Wang, M., Zhou, Y., Yin, H., Jiang, W., Wang, H., Ai, S., 2018. Signal-on electro-chemiluminescence biosensor for microRNA-319a detection based on two-stage iso-thermal strand-displacement polymerase reaction. Biosens. Bioelectron. 107, 34–39.

Wang, Z.G., Ding, B., 2014. Engineering DNA self-assemblies as templates for functional nanostructures. Acc. Chem. Res. 47 (6), 1654–1662. https://doi.org/10.1021/ar400305g.

Wang, Z.G., Elbaz, J., Willner, I., 2011. DNA machines: bipedal walker and stepper. Nano Lett. 11 (1), 304–309. https://doi.org/10.1021/nl104088s.

Wei, Y., Zhou, W., Li, X., Chai, Y., Yuan, R., Xiang, Y., 2016. Coupling hybridization reaction with catalytic hairpin assembly enables non-enzymatic and sensitive fluor-escent detection of microRNA cancer biomarkers. Biosens. Bioelectron. 77, 416–420. https://doi.org/10.1016/j.bios.2015.09.053.

Wen, Y., Xu, Y., Mao, X., Wei, Y., Song, H., Chen, N., Li, D., 2012. DNAzyme-based rolling-circle amplification DNA machine for ultrasensitive analysis of microRNA in Drosophila larva. Anal. Chem. 84 (18), 7664–7669. https://doi.org/10.1021/ac300616z.

Wu, H., Liu, Y., Wang, H., Wu, J., Zhu, F., Zou, P., 2016. Label-free and enzyme-free colorimetric detection of microRNA by catalyzed hairpin assembly coupled with hybridization chain reaction. Biosens. Bioelectron. 81, 303–308. https://doi.org/10.1016/j.bios.2016.03.013.

Wu, X., Chai, Y., Zhang, P., Yuan, R., 2015. An electrochemical biosensor for sensitive detection of microRNA-155: combining target recycling with cascade catalysis for signal amplification. ACS Appl. Mater. Interfaces 7 (1), 713–720. https://doi.org/10.1021/am507059n.

Wu, Z., Fan, H., Satyavolu, N.S.R., Wang, W., Lake, R., Jiang, J.H., Lu, Y., 2017. Imaging endogenous metal ions in living cells using a DNAzyme–catalytic hairpin assembly probe. Angew. Chem. 129 (30), 8847–8851.

Xia, N., Zhang, Y., Wei, X., Huang, Y., Liu, L., 2015. An electrochemical microRNAs biosensor with the signal amplification of alkaline phosphatase and electrochemical-chemical-chemical redox cycling. Anal. Chim. Acta 878, 95–101. https://doi.org/10.1016/j.aca.2015.04.018.

Xiong, E., Li, Z., Zhang, X., Zhou, J., Yan, X., Liu, Y., Chen, J., 2017a. Triple-helix mo-lecular switch electrochemical ratiometric biosensor for ultrasensitive detection of nucleic acids. Anal. Chem. 89 (17), 8830–8835. https://doi.org/10.1021/acs.analchem.7b01251.

Xiong, E., Wu, L., Zhou, J., Yu, P., Zhang, X., Chen, J., 2015a. A ratiometric electro-chemical biosensor for sensitive detection of Hg2+ based on thymine-Hg2+-thy-mine structure. Anal. Chim. Acta 853, 242–248. https://doi.org/10.1016/j.aca.2014.10.015.

Xiong, E., Yan, X., Zhang, X., Li, Y., Yang, R., Meng, L., Chen, J., 2018. A new photo-electrochemical biosensor for ultrasensitive determination of nucleic acids based on a three-stage cascade signal amplification strategy. Analyst 143 (12), 2799–2806. https://doi.org/10.1039/c8an00609a.

Xiong, E., Yan, X., Zhang, X., Liu, Y., Zhou, J., Chen, J., 2017b. Exonuclease III–assisted cascade signal amplification strategy for label-free and ultrasensitive electrochemical detection of nucleic acids. Biosens. Bioelectron. 87, 732–736.

Xiong, E., Zhang, X., Liu, Y., Zhou, J., Yu, P., Li, X., Chen, J., 2015b. Ultrasensitive electrochemical detection of nucleic acids based on the dual-signaling electro-chemical ratiometric method and exonuclease III-assisted target recycling amplifi-cation strategy. Anal. Chem. 87 (14), 7291–7296. https://doi.org/10.1021/acs.analchem.5b01402.

Xue, Q., Lv, Y., Zhang, Y., Xu, S., Li, R., Yue, Q., Liu, J., 2014. Ultrasensitive fluorescence detection of nucleic acids using exonuclease III-induced cascade two-stage isothermal amplification-mediated zinc (II)-protoporphyrin IX/G-quadruplex supramolecular fluorescent nanotags. Biosens. Bioelectron. 61, 351–356. https://doi.org/10.1016/j.bios.2014.05.047.

Yan, Y., Shen, B., Wang, H., Sun, X., Cheng, W., Zhao, H., Ding, S., 2015. A novel and versatile nanomachine for ultrasensitive and specific detection of microRNAs based on molecular beacon initiated strand displacement amplification coupled with cata-lytic hairpin assembly with DNAzyme formation. Analyst 140 (16), 5469–5474. https://doi.org/10.1039/c5an00920k.

Yin, P., Choi, H.M., Calvert, C.R., Pierce, N.A., 2008. Programming biomolecular self-assembly pathways. Nature 451 (7176), 318–322. https://doi.org/10.1038/nature06451.

Yu, C.-Y., Yin, B.-C., Wang, S., Xu, Z., Ye, B.-C., 2014. Improved ligation-mediated PCR method coupled with T7 RNA polymerase for sensitive DNA detection. Anal. Chem. 86 (15), 7214–7218.

