Advances in DNA/RNA detection using nanotechnology

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Contents

Abstract

Specific nucleic acid detection in vitro or in vivo has become increasingly important in the discovery of genetic diseases, diagnosing pathogen infection and monitoring disease treatment. One challenge, however, is that the amount of target nucleic acid

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in specimens is limited. Furthermore, direct sensing methods are also unable to provide sufficient sensitivity and specificity. Fortunately, due to advances in nanotechnology and nanomaterials, nanotechnology-based bioassays have emerged as powerful and promising approaches providing ultra-high sensitivity and specificity in nucleic acid detection. This chapter presents an overview of strategies used in the development and integration of nanotechnology for nucleic acid detection, including optical and electrical detection methods, and nucleic acid assistant recycling amplification strategies. Recent 5 years representative examples are reviewed to demonstrate the proof-of-concept with promising applications for DNA/RNA detection and the underlying mechanism for detection of DNA/RNA with the higher sensitivity and selectivity. Furthermore, a brief discussion of common unresolved issues and future trends in this field is provided both from fundamental and practical point of view.

1. Introduction

Nucleic acid, including DNA (deoxyribonucleic acid) and RNA (ribonucleic acid), are polymeric biologic molecules composed of nucleotide monomers. Each nucleotide consists of three-components: a phosphate group, a nitrogenous base and a five-carbon sugar (deoxyribose for DNA and ribose for RNA). Nucleic acids are critical biomolecules in life due to their capacity to encode genetic information and regulate the synthesis of protein. Thus, genetic variation resulting from some minor nucleic acid sequence change has significant biomedical and biologic implications, i.e., cancer [1]. RNA also plays a key role in cancer development and further detection of diseases. In addition, expression of microRNA or messenger RNA appears related to cancer growth and development [2]. Therefore, sensitive, accurate and selective detection of nucleic acid is highly important and fundamental to biomedical research, clinical diagnosis and efficient treatment.

In support thereof, various DNA/RNA detection technologies have been developed in recent years [3,4]. Despite this continuing evolution, many of these approaches are remain challenged by acceptable practicality, sufficient sensitivity and resistance to interferents in biologic material, i.e., serum, saliva, urine and cell extracts. To improve the limitations inherent to traditional DNA/RNA detection methods, nanomaterials have received particular attention due to their unique chemical and physical properties as signal amplification carriers and as direct signal generating biosensor elements. Moreover, nanomaterials provide unlimited opportunity for novel combinations of various materials or molecules of different composition,

size, shape and dimension. When coupled with different biomolecules, these nanocomposites can provide unique probes having the desired properties for signal transfer and biosensing [5,6]. Advances in nanotechnology include the use of noble metal nanoparticles [7], magnetic nanoparticles (MNPs) [8], quantum dots (QDs) [9], two dimensional (2D) nanomaterials [10], metal-organic frameworks (MOFs) [11] and up-conversion phosphors (UCPs) [12]. These technologic breakthroughs have significantly enabled the development of electro/optical biosensors possessing exceptional ability to detect DNA/RNA. The use of nanomaterials also enhances signal amplification because of their large specific surface area which could then be loaded with more signal tags, as well as other unique photo/electric properties for direct signal transfer and collection. In addition, the flexibility and designability during the construction of the nanobiosensing interfaces provide a promising research tool for ultrasensitive detection of DNA/RNA.

In this chapter, we review current developments in smart nanobiosensing strategies, including electrochemical, electrochemiluminescence (ECL), photoelectrochemistry (PEC), fluorescence, surface-enhanced Raman scattering (SERS) assays, as well as colorimetric and other plasmonic-based sensors. Their use in DNA/RNA detection and signal-enhancing ability and mechanism of action will be discussed. The advantages and shortcomings of specific nanomaterials such as noble metal nanoparticles, MNPs, QDs, 2D nanomaterials, MOFs and UCPs will be highlighted. Finally, we discuss unresolved challenges and future trends for nucleic acid detection from both a fundamental and practical point of view.

2. Metallic nanoparticle strategies

Because of their unique optical, chemical, electrical and catalytic properties, gold (Au) and silver (Ag) nanoparticles have been extensively studied and used for DNA/RNA detection in combination with electrochemistry, electrochemiluminescence (ECL), photoelectrochemistry (PEC), fluorescence, SERS, colorimetric assays and surface plasmon resonance (SPR) sensing approaches.

2.1 Metallic nanoparticle electrochemical assays

Recently, metallic nanomaterial-based electrochemical detection strategies offered new opportunities for highly sensitive nucleic acid detection. Because of their excellent conductivity, high surface area and catalytic properties,

metallic nanoparticles were found to ideal platforms for electrochemical-based detection. For example, the metal surface is suitable for binding of biomolecules and the metal itself facilitates direct and rapid electron transfer that decrease the overpotentials of many electrochemical reactions, thus maintaining redox reaction reversibility. In addition, they can be used to amplify signal detection via increased loading density of signal probes.

Gold nanoparticles (AuNP), one of the most popular metal nanoparticles, have become suitable nanomaterials for sensitive electrical transduction during biomolecular recognition events due to their attractive electrical properties, excellent biocompatibility and versatile bioconjugation [7]. More interesting is that different properties would be shown from DNA-Au NPs composite after interaction with single- (ssDNA) and double-stranded DNA (dsDNA). For example, Zhang et al. [13] demonstrated that catalytic sites of Au NPs could be fully blocked by ssDNA due to the noncovalent interaction with nucleotide bases. In contrast, dsDNA cannot be adsorbed onto the surface of Au NPs due to electrostatic interaction. As such, unmodified Au NPs exhibited excellent glucose oxidase-like activity thus enlarging Au NP size in the presence of glucose and $HAuCl_4$ solution. The formation of large size of Au NPs could result in a conductive gold film formation with a dramatically increased conductance of Au NPs. This proposed self-catalytic growth of unmodified Au NPs has been successfully employed for detection of DNA hybridization at pmol/L concentration via a conductive bridge mediated gap-electrical signal transduction. Assembly of different diameter of Au NPs or layer-by-layer assembly of Au NPs of the same diameter also showed enhanced overall DNA sensor performance [14]. Employing Au NPs of two diameters, i.e., 20 and 5 nm, Wang et al. [15], designed and assembled a super-lattice on a glassy carbon electrode. Compared with random packed nanoparticles, the Au NP super-lattice ($CaCu_5$- and NaCl-type) showed a higher surface area and excellent conductivity for signal amplification via greatly increased electron transfer.

To further assist nucleic acid isothermal amplification strategies, more efficient signal-amplified detection could be achieved by a cascade signal amplification platform through specific nuclease-assisted target recycling. For example, Yu et al. [16] recently designed catalytic hairpin assembly (CHA) reaction assistant Au NP network architecture on an electrode for signal-on electrochemical detection of microRNA-141 (Fig. 1). The target recycling process driven by DSN resulted in highly amplified translation of target miRNA to single-stranded connector DNA fragments. The CHA reaction is further initiated by connector DNAs using hairpin-modified gold

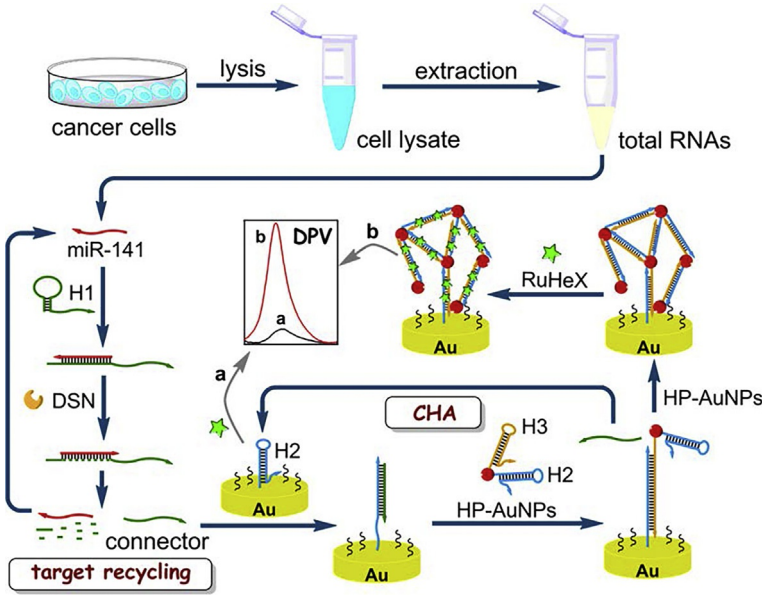

Fig. 1 Schematic illustration of cascade amplification of DSN-assisted target recycling and CHA reaction. *Reprinted with permission S. Yu, Y. Wang, L.P. Jiang, S. Bi, J.J. Zhu, Cascade amplification-mediated in situ hot-spot assembly for microRNA detection and molecular logic gate operations, Anal. Chem. 90 (2018) 4544–4551.*

nanoparticles (HP-AuNPs) as the sensing unit. This approach enabled electrochemical detection to 25.1 amol/L miRNA-141. Another example employing hairpin assembly target recycling strategy for cascade electrocatalysis of micro RNA was demonstrated by Yuan et al. [17]. In this report, target recycling was achieved via a nuclease-free strand displacement process. The novel porous graphene oxide/Au composites showed much improved specific surface area, excellent electrical conductivity and unique biocompatibility providing detection of miRNA-155 from 0.8 fmol/L to 1.0 nmol/L with a lower detection limit of 0.35 fmol/L. Using well-designed bridge DNA-AuNPs, the aggregation of three Au NPs could be accurately controlled by DNA sequence. Thus a triple signal amplification strategy in combination with DSN cleavage cycles could be obtained thus providing miRNA detection of ultrahigh sensitivity [18]. Au NPs could be modified on the surface of electrode via electrochemical deposition by immersing the gold electrode in $HAuCl_4$ solution containing 0.1 mol/L KNO_3. Subsequent cyclic enzymatic amplification strategy on the modified electrode resulted in ultrasensitive electrochemical DNA or miRNA detection [19].

The ability to detect DNA/RNA is closely associated with the interfacial structure or micro-environment of a biosensor, i.e., characteristics that profoundly affect interfacial efficient area, thermodynamics and kinetics of the assembly, binding and signal transduction of biomolecules. For example, gold nanostructures of various shapes show different biosensing properties. Recently, Fan et al. [20], demonstrated this phenomenon using shape-controlled gold nanostructures on indium tin oxide substrates. These hierarchical flower-like gold nanostructures possessed a large surface area that readily accommodated the assembly of DNA probes for subsequent detection of nucleic acid by electrochemical hybridization. Differently shaped gold nanostructures combined with graphene or other 2D material, such as graphene oxide@gold nanorod (Au NRs) [21], gold nanocages (Au NCs) @graphene nanoribbons [22] and Au NPs functionalized MoS_2 nanosheets [23] were reported to have large surface area with high sensing conductivity and excellent biocompatibility, chemical stability and fast electron transfer ability. For example, Dey et al. [14], designed a three-dimensional (3D) alternately-layered nanoarchitecture through layer-by-layer assembly of Au NPs and reduced graphene oxide on the surface of a glassy carbon electrode. Using this approach, they achieved label-free ultrasensitive electrochemical impedance sensing of DNA hybridization of wide range and a lower detection limit of 3.9×10^{-14} g/mL.

In addition to commonly used Au NPs, other metal nanoparticles or metal nanoclusters (MNCs) have been widely reported. For example, Crook et al. [24], developed ssDNA modified platinum (Pt) NPs through a linker consisting of a thiol group and a short alkyl chain for complementary target micro RNA-203 detection. Because the ssDNA modified on Au NP−DNA probes was complementary to the miRNA target, DSN could selectively cleave dsDNA whereas DNA in DNA:RNA duplexes was employed to cleave the ssDNA:miRNA conjugate. The digestion process resulted in significant collision signals produced by the Au NP-DNA conjugates before and after hybridization with target miRNA. Ultra-microelectrode measurement of current vs time (i − t) transients demonstrated a robust and simple strategy for RNA detection which could also be adapted to other molecules. Metal nanoclusters (MNCs), consisting of several or dozens of metal atoms approximately 2 nm diameter, have also been reported [25]. These unique structures have been shown to possess high surface atom activity, excellent conductivity and quantum effect. A common MNC is Ag NCs has been widely used in the detection of various small molecules [26] and DNA/RNA [27,28] following reports by Dickson et al. [29], using a

DNA-templated synthesis method in 2004. Similar to Ag NPs, Ag NCs could also be employed as electrochemical tags for amplified detection [30–32]. For example, Yuan et al. [33], designed an in situ growth strategy of Ag NCs on electrodes combined with a target-assisted polymerization nicking reaction and hybridization chain reaction for sub-femtomolar microRNA-199a detection. Using a similar hybridization chain reaction for signal amplification, Wang et al. [34], prepared copper (Cu) nanoclusters (Cu NCs) in situ. This approach was supplemented with exonuclease T7 triggered target recycling for ultrasensitive electrochemical detection of microRNA-21 to 10 amol/L [34]. A comparison of different nanoparticle based electrochemical sensing assays is shown (Table 1). As can be expected, these nanoparticle electrochemical biosensing approaches showed different DNA/RNA detection limits. Generally, the sensitivity of a biosensing assay was related not only to the inherent nanoparticle properties but also to the protocols integrated with other amplification techniques, i.e., isothermal nucleic acid recycling reaction. Moreover, the construction process of sensing interfaces and modification environment also greatly influence detection limit.

2.2 Metallic nanoparticle electrochemiluminescence (ECL) assays

Electrochemiluminescence (ECL) is produced by electrochemical oxidation or reduction [35,36]. This approach integrates the advantages of electrochemistry and spectroscopy thus improving sensitivity and specificity. For example, the absence of a light source greatly reduces background signals from scattered light and luminescent impurities. Furthermore, high specificity was an additional benefit due to the adjustable excited states and corresponding co-reactant. Years of development has resulted in ECL technology possessing high stability as well as satisfactory sensitivity and specificity.

By employing ECL-active molecules as signal tags, ECL became a powerful analytical method for biomolecular detection. Although luminol has become one of the most important ECL reagents because of a high light efficiency, it has weak signal and poor solubility in neutral aqueous solution [37,38]. Because of this limitation, Xu et al. [39,40], developed luminol-functionalized Au NPs and Pt NPs. This approach greatly enhanced ECL intensity due to the relatively larger specific surface area as well as improved nanoparticle catalytic activity. Using luminol-functionalized Au NPs, Lu et al. [41], developed a "dual-potential" ratiometric ECL sensing method

Table 1 Comparison of nanoparticle based electrochemical nanobiosensors for DNA/RNA detection.

