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Recent progresses in DNA nanostructure-based biosensors for detection of tumor markers

Rongrong Huang[a], Nongyue He[a,b,*], Zhiyang Li[c,**]

[a] State Key Laboratory of Bioelectronics, School of Biological Science and Medical Engineering, National Demonstration Center for Experimental Biomedical Engineering Education (Southeast University), Southeast University, Nanjing 210096, PR China

[b] Economical Forest Cultivation and Utilization of 2011 Collaborative Innovation Center in Hunan Province, Hunan Key Laboratory of Green Chemistry and Application of Biological Nanotechnology; Hunan University of Technology, Zhuzhou 412007, PR China

[c] Department of Clinical Laboratory, The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing 210008, PR China

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ABSTRACT

DNA has emerged as a promising biomaterial for assembling a variety of nanostructures based on its programmable base pairing. It also has other remarkable properties including stability, prominent biocompatibility, and can easily be modified with functional groups for further applications. In the past few decades, researchers have established various design rules and assembly technologies to improve the stability and complexity of DNA nanostructures. The detection of cancer-associated biomarkers has significant importance in identifying patients with different clinical stages and also in developing adaptive therapeutic strategies. Due to their unique advantages, DNA nanostructures can be designed to serve as universal units to form biosensors for the detection of tumor biomarkers. In this review, we first present a brief introduction of the development of structural DNA nanotechnology. Then we summarize recent strategies for DNA nanostructure-based optical, electrochemical and mass sensitive biosensors in cancer detection. Finally, we discuss the challenges and opportunities these technologies provide.

1. Introduction

It is well known that DNA plays a significantly important role in storing and transmitting genetic information (Crick, 1970; Watson and Francis, 1953). The Watson-Crick base pairing rules guide single strand DNA (ssDNA) assembling into double strand helical structures. DNAs have been considered as novel building blocks for bottom-up fabricating construction at the nanoscale since Seeman first performed pioneering research in the early 1980s (Seeman, 1982). Self-assembled DNA structures began with crossovers and other topological structures such as branched junction (Kallenbach et al., 1983) and knots (Wang et al., 1993), progressing to higher-order periodic and aperiodic structures *via* DNA crossover tiles (LaBean et al., 2000; Li et al., 1996; Mathieu et al., 2005; Winfree et al., 1998). The introduction of DNA origami which used long-stranded DNA chain to fold into a desired shape with the help of a set of designed 'staple strands' brought structural DNA nanotechnology to a new level in 2006 (Rothemund, 2006). This technique led to well-formed 2D structures in near-quantitative yields, even when unpurified staple strands are used (Zhang et al., 2014a, 2014b). The scalability and complexity of DNA nanostructures are also markedly improved (Hong et al., 2017). Substantial efforts have more recently been taken to extend the DNA origami fabrication to the third dimension (Andersen et al., 2009; Hendrik Dietz and William, 2009). Through different strategies, multifarious nanostructures have been created, such as wireframe (Benson et al., 2015; Zhang et al., 2015) and supracolloidal fibrils (Tigges et al., 2016). Nowadays, the rapid growth of technology makes it possible to design one-, two- and three-dimensional DNA nanomaterials for a broad range of applications in biochemistry, materials science and medical science.

Cancer is a leading cause of premature death and disability worldwide. Cancer-associated biomarkers including DNA, RNA, proteins, lipids, metabolites, etc, are quantifiable indicators of specific cancer states and their detection has significant importance in identifying patients with different clinical stages and also in developing adaptive therapeutic strategies (Huang et al., 2017a, 2017b). These biomarkers can be classified into three categories: predictive biomarkers, prognostic biomarkers and diagnostic biomarkers. However, due to the structural characteristics of nucleic acids, specific protein signatures

* Corresponding author at: State Key Laboratory of Bioelectronics, School of Biological Science and Medical Engineering, National Demonstration Center for Experimental Biomedical Engineering Education (Southeast University), Southeast University, Nanjing 210096, PR China.

** Corresponding author.

E-mail addresses: nyhe@seu.edu.cn (N. He), lizhiyangcn@qq.com (Z. Li).

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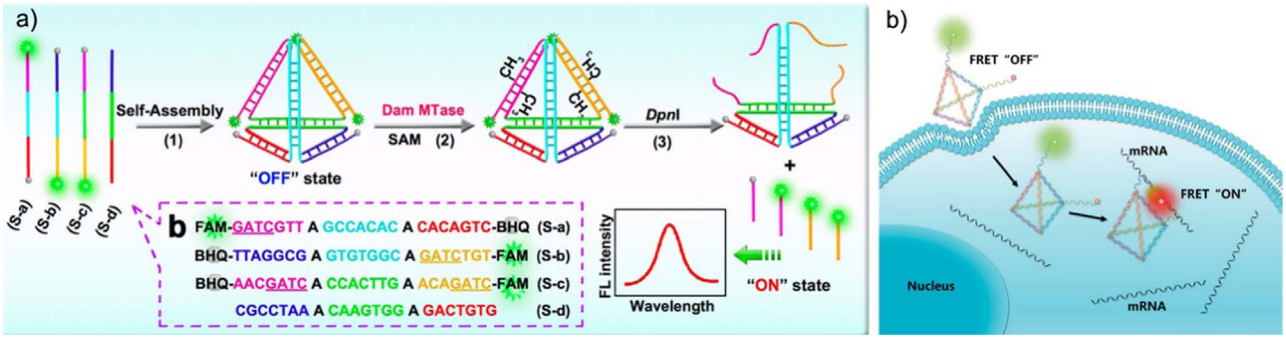