Yu, Y., Yu, C., Niu, Y., Chen, J., Zhao, Y., Zhang, Y., He, J., 2018. Target triggered cleavage effect of DNAzyme: relying on Pd-Pt alloys functionalized Fe-MOFs for amplified detection of Pb(2). Biosens. Bioelectron. 101, 297–303. https://doi.org/10.1016/j.bios.2017.10.006.

Zang, Y., Lei, J., Hao, Q., Ju, H., 2016. CdS/MoS2 heterojunction-based photoelec-trochemical DNA biosensor via enhanced chemiluminescence excitation. Biosens. Bioelectron. 77, 557–564.

Zang, Y., Lei, J., Ling, P., Ju, H., 2015. Catalytic hairpin assembly-programmed por-phyrin-DNA complex as photoelectrochemical initiator for DNA biosensing. Anal. Chem. 87 (10), 5430–5436. https://doi.org/10.1021/acs.analchem.5b00888.

Zhang, D., Peng, Y., Qi, H., Gao, Q., Zhang, C., 2010. Label-free electrochemical DNA biosensor array for simultaneous detection of the HIV-1 and HIV-2 oligonucleotides incorporating different hairpin-DNA probes and redox indicator. Biosens. Bioelectron. 25 (5), 1088–1094. https://doi.org/10.1016/j.bios.2009.09.032.

Zhang, D., Yan, Y., Li, Q., Yu, T., Cheng, W., Wang, L., Ding, S., 2012. Label-free and high-sensitive detection of Salmonella using a surface plasmon resonance DNA-based biosensor. J. Biotechnol. 160 (3–4), 123–128.

Zhang, D.Y., Seelig, G., 2011. Dynamic DNA nanotechnology using strand-displacement reactions. Nat. Chem. 3 (2), 103–113. https://doi.org/10.1038/nchem.957.

Zhang, H., Wang, Q., Yang, X., Wang, K., Li, Q., Li, Z., Zheng, Y., 2017. An isothermal electrochemical biosensor for the sensitive detection of microRNA based on a cata-lytic hairpin assembly and supersandwich amplification. Analyst 142 (2), 389–396. https://doi.org/10.1039/c6an02390h.

Zhang, X., Wu, D., Liu, Z., Cai, S., Zhao, Y., Chen, M., Chen, J., 2014. An ultrasensitive label-free electrochemical biosensor for microRNA-21 detection based on a 2'-O-methyl modified DNAzyme and duplex-specific nuclease assisted target recycling. Chem. Commun. 50 (82), 12375–12377. https://doi.org/10.1039/c4cc05541a.

Zhang, X., Yang, Z., Chang, Y., Qing, M., Yuan, R., Chai, Y., 2018a. Novel 2D-DNA-na-noprobe-mediated enzyme-free-target-recycling amplification for the ultrasensitive electrochemical detection of microRNA. Anal. Chem. 90 (15), 9538–9544. https://doi.org/10.1021/acs.analchem.8b02251.

Zhang, X.F., Xu, H.M., Han, L., Li, N.B., Luo, H.Q., 2018b. A Thioflavin T-induced G-quadruplex fluorescent biosensor for target DNA detection. Anal. Sci. 34 (2), 149–153. https://doi.org/10.2116/analsci.34.149.

Zhang, Y., Luo, S., Situ, B., Chai, Z., Li, B., Liu, J., Zheng, L., 2018c. A novel electro-chemical cytosensor for selective and highly sensitive detection of cancer cells using binding-induced dual catalytic hairpin assembly. Biosens. Bioelectron. 102, 568–573. https://doi.org/10.1016/j.bios.2017.12.010.

Zhao, J., Jing, P., Xue, S., Xu, W., 2017. Dendritic structure DNA for specific metal ion biosensor based on catalytic hairpin assembly and a sensitive synergistic amplifica-tion strategy. Biosens. Bioelectron. 87, 157–163. https://doi.org/10.1016/j.bios.2016.08.032.

Zhao, J., Zheng, T., Gao, J., Xu, W., 2018. Toehold-mediated strand displacement reaction triggered by nicked DNAzymes substrate for amplified electrochemical detection of lead ion. Electrochim. Acta 274, 16–22.

Zhao, W.-W., Xu, J.-J., Chen, H.-Y., 2014. Photoelectrochemical DNA biosensors. Chem. Rev. 114 (15), 7421–7441.

Zhao, W.W., Wang, J., Xu, J.J., Chen, H.Y., 2011. Energy transfer between CdS quantum dots and Au nanoparticles in photoelectrochemical detection. Chem. Commun. 47 (39), 10990–10992. https://doi.org/10.1039/c1cc13952e.

Zheng, J., Jiao, A., Yang, R., Li, H., Li, J., Shi, M., Tan, W., 2012. Fabricating a reversible and regenerable Raman-active substrate with a biomolecule-controlled DNA nano-machine. J. Am. Chem. Soc. 134 (49), 19957–19960. https://doi.org/10.1021/ja308875r.

Zhuang, J., Fu, L., Xu, M., Zhou, Q., Chen, G., Tang, D., 2013. DNAzyme-based magneto-controlled electronic switch for picomolar detection of lead (II) coupling with DNA-based hybridization chain reaction. Biosens. Bioelectron. 45, 52–57. https://doi.org/10.1016/j.bios.2013.01.039.

Zhu, J., Ding, Y., Liu, X., Wang, L., Jiang, W., 2014. Toehold-mediated strand displace-ment reaction triggered isothermal DNA amplification for highly sensitive and se-lective fluorescent detection of single-base mutation. Biosens. Bioelectron. 59, 276–281.