Target	Applied nanomaterial	Electrochemical method	Linear range	Detection Limit	References
DNA	Au NP/rGO/Au NP	CV and EIS	10^{-9}–10^{-13} g mL^{-1}	39 fg mL^{-1}	[14]
MiR-21	Au NPs superlattices	DPV	100 aM–1 nM	78 aM	[15]
miRNA-155	GO/Au NPs and p-TiO2@PtNPs	DPV	0.8 fM–1 nM	0.35 fM	[17]
MiR-21	Bridge DNA-Au NPs	CC	10 aM–10 pM	6.8 aM	[18]
MiR-21	Au NPs	DPV	1 fM – 100 pM	0.36 fM	[19]
MiR-21	Flower-like Au nanostructures	SWV	0.1 fM–100 fM	0.1 fM	[20]
MiR-155	GO/Au NRs	DPV	2 fM–8 pM	0.6 fM	[21]
DNA	Au nanocages@graphene	DPV	1 fM–100 pM	600 aM	[22]
MiR-21	Thionines/AuNPs/MoS_2	SWV	1 pM–10 nM	0.26 pM	[23]
DNA	Ag NCs	DPV	0.2 fM–1 pM	0.16 fM	[32]
MiR-21	Cu NCs	DPSV	10 pM–0.1 fM	10 aM	[34]

through fabrication of target DNA and Hemin/Au-Luminol NPs on Thioglycolic acid (TGA)/CdSe/ZnS QDs/MWNTs modified GCE. Due to the enhancing effect of luminol and the quenching effect of CdSe/ZnS by G-quadruplex/hemin, DNA detection to fmol/L concentration was achieved. The "dual-potential" ratiometric approach also minimized any false positive signal. In combination with nucleic acid amplification, ECL has attracted intense attention and has led to more simple and sensitive biomolecule analysis. In addition, novel sensor interfaces have been developed in combination with ECL and nucleic acid isothermal amplification. In this strategy, ECL signal was induced by hybridization between DNA modified on ECL materials and DNA modified on the electrode. The signal could be further enhanced by nucleic acid isothermal amplification, i.e., strand displacement amplification (SDA), DNAzyme-mediated DNA hydrolysis, nicking enzymes and nuclease assistant cyclic enzyme amplification and target-catalyzed hairpin assembly. Previously, Xu et al. [42], explored a ratiometric ECL biosensing method for microRNA at fmol/L concentration by combining cyclic enzyme amplification and distance dependent resonance energy transfer between Au NPs, luminol-Au NPs and CdS semiconductor nanocrystals. In this report, duplex-specific nuclease (DSN) was employed to realize target recycling amplification which showed selective cleaving to dsDNA or DNA in DNA-RNA heteroduplexes and no effect to ssDNA or ss (ds) RNA. Using the DSN and Au NP approach, they recently proposed a nanopore-based ECL sensor based on an anodized aluminum oxide (AAO) nanopore electrode with luminol anion as probes for detecting target miRNA-107 [43]. The DNA-Au NP-modified AAO electrode exhibited a strong repulsion effect for the negatively charged luminol anion probe due to the electrostatic repulsion and volume exclusion effect (Fig. 2). However, the presence of a small amount of miRNA can bring about the removal of a mass of DNA-Au NPs after target recycling amplification. As such, a lower detection limit of 1 fmol/L miRNA could be obtained. The use of nuclease assistant cyclic enzyme amplification led to the development of a DNA walking machine as a target-recycling amplification strategy. This approach has attracted much attention due to its ability to transform external stimuli such as energy-first DNA strands hybridization or the existence of ions to cargoes transit and detection signal. Yuan et al. [44], reported an ultrasensitive ECL biosensing strategy for microRNA detection based on the 3D DNA walking machine and distance-controlled signal quenching and enhanced CdS:Mn QDs and Au NPs. This work demonstrated that is was possible

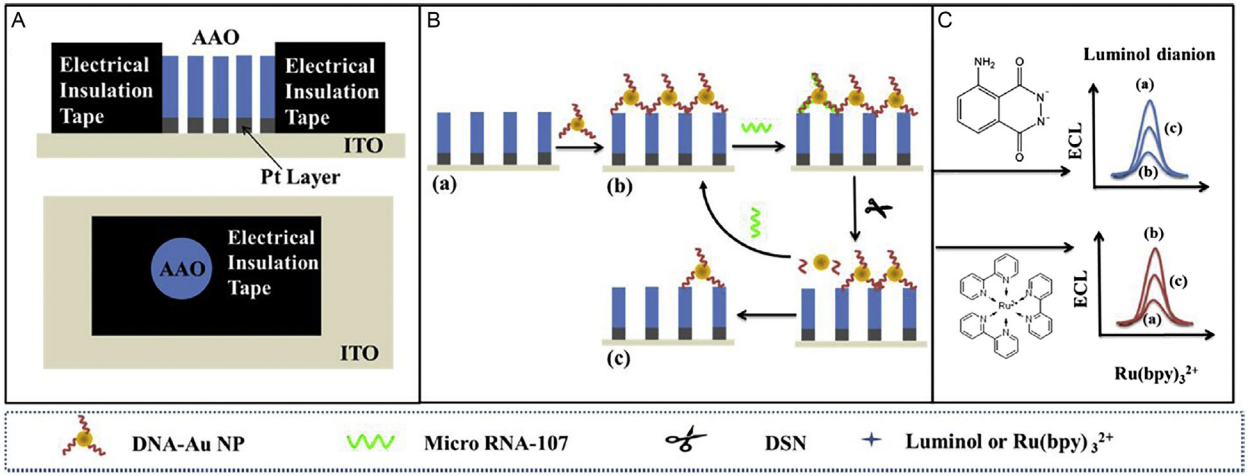

Fig. 2 Schematic illustration of (A) Construction of nanopore-based electrode, (B) Preparation of nanopore-based ECL platform, and (C) ECL detection using luminol or $Ru(bpy)_3^{2+}$. *Reprinted with permission X.L. Huo, H. Yang, W. Zhao, J.-J. Xu, H.-Y. Chen, Nanopore-based electrochemiluminescence for detection of microRNAs via duplex-specific nuclease-assisted target recycling, ACS Appl. Mater. Interfaces 9 (2017) 33360–33367.*

to apply the 3D walker in combination with ECL for effective microRNA and DNA analysis. Recently, Kuang et al. [45] reported another ECL biosensor also based on smart DNA walker on Au NPs modified electrode for signal amplification. The nicking endonuclease powered movement of DNA walker could cleave multiple QDs probes on the electrode, thus resulting in significantly amplified ECL signal changes.

Combination of Au NPs with other 2D or 3D nanomaterials may enhance ECL biosensing performance by maximizing nanomaterial properties via complementary approaches. Many carbon nanomaterials, i.e., graphene oxide (GO), carbon nanohorns and graphite-like carbon nitride nanosheet, have been used as efficient carriers [46]. Because of their large surface area, excellent conductivity and ability to adsorb biomolecules, they have greatly improved the intensity and biocompatibility of ECL biosensors. For example, a target recycling SDA and co-reactant tris(2-aminoethyl) amine (TAEA)-based ECL system was developed by Zhuo et al. [47]. This approach was successfully used via a DNA/Au NPs/Ru(II) complex-TAEA@GO composite modified GCE to obtain a stable and sensitive self-enhanced ECL biosensing method for miRNA21. Further studies reported that Au NPs could be in situ decorated on surface of GO by the reduction of Au (III) complex with sodium citrate in GO solution to form a GO/Au nanocomposite. This material showed improved performance for constructing a more sensitive and selective ECL biosensor for DNA/RNA. Mao et al. [48] immobilized hairpin DNA probe on GO/Au composite modified electrode surface for electric transmission and then obtained greatly enhanced initial ECL intensity through nicking enzymes Nb.BbvCI mediated signal amplification. Another study employed Au NPs functionalized reduced graphene oxide (Au-rGO) as nanocarriers with self-enhanced ruthenium complex (PEI-Ru(II)) and hairpin DNA sequentially anchored on nanocomposite surface as signal probes [49]. By coupling intramolecular co-reaction amplification of PEI-Ru(II) and intermolecular co-reaction amplification of thiosemicarbazide toward the PEI-Ru(II) complex, high ECL intensity could be achieved with sub-femtomolar miR-21 detection and a linear response about six orders of magnitude.

Some interesting interactions have been noted between metal nanoparticles and semiconductor nanocrystals due to surface plasmon resonance (SPR) of metal nanoparticles and the enhanced or suppressed ECL response of nanocrystals by the induced SPR. For example, ECL-resonance energy transfer (RET) between CdS:Mn nanocrystals (NCs) and Au NPs within short distances was first discovered by Xu et al. in 2009 [50].

Subsequent work using RET has been reported to greatly improve ECL biosensing platforms. In fact, RET combined with Au NPs and nanocrystals has become one of most powerful tools for ECL biosensor construction [51–55]. When designing a RET based ECL system, dual independent emissions of two ECL emitters should be integrated with spectral overlap between donor ECL spectrum and acceptor absorption spectrum. In addition to Au NPs, subsequent studies found that Ag NCs were good candidates as the energy acceptor of nanocrystals with an absorption peak of 492 nm in the ultraviolet-visible range, i.e., overlapped absorption and emission spectrum [56]. Moreover, such nanoclusters with sizes about or below 2 nm diameter showed size-dependent discrete energy levels. This finding suggests unique "molecular" properties possibly providing enhanced performance for smart ECL biosensors. Xu et al. [57] prepared oligonucleotide encapsulated Ag NCs and demonstrated that these could quench ECL emissions from CdS NCs via ECL RET and rapid catalysis of ECL co-reactant $K_2S_2O_8$ thereby providing sensitive miRNA detection. Subsequently, Yuan et al. [58] introduced target-cycling synchronized rolling circle amplification (RCA) for ultrasensitive detection of miR-21down to 22 amol/L [58].

2.3 Metallic nanoparticle photoelectrochemistry (PEC) assays

The photoelectrochemistry (PEC) process is characterized as light-electrochemistry interaction under an applied light which generates electron excitation following charge transfer from photoexcited material. It is noteworthy that the PEC process is the reverse of ECL, i.e., photocurrent excitation and light as the detection signal [59]. Unlike ECL, PEC-active material was only modified directly on the electrode interface or by DNA hybridization to produce electrical signal. The newly emerged technology is of special interest for its potential in biologic analysis. It has inherently low background signal and improved sensitivity due to complete separation of the excitation source and detection signal in contrast to traditional optical and electrochemical methods. Similar to ECL, various metal nanomaterials, including Au NPs, Au NPs based composite, iridium complex, Pt NPs, and Ag NCs have shown potential as versatile PEC biosensors due to their unique plasmonics and physicochemical properties. For example, it has been reported that Ag NCs demonstrate efficient quenching to nearby CdS QDs through energy transfer between NCs and QDs in PEC biosensors. Using this approach, DNA detection could be achieved with a linear range from 1.0 pmol/L to 10 nmol/L having a detection limit

of 0.3 pmol/L [60]. Efficient photocurrent quenching through energy transfer is one type of exciton-plasmon interaction (EPI) between noble metal NPs and QDs [61]. In fact, recent studies investigating this phenomenon have proven promising for EPI in biosensing [62]. In one report, Cao et al. [62] evaluated the use of EPI with CdS@g-C_3N_4 nanowires and Au@Ag NPs coupled to DNAase-triggered signal amplification. As a photoelectrode, the CdS@g-C_3N_4 heterojunction electrode matrix could generate photocurrent. The natural absorption overlap between the exciton of CdS@g-C3N4 and the plasmon of Au@Ag NPs resulted in greatly decreased PEC intensity. Subsequent work from Dai et al. [63] reported an RET process between ZnSe-COOH nanoflakes (NFs) and Au NPs due to the overlapped spectrum between UV−visible spectrum of Au NPs and emission spectrum of ZnSe-COOH NFs (Fig. 3). RET greatly improved photoelectric conversion efficiency of ZnSe-COOH NFs resulting in significantly amplified PEC signal for target microRNA-122a. Despite the enormous advances in PET biosensing and use in nucleic acid detection, there remain technologic issues including high background, low

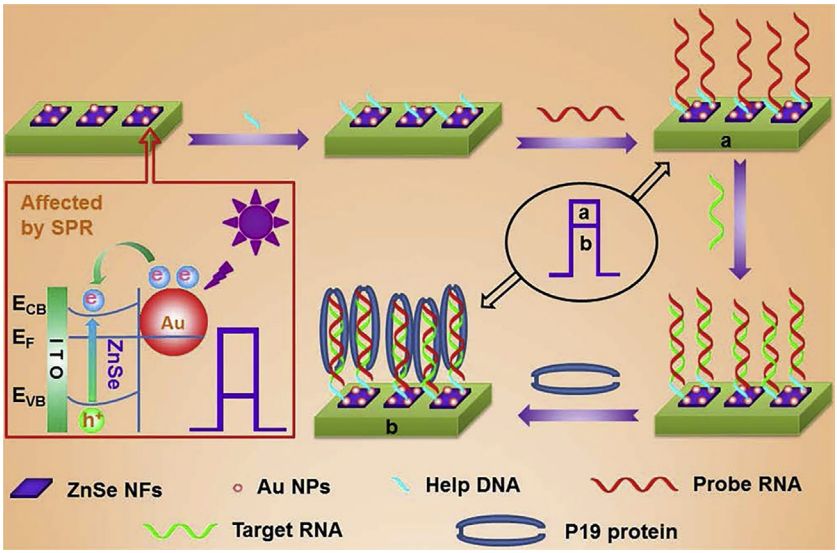

Fig. 3 Schematic illustration of the PEC biosensing platform based on SPR of Au NPs enhanced RET and remarkable steric hindrance of p19 protein as dual signal amplification. *Reprinted with permission W. Tu, H. Cao, L. Zhang, J. Bao, X. Liu, Z. Dai, Dual Signal Amplification using gold nanoparticles-enhanced zinc selenide nanoflakes and P19 Protein for ultrasensitive photoelectrochemical biosensing of microRNA in cell, Anal. Chem. 88 (2016) 10459–10465.*

sensitivity and poor detection limit. To mitigate these limitations, much research has focused on the design of advanced photoelectric materials with excellent PEC performance as well as the use of nucleic acid assistant cascade amplification strategies [64–66]. The PEC biosensor provided highly sensitive microRNA-21 detection at sub-femtomolar concentration (0.05 fmol/L) with DSN mediated target recycling amplification [67]. Recent work from Tang et al. [68], demonstrated an advanced photoelectric material defect-engineered TiO_{2-x} nanobars ($dTiO_{2-x}$) with improved visible light photoelectric response for sensitive PEC biosensing with ultralow background. Combined with exonuclease III-assisted target recycling amplification, the target-induced plasmonic enhancement PEC biosensing platform demonstrated excellent DNA detection under visible light irradiation and low background. Tang et al. [69] synthesized an Ir(III) complex as an intercalated reporter combined with PEC sensing for DNA detection at femtomolar concentration using hybridization chain reaction amplification. Recently, Chen et al. [70] reported on PEC nanomaterial semiconducting polymer dots (Pdots) as a novel strategy for PEC bioanalysis due to its excellent light-harvesting characteristics. In addition, they found that the cathodic photocurrent of Pdots was reduced when Au NPs were in proximity to Pdots. Advanced functional materials such as PEC nanomaterials with efficient quenching and/or enhancement phenomenon have been key in the evolution of DNA/RNA detection technology.

2.4 Metallic nanoparticle fluorescence assays

Due to its inherent advantages, fluorescence has been widely applied to the detection of biomolecules. Recently, fluorescence detection methods have been integrated with noble metal nanomaterials and various isothermal amplification reactions for constructing a series of analysis interfaces and fabricating novel analysis strategies. Together, these have combined to achieve sensitive and selective detection of biomolecules including tumor markers.