Fig. 1. DNA nanostructure based fluorescence sensing. (a) Schematic illustration of DNA tetrahedron nanostructure to detect DNA methyltransferase activity. With the aid of SAM, the sequences used to assemble DNA tetrahedron was methylated and cleaved. Which led to the recovering of the fluorescence signal. (b) Schematic illustration of DNA tetrahedron nanotweezer to detect intracellular mRNA. The structure of DNA tetrahedron altered in the presence of target mRNA and led to the change of fluorescence signal. Adapted with permission from Ref. (Zhou et al., 2017a, 2017b) and (He et al., 2017).

caused by tumor heterogeneity and difficulty to achieve sample concentration, sensitive detection of cancer biomarkers represents a challenge. DNA nanostructures provide effective platforms in the bioanalytical field. Much attention has been paid to DNA nanostructures for cancer detection in the last three decades. First, the strict base-pairing principle (A-T and G-C) endows the DNA with precise predictability and reproducibility. Second, DNA nanostructures exhibit strong nuclease resistance compared with ssDNA and dsDNA (Song et al., 2017a, 2017b). Third, DNA nanostructures are natural biopolymers with prominent biocompatibility and biodegradability, indicating a great potential for their *in vivo* application (Kumar et al., 2016; Li et al., 2017a; b, c, d, e, f, g; Zhang et al., 2014a, 2014b). Forth, DNA nanostructures can be further modified with quantum dots (Wen et al., 2018), fluorescent dyes (Domljanovic et al., 2017; Schlichthaerle et al., 2016), antibodies (Wang et al., 2017a, b, c, d, e), and cancer-targeting organic compounds including peptides and aptamers (Jiang et al., 2016; Li et al., 2017a; b, c, d, e, f, g; Song et al., 2017a, 2017b) to achieve versatile applications. Thus, DNA nanostructures can be designed and modified to serve as universal units to form biosensors for detection of cancer related biomarkers (Xie et al., 2017). This review therefore focuses on recent progress on application of DNA nanostructure-based biosensors in different classifications for the detection of cancer. We also attempt to discuss the challenges and potential applications regarding these biosensors.

2. DNA nanostructure-based biosensors

Biosensors possess several preponderances including strong specificity to their targets, high sensitivity, simple operation, transportable and able to perform real-time detection compared with traditional analytical approaches like enzyme-linked immunosorbent assay (ELISA) and chromatography (Salek-Maghsoudi et al., 2018). A classical biosensor is formed by a biological recognition unit which specifically recognizes target and transducer which converts the biologic interaction into physical signals to determine the quantities of the target (Chao et al., 2016; Meng et al., 2016). Based on the transduction mechanism, biosensors can be categorized based on the transduction mechanism: optical, electrochemical, thermal, resonant and ion-sensitive biosensors (Chaubey and Malhotra, 2002). Among them, optical and electrochemical biosensors are the most widely used types in the field of tumor biomarker detection and will be discussed in details in the next sections.

The main components of an optical biosensor are illumination supply, optical transducer and detecting system (Patel et al., 2010). The output transducer signals of optical biosensors are based on fluorescence, absorption, luminescence, surface plasmon resonance (SPR), reflection and other optical phenomena (Jayanthi et al., 2017).

2.1. Fluorescence detection

Fluorescence-based device measuring the fluorescence emission of the fluorescent tags labeled target is one of the most sensitive strategies in biosensing. Among the various DNA nanostructures fabricated in the recent years, a classical 3D framework named DNA tetrahedron holds prominent mechanical properties, including simplicity, flexibility, structural stability, and ability to modify with functional decorations or to load drugs and other molecules (Goodman et al., 2005; Xie et al., 2017; Li et al., 2014). Goodman and co-workers first reported a single-step synthesis of tetrahedron (Goodman et al., 2004). In their experiment, four designed oligonucleotides were mixed in salt-containing buffer followed by an annealing process. Since then, DNA tetrahedron has been utilized in the study of cancer mechanisms, tumor biomarker detection and cellular imaging. Zhou and co-workers described an 'off-on' fluorescence system based on DNA tetrahedron to monitor DNA methyltransferase (MTase) activity which plays a crucial role in cancer suppressor gene expression, cancer growth and therapeutics (Hossain et al., 2017). In their experiment, three of the oligonucleotides used to form the DNA tetrahedron were modified with fluorescein and quencher at their 5′ and 3′ ends (Zhou et al., 2017a, 2017b). In the presence of MTase, methyl groups were transferred from S-adenosyl methionine (SAM) to induce methylation of three labeled strands. The strands were then removed from the DNA tetrahedron with the help of *Dpn*I to provide measurable fluorescence signal (Fig. 1a). The detection limit for the fluorescence system reached as low as 0.045 U mL^{-1}.