Noble metal nanoclusters have attracted much attention in the development of efficient fluorescence biosensors. For example, nucleic acid-stabilized Ag NCs (DNA-Ag NCs), due to their fluorescence intensity, have become a fluorophore of choice in many studies [71]. Furthermore, DNA provided an ideal scaffold for the synthesis of Ag NCs resulting in good water solubility, excellent biocompatibility and relatively low toxicity. Moreover, the fluorescence properties of this nanomaterial could be adjusted by changing the length, sequence and structure of DNA template to obtain a

satisfactory probe [72–74]. Subsequently, Zhu et al. [75] designed a versatile DNA molecular beacon structure for parallel detection of two target genes (Influenza A virus genes H1N1 and H5N1). Using two DNA-Ag NCs containing different DNA structures, this approach demonstrated fluorescence response at two wavelengths (520 and 600 nm). Yeh et al. [76,77] demonstrated that DNA-Ag NCs nucleated by a cytosine (C)-rich sequence showed greatly enhanced fluorescence (500-fold) upon hybridization to a G-rich overhang strand. This G-rich fluorescence enhancement was subsequently combined with SDA amplification by Cui et al. [78], as a light-up fluorescence method for rapid detection of miR-16-5p and miR-19b-3p. In addition to SDA, other DNA recycling amplification strategies could be successfully introduced in this AgNC-based fluorescence sensing system for bioanalysis, i.e., nucleases [26], DNAzymes assistant target recycling and dynamic DNA self-assembly signal-amplification [79]. Chameleon Ag NC showed a structure-dependent orange-to-green fluorescence transformation thus providing a potentially new approach for ratiometric target detection. To mitigate labor-intensive and time-consuming preparation during target-induced variation of DNA templates, Dong et al. [80] designed a simple but powerful chameleon DNA-Ag NC showing dramatic color variations upon DNA hybridization with nonfluorescent assistant Ag NC or Mg^{2+}. Using different Ag NC based fluorescent probes, a ratiometric biosensing method was demonstrated at nanomolar HIV and HBV due to exponential signal response. In addition, dsDNA-template copper (Cu) NPs also showed great promise for quantitative DNA/RNA detection when combined with DNA amplification including hybridization chain reaction (HCR) [81], DSN assistant target recycling [82] and enzymatically engineered primer extension poly-thymine [83]. A problem in nucleic acid biosensing is difficulty in obtaining quantitative results for intracellular RNA. This is generally due to the presence of multiple RNAs of similar sequences, as well as, their relatively small size, low abundance and vulnerability to degradation. Recently, fluorescence microscopy-based molecular imaging techniques with high resolution, excellent selectivity and noninvasive capability have provided powerful approaches for in situ intracellular DNA/RNA visualization. Among these, Au NPs and functionalized Au NPs have been used to detect low expression DNA/RNA. This approach has benefited from improved cellular transfection, high DNA loading of Au NPs and fluorescence RET with other nanomaterials. Since the first example of Au NPs based nanoflares reported by Mirkin et al. in 2007 [84], the usefulness of nucleic acid-Au NPs for RNA detection in living cells has been

widely reported [85–88]. Subsequent studies demonstrated the application of smart DNA tracks and DNA walking strategies powered by DNA assistant events including DNA hybridization, hydrolysis and conformational transition. In addition, others have examined the principles of DNA motors in vitro and in vivo for DNA walking or biosensing [89–91]. For example, a target miRNA induced hybridization reaction generated unlocked DNAzyme strand via strand displacement reaction as shown (Fig. 4). The unlocked DNAzyme strand could subsequently hybridize with its substrate. In the presence of cofactor Mn^{2+}, DNAzyme was active and cleaved its substrate strand, generating two DNA segments (F1 and F2). FAM modified on

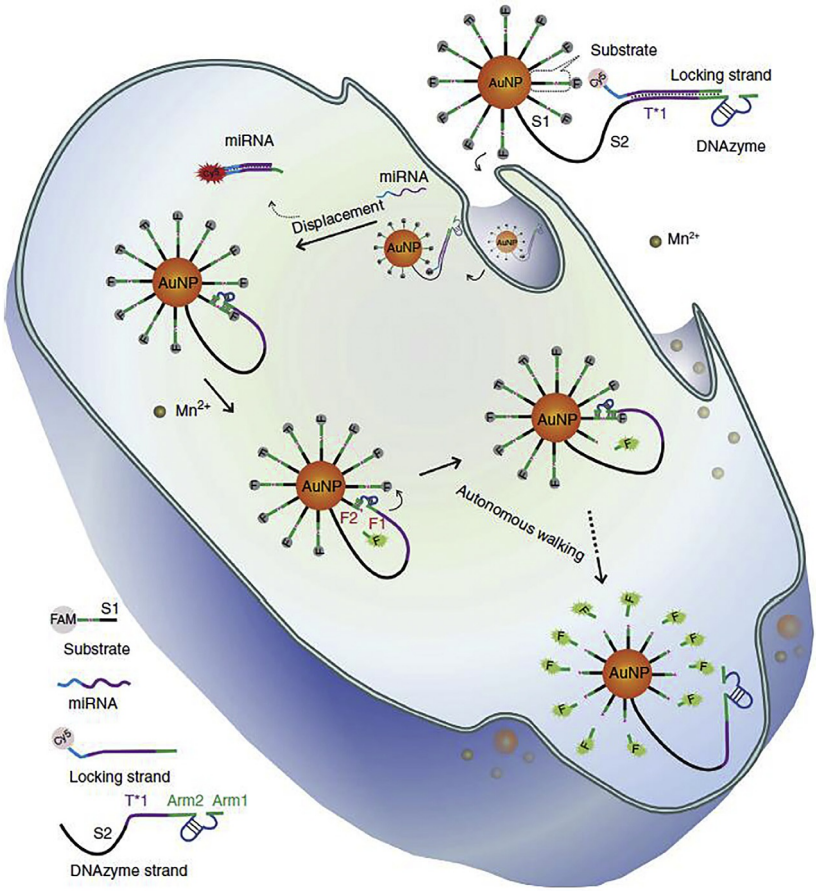

Fig. 4 Intracellular operation of a DNAzyme motor initiated by a specific miRNA. *Reprinted with permission H. Peng, X.F. Li, H. Zhang, X.C. Le, A microRNA-initiated DNAzyme motor operating in living cells, Nat. Commun. 8 (2017) 14378.*

the F1 segment demonstrated its recovered fluorescence due its relative distance from the Au NP surface. Furthermore, the separated DNAzyme from F2 could subsequently react circularly with substrate strands, thus obtaining a greatly enhanced fluorescent signal intracellularly. This DNAzyme motor system on Au NP provided real-time imaging of miRNA induced motor operation [89]. Wang et al. constructed efficient and versatile DNA-Au NP probes for accurate and amplified low-abundance miRNA imaging inside cells employing hairpin-locked-DNAzyme strand [92], hairpin-fueled catalytic nano beacons and fluorescence RET (FRET) nanoflares [93]. Subsequent work to address the complicated preparation and unsatisfactory sensitivity resulted in the development of an Au NP loaded split-DNAzyme probe for miRNA-21 at physiologic magnesium [94]. Ye et al. [95] further engineered a smart DNA-AuNP conjugate assistant entropy-driven DNA nanomachine for intracellular miRNA imaging in the absence of a DNA tool enzyme. This nanomachine was driven by the negative free energy change of base pair formation and thus did not need HCR or CHA support. This novel approach resulted in good stability, low immunogenicity and high signal-to-noise ratio. Toehold DNA was employed to achieve smart hybridization using a displacement reaction similar to automatic DNA walking, i.e., a non-enzymatic catalytic substrate disassembly. By employing toehold DNA mediated SDR, Xiang et al. [96] developed a DNA-fueled target recycling signal amplification approach for monitoring under-expressed miRNA in living cells. These dsDNA-Au NP nanoprobes showed good nuclease stability, low cytotoxicity, reduced background noise and high sensitivity.

In contrast to single RNA detection, simultaneous monitoring of multiple RNA targets could provide a more comprehensive and accurate assessment of disease state especially in early stage cancer. As such, many multiplexed or multicolor DNA-Au NPs have been designed for detection and/or imaging of tumor-related intracellular mRNAs [97–99]. Tang et al. [100] recently demonstrated the use of Fluorescence-Raman dual-signal switchable DNA-Au NPs nanoprobe for intracellular imaging and detection of miR-21 and miR-203 in living MCF-7 cells. By combining the advantages of fluorescence with SERS this approach provided a new detection platform. The use of smart DNA probes built on spherical Au NPs further improved the mobility and processivity of the DNA motors. Accordingly, the performance of DNA probes immobilized on Au NP of various shapes and other metal nanomaterials have been studied. For example, Sun et al. [101] examined the use of oriented gold nanocross (AuNC)-decorated gold

nanorod (AuNR) nanoconjugates. This study resulted in the development of an OFF-enhanced ON fluorescence switching sensing strategy via FRET for in vitro detection and intracellular tracking of miRNA-34a from the HepG2 and H9C2 cells stimulated by AFB1 and TGF-β1. Fluorescent sensing strategies using Au NP based nanocomposites or Au NPs with other nanoparticles has gradually come into use [102]. For example, Kelley et al. [103] developed a programmable metal/semiconductor nanostructure composed of a central core gold nanoparticle surrounded by a layer of DNA-capped quantum dots for mRNA-modulated molecular delivery. This "core-satellite" composite provided an efficient superstructure to specifically bind mRNA encoding MRP1, an important drug resistance factor, inside cancer cells and release of doxorubicin, an anticancer drug. Recently, Zhu et al. [104] introduced up-conversion material (UCNPs) into DNA-Au NPs and provided a platform for the sensitive detection of tumor-related ncRNA (HOTAIR segment, miR-21) assisted by Exo III-mediated cycling amplification strategy. The work takes advantage of both DNA-Au NPs conjunction and UCNPs thus showing minimal background fluorescence, low photodamage and high photostability.

DNA-nanomaterial conjunctions based nanomachines or nanoflares greatly accelerate the rates from the intra- and inter-molecular reaction. This approach leads to high local effective concentration and stable signal outputs due to the controlled hybridization or release of DNA substrates, as well as excellent stability, biocompatibility and adjustable optical properties. Despite the achievements in metal nanoparticle based fluorescence biosensing, more studies on enzyme-free smart amplification and the use of other metal nanoparticles are clearly required to explore this new technology.

2.5 Metallic nanoparticle SERS assays

In biologic systems, SERS is a superior approach because of its ability to provide significantly improved signal intensity [105]. To achieve ultrasensitive detection of cancer biomarkers, a novel SERS biosensing interface was introduced. Nanoparticles for label-free Raman based techniques were constructed to eliminate the complexity associated with preparation and attachment of appropriate Raman labels. Ag NPs grown along the DNA skeleton induced sufficient interaction between the bases and the substrate to yield a sensitive Raman signal and were successfully used for label-free SERS detection of DNA at picomolar concentration [106,107]. Although Raman

spectroscopy of Ag NPs has above unique advantages [108], further development of SERS-active nanoparticles, metal nanoparticle based nanocomposites or nanoconjunctions and oligonucleotide modified nanoparticles have stimulated broad interest in DNA/RNA detection due to their improved SERS effect [109,110]. One promising nanocomposite is Au-Ag nanocomposite having a stable SERS signal and much broader wavelengths as a SERS nanoprobe [111]. For example, Song et al. [112] developed a DNA-mediated multicolor Au@Ag nanomushroom structure with interior nanogaps and employed it as ready-to-use SERS nanoprobes for multiplex and ultrasensitive SERS detection of various DNA/RNA targets. Recently, Li et al. [113] synthesized Raman dyes modified Au@Ag nanosnowmen structure grown via a DNA-mediated approach as bimetallic SERS nanoprobe for ultrasensitive detection of three prostate carcinoma-related genes at femtomolar concentration. Another example was reported by Yang et al. [114]. As shown (Fig. 5), Cu NPs in situ grown on the surface of SWNTs improved the SERS effect due to the electromagnetic enhancement effect associated with the large local E field between Cu NPs and SWNTs. They also found this CuNP-enhanced SERS effect of SWNTs was dependent on the amount of T-rich ssDNA, thus providing an efficient biosensing method for target circulating tumor DNA (ctDNA). Recent work from Halas et al. [115] reported that aluminum

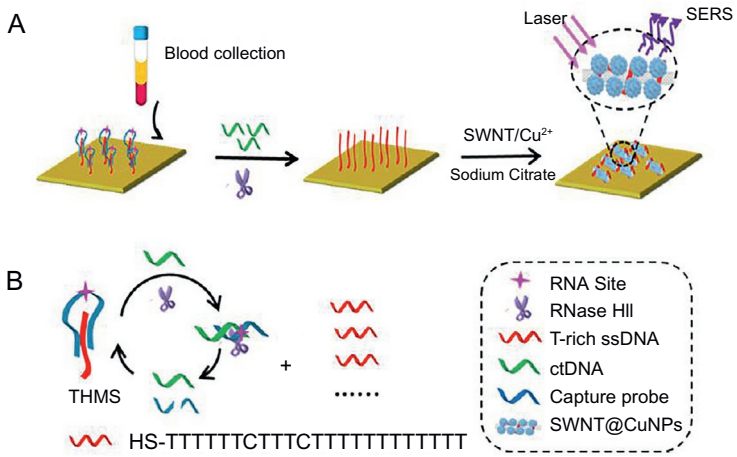

Fig. 5 Construction of SWNT-based SERS assay coupling with RNase HII-assisted amplification for highly sensitive detection of ctDNA in human blood. *Reprinted with permission Q. Zhou, J. Zheng, Z. Qing, M. Zheng, J. Yang, S. Yang, L. Ying, R. Yang, Detection of circulating tumor DNA in human Blood via DNA-mediated surface-enhanced Raman spectroscopy of single-walled carbon nanotubes, Anal. Chem. 88 (2016) 4759–4765.*

(Al) nanocrystal aggregates showed substantial near-infrared SERS enhancement as an inexpensive, highly abundant and sustainable devise for SERS resulting in label-free ssDNA detection with no pre-modification. The performance Al NC aggregates opened the possibility for non-noble SERS substrates having many of the same advantages such as low-cost, ease of disposal and potential to recyle.

Although metal nanoparticle based SERS technology is characterized by high sensitivity, additional signal enhancement remains necessary for trace DNA/RNA. This includes rolling-circle DNA polymerization [116,117], ion-mediated cascade amplification [118], DNA tool enzyme based exponential amplification reaction [119], and DSN assistant target-responsive DNA hydrogels [120]. Despite these approaches to enhance SERS biosensing, more studies are clearly needed to explore the interaction between DNA configuration and distinctive shaped nanoparticles as well as development of a smart SERS platform employing DNA-metal nanostructures for molecular recognition and biosensing. The SERS-active nanostructure performance is generally influenced by nanoparticle geometry, type of material or composite and interparticle distance. Au NP dimers, multibranched Au nanoflowers and Au nanostars [121–123] appear applicable for SERS biosensing at single-molecule level [124,125] and cell imaging [126]. This is due, in large part, to the relatively large surface area and unique optical and physical properties of these nanostructures. Although promising, it is clear that additional work is needed to more fully assess the application of SERS technology for detection and intracellular imaging of DNA/RNA.

2.6 Metallic nanoparticle plasmon assays

When excited by electromagnetic radiation, plasmonic nanomaterials (e.g., Au NPs or Ag NPs) can confine and manipulate photons at the nanoscale by the collective oscillation of conduction electrons, i.e., localized surface plasmon resonance (LSPR) [127]. Importantly, the absorbance (color) of the nanoparticle is easily modulated by their shape/morphology, size, distribution, composition, as well as the surrounding environment. When in close proximity, there exists strong interparticle plasmon coupling and an associated perturbation in the LSPR band of the ensemble, leading to a red-shift in the absorbance peak. Capitalizing on this feature, many noble metal nanoparticle-based colorimetric or other plasmonic-based sensors have been developed for detecting nucleic acid [128].

Using SPR properties of noble metal nanoparticles, DNA/RNA induced molecular recognition events could be transformed into color change snf thus be observed by simple colorimetric assay. AuNPs based colorimetric assays via target-induced aggregation have been used for DNA/RNA detection due to their ease of synthesis and surface modification, tunable optical properties, strong photostability [129–132]. Some have been combined with DNA nuclease or DNAzymes assisted signal amplification to improve sensitivity. To enable point-of-care (POC) testing, a simple paper-based colorimetric assay using AuNP-DNA conjugates or peroxidase-mimicking DNAzyme structure has been constructed for microRNA detection [133].