Furthermore, reports showed that the DNA tetrahedron is able to penetrate cellular membrane without a transfection reagent (Walsh et al., 2011) so that it can be used for cellular detections. He and co-workers reported a DNA tetrahedron nanotweezer for the detection of cancer-related mRNA in living cells (He et al., 2017). The presence of target mRNA caused a structural change for the nanoprobe which led to a high fluorescence resonance energy transfer (FRET) (Fig. 1b). The method they described had the potential to be applied in biomedical research and clinical field. Other than linking the vertexes of tetrahedron with functional groups (Feng et al., 2016; Wang et al., 2017a, b, c, d, e), modificators such as molecular beacons and selective DNAzyme can also be integrated into DNA tetrahedron (Xie et al., 2016; Zhou et al., 2016a, 2016b). Xie and co-workers encoded a molecular beacon into the DNA tetrahedron to detect cancer-associated mRNA in living cells. The target mRNA would induce a configuration change of the DNA tetrahedron, which resulted in the rise of fluorescence intensity (Xie et al., 2016).

In addition to DNA tetrahedron, other DNA nanostructures such as DNA nanohydrogel and DNA origami scaffolds are also applied for bioanalytical application (Fu et al., 2016; Wang et al., 2017a, b, c, d, e; Wang et al., 2015; Wang et al., 2014). These materials are not only utilized to immobilize functional molecules but also participate in the

reaction between the target and biological recognition unit. As miRNAs are able to regulate gene expression, they specifically have been considered as biomarkers in a variety of malignancies, for example; Wang and co-workers described a DNA walker biosensor specifically responsive to colon and lung cancer-associated microRNA named let-7a (Wang et al., 2015). The target miRNA would cause the DNA walker to perform rolling circle amplification (RCA), which is a single-temperature method using small circular oligonucleotide template to produce long repeating strands (Mohsen and Kool, 2016). Then hybridization of RCA product and the molecular beacon modified with 5′-fluorophore and 3′-quencher was cleaved to generate a measurable fluorescence signal.

2.2. Colorimetric detection

Colorimetric biosensors utilizing the high extinction coefficient of color reporting groups such as chromogen coupled enzymes, metallic nanoparticles and small organic dyes to achieve detection have been proved to be convenient tools to analyze biomolecules (Nazmul Islam et al., 2017). Controllable DNA nanostructures are excellent choice for organizing precise spatial arrangement in biosensors.

Functional nucleic acids,including DNAzymes and aptamers, show strong specificity and affinity to their targets and have been widely applied for the detection of various analytes (Nimjee et al., 2017; Wang et al., 2017a, b, c, d, e; Wu et al., 2017). DNAzymes are ssDNA molecules able to catalyze various reactions with high efficiency, designability and versatility and have gained much attention in fabrication of biosensors (Cai et al., 2017; McGhee et al., 2017; Xiang et al., 2016). Li and co-workers designed a functional nucleic acid-based machine which could establish a G-quadruplex/hemin DNAzyme to mimic horseradish peroxidase (HRP) to achieve visual detection of microRNAs (Li et al., 2016b). The colorimetric machine was demonstrated to provide strong sensitivity to target miRNA with a wide dynamic range from 10 aM to 1.0 nM. The high sensitivity and simplicity made this platform ideal for multianalysis of miRNAs.

Aptamers are short ssDNA or RNA molecules which can specifically bind to their target *via* 3D structures so that they can either serve as building blocks to form the DNA nanostructure or be considered as functional groups to achieve specific recognition (Meng et al., 2016). Chang and co-workers reported an aptamer-based biosensor to detect vascular endothelial growth factor (VEGF), a protein important for the growth and spread of tumors (Roskoski, 2017). Gold nanoparticles were used to generate a colorimetric signal in their method. The binding of the VEGF and hairpin probe containing VEGF specific aptamer sequence would trigger a nonlinear hybridization chain reaction (HCR) to assemble a DNA dendritic nanostructure. The DNA strands used to perform HCR were released from the gold nanoparticles (AuNPs). The naked AuNPs were susceptible to salt-induced aggregation so that the color of solution would change from wine red to purple (Chang et al., 2016).

Colorimetric detection methods that make use of AuNPs aggregation and DNA programmable assembly have gained much attention lately, due to their low-cost, simplicity, and being easy to operate (Lam et al., 2016) (Fig. 2a). Besides the aptamer-based biosensor mentioned above, He et al. and Li et al. (Fig. 2b) also developed DNA polymer chains nanostructures for the detection of nucleic acids (He et al., 2016; Li et al., 2017a; b, c, d, e, f, g). Moreover, Zeng et al. recently described colorimetric detection of DNA (Zeng et al., 2017a, 2017b). The detection limit was as low as 0.6 pM and could be applied to numerous other targets including cancer-related DNAs in real samples.

2.3. Chemiluminescence detection

Chemiluminescence detection has been considered a convenient tool in biochemical analysis, as no external light source is needed (Table 1). As mentioned above (Li et al., 2016), G-quadruplex, which is a 3D nanostructure containing G-rich DNA sequences, has been widely used to amplify the output of biosensor as it can increase the peroxidase activity of hemin (Liu et al., 2017a; b, c). Xu and co-workers described a G-quadruplex DNAzyme based chemiluminescence method to detect BCR/ABL fusion gene which is the cause of chronic myelogenous leukemia (Xu et al., 2016). They designed a DNA junction probe to specifically recognize the BCR/ABL fusion gene, leading to the synthesis of DNAzyme subunits. A chemiluminescence signal was then induced by the conjugation of DNAzyme and hemin. Furthermore, Li and co-workers utilized G-quadruplex DNAzyme for low background sensing of microRNA (Fig. 3a). The biosensor they developed showed significant sensitivity improvement in comparison with the traditional fluorescence method (Li et al., 2017a; b, c, d, e, f, g). Besides the microRNAs (Li et al., 2016a) (Fig. 3b), other tumor biomarkers such as proteins (Yang et al., 2017) can also be the targets for inducing the fabrication of G-quadruplex DNAzyme.

Another strategy to achieve the amplification of chemiluminescence signal is HCR (Liu et al., 2017a; b, c). For example, Zhou and co-workers described a ‘sandwich-like’ biosensor to detect specific DNAs related to disease (Zhou et al., 2017a, 2017b). First the target DNAs were bound to the capture probe immobilized on magnetic beads and the report probe modified polystyrene microspheres, respectively. Then the two designed monomers were added to trigger the HCR to generate chemiluminescence with the assistance of 3,4,5-trimethoxylphenylglyoxal. This simple method can be applied to the development of powerful techniques for the early diagnoses of cancers.

2.4. SPR detection

SPR sensors measuring the binding kinetics and affinity exhibit distinct advantages over fluorescence-based assays such as label-free and real-time (Singh, 2016). Due to their biocompatibility, well-formed nanoscale shapes and precise predictability, DNA origami has the ability to arrange nanocomponents self-assembling, which makes it promising technology to develop programmed plasmonic nanoparticles for the enhancement of fluorescence spectroscopy (Acuna et al., 2012; Puchkova et al., 2015), infrared (Ataka et al., 2013) and Raman signals (Heck et al., 2017; Prinz et al., 2016). The unique advantages these novel DNA origami-based nanocomponents exhibit in terms of programmability and sensitivity make them be multifunctional tools for *in vivo* detection. Du and co-workers constructed a DNA-origami-gold-nanorod hybrid nanoprobe for optoacoustic imaging and diagnostic applications (Du et al., 2016). First, they used DNA scaffold to fold into a triangular nanostructure with the help of designed staple strands to capture strands. Then the gold nanorods coated with DNA strands complementary to the capture strands were attached to the scaffolds. The nanoprobes were excellent agents for *in vivo* imaging due to their localized surface plasmon resonances. Finally, optoacoustic imaging was performed on the tumor bearing mouse under near-infrared laser light. Their results demonstrated the nanoprobe exhibited better tumor accumulation and higher contrast ratio than bare gold nanorods. Besides, the AuNPs (Matsishin et al., 2017; Zhang et al., 2017a, 2017b), copper nanoparticles synthesized with the template of DNA origami were also utilized to form enhanced SPR sensor (Yuan et al., 2017).

2.5. Electrochemical detection

Electrochemical biosensors are among the most widely used biosensors which quantify the measurable electrical signals caused by the ions or electrons produced by the chemical reactions between the biorecognition element and target analyte (Krejcova et al., 2017). The main advantages of electrochemical biosensors are quickness, sensitivity and low-prices (Salek-Maghsoudi et al., 2018).

Exosomes are nanoscale extracellular vesicles containing cell-type specific features considered as biomarkers in various diseases including cancer (Cappello et al., 2017). Wang and co-workers linked a HepG2

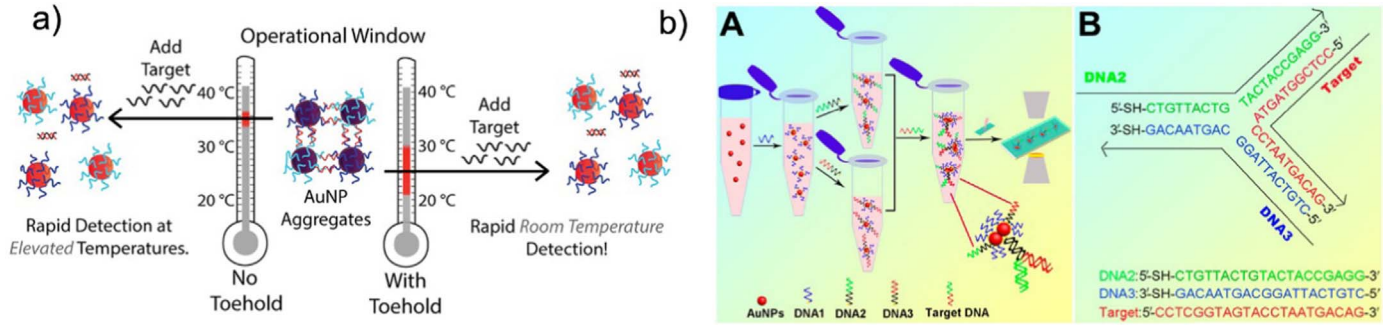

Fig. 2. DNA nanostructure based colorimetric sensing. a) Schematic illustration of DNA detection based on AuNPs aggregation and DNA hybridization. Use toehold mediated stand displacement and aggregation of AuNPs to achieve rapid detection of target DNA. b) Schematic illustration of Y-shaped DNA nanostructure-based biosensor to detect nucleic acid. The presence of target DNA triggered the assembly of complementary DNA with a Y shape and led to the formation of AuNP dimers. DNA Adapted with permission from Ref. (Lam et al., 2016) and (Li et al., 2017a; b, c, d, e, f, g).