Despite the simplicity of noble metal nanoparticle colorimetry, this technology was limited by relatively poor sensitivity and susceptibility to environmental influence, i.e., temperature, pH and salt concentration. As such, other plasmonic-based sensing technologies such as dark-field light scattering imaging has received considerable interest. This approach that monitors biological events related SPR scattering change via dark-field microscope (DFM). Following this model, biosensing platforms using SPR responses of Au NP based nanoparticles or nanocomposites were designed and found to detect DNA/RNA at the single molecule level [134,135]. Due to the existence of hot spots in a single plasmonic assembly, a multitude of nanoassembled AuNP, such as dimers or trimers, Janus NPs, nano-oscillators [136], core–satellite constructs [137], or network [138] have been evaluated as optical sensing nanostructures. For example, Xu et al. [139] used Au NP based core-satellite plasmon rulers and explored the dynamic process of toehold-mediated strand displacement. Target microRNA-21 (in vitro or in living cells) induced strand displacement accompanied by blue shift of scattering wavelength. Subsequently, Chen et al. [140] designed Au NP dimers triggered by Y-shaped DNA duplex provided ultrasensitive DNA colorimetric detection under DFM. In comparison to traditional colorimetric sensors, this strategy exhibited significantly increased sensitivity, i.e., 5–9 orders of magnitude. Nam et al. [141] sought to improve Au NP dimer performance to maximize detection signals and minimize nonspecific signals. This study led to the development of associating and dissociating nanodimer analysis for ultra-low DNA targets on a lipid micropattern.

Besides DMF, other plasmonic-based nanosensor via monitoring extinction intensity or the peak shift of the plasmonic coupling resonance band arising from the probe-target DNA binding event have been designed.

For example, Long et al. [142] combined DFM and Rayleigh scattering spectroscopy for the dual-channel detection of tumor-related TK1 mRNA in living cells. As shown (Fig. 6), the scattering spectrum of Au NP was quenched when assembled with probe DNA and dye-labeled nanoflares. In the presence of target mRNA, the specific binding between probe DNA and target led to the release of the dye-labeled nanoflares thus resulting in recovery of the scattering intensity. Recently, Zhu et al. [136], reported a light-driven nano-oscillator with a subnanoscale gap distance for single-molecule miRNA detection. The nano-oscillator consisted of mechanoresponsive polymeric poly(*N*-isopropylacrylamide) modified on an Au-coated glass slide and Au NPs deposited by van der Waals force. The complementary DNA strand was immobilized in the gap between the Au NP and the Au surface. Single-molecule miRNA monitoring was achieved via oscillation (scattering amplitude of Au NP) from the rigid dual-strand structure formed from hybridization of immobilized DNA and target miRNA.

Plasmonic sensors have shown wide potential applications for oligonucleotide screening at single-molecule and subnanoscale level. Further development of smart strategies based on DNA-noble SPR technology are expected to provide additional tools for single-molecule detection of DNA/RNA, other small molecules and proteins in vitro and in vivo.

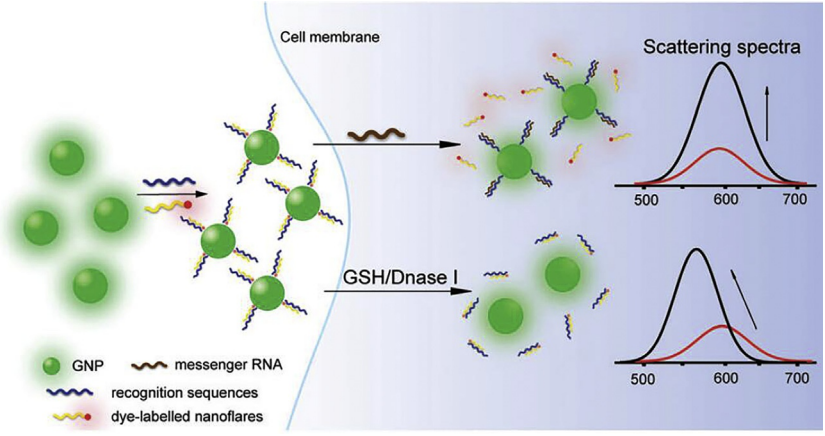

Fig. 6 Schematic illustration of the interaction between PRET-based nanosensors and intracellular mRNA. *Reprinted with permission T. Xie, M. Li, Y.T. Long, Dual-channel signals for intracellular mRNA detection via a PRET nanosensor, Chem. Commun. 53 (2017) 7768–7771.*

3. Magnetic nanoparticle strategies

Magnetic nanoparticles possessing excellent separation ability have been widely used in biosensors for DNA/RNA detection. In addition, magnetic nanoparticles could be functionalized with active groups such as hydroxyl, amine, carboxyl, aldehyde, and epoxy moieties improve target DNA binding via a stable covalent link. To date, a large number of magnetic nanoparticle based nucleic acid sensing approaches have been reported. These include SERS [143], fluorescence [144], CL [145], ECL [146], PEC [147], SPR [148], QCM [149] and electrochemistry [150]. In SERS sensing, researchers employed magnetic beads or an Fe_3O_4@Ag NP composite coupled with strand-displacement polymerization [151], HCR [152] or PCR [153] for signal amplified detection of DNA/RNA with a low detection limit. Zhen et al. [151] designed a new signal amplification strategy for miRNA detection based on a label-free multifunctional probe that recognized target miRNA and then initiated exponential amplification. The combination of SERS technology with multiple amplification modes and Au NP-DNA and magnetic beads enabled rapid amplification process and thus the sensitive detection of 6.3 fmol/L miR-203 in a complex biological matrix. Ye et al. [152] proposed another SERS signal amplification strategy that combined a magnetic bead based bifunctional probe with HCR amplification and achieved simultaneous detection of multiple cancer biomarkers (microRNA and ATP with detection limit of 0.15 fmol/L and 20 nmol/L, respectively) with a concentration difference >11 orders of magnitude. This highly sensitive technology would be of interest for detection of circulating tumor DNA (ctDNA). As such, Trau et al. [153] designed an SERS assay for multiplex detection of clinically relevant mutations in ctDNA from melanoma patients. This ultra-sensitive approach was shown to reproducibly detect to 10 copies of target sequence.

New types of magnetic materials or magnetic nanocomposite have also been developed in order to meet increasing detection sensitivity. For example, Chai et al. [154] proposed an "OFF-ON" SERS sensing system on magnetically active substrate (Co@C/PEI/Ag) assisted by specific padlock probe-based exponential RCA (P-ERCA) strategy for miRNA detection. Cy5 modified Thiol-hairpin DNA (H1) as a Raman label was immobilized on the surface of Co@C/PEI/Ag showing a strong Raman signal. This Raman signal could be crippled by DNA P2 as placeholder DNA through a hybridization event. In the presence of target miRNA 155, Raman signal

recovered as "ON" status after a series target-induced hybridization and exponential amplification reactions. This work demonstrated a wide linear range (100 aM–100 pM) and a lower detection limit of 70.2 amol/L for miRNA.

Besides SERS, many new ideas being brought forward using magnetic nanoparticle for other sensing technologies. This includes fluorescence detection. For example, Zhang et al. [144] designed carboxyl-modified magnetic beads and liposome encapsulated QDs for amplification-free single-particle DNA detection. In this work, they prepared liposomes/QDs (L/QD) complexes with hundreds of QD particles encapsulated inside liposomes. The target DNA simultaneously bound to the L/QD complex-labeled reporter probe and the magnetic bead-modified capture probe, thus generating a sandwich hybrid which could be separated from the free reporter probe through magnetic separation. Using this method, sensitive and simultaneous detection of HIV-1 and HIV-2 DNA sequences could be obtained at attomolar concentration. To improve sensitivity, several magnetic microbead-assisted isothermal amplification strategies have been developed for fluorescent detection of nucleic acid. Various isothermal amplification reactions have been studied including HCR [155], RCA [156] and CHA [157]. Magnetic microbead-assisted isothermal amplification strategies have been successfully used in chemiluminescence [145,158], ECL [42,146,159], PEC [147], SPR [148,149,160], and electrochemical [161,162] detection of DNA/RNA. For example, Bi et al. [158] developed an ultrasensitive and selective CL imaging array for high-throughput and simultaneous detection of miR-155, miR-let-7a and miR-141. This array combined exponential signal amplification from a DNA polymerase/NEase-assisted DNA machine and magnetic beads-assisted separation technique, through programmable DNA toehold-mediated strand displacement (TMSD) reactions. By introducing a magnetic nanoparticle to ECL analysis, Xu et al. [42] proposed a target induced dual recycling amplification method for sensitive microRNA detection. This study used DSN to cyclically cleave the complementary section of the DNA probes on the surface of magnetic beads in the presence of miRNA-21 thus obtaining changes in ECL intensity. Using PEC with DSN enzyme-assisted target recycling, Yuan et al. [147] proposed a ratiometric PEC assay for ultrasensitive and highly accurate determination of miRNA-141 in complex biological matrices. This study integrated target-nucleotide transduction-amplification with a binding-induced four-way junction DNA nanomachine.

Zhang et al. [160] combined SPR bioassay with the target-triggered amplification reaction and magnetic nanoparticle-based RCA for detection

of DNA and Ramos cells. Recently, Chai et al. [161] synthesized magnetic nanoparticles (Fe_3O_4@CeO_2 − PtNPs) with magnetic cores close to the substrate through the assistance of DNA structures. Target recycling-based Y-shaped DNA (Y-DNA) could regulate the electrocatalysis of Fe_3O_4@CeO_2 − Pt nanoparticles to methylene blue for signal enhancement and sensitive electrochemical detection of target DNA (10 fmol/L–50 nmol/L) with a detection limit of 3.5 fmol/L. Due to the complexity of DNA-assisted amplification reactions, PingarrÒn et al. [163], did not use nucleic acid amplification and proposed a thorough comparison of 11 methods involving various assay formats and labeling strategies. This study used conventional sandwich and competitive hybridization assays on the surface of magnetic beads (MBs) coupled with amperometric transduction at screen-printed carbon electrodes (SPCEs). Gooding et al. [150] reported a highly sensitive sensor for direct DNA analysis in whole blood through electric-field-induced reconfiguration of a network of probe DNA modified Au@magnetic NPs (DNA-Au@MNPs). As shown (Fig. 7), probe DNA sequences complementary to target miR-21 were modified on the surface of Au@MNPs with a thiol group and methylene blue redox label at the two ends. Excess DNA–Au@MNPs (threefold) relative to the amount of miR-21 was added to minimize response impact due to any variation in nanosensor concentration. Following 30 min incubation with analyte, nanosensors were magnetically separated and non-hybridized sequences washed away. DNA-Au@MNPs were then magnetically collected on an Au macroelectrode. Ten cycles of square-wave voltammetry was then conducted whereupon the current remained unchanged. This approach resulted in substantially improved detection limit (>1000-fold vs conventional gold macroelectrode).

In addition to the above, new sensing strategies based on magnetic nanoparticles have been developed. These include quartz crystal microbalance (QCM) [164], inductively coupled plasma mass spectrometry (ICP-MS) [165], magnetic relaxation switch sensing (MRS) [166] and optomagnetic [167].

4. Quantum dot (QD) strategies

In recent years, quantum dot (QD) semiconductor nanocrystals have been reported to have many unique and promising optical/electronic properties superior to those of large particles, making them attractive nanomaterials for optical biosensing [168]. QD-based Förster resonance

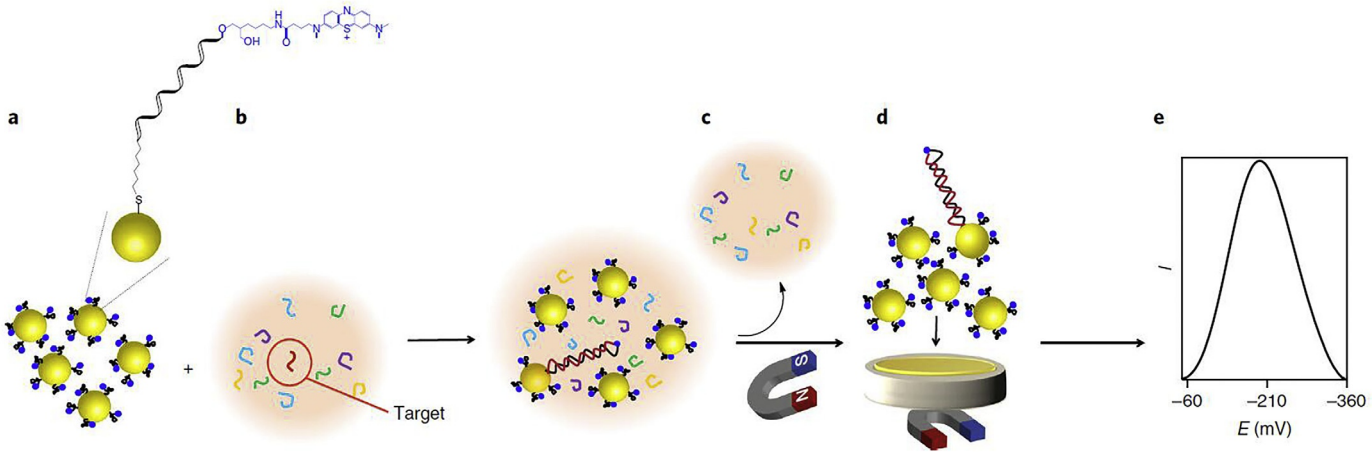

Fig. 7 Schematic representation of the steps involved in the proposed sensing strategy for detecting miRNA. *Reprinted with permission R. Tavallaie, J. McCarroll, M. Le Grand, N. Ariotti, W. Schuhmann, E. Bakker, R.D. Tilley, D.B. Hibbert, M. Kavallaris, J.J. Gooding, Nucleic acid hybridization on an electrically reconfigurable network of gold-coated magnetic nanoparticles enables microRNA detection in blood, Nat. Nanotechnol. 13 (2018) 1066–1071.*

energy transfer (FRET) biosensors have attracted significant interest for the direct detection of target analytes in solution. This property effectively mitigates typical biosensing problems such as long preparation time and immobilization, target incubation, need for multiple wash steps and construction of recognition system. Compared with traditional organic dyes, QDs as donors in FRET applications exhibit much better spectral overlap with different acceptors, a stronger FRET efficiency due to a higher acceptor density on the QD surface, and a wider excitation wavelength range of QD donors. As such, many QDs donor based FRET strategies has been applied for homogeneous detection of DNA/RNA with different nanoparticles or molecules as acceptors including Cy5 [169,170], Cy3 [171], Tamra [172], AF_{594} [173], BHQ [174,175], C60 [176] and Al-GFLX [177]. Recently, Seitz et al. [170] designed a FRET system on the basis of peptide nucleic acid (PNA) probes for rapid detection of RNA. This FRET pair consisted of a red emissive QD as donor and a NIR dye (Cy5) as fluorescent acceptor. This QD-PNA nanoconjugate demonstrated good PNA labeling density and thus achieved sensitive and selective RNA detection with good range (10 pmol/L–100 nmol/L) within 5 h. Integration of hyperbranched RCA (HRCA) with QD-based FRET strategy resulted in simultaneous biosensing of miR-21 and miR-221 with a single-color QD and two fluorescent dyes (Cy3 and Texas Red) acting as donors and the acceptors, respectively [171]. As shown (Fig. 8), target miR-21 and miR-221 as primers specifically trigger HRCA in the presence of corresponding circular templates. Numerous single-stranded amplification products were formed which can then be sandwiched by biotin-labeled capture probes and Cy3/Texas Red-labeled reporter probes. The biotinylated sandwich hybrids were subsequently assembled on the surface of QDs thus generating an efficient FRET signal (Cy3 for miR-21 and Texas Red for miR-221). This assay was very simple to construct and exhibited good specificity and high sensitivity under isothermal conditions using the same reverse primer and same capture probe. The assay had a lower detection limit of 0.72 fmol/L and 16 amol/L for miR-21 and miR-221, respectively. Moreover, the assay could be successfully employed for intracellular microRNA targets in cancer cells. Shamsipur et al. [172] developed a QD-based FRET biosensor for Helicobacter pylori DNA. In this study, two sets of detection probes were labeled using QD and Tamra as the donor and the acceptor, respectively. Target DNA could trigger the formation of a QD-DNA-Tamra sandwiched hybrid generating an efficient FRET signal between QD and Tamra. In the absence of target DNA, no sandwiched hybrid was obtained

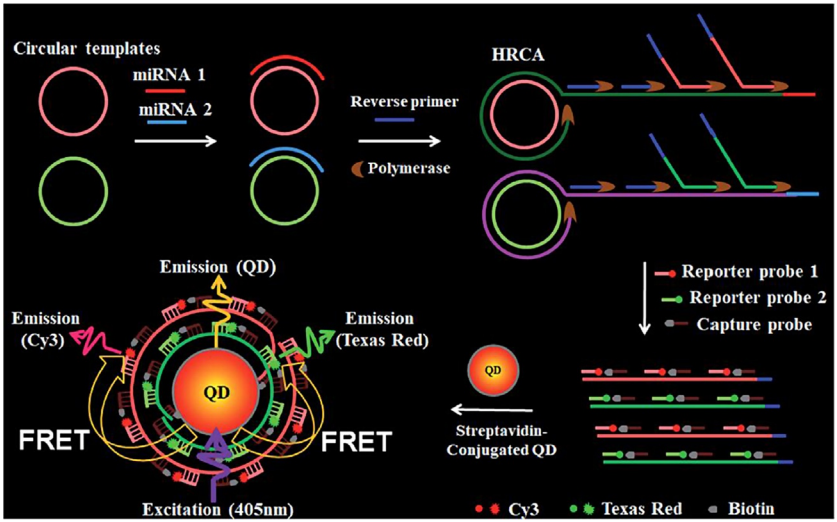

Fig. 8 Schematic illustration of the integration of HRCA with the QD-based FRET for simultaneous detection of miR-21 and miR-221. *Reprinted with permission J. Hu, M.H. Liu, C.Y. Zhang, Integration of isothermal amplification with quantum dot-based fluorescence resonance energy transfer for simultaneous detection of multiple microRNAs, Chem. Sci. 9 (2018) 4258–4267.*

and no FRET detected. This simple and rapid assay showed ultrahigh sensitive detection of Helicobacter pylori DNA at nanomolar level.

Advances in nanotechnology have brought new opportunities for the design of next-generation nucleic acid biosensors and disease diagnosis by combining advanced functional nanoparticles, DNA nanotechnology and nuclease-based target recycling amplification. Stevens et al. [173] employed DSN nuclease, bright fluorescent QDs as a donor and Alexa Fluor 594 (AF594) dye as an acceptor to develop an isothermal target-recycling assistant FRET sensing method. Using DSN-based cleavage reaction and QD-FRET-based signal readout, this method achieved a miR-148 detection limit of 42 fmol/L with excellent selectivity against mismatched sequences and other miRNAs. Using DSN, which specifically digests DNA in the DNA/RNA duplex, a QD-based FRET biosensor using BHQ2-labeled DNA functionalized QDs was developed for miR-141 detection in prostate cancer [174]. In the absence of miR-141, the fluorescence of QDs was efficiently quenched by BHQ2. When target miR-141 bound DNA on the QD surface, i.e., formation of DNA/RNA duplex, the DNA strand could be digested by DSN, resulting in the separation of BHQ2 and QD and recovery of QD fluorescence. This approach could identify

target miR-141 in serum from healthy individuals as well as prostate cancer carriers and, as such, may be clinically useful. Using similar FRET strategies between QD and BHQ, a CdTe/CdS core–shell QD-based FRET biosensor was developed for detection of DNA and microRNA [175]. Target nucleic acid (DNA and microRNA) can trigger the formation of sandwich hybrids, thus resulting in efficiently quenched fluorescence of QD due to close proximity between QD and BHQ2. A detection limit of 1 fmol/L and good selectivity demonstrated its ability to distinguish single-base-mismatched as well as random nucleic acid sequences.

In addition to BHQ2, recent research demonstrated that spherical fullerene (C_{60}) also exhibited a quenching effect to the fluorescence of QD via energy-transfer and charge-transfer processes and the quenching efficiency could be regulated by the number of proximate C_{60} on the QD surface [176]. High signal-to-noise ratio obtained from QD-C_{60} pairs and magnetic concentration yielded a detection limit of 100 fmol/L ($\sim 10^6$ target DNA copies per 10 μL sample). Recently, others reported a NIR fluorescence nanoprobe (QD-Al-GFLX) composed of NIR quantum dots (QDs) and Al(III)-gatifloxacin (Al-GFLX) complexes for the sensitive in vitro and in vivo detection of dsDNA [177]. They demonstrated that the initial strong NIR fluorescence of QDs in QD-Al-GFLX could be quenched by Al-GFLX complex via a photoinduced electron transfer mechanism. Upon interaction with target dsDNA, the high binding affinity between dsDNA and Al-GFLX complex could trigger dissociation of QD-Al-GFLX, thus eliminating the photoinduced electron transfer process and following significant enhancement of NIR fluorescence. This novel sensing approach provided a dsDNA detection limit of 6.83 ng/mL in aqueous solution.

Interestingly, in FRET biosensors, QDs can serve as donors as well as acceptors. For example, using a luminescent Tb complex as a donor and three semiconductor QDs as acceptors, Hildebrandt and Qiu et al. developed a Tb-to-QD FRET-based biosensor for sensitive multiplexed miRNA detection from a single 150 μL sample with 1 nM detection limit [178]. Employing CdSe@ZnS QDs as an acceptor, Yuan et al. proposed an ECL-RET based RNA biosensor within a nanostructure containing $Ru(dcbpy)_3^{2+}$ and CdSe@ZnS QDs acting as donor and acceptor, respectively [179]. This QDs-$Ru(dcbpy)_3^{2+}$ pair represented a new FRET based ECL biosensing system and achieved an ultralow detection limit of microRNA-141 (33 amol/L) via target recycling amplification and double-output conversion strategies.

In addition to their optical properties, QDs also possess distinct PEC activity [9,59,180]. After immobilization on a conductive electrode, the

excitation of QDs by light is able to activate an electron-transfer reaction between QDs and the electrode and then generate a photocurrent signal. Although the QD-based PEC biosensors emerged later than optical biosensors, they have been widely used due to their excellent sensitivity and low expense. For example, Wang et al. [181] developed a "switched-on" PEC biosensing platform for target DNA based on integration of p-type PbS QDs photocathode with the versatile function of the G-quadruplex/hemin configuration. Unfortunately, limited sensitivity was obtained due to the use of a single QD as sensitizer. Subsequently, Zhu et al. [182] synthesized two CdTe QDs with different sizes as the sensitizers and developed a new PEC biosensor for DNA. In this study, the TiO_2/CdS:Mn hybrid structure was prepared by successive adsorption and reaction of Cd^{2+}/Mn^{2+} and S^{2-} ions on the surface of TiO_2 film and then was employed as matrix for further hairpin DNA probe modification. Two sizes of QDs (CdTe-COOH QDs with a larger size and $CdTe-NH_2$ QDs with a smaller size) labeled on the terminal of hairpin DNA probe were designed as signal amplification elements. Upon hybridization between target DNA and hairpin DNA probe, hairpin DNA probe showed conformation change generating photocurrent change. This new biosensing strategy detected target DNA to 27 amol/L. To further improve sensitivity, several isothermal amplification strategies such as CHA [183,184], DNase I [185],λ-exonuclease [186] and restriction endonuclease [187] assisted target recycling signal amplification have been introduced.

5. Two-dimensional layered nanomaterial strategies

Since the discovery of mechanically exfoliated graphene in 2004 [188], numerous studies have been conducted on graphene and other two-dimensional (2D) layered nanomaterials for use in material science, biochemistry and nanotechnology [10]. Graphene, as one of most common used 2D materials, has showed promise in nucleic acid detection due to its unique low-dimensional physical properties, excellent electrochemical performance and high fluorescence quenching efficiency [189]. Further studies demonstrated that GO showed much higher efficient adsorption ability for ssDNA vs dsDNA because of the shielded π–π interactions from the helical structure of the latter [190]. Based on this difference, Tang et al. [191] recently employed GO as a nanocarrier for the simultaneous fluorescent imaging analysis of miR-21 and PDCD4 mRNA in MCF-7 human breast cancer cells and also developed a new fluorescence and photoacoustic

dual-mode probe for mRNA detection in living cells [192]. Integration with isothermal amplification remarkably amplified signals for ultrasensitive nucleic acid detection. Many recent studies have shown that the assistance of RCA [193,194] or HCR [195] on GO substrate has become a promising tool in the field of fluorescence biosensing of miRNA. For example, Kim et al. [196] developed a facile GO based fluorescence method for the quantitative detection of miRNA coupled with RCA mediated isothermal gene amplification. This strategy could reliably detect miRNA as low as 0.4 pmol/L. Using RCA and self-assembled nucleic acid molecules on GO nanoplates, Zhang et al. [197] developed a triple-helix probe that could provide low-abundance miRNA imaging in single cells. Another example by the same group, utilized an enzyme-free HCR strategy on GO carrier and simultaneously obtained imaging of multiple miRNA in living cells thereby providing a more comprehensive assessment of intracellular events [198]. Besides fluorescence analysis, nucleic acid assistant isothermal amplification strategies on GO interfaces have also become powerful tools during the construction of PEC DNA assays [199], field-effect DNA biosensors [200], chemiluminescence DNA detection [201] and ECL DNA biosensor [202].

Other graphene-like ultrathin 2D nanomaterials including MoS_2 [203], WS_2 [204], and MnO_2 [205], WSe_2 [206], Ta_2NiS_5 [207] and nanosheets have also been used in DNA/RNA biosensor technology because of their large surface area and ease of functionalization. Fluorophore-labeled ssDNA can be adsorbed by van der Waals interaction between nucleobases and the nanomaterial plane with good fluorescence quenching. Inspired by the unique properties of transition metal dichalcogenides, Zhang et al. [208] demonstrated that a single-layer MoS_2 nanosheet possessed high fluorescence quenching efficiency and variable affinity for ssDNA vs dsDNA. In subsequent work, Xiao et al. [209,210] combined super quencher MoS_2 nanosheet-loaded molecular beacons with DSN assistant signal amplification for simple, sensitive and multiplexed miRNA detection. For in situ detection of target miRNA in living cells, MoS_2 nanosheets were proven to be particularly useful due to their low cytotoxicity and high stability. For example, Yang et al. [211] used MoS_2 a nanosheet-based nanoprobe for one-step monitoring of endogenous miRNA single cell expression. Recent studies have shown that biodegradable MnO_2 nanosheets were also useful as in situ biosensors for intracellular targets [212]. For example, Xiang et al. [213] developed an intracellular signal amplification strategy based on a biodegradable MnO_2 nanosheet, target-triggered assembly of hairpins and

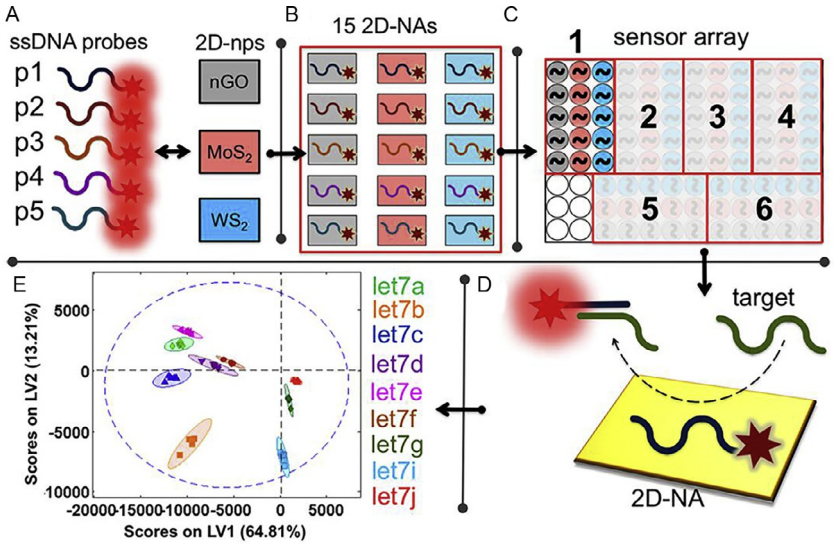

Fig. 9 Schematic illustration of the combinatorial nanosensor array for miRNA analyses with two-dimensional nanoparticles. *Reprinted with permission M.S. Hizir, N. Nandu, M.V. Yigit, Homologous miRNA analyses using a combinatorial nanosensor array with two-dimensional nanoparticles, Anal. Chem. 90 (2018) 6300–6306.*

FRET. Using this approach it was possible to monitor down-regulated miRNA-21 in living cells. In combination with DNAzyme, Zhao et al. [214] developed a MnO_2 nanosheet/DNAzyme as nanomaterial/DNA integrated nanozymes which acted as a catalytic DNA circuit generator for intracellular signal amplification and versatile imaging of DNA base-excision repairs in living cells. As shown (Fig. 9), a combination of three two-dimensional nanoparticles (WS_2, MoS_2, and GO) and five rationally designed fluorescently labeled 15-nt-long ssDNAs (probes), a novel combinatorial nanosensor array was developed for simultaneous detection of nine let-7 miRNA analogues [215]. This work demonstrated the usefulness of two dimensional nanoparticles for analysis of biologic matrices.

6. Other nanoparticle strategies

In addition to common nanoparticles listed above, others have been developed including metal-organic frameworks (MOFs), silica nanoparticles, polydopamine nanomaterials, UCNPs, DNA-tagged liposomes and carbon dots. All have been successfully employed in the construction of bioanalytical methods for sensitive DNA/RNA detection.

MOFs are an emerging class of hybrid porous materials self-assembled from metal-containing nodes and organic linkers that have attracted tremendous attention over the past two decades [216]. MOF are based on crystalline molecular materials possessing open crystalline supramolecular coordination architectures with unprecedentedly large and permanent inner porosity. Because of these characteristics, MOFs have unique physical and chemical properties such as advanced signal transduction which is essential for sensory materials [11]. MOF biosensing strategies primarily rely on their excellent optical or catalytic properties during signal transduction. For example, several recent MOFs have been used as effective fluorescence sensing platforms for DNA detection. In this application, MOFs are coupled with dye-labeled ssDNA probe through electrostatic, π-stacking or hydrogen-bonding. MOF materials showed quenching effect to the fluorescence response of the dye due PET. Many 2D or 3D MOFs demonstrate excellent fluorescence quenching ability toward DNA labeled fluorescence dye, including 2D Zn-TCPP MOF [217], 3D dysprosium (Dy) MOF [218], UiO-66-NH_2 [219], H_2dtoaCu MOF [220], MIL-101 [221,222], MIL-88B [223] and MOCPS [224]. Because of these characteristics, it is possible to achieve discrimination of target DNA by synchronous scanning fluorescence spectrometry. Meanwhile, porous MOFs act as a scaffold with signal dyes loaded on it as well as with hairpin DNA structure as capping shell [225]. In the presence of target DNA or RNA, fluorophores released from MOF pores was trigged by competitive displacement reaction thereby significantly enhancing the fluorescent signal. Due to MOF high loading capacity, DNA targets could be detected to 20 fmol/L and could effectively discriminate single-base mismatch via stimuli-responsive nanoprobes. To take advantage of the catalytic properties of MOFs nanomaterials, Ling et al. [226], synthesized FeTCPP@MOF composites. These acted as electrochemical indicators for signal readout which can mimetically catalyze the oxidation of *o*-phenylenediamine (o-PD) to 2,2′-diaminoazobenzene. This "signal-on" electrochemical sensor showed a satisfactory detection limit of target DNA to 0.48 fmol/L and a linear range of 10 fmol/L–10 nmol/L.