exosome specific aptamer on top of a DNA tetrahedron, which was then attached to the gold electrodes for electrochemical detection of exosomes (Wang et al., 2017a, b, c, d, e) (Fig. 4a). Furthermore, Lin and co-workers developed a DNA nanostructure-based universal biosensing platform to detect small molecules and cells (Lin et al., 2016). They immobilized tumor biomarker specific aptamers or antibodies conjugated tetrahedron nanostructures on gold electrode surface. In their experiment, the electro-catalytic signal produced by single avidin-HRP conjugate could be further amplified by poly-HRP or multibranched hybridization chain reaction. More recently Shen and co-workers used a specific aptamer for breast tumor biomarker human epidermal growth factor receptor (HER2) to accomplish analysis of target protein in serum (Shen et al., 2017). Construction of the electrochemical biosensor is described in Fig. 3. TheHER2 specific peptide attached to the gold electrode and HER2 specific aptamer were utilized to form a sandwich-like structure in the presence of target protein. Then the self-assembly reaction was carried out by two strands containing complementary sequences to produce electrochemical current which was finally analyzed using an electrochemical workstation. To further demonstrate the clinical value of the biosensor, serum samples were collect from 4 breast cancer patients and 2 healthy donors. Results showed that this biosensor was of excellent accuracy compared with the classic ELISA test.

With assistance of the HRP mimicking DNAzyme, Zhao and co-workers introduced a DNA-tetrahedron based electrochemical biosensor. First, they immobilized the capture DNA modified DNA tetrahedron on the surface of the gold electrode (Zhao et al., 2016). The target DNA was then cut from the biosensor, leading to a non-signal state. The presence of MTase could cause the methylation of capture DNA, leaving the target unremoved. The target was then converted to DNAzyme and catalyzed the deposition of polyaniline on the gold surface to induce the electrochemical signal. This method exhibited excellent accuracy and sensitivity when applied in complex samples, which made it promising in the field of clinical field.

There are still other explorations for DNA nanostructures-based biosensors on detection of cancer-associated biomarkers (Su et al., 2016). Among the microRNAs exploited in cancer therapeutics (Bahrami et al., 2018), MiR-21 is of significant importance in cancer progression (Li et al., 2017a; b, c, d, e, f, g). Liu and co-workers developed an enzyme-free electrochemical biosensor to quantify the concentration of miR-21 (Liu et al., 2016). The presence of miR-21 would induce hybridization chain reaction of two hairpin strands, followed by the progress of a long double strand with assistance of two designed aid DNAs. As one of the aid DNA was modified with CdTe quantum dots, the long strand was able to provide Cd ions and produce measurable electrochemical signals. Moreover, Huang and co-workers also described a DNA nanostructure based electrochemical biosensor to analyze miR-21 (Huang et al., 2017a, 2017b). In their experiment, guanine nanowire was used to amplify the signals. Moreover, Zeng and co-workers reported a sensitive biosensor to accomplish multiple detection of pancreatic cancer associated miRNA (Zeng et al., 2017a, 2017b) (Fig. 4b). Results showed that the detection limit of this biosensor reached 10fM.

Electrochemiluminescence (ECL) generated by electrochemical high-energy electron transfer reactions has currently been applied in the formation of biosensors with extremely high sensitivity (Feng et al., 2017, 2018; Zhai et al., 2017). The use of DNA nanostructures with mechanical operations as a signal amplification platform is increasing (Li et al., 2017a; b, c, d, e, f, g; Zhang et al., 2017a, 2017b). For example, Xu and co-workers described a DNA walking machine-based biosensor to detect microRNA (Xu et al., 2017). First, they utilized the DNA machine to convert target microRNA to intermediate DNA, which was then conjugated to hairpin DNA modified AuNPs. Consequently, the distance between quantum dots and AuNPs was increased and triggered the 'super-on' state of the biosensor (Fig. 5a). Similarly, Peng and co-workers also designed a distance-based electrochemiluminescence biosensor to detect microRNAs (Peng et al., 2017). However, the DNA machine they used was designed to walk bidirectionally to achieve multiple targets detection (Fig. 5b).

2.6. Mass sensitive detection

Mass-based biosensors record the mass changes caused by modifications in resonance frequencies of the sensor surface (Salek-

Table 1
Advantages and disadvantages of each type of biosensor.

Transduction type	Advantages	Disadvantages
Fluorescent	High sensitivity	Costly equipment, fluorescent label may impair binding
Electrochemical	High sensitivity, simplicity, rapid, inexpensive	sensor surface functionalization challenging, redox species required to increase current production, no real-time detection, sensitive to sample matrix effects, bulky equipment
Colorimetric	Simplicity, low cost	high detection limit
Chemiluminescent	Simplicity, low cost, high sensitivity	Back ground absorption, sensor surface functionalization challenging
QCM	Real time, label-free	Not applicable for small analytes, careful control of temperature and stress is essential
SPR	Real-time, label-free, high sensitivity	suffers from interferences

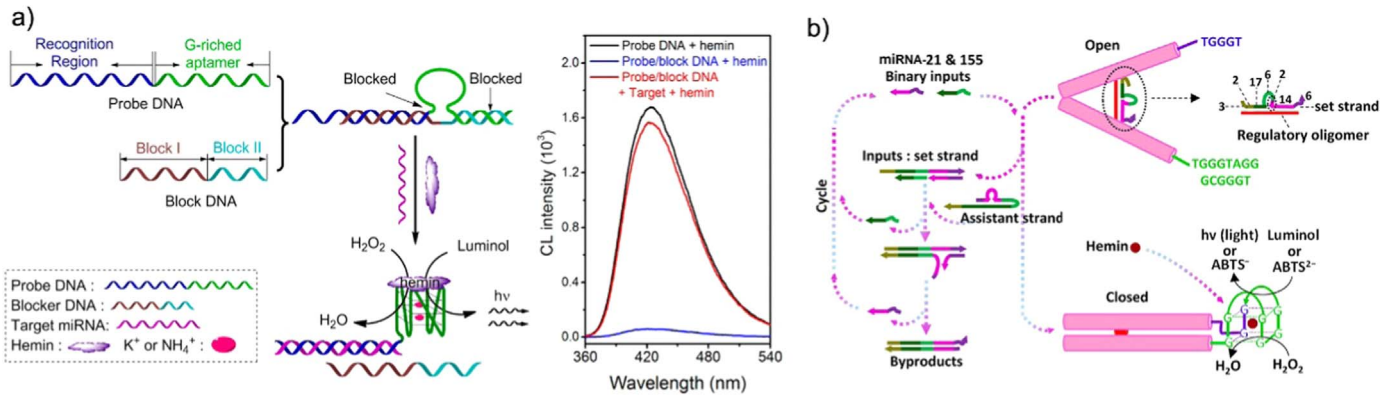

Fig. 3. DNA nanostructure based colorimetric sensing. a) Schematic illustration of a G-quadruplex DNAzyme based chemiluminescence biosensor to detect BCR/ABL fusion gene. b) Schematic illustration of a DNA nanotweezer for multiple miRNA detection. The structure of DNA nanotweezer altered from open to a closed state in the presence of target miRNA and led to the formation of proximity-dependent DNAzyme. Adapted with permission from Ref. (Li et al., 2017a; b, c, d, e, f, g) and (Li et al., 2016a).

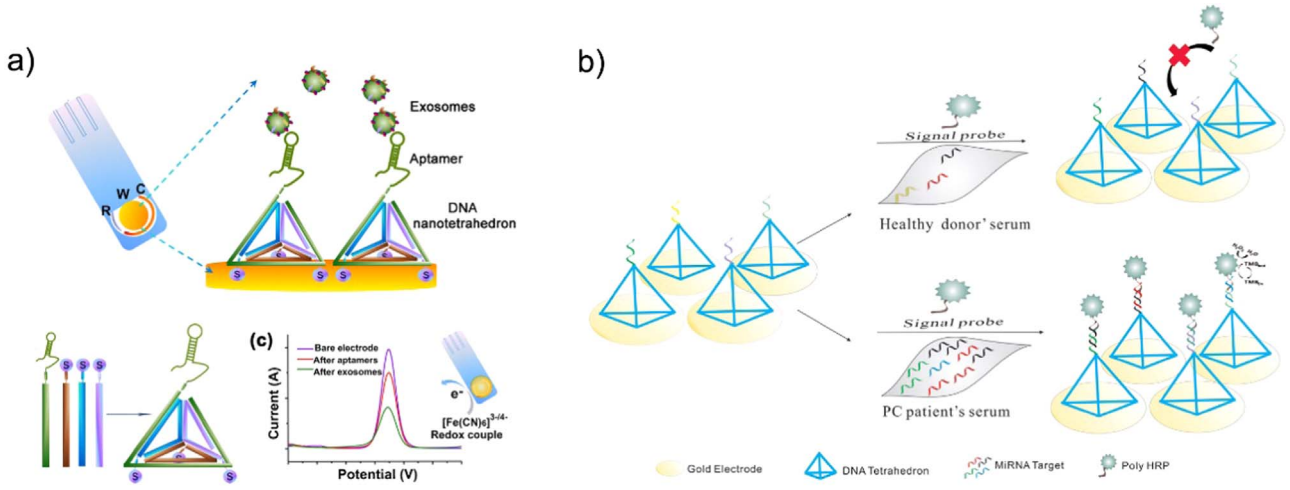

Fig. 4. DNA nanostructure based electrochemical sensing. a) Schematic illustration of an aptamer based biosensor to detect exosomes. The immobilization of aptamer modified DNA tetrahedral and the binding of exosome led to the redox signal changes. b) Schematic illustration of a DNA tetrahedron based biosensor to detect miRNA. Adapted with permission from Ref. (Wang et al., 2017a, b, c, d, e) and (Zeng et al., 2017a, 2017b).