Silica nanoparticles (SNPs) are the second most commonly used nanomaterial. SNPs possess incomparable properties such as hydrophilic surface, ease of modification and/or surface functionalization, high stability and good biocompatibility. These characteristics have shown SNPs to be one of the most important and promising nanomaterials for biosensing. These are generally divided into two categories, nonporous (solid) silica

nanoparticles (NSNPs) and mesoporous silica nanoparticles (MSNPs), both of which bear an amorphous silica structure. MSNPs have been widely employed as nanocarriers for the delivery of small molecules or drugs via physical or chemical adsorption due to their size (2–50 nm). In contrast, NSNPs have been employed as nanocarriers via encapsulation or conjugation approaches. For example, Yang et al. [227] developed a target miRNA-induced HCR amplification reaction on the surface of silicon microbeads to produce long self-assembled DNA polymers on which could be further fabricated with Ag NP. Because of the miRNA triggered hybridization chain reaction and Ag^{+}-mediated cascade amplification, very low circulating miRNA (0.3 fmol/L) could be detected in serum collected from different stage chronic lymphocytic leukemia (CLL). Functionalized with other nanomaterial, such as CdTe QDs, silica nanospheres also exhibit positive effect for highly sensitive fluorescent biosensing target DNA (10 amol/L–10 pmol/L) with a detection limit to 50 copies [228].

With respect to controlled drug delivery or DNA modification, MSNPs have attracted much attention due to their mesoporous nature. In fact, others have taken advantage of this characteristic as well as adsorption capacity to develop smart sensing MSNPs, i.e., nano-carrier/amplifier in various electro/optical sensing methods for controlled release or sensitive detection of DNA and small molecules [229,230]. With the integration of a nicking endonuclease based amplification reaction on the surface of MSNPs, Zhang et al. [231], developed a SERS based approach for DNA methyltransferase detection. By incorporating nanoporous materials, traditional label-free and enzyme-free electrochemical methods showed ultrasensitive miRNA sensing with a detection limit of 33 amol/L [232]. In this study, $[Ru(NH_3)_6]^{3+}$, as one of the electroactive probes, was pre-entrapped in the pores of positively charged MSNPs, while $[Fe(CN)_6]^{3-}$ was selected as another electroactive probe to facilitate redox recycling of target-triggered release of $[Ru(NH_3)_6]^{3+}$. Subsequent work presented a self-powered ratiometric biofuel cell electrochemical biosensor for ultrasensitive microRNA-21 detection with a detection limit of 2.7 amol/L [233]. In this approach, the cathodic electron acceptor $[Fe(CN)_6]^{3-}$ was entrapped in the pores of positively charged MSNPs and then capped with DNA as a biogate. In the presence of target miRNA, entrapped $[Fe(CN)_6]^{3-}$ was released resulting in a dramatically increased circuit voltage. The designed "signal-on" homogeneous self-powered biosensor presented an ingenious approach as an ultrasensitive, easy-to-use, portable and on-site biosensing platform. In addition to traditional electrochemical biosensing methods, ECL, as a modern

electrochemical approach, also demonstrated improved performance in combination with MSN signal amplification. For example, Chen et al. [234] developed a facile ECL assay using a DNA bio-gate and DSN assisted target recycling for survivin mRNA detection [234]. As shown (Fig. 10), a large amount of $Ru(bpy)_3^{2+}$ were first encapsulated into the MSNs via physical adsorption and then NH_2-MSNs formed with further functionalization with 3-aminopropyltriethoxysilane (APTES) on the external surface. Thus negatively charged ssDNA could be electrostatically adsorbed onto the positively charged NH_2-MSNs as a DNA biogate. After hybridization between target survivin mRNA and ssDNA, dsDNA would move away from NH_2-MSN leading to release of pre-entrapped $Ru(bpy)_3^{2+}$ and generation of ECL signal with TPA co-reactant. Using this strategy, it was possible to reproducibly quantify cancer cell survivin mRNA to a detection limit of 0.1 fmol/L. MSN-based in situ amplification strategies for detection of intracellular analytes has attracted much attention due to the target-stimulation induced release process. On the surface of silica-coated gold nanorods, Zhu et al. [235] designed multicomponent nucleic acid enzymes for in situ controlled drug release and logic imaging of multiplexed targets (miR-21 and miR-145). This work provided a general

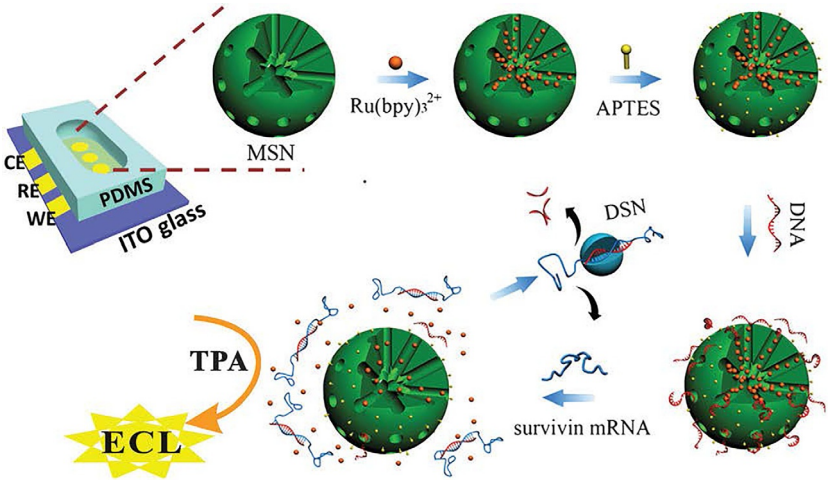

Fig. 10 Schematic illustration of the ECL microreactor for detection of survivin mRNA in cells based on DNA bio-gates of MSNs and the DSN amplification mechanism. *Reprinted with permission J. Wang, X.L. Li, J.D. Zhang, N. Hao, J.-J. Xu, H.-Y. Chen, Integration of DNA bio-gates and duplex-specific nuclease signal amplification: toward electrochemiluminescence detection of surviving mRNA, Chem. Commun. 51 (2015) 11673–11676.*

approach for disease diagnosis, synergistic chemotherapy and gene therapy and prognosis. In another example, Zhang et al. [236], proposed a smart autonomous ATP self-powered strand-displacement cascade amplification (SDCA) system for highly sensitive intracellular multiple miRNA detection.

Up-conversion nanoparticles (UCNPs), a lanthanide-doped nanomaterial that converts near-infrared (NIR) radiation into visible radiation (anti-Stokes optical properties), has become another useful nanomaterial for biosensing [237]. Using UCNPs (the donor) and multiple luminescent RET (LRET, energy transfer between the donor and acceptor) strategies, a series of biosensors for nucleic acid have been successfully developed. It is important to note, however, that an effective and suitable acceptor for up-conversion fluorescence is critical. Au NPs [238,239], GO [240], Cy3 [241], TAMRA [242], PMPD nanospheres [243], Ir(III) complex@Au NPs [244] are ultra-efficient acceptors for UCNPs. Moreover, signal amplification strategies have been introduced and showed positively impacted DNA/RNA detection via amplified signal collection. For example, Zhu et al. [104], combined UCNPs (as donors) and Au NPs (as acceptors) to develop a universal UCNP-based FRET sensing system for highly sensitive tumor-related ncRNA detection using enzymatic signal amplification. On the other hand, the excitation wavelength of UCNPs (~980 nm) in the near IR region can also be used because biomolecular auto-fluorescence can be successfully avoided thus enhancing signal to noise ratio. This property is considered to be one of the most significant advantages in avoiding autofluorescence interference common to traditional fluorescence biosensing systems. As such, UCNPs based nanoprobe assemblies have great potential for detecting target mRNA in living cells [245]. For example, Kuang et al. [246] developed a DNA-driven gold nanorod coated platinum-UCNP satellite assemblies (Au NR@Pt-UCNP satellites) for detection of intracellular thymidine kinase 1 (TK1) mRNA (1.17–65.21 fmol/10 μg RNA) with a detection limit of 0.67 fmol. Using a nonenzymatic signal amplification strategy, Zhu et al. [247], employed a target cycling amplification strategy to trigger disassembly of Au NPs and UCNPs to achieve highly sensitive detection of low abundance microRNA in vitro as well as in vivo. Although UCNP based biosensors show great promise, remaining challenges include energy-transfer efficiency, complicated preparation, and poor specificity in UCNP-based FRET. To mitigate these issues, UCNPs were improved to form confined core−shell structures that emit ions located in the thin shell. This modification greatly improved FRET efficiency due to close distance between UCNPs and

external energy acceptors. For example, Na et al. [248] developed a new UCNP with a core−shell structure that remarkably increased energy-transfer efficiency for miR-122 detection. Similarly, Chu et al. [249] designed a multifunctional core-shell-shell structured polydopamine (PDA) modified UCNP and developed a platform for intracellular tumor-related mRNAs detection, near IR light triggered photodynamic and photothermal synergistic therapy.

Polydopamine nanospheres (PDANSs) have been widely reported as effective FRET energy acceptor for nucleic acid. This biopolymerized material has many advantages including biocompatibility, biodegradability and ease of synthesis. For example, Xu et al. [250] reported that PDANSs possessed high fluorescence quenching efficiency and, interestingly, showed completely different affinities toward various ssDNA conformations. On the basis of this discovery, PDANSs could be employed as an essential sensing component for DNA and protein detection. Due to excellent adsorption of DNA on PDANs, Meng et al. [251] demonstrated robust DNA/PDAN sensors in biologic samples. In this work, DNA/PDANs acted as probes, and demonstrated sensitive detection and imaging of target DNA in serum or in living cells with a detection limit of 1 nmol/L target DNA. In a subsequent study, Luo et al. [252] employed PDANSs (acceptors) and dual-colored Au NCs (donors) to develop a novel FRET-based platform for simultaneous detection of multiple tumor-related microRNAs with amplified signals from DNase-I-assistant target recycling amplification. By monitoring the changes of the recovered fluorescence intensity at 445 and 575 nm, miRNA-21 and let-7a were simultaneously detected with detection limits of 4.2 and 3.6 pmol/L, respectively, [252]. Choi et al. [253] proposed a PDANs@Au NPs composite as a fluorescence quencher with DNA strands as molecular probes for multiplexed detection of two types of miRNAs in differentiating stem cells. Recently, Li et al. [254] designed a ZnO@PDANs–DNA nanosystem for ultrasensitive imaging of mRNA in live cells. Four functional hairpin DNA probes were employed (H0, H1, H2 and H3) and modified on the surface of ZnO@PDANs as a nanosensing system. H1 and H2 possessed two separate single-strand tails with inactive Mg^{2+}-dependent DNAzyme sequences at their 5′ and 3′ ends, respectively. Following live cell entry and facing target mRNA, a target-triggered, wire-shaped DNAzyme nanostructures could form resulting in fluorescent detection of tumor survivin mRNA. In addition, PDAN-based novel chemiluminescence RET method for microRNA detection has been reported by Ye et al. [255]. In this work, they proposed a PDAN

nanosphere-assisted chemiluminescence resonance energy transfer (CRET) platform coupled with a DSN-assisted signal amplification strategy and developed a powerful method for specific miRNA detection. The target miRNA could trigger DSN to partially degrade the sensing probe in the DNA-miRNA hetero duplex to repeatedly release G-quadruplex formed by G-rich sequence from PDANs, generating a chemiluminescence signal. The method quantitated target miRNA in the range of 80 pmol/L–50 nmol/L with a detection limit of 49.6 pmol/L. Other nanoparticles, such as DNA-tagged liposomes [256], single-walled carbon nanotubes [257], carbon dots [258], luminescent polymer dots [259] and Ti^{4+}@spore microspheres [260] have also been successfully employed. These strategies have shown promise as bioanalytical tools for DNA/RNA detection.

7. DNA/RNA detection based on nucleic acid nanotechnology

Strict Watson-Crick base-pairing rules for DNA strand hybridization make the use of DNA to be a powerful approach in the construction of nanotechnology strategies [261]. For example, employing sequence programmability and highly specific molecular recognition from DNA molecules, a large amount of DNA-based nanomaterials or frameworks have been designed and successfully applied in sensing [262]. To date, the rapid growth of technology has enabled the design and construction of elaborate DNA nanostructures with different dimensions (1D, 2D and 3D) and broad applications in materials science, biochemistry and biosensing [263,264].

7.1 Nucleic acid nanotechnology in vitro assays

In vitro diagnostics assays aim to find information regarding a target analyte in a biological sample such as whole blood, serum/plasma, urine and tissue. DNA nanostructures have been successfully used in a variety of bioanalytical and biomedical applications due to their simplicity, flexibility, structural stability and ability to modify with functional decorations or to load drugs and other molecules [261–264].

For example, the first 3D framework, a DNA tetrahedron, was reported by Goodman and co-workers using a single step synthesis process [265]. The DNA tetrahedron consisted of four designed oligonucleotides was used to evaluate biomarkers and perform cellular imaging in cancer. Subsequently, Ju et al. [266] described an “off-on” fluorescence system for monitoring

DNA methyltransferase (MTase), an enzyme integral to cancer suppressor gene expression, tumor growth and therapeutics. Interestingly, the DNA tetrahedron can also act as a nanoscaffold to provide an amplified signal due to spatially loaded HRP enzymes at three vertices, and one recognition domain at the fourth vertex for target breast cancer 1 (BRCA1) DNA binding [267]. Using this strategy, an ultralow DNA detection limit (10 fmol/L) was achieved using a portable magnetic bead colorimetric assay. Subsequent studies showed that tetrahedral DNA nanostructures modified on Au NPs could greatly increase reactivity and accessibility. On this basis, Dong et al. [268], designed Au NPs tetrahedral DNA probes labeled with different dyes. Initially, fluorescence of vertical dyes was quenched due to close distance to the gold surface. Upon target miRNA hybridization and subsequent DSN assistant digestion, heteroduplex DNA was selectively digested, leading to the release of dyes and fluorescent signal. Using this approach, ultrasensitive detection of multiplexed miRNA was achieved with a detection limit to attomolar concentration. In contrast to ss or dsDNA probes, the DNA tetrahedron nanostructures provided smart and designable sensing interfaces with lateral interprobe spacing controlled by scaffold size [262,269–271]. For example, Fan et al. [272] designed multiple tetrahedron structured probes (TSP) with side length ranging from 2.4 to 12.6 nm in order to tune the probe distance. By simply changing TSP size it was possible to decrease hybridization time and increase hybridization efficiency. This approach resulted in excellent sensitivity (1 fmol/L–10 pmol/L) and low detection limit (1 fmol/L) for target DNA. When coupled to an HCR signal amplification reaction, the TSP electrochemical sensor could achieve ultralow detection limits for DNA (100 amol/L) and microRNA (10 amol/L) [273]. Recently, Zhao et al. [274] proposed an electrochemical method to detect circulating methylated DNA. This approach which integrated TSP with asymmetric methylation-specific PCR resulted in ultra-low methylated DNA detection at single copy level. Besides DNA, various miRNAs have been readily detected as few as attomolar concentration (<1000 copies) with high single-base discrimination ability using TSP based biosensing methods, i.e., electrochemical sensors via hybridization identification [275,276]. Third generation electrochemical-DNA biosensors provided improved detection limit (pmol/L to fmol/L) for RNA of low abundance and small size [277]. Electrochemical tags could be labeled on free domains of the DNA tetrahedron as signal reporter probes and when combined enzymatic amplification, nonenzymatic HCR, target-catalytic recycling, RCA, and nanoparticle assistant signal-amplification,

it was possible to detect microRNA to attomolar concentration [278–280]. To improve signal readouts for simultaneous detection of multiple miRNAs, a disposable screen-printed gold electrode array (16-channel) with sequence-specific TSPs was developed [281]. This approach successfully detected four pancreatic carcinoma miRNAs at femtomolar concentration.