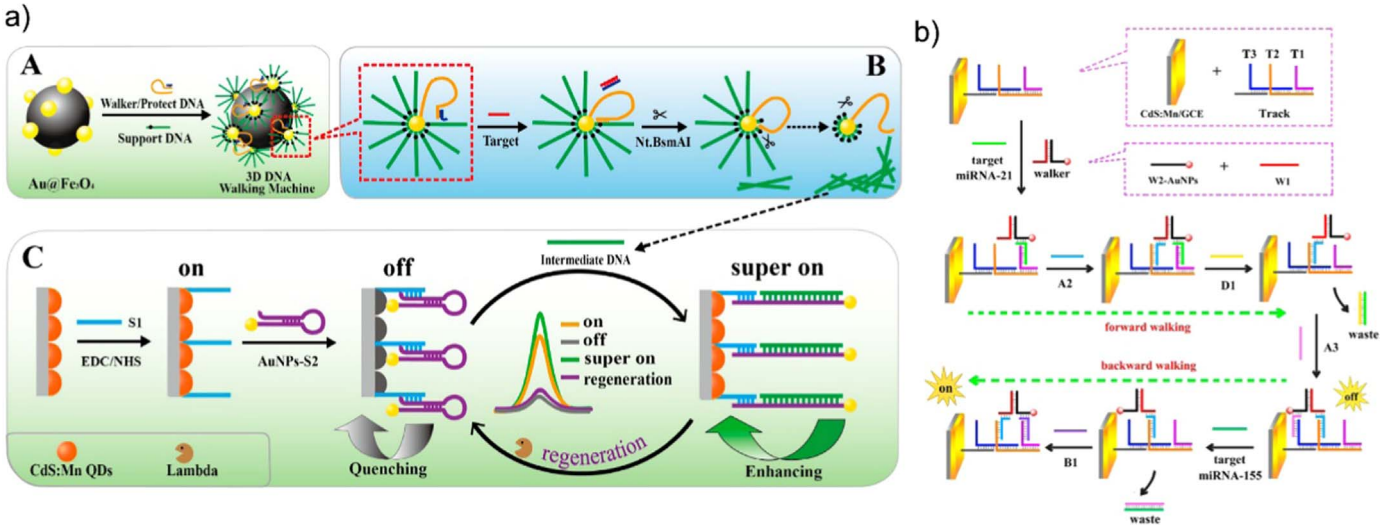

Fig. 5. DNA nanostructure based electrochemiluminescence sensing. a) Schematic illustration of a DNA walker to detect miRNA. The presence of target microRNA could induce the increase in distance between quantum dots and AuNPs and then trigger the 'super-on' state of the biosensor. b) Schematic illustration of a bi-directional DNA walker for the multiplex detection of miRNAs. The DNA walker could move forth and backward along the track in the presence of different target miRNAs and led to detectable ECL signal. Adapted with permission from Ref. (Xu et al., 2017) and (Peng et al., 2017).

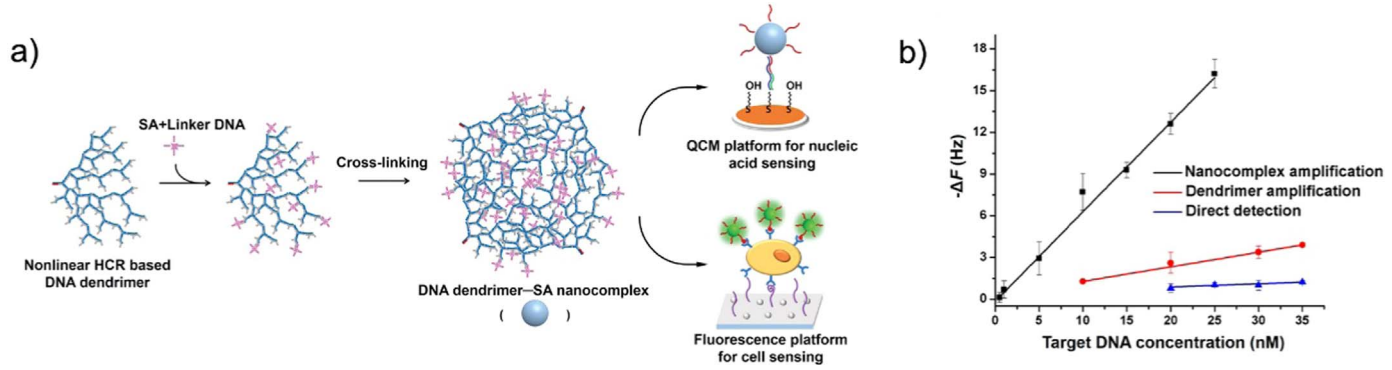

Fig. 6. (a) Schematic illustration of DNA dendrimer-streptavidin (SA) nanostructure-based biosensors to detect cancer-related gene. (b) Linear relationship between frequency responses of the DNA nanostructure amplified QCM platform and target DNA concentrations. Adapted with permission from Ref. (Zhao et al., 2017).

Maghsoudi et al., 2018). These biosensors were once more frequently applied in the detection of large targets such as cells. However, with the advancement of technology, mass-based biosensors for sensitive detection of small analytes have been explored.

Quartz crystal microbalance (QCM) is a label-free, real time and non-invasive technology which has been considered as a powerful tool for biological and chemical research (Chen et al., 2018; Sun et al., 2014). The sensitivity and practicality of the QCM-based biosensors have more recently been further improved by employing DNA nanostructures (Liu et al., 2017a; b, c; Zhao et al., 2015). For example, Zhao and co-workers constructed the DNA dendrimer-streptavidin (SA) nanostructure to amplify the output signal for the QCM platform, for quantitative determination of cancer-related genes (Zhao et al., 2017). First, they operated nonlinear HCR to build a DNA dendrimer which was then cross-linked to SA-coupled DNA to construct the complex nanostructure to assist QCM detection (Fig. 6). Besides the HCR, the DNA-conjugated nanomaterials such as metal nanoparticles and quantum dots are also excellent mass contribution amplifiers (Kuewhan et al., 2016; Premaratne et al., 2017; Zhou et al., 2016a, 2016b). The combination of QCM and DNA nanotechnology can be utilized for effective detection of small molecular biomarkers with quantitative insights. However, the drawback of mass-sensitive detectors is non-specific adsorption which may affect the results.

3. Conclusions

Despite the remarkable development of DNA nanostructure-based tumor biomarker detection in the past few decades (Table 2), there are still challenges which need to be overcome for making the DNA nanotechnology practical in constructing biosensors for clinical use. First of all, the technology is still expensive for synthesis of DNA templates and fabrication of large scale and complex nanostructures, especially the DNA origami which uses 7176-nt sequence as scaffold to create structures of approximately 100 nm size (Rothemund, 2006). Although chemical modification with groups, such as thiol groups, antibodies and fluorescence dyes, improves the functional potential of DNA nanostructures, it also raises the cost. Besides, the position and orientation of the functional groups should be controlled precisely (Pinheiro et al., 2011). Efforts should be aimed at forming large scale nanostructures at lower cost. Second, a large number of transducers employed in biosensors are inorganic materials such as AuNPs, carbon nanotubes and quantum dots. Coupling of DNA nanostructures with these inorganic materials or producing DNA patterns at arbitrary locations while retaining the stability and biological functions of DNA proves to be difficult (Zhang et al., 2013). Improvements on the efficiency of conjugating DNA with inorganic surface are therefore also required. Apart from these two main challenges, there are still other challenges that remain to be solved. For example, as mentioned above, exosomes which

Table 2
Overview of DNA nanostructure-based biosensors applied in tumor biomarker detection.

DNA nanostructure	Tumor biomarker	Transduction type	Detection limit	References
DNA Tetrahedron	DNA methyltransferase	Fluorescent	0.045 U mL^{-1}	Zhou et al. (2017a), (2017b)
		Electrochemical	0.03 U mL^{-1}	Zhao et al. (2016)
	intracellular metal ions	Fluorescent	UO_2^{2+}: 0.6 nM, Pb^{2+}: 3.9 nM	Zhou et al. (2016a), (2016b)
	Exosomes	Electrochemical	2.09 × 10^4 mL^{-1}	Wang et al. (2017a, b, c, d, e)
	miRNA – 21	Electrochemical	176 fM	Huang et al. (2017a), (2017b)
	DNA	Electrochemiluminescence	20 aM	Feng et al. (2017)
DNA walker	miRNA let – 7a	Fluorescent	58 fM	Wang et al. (2015)
	miRNA – 141	Electrochemiluminescence	3.3 fM	Xu et al. (2017)
	miRNA – 21, miRNA – 155	Electrochemiluminescence	miRNA – 21:1.51 fM, miRNA – 155: 1.67 fM	Peng et al. (2017)
DNA G-Quadruplex	miRNA – 21	Colorimetric	5 a.M.	Li et al. (2016a, 2016b)
		Chemiluminescent	0.5 nM	Li et al. (2017a; b, c, d, e, f, g)
	Carcinoembryonic antigen	Chemiluminescent	80 fM	Yang et al. (2017)
DNA dendrimer	Vascular endothelial growth factor	Colorimetric	370 p.M.	Chang et al. (2016)
	DNA	Colorimetric	0.6 p.M.	Zeng et al. (2017a), (2017b)
	KRAS gene	QCM	0.062 nM	Zhao et al. (2017)
Y-shaped DNA structure	DNA	Colorimetric	9 p.M.	He et al. (2016)
DNA Nanotweezer	miRNA – 21	Chemiluminescent	30 fM	Li et al. (2016b)
		Electrochemiluminescence	0.03 fM	Zhang et al. (2017a), (2017b)
DNA hybridization	DNA	SPR	3.21 fM	Yuan et al. (2017)
		QCM	0.1 nM	Zhou et al. (2016a), (2016b)
	miRNA – 21	QCM	28 fM	Premaratne et al. (2017)
DNA chain	miRNA – 21	Electrochemical	33 a.M.	Liu et al. (2016)
DNA origami	prostate-specific antigen	Chemiluminescent	50 a.M.	Yan et al. (2015)

could be obtained from most bodily liquids have recently been considered as ideal tumor markers and therapeutic targets (Cappello et al., 2017; Tomasetti et al., 2017). With advances in extraction, purification and analysis techniques for exosomes, a variety of exosome-shuttled molecules, including proteins and miRNA which play critical roles in the modulation of cancer progress, have been identified (Li et al., 2017a; b, c, d, e, f, g). However, the detection sensitivity of exosome levels in biological samples remains to be improved (Wang et al., 2017a, b, c, d, e).

4. Future perspectives

Predictability, reproducibility, stability, biocompatibility, biodegradability and the ability to be easily modified are the most important advantages of DNA nanostructures. With researchers majoring in different fields working together to solve the problems mentioned above, programmable systems such as DNA nanostructure based nanomachines capable of individual treatment can be designed. As the DNA nanotechnology develops, we expect the bright future for DNA nanostructure-based biosensors in tumor marker detection.

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