In addition to electrochemical methods, a DNA tetrahedron structure-based ECL biosensor has been constructed and used for DNA/RNA detection. Xu et al. [282,283], developed sensitive tetrahedron DNA structure ECL sensing platform for DNA detection combined with DNA cyclic amplification and in situ generation of H_2O_2 as $Ru(bpy)_3^{2+}$ ECL quencher. Using plasmon coupling effect of gold nanodendrites (Au NDs), the same group recently reported a novel LSPR enhanced ECL emission from CdTe nanocrystals (NCs) by Au NDs for nucleic acid detection [284]. In this work, a thin film of CdTe NCs modified on glassy carbon electrode served as an anodic ECL emitter with Au NDs as plasmon enhancer. A DNA tetrahedron embedded with a stem-loop hairpin structure on one edge was prepared as a switch to regulate the distance between CdTe NCs and Au NDs. Initially, the hairpin structure was closed with relaxed DNA tetrahedron structure on CdTe NCs film. In this setting, ECL emission of CdTe NCs was greatly quenched as a "turn-off" mode by proximal Au NDs via FRET effect. Following hybridization with target DNA, the hairpin structure changed to a rodlike configuration resulting in enhanced ECL as a "turn-on" mode due to an increased distance between CdTe NCs and Au NDs. Various nanoparticle ECL-active materials and ECL donor-acceptor pairs have been reported. These approaches have utilized the tetrahedron DNA structure as a biosensing interface to control the distance between the ECL donor-acceptor pairs. For example, $Ru(bpy)_3^{2+}$-doped silica nanoparticles and hollow Au nanocages were used as the ECL donor and acceptor, respectively, for detection of femtomolar miRNA141 [285]. Using copper nanoclusters (Cu NCs) as ECL signal label and tetrahedron DNA structure to modulate luminous efficiency of Cu NCs, Yuan et al. [286], reported a DNA nanocrane for enhanced ECL detection of microRNA-155.

Due to its versatility as a molecular scaffold, the tetrahedron DNA structure is compatible with glass-based optical analysis. For example, Li et al. [287] immobilized the DNA tetrahedron on the epoxy-functional glass slide via epoxy-amine linkage. This QD imaging platform enabled

a toehold-mediated sensitive miRNA fluorescent imaging to 5 fmol/L. For detection of microRNA at single molecule level, Wang et al. [288], developed a plasmonic nanobiosensor employing single TSP-modified Au@Ag core-shell nanocube as a plasmonic probe to capture target microRNA, meanwhile inducing the localized surface plasmon resonance (LSPR) in tetrahedron-structured DNA (Fig. 11). Using this LSPR nanoplasmonic sensor, a single miRNA21 binding event can generate ~4 nm wavelength shift of LSPR scattering spectral for ultrasensitive logic detection. For multiple targets, a TSP microarray platform was developed by substituting the pendant recognition domain with the corresponding target-responsive probes [289]. Besides direct anchoring on sensing surface, TSP could also serve as a signal-amplified nanolabel for quantitative detection various DNA, including HIV related DNA or human IgG at the single molecule level [290,291]. Other DNA nanostructures such as DNA nanomachines [292–294], DNA walker [295–297] and DNA nanoparticles [298,299] have also been successfully used in nucleic acid detection.

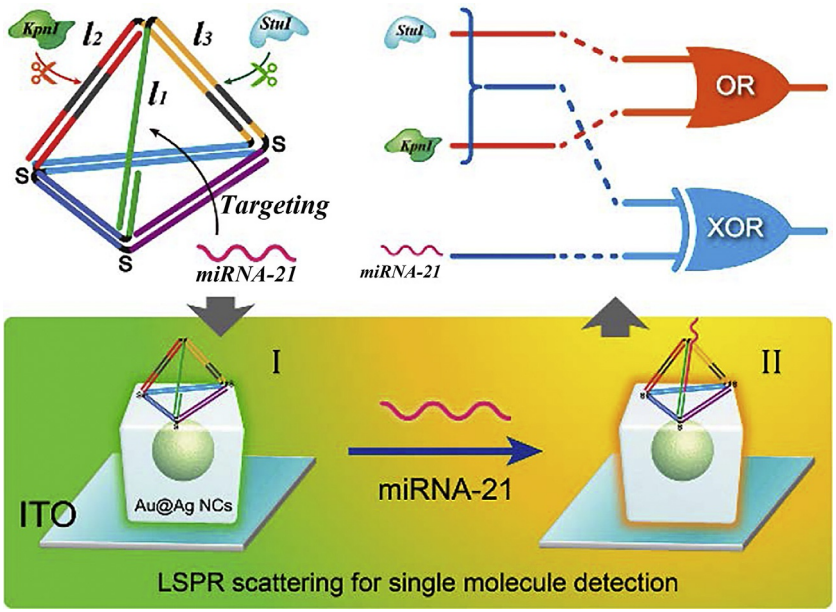

Fig. 11 Schematic illustration of single-molecule microRNA analysis and logic operations using a smart plasmonic nanobiosensor. *Reprinted with permission Y. Zhang, Z. Shuai, H. Zhou, Z. Luo, B. Liu, Y. Zhang, L. Zhang, S. Chen, J. Chao, L. Weng, Q. Fan, C. Fan, W. Huang, L. Wang, Single-molecule analysis of microRNA and logic operations using a smart plasmonic nanobiosensor, J. Am. Chem. Soc. 140 (2018) 3988–3993.*

7.2 Nucleic acid nanotechnology in situ assays

As discussed above, the concentration of and spatiotemporal distribution of intracellular DNA or RNA could provide important information with respect to the state of living cells as well as disease progression. Unfortunately, many challenges remain in accurate detection and monitoring of DNA/RNA mediated intracellular processes. DNA nanostructures, as natural biopolymers with excellent biocompatibility and biodegradability, provide a promising tool as an in vivo biosensor. For example, DNA nanostructures are idea carrier platforms for the delivery of drugs and probes intracellularly. In fact, some have successfully used the DNA tetrahedron and the factionalized DNA tetrahedron due to their ease of penetration across cellular membranes in the absence of a transfection reagent [300]. For example, Tan et al. [301] proposed a single-step DNA tetrahedral nanotweezer utilizing mRNA-induced FRET for intracellular imaging of tumor TK1 mRNA in HepG2 cells. To enhance signal, an entropy-driven tetrahedron DNA amplifier (EDTD) was used [302]. As shown (Fig. 12), mRNA target could trigger the EDTD interaction and initiate an entropy-driven force assistant autonomous DNA circuit inside living cells, thus providing greatly amplified fluorescence signal for ultrasensitive detection of intracellular mRNA. Due to the molecular engineering of the DNA tetrahedral framework, this work demonstrated excellent cellular uptake with high biocompatibility and biostability indicating its potential application as a smart DNA machine in vivo. Subsequently, Leong et al. [303] designed a functionalized DNA tetrahedron with a GAPDH mRNA-specific molecular beacon at one vertex. With the protection of TSP nanoshell, this approach showed good cell entry without transfection and was resistant to nonspecific enzymatic degradation in detecting nanomolar GAPDH mRNA in DLD-1 cells. For multiple intracellular RNA targets, TSP assistant simultaneous detection was developed via a dual-color-encoded reconfigurable tetrahedron nanoprobe [304] multicolor encoded nanoprobe [305].

In contrast to fluorescent dye DNA tetrahedral biosensing, high-photostability nanoparticles (UCNPs and Ag_2S NP) could also be incorporated into the DNA frame for ultrasensitive intracellular miRNA quantification [306]. Kuang et al. [307] demonstrated that the DNA tetrahedron provided a geometric framework to precisely distance AuNPs and luminescent UCNPs using a rational spatial spacer. Multifunctional nanopyramids

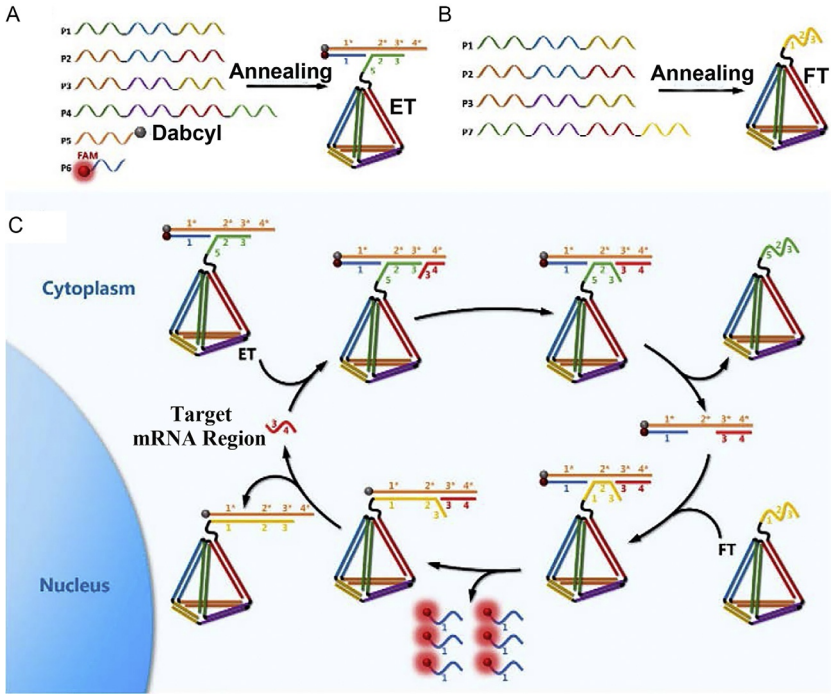

Fig. 12 Schematic illustration of entropy-driven 3D DNA amplifier for catalytic signal enhancement of specific mRNA expression in living cells. *Reprinted with permission L. He, D. Lu, H. Liang, S. Xie, X. Zhang, Q. Liu, Q. Yuan, W. Tan, mRNA-initiated, three-dimensional DNA amplifier able to function inside living cells, J. Am. Chem. Soc. 140 (2018) 258–263.*

containing Au-Cu_9S_5 NPs, UCNPs and Ag_2S NPs were loaded with target-specific sequences for miR21 detection in HeLa cells. Other DNA nanostructures such as DNA nanostring light [308], DNA nanowire [309] and assembly of Y-shaped DNA [310] are also been successfully used for nucleic acid detection.

DNA nanostructures are uniquely qualified intracellular molecular detection. First, negatively charged DNA nanostructures provide transfection-free endocytotic internalization and enable molecular recognition inside different cellular compartments. Second, DNA nanostructures show high enzyme-resistance, intrinsic biocompatibility and non-cytotoxicity thus facilitating intracellular transport. In addition, DNA nanoarchitecture has been widely used for the precise molecular recognition and detection of disease-related nucleic acid intracellularly.

8. Point-of-care-testing (POCT) of nucleic acid

Interestingly, point-of-care-testing (POCT) systems have become one of the most rapidly growing tools in the field of nucleic acid detection and identification. Compared to conventional biologic/biochemical approaches, POCT of nucleic acid can facilitate the detection of infectious agents [311]. As such, much research has been performed to miniaturize devices and develop portable microchips. These novel POCT devices include paper chips, microfluidic chips and capillary devices.

The paper chip has gained considerable interest due to its low price, simplicity, biocompatibility and ease of disposal [312,313]. The inherently porous structure of paper provides many advantages during sequential delivery of reagent, sample mixing and multi-step processing to provide a sensitive and specific approach for a number of analytes [314,315]. As such, these paper-based devices have been further optimized by integration with electro/optical sensing technology including electrochemistry, chemiluminescence, ECL, PEC, colorimetry, fluorescence and SERS.

One of the most significant components of paper-based POC sensors is the label or tracer used to influence signal generation. The ideal label or tracer must be specific, easy to conjugate and possess high activity following target recognition. Because of their high surface-to-volume ratio, good electrical properties and chemical stability, nanoparticles are ideal for DNA detection in paper-based POCT systems. For example, Au NPs, QDs and carbon nanotubes as well as nanocomposites have been evaluated in paper-based POCT biosensors. Among these, Au NPs have particularly favorable optoelectronic properties, i.e., surface plasmon resonance and SERS, influenced by size, shape and the surrounding chemical environment to provide optimal detection. For example, DNA-Au NPs probe and DNA-Au NP aggregates incorporated into a lateral flow device were shown to improve sensitivity in nucleic acid POCT [316,317]. Additional amplification strategies are, however, necessary to improve sensitivity, especially of low abundance targets, and decrease the impact of interfering substances typical of clinical specimens. This may involve the use of loop-mediated isothermal amplification (LAMP), an approach successfully used for rapid pathogen diagnosis. For example, Chen et al. [318] proposed an instrumentation-free sensing method for detection of 20 CFU/mL *Pseudomonas aeruginosa* and its toxin genes. In contrast to conventional PCR, LAMP-based isothermal amplification technologies have proven promising in POCT [319,320].

LAMP, strategies including RCA [321] and SDA [322] assistant isothermal amplification have been successfully used. For example, Li et al. [321] used netlike rolling circle amplification (NRCA) to design a pH-responsive miRNA amplification method. Interestingly, the large amounts of H^+ produced as byproduct during amplification were sufficient to induce a pH change and could thus be detected directly or with pH-sensitive indicators. Although Au NPs-assistant paper-based colorimetry has been extensively used for POCT, this approach is limited by low sensitivity due to the need for visual color change detection, i.e., signal readout. To mitigate these issues, Choo et al. [323] used SERS-based strip assay technology and Raman reporter-labeled AuNPs as SERS nanotags for HIV-1 DNA with a detection limit of 0.24 pg/mL, a 1000-fold increase in sensitivity vs colorimetric or fluorescent methods.

Although Au NP paper lateral strip technology has been highly successful for nucleic acid POCT, assay performance may be improved by incorporating QDs or UCNPs due to the characteristically narrow wavelengths and intense luminescence. Using QD FRET, Krull et al. [324–326] developed efficient sensing proposals for nucleic acid on chemically derivatized paper substrates. In this work, the paper surface was chemically derivatized with imidazole and then conjugated to two QD-DNA probes that were green- and red-emitting with detection limits of 50 nmol/L and 80 nmol/L, respectively. As shown (Fig. 13), subsequent work involved non-enzymatic

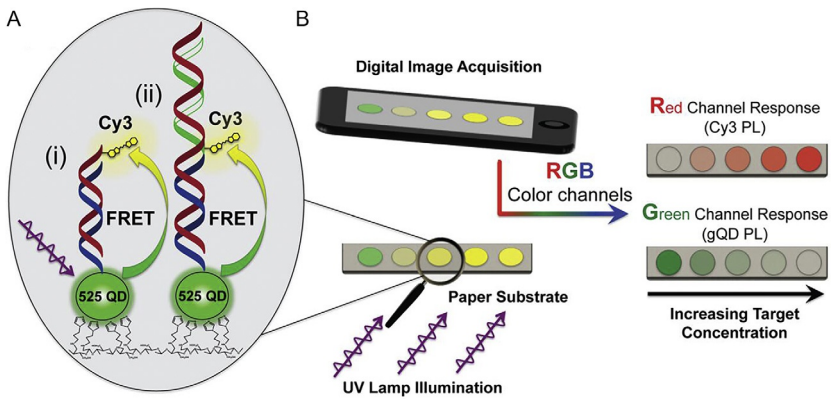

Fig. 13 Schematic illustration of a digital camera for quantitative ratiometric transduction of nucleic acid hybridization on a paper-based platform. *Reprinted with permission M.O. Noor, U.J. Krull, Camera-based ratiometric fluorescence transduction of nucleic acid hybridization with reagentless signal amplification on a paper-based platform using immobilized quantum dots as donors, Anal. Chem. 86 (2014) 10331–10339.*

signal enhancement for QD-FRET by drying the paper before data acquisition and digital signal collection using an iPad [327]. This modification resulted in a 10-fold improvement in limit of detection vs hydrated paper substrates. The compaction of dried paper fibers resulted in closer proximity of immobilized QDs and dye and increased crosstalk. Wang et al. [328] integrated SDA into QD test strips thereby recycled HIV-DNA for signal amplification. This approach eliminated the hook effect due to target drop out on the test zone resulting in a lower detection limit of 0.76 pmol/L. Recently, Xing et al. [329] constructed a paper fluidic chip device using QDs as signal labels for multiplex miRNA analysis in various human cancer cells through integrating hairpin probe-exponential amplification reaction with optical detection. This approach was rapid (90 min) and had a detection limit of 3×10^6 copies and as such may be applicable clinically.

Recently, fluorescent carbon nanoparticles (FCNs) and carbon nanotubes (CNTs) have been employed as labels. Liu et al. [330,331] successively demonstrated a FCN and a multi-walled carbon nanotube (MWCNT) lateral flow sensor for ultrasensitive DNA detection. UCNPs can be excited by NIR radiation, thus minimizing background typical of most QDs or molecular dyes testing systems with UV–visible excitation. Krull et al. [332], applied poly(acrylic acid) (PAA) modified LiYF4 UCNPs as a bioprobe for target DNA detection via sandwich hybridization on a paper platform. UCNP luminescence generated a limit of detection of 1.8 fmol DNA target.

In addition to paper devices, microfluidic and microchip technologies also show great potential for clinical POCT [333]. Miniaturized chips have many advantages including the use small sample volumes and the numerous biochemical recognition reactions that can be incorporated into the device. Nucleic acid detection can be transformed to a variety of output signals, i.e., optical, electrochemical, calorimetric as well as changes in pH. Microbead [334] and multi-walled carbon nanotube [335] modified micro-array chips have proven to be simple, inexpensive, sensitive and portable nucleic acid detection devices. Kelley et al. [336–339] designed many functionalized nanostructured microelectrode assays for electrochemical detection of specific mutant DNA sequence and mRNA profiling of circulating tumor cells. Rapid on-chip gene expression analysis was suitable for clinical evaluation of complex blood samples. Subsequently, they further reported a high-throughput electrochemical array approach that provided direct molecular analysis with large panels of sequence alterations in ctDNAs [340]. In this work, combinatorial probes were designed to screen all possible mutations present in the same gene region with high fidelity.

Additionally, some nanoparticles enhanced meter-based POCT were also reported as inexpensive such as using gas pressure meters readout [341] or glucose meters [342]. Overall, POCT using this technology is inexpensive, rapid, labor sparing and ease of commercialization.

9. Summary and future perspectives

The accurate and sensitive detection of nucleic acid is an important diagnostic tool. As described above, the use nanotechnology including nanomaterial-based signal transfer and amplification strategies have shown great promise for DNA/RNA detection in vitro and in vivo. The unique physical, chemical, optical, electrical, and catalytic properties of these devices are synergistic in accelerating signal transduction at much lower detection limits than traditional approaches. Nanomaterials efficiently protect nucleic acid probes from enzymatic degradation in complicated biologic samples, characteristic vital to clinical use as well as in vivo cell assays. Integration with isothermal amplification strategies will further enhance device performance with respect to analytical sensitivity and specificity. Furthermore, the potential for miniaturization provides a distinct advantage over traditional approaches.

Although nanomaterial enhanced DNA/RNA biosensing platforms have shown great promise, many challenges remain. Technical issues include reproducibility, stability, biocompatibility, susceptibility to interference and cost. As such, functionalized biocompatible nanomaterials need to be developed especially for in vivo applications. It is likely that continued development of nanotechnology including smart nanoparticle enhanced POCT devices will evolve as novel diagnostic nucleic acid sensors.

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Conflicts of interest

The authors declare no competing financial interest.

References

[1] E. Chargaff, The Nucleic Acids, Elsevier, 2012.
[2] H. Dong, J. Lei, L. Ding, Y. Wen, H. Ju, X. Zhang, MicroRNA: function, detection, and bioanalysis, Chem. Rev. 113 (2013) 6207–6233.

[3] Y. Du, S. Dong, Nucleic acid biosensors: recent advances and perspectives, Anal. Chem. 89 (2017) 189–215.
[4] R.M. Graybill, R.C. Bailey, Emerging biosensing approaches for microRNA analysis, Anal. Chem. 88 (2016) 431–450.
[5] H. Zhou, J. Liu, J.J. Xu, S.S. Zhang, H.Y. Chen, Optical nano-biosensing interface via nucleic acid amplification strategy: construction and application, Chem. Soc. Rev. 47 (2018) 1996–2019.
[6] X. Huang, Y. Liu, B. Yung, Y. Xiong, X.Y. Chen, Nanotechnology-enhanced no-wash biosensors for in vitro diagnostics of cancer, ACS Nano 11 (2017) 5238–5292.
[7] W. Zhou, X. Gao, D. Liu, X.Y. Chen, Gold nanoparticles for in vitro diagnostics, Chem. Rev. 115 (2015) 10575–10636.
[8] T.A.P. Rocha-Santos, Sensors and biosensors based on magnetic nanoparticles, Trends Anal. Chem. 62 (2014) 28–36.
[9] H. Zhou, J. Liu, S. Zhang, Quantum dot-based photoelectric conversion for biosensing applications, TrAC-Trends Anal. Chem. 67 (2015) 56–73.
[10] C. Tan, X. Cao, X.J. Wu, Q. He, J. Yang, X. Zhang, J. Chen, W. Zhao, S. Han, G.H. Nam, M. Sindoro, H. Zhang, Recent advances in ultrathin two-dimensional nanomaterials, Chem. Rev. 117 (2017) 6225–6331.
[11] W.P. Lustig, S. Mukherjee, N.D. Rudd, A.V. Desai, J. Li, S.K. Ghosh, Metal–organic frameworks: functional luminescent and photonic materials for sensing applications, Chem. Soc. Rev. 46 (2017) 3242–3285.
[12] M.-K. Tsang, G. Bai, J. Hao, Stimuli responsive upconversion luminescence nanomaterials and films for various applications, Chem. Soc. Rev. 44 (2015) 1585–1607.
[13] J. Zhang, H. Nie, Z. Wu, Z. Yang, L. Zhang, X. Xu, S. Huang, Self-catalytic growth of unmodified gold nanoparticles as conductive bridges mediated gap-electrical signal transduction for DNA hybridization detection, Anal. Chem. 86 (2014) 1178–1185.
[14] J. Kumarasamy, M.B. Camarada, D. Venkatraman, H. Ju, R.S. Dey, Y. Wen, One-step coelectrodeposition-assisted layer-by-layer assembly of gold nanoparticles and reduced graphene oxide and its self-healing three-dimensional nanohybrid for an ultrasensitive DNA sensor, Nanoscale 10 (2018) 1196–1206.
[15] L. Tian, K. Qian, J. Qi, Q. Liu, C. Yao, W. Song, Y. Wang, Gold nanoparticles superlattices assembly for electrochemical biosensor detection of microRNA-21, Biosens. Bioelectron. 99 (2018) 564–570.
[16] S. Yu, Y. Wang, L.P. Jiang, S. Bi, J.J. Zhu, Cascade amplification-mediated in situ hot-spot assembly for microRNA detection and molecular logic gate operations, Anal. Chem. 90 (2018) 4544–4551.
[17] X. Wu, Y. Chai, P. Zhang, R. Yuan, An electrochemical biosensor for sensitive detection of microRNA-155: combining target recycling with cascade catalysis for signal amplification, ACS Appl. Mater. Interfaces 7 (2015) 713–720.
[18] B. Bo, T. Zhang, Y. Jiang, H. Cui, P. Miao, Triple signal amplification strategy for ultrasensitive determination of miRNA based on duplex specific nuclease and bridge DNA-gold nanoparticles, Anal. Chem. 90 (2018) 2395–2400.
[19] B. Li, F. Liu, Y. Peng, Y. Zhou, W. Fan, H. Yin, S. Ai, X. Zhang, Two-stage cyclic enzymatic amplification method for ultrasensitive electrochemical assay of microRNA-21 in the blood serum of gastric cancer patients, Biosens. Bioelectron. 79 (2016) 307–312.
[20] S. Su, Y. Wu, D. Zhu, J. Chao, X. Liu, Y. Wan, Y. Su, X. Zuo, C. Fan, L. Wang, On-electrode synthesis of shape-controlled hierarchical flower-like gold nanostructures for efficient interfacial DNA assembly and sensitive electrochemical sensing of microRNA, Small 12 (2016) 3794–3801.

[21] M. Azimzadeh, M. Rahaie, N. Nasirizadeh, K. Ashtari, H. Naderi-Manesh, An electrochemical nanobiosensor for plasma miRNA-155, based on graphene oxide and gold nanorod, for early detection of breast cancer, Biosens. Bioelectron. 77 (2016) 99–106.
[22] Q. Feng, X. Zhao, Y. Guo, M. Liu, P. Wang, Stochastic DNA walker for electrochemical biosensing sensitized with gold nanocages@graphene nanoribbons, Biosens. Bioelectron. 108 (2018) 97–102.
[23] D. Zhu, W. Liu, D. Zhao, Q. Hao, J. Li, J. Huang, J. Shi, J. Chao, S. Su, L. Wang, Label-free electrochemical sensing platform for microRNA-21 detection using thionine and gold nanoparticles co-functionalized MoS2 nanosheet, ACS Appl. Mater. Interfaces 9 (2017) 35597–35603.
[24] A.D. Castaneda, N.J. Brenes, A. Kondajji, R.M. Crooks, Detection of microRNA by electrocatalytic amplification: a general approach for single-particle biosensing, J. Am. Chem. Soc. 139 (2017) 7657–7664.
[25] Y. Tao, M. Li, J.S. Ren, X.G. Qu, Metal nanoclusters: novel probes for diagnostic and therapeutic applications, Chem. Soc. Rev. 44 (2015) 8636–8866.
[26] H. Dong, K. Hao, Y. Tian, S. Jin, H. Lu, S.F. Zhou, X.J. Zhang, Label-free and ultrasensitive microRNA detection based on novel molecular beacon binding readout and target recycling amplification, Biosens. Bioelectron. 53 (2014) 377–383.
[27] L. Zhang, J. Zhu, Z. Zhou, S.J. Guo, J. Li, S.J. Dong, E.K. Wang, A new approach to light up DNA/Ag nanocluster-based beacons for bioanalysis, Chem. Sci. 4 (2013) 4004–4010.
[28] H. Dong, S. Jin, H. Ju, K. Hao, L.-P. Xu, H. Lu, X.J. Zhang, Anal. Chem. 84 (2012) 8670–8674.
[29] J.T. Petty, J. Zheng, N.V. Hud, R.M. Dickson, DNA-templated Ag nanocluster formation, J. Am. Chem. Soc. 126 (2004) 5207–5212.
[30] B. Zhang, B. Liu, J. Zhou, J. Tang, D.P. Tang, Additional molecular biological amplification strategy for enhanced sensitivity of monitoring low-abundance protein with dual nanotags, ACS Appl. Mater. Interfaces 5 (2013) 4479–4485.
[31] L. Chen, L. Sha, Y. Qiu, G. Wang, H. Jiang, X. Zhang, An amplified electrochemical aptasensor based on hybridization chain reactions and catalysis of silver nanoclusters, Nanoscale 7 (2015) 3300–3308.
[32] Z. Chen, Y. Liu, C. Xin, J. Zhao, S. Liu, A cascade autocatalytic strand displacement amplification and hybridization chain reaction event for label-free and ultrasensitive electrochemical nucleic acid biosensing, Biosens. Bioelectron. 113 (2018) 1–8.
[33] C. Yang, K. Shi, B. Dou, Y. Xiang, Y. Chai, R. Yuan, In situ DNA-templated synthesis of silver nanoclusters for ultrasensitive and label-free electrochemical detection of microRNA, ACS Appl. Mater. Interfaces 7 (2015) 1188–1193.
[34] Y. Wang, X. Zhang, L. Zhao, T. Bao, W. Wen, X. Zhang, S. Wang, Integrated amplified aptasensor with in-situ precise preparation of copper nanoclusters for ultrasensitive electrochemical detection of microRNA 21, Biosens. Bioelectron. 98 (2017) 386–391.
[35] Z.Y. Liu, W.J. Qi, G.B. Xu, Recent advances in electrochemiluminescence, Chem. Soc. Rev. 44 (2015) 3117–3142.
[36] Z.F. Ding, B.M. Quinn, S.K. Haram, L.E. Pell, B.A. Korgel, A.J. Bard, Electrochemistry and electrogenerated chemiluminescence from silicon nanocrystal quantum dots, Science 296 (2002) 1293–1297.
[37] Y.-P. Dong, J. Zhang, Y. Ding, X.-F. Chu, J. Chen, Electrogenerated chemiluminescence of luminol at a polyaniline/graphene modified electrode in neutral solution, Electrochim. Acta 91 (2013) 240–245.
[38] S. Wang, L. Ge, M. Yan, J. Yu, X. Song, S. Ge, J. Huang, 3D microfluidic origami electrochemiluminescence immunodevice for sensitive point-of-care testing of carcinoma antigen 125, Sens. Actuators B 176 (2013) 1–8.

[39] H.-R. Zhang, M.-S. Wu, J.-J. Xu, H.-Y. Chen, Signal-on dual-potential electrochemiluminescence based on luminol–gold bifunctional nanoparticles for telomerase detection, Anal. Chem. 86 (2014) 3834–3840.
[40] H.-R. Zhang, J.-J. Xu, H.-Y. Chen, Electrochemiluminescence Ratiometry: a new approach to DNA biosensing, Anal. Chem. 85 (2013) 5321–5325.
[41] Y. Wang, D. Shan, G. Wu, H. Wang, F. Ru, X. Zhang, L. Li, Y. Qian, X. Lu, A novel "dual-potential" ratiometric electrochemiluminescence DNA sensor based on enhancing and quenching effect by G-quadruplex/hemin and Au-luminol bifunctional nanoparticles, Biosens. Bioelectron. 106 (2018) 64–70.
[42] N. Hao, X.L. Li, H.R. Zhang, J.-J. Xu, H.-Y. Chen, A highly sensitive ratiometric electrochemiluminescent biosensor for microRNA detection based on cyclic enzyme amplification and resonance energy transfer, Chem. Commun. 50 (2014) 14828–14830.
[43] X.L. Huo, H. Yang, W. Zhao, J.-J. Xu, H.-Y. Chen, Nanopore-based electrochemiluminescence for detection of microRNAs via duplex-specific nuclease-assisted target recycling, ACS Appl. Mater. Interfaces 9 (2017) 33360–33367.
[44] Z. Xu, L. Liao, Y. Chai, H. Wang, R. Yuan, Ultrasensitive electrochemiluminescence biosensor for microRNA detection by 3D DNA walking machine based target conversion and distance-controllable signal quenching and enhancing, Anal. Chem. 89 (2017) 8282–8287.
[45] Q. Kuang, C. Li, Z. Qiu, G. Jie, S. Niu, T. Huang, Three-way DNA junction structure combined with enzyme-powered cascade amplification for ultrasensitive electrochemiluminescence detection of microRNA via smart DNA walker, Sens. Actuators B 274 (2018) 116–122.
[46] Q.M. Feng, Y.Z. Shen, M.X. Li, Z.L. Zhang, W. Zhao, J.J. Xu, H.Y. Chen, Dual-wavelength electrochemiluminescence ratiometry based on resonance energy transfer between Au nanoparticles functionalized g-C3N4 nanosheet and $Ru(bpy)_3^{2+}$ for microRNA detection, Anal. Chem. 88 (2016) 937–944.
[47] A. Chen, G.F. Gui, Y. Zhuo, Y.Q. Chai, Y. Xiang, R. Yuan, Signal-off electrochemiluminescence biosensor based on Phi29 DNA polymerase mediated strand displacement amplification for microRNA detection, Anal. Chem. 87 (2015) 6328–6334.
[48] Q. Liu, C. Ma, X.P. Liu, Y.P. Wei, C.J. Mao, J.J. Zhu, A novel electrochemiluminescence biosensor for the detection of microRNAs based on a DNA functionalized nitrogen doped carbon quantum dots as signal enhancers, Biosens. Bioelectron. 92 (2017) 273–279.
[49] Y.Q. Yu, J.P. Wang, M. Zhao, L.R. Hong, Y.Q. Chai, R. Yuan, Y. Zhuo, Target-catalyzed hairpin assembly and intramolecular/intermolecular co-reaction for signal amplified electrochemiluminescent detection of microRNA, Biosens. Bioelectron. 77 (2016) 442–450.
[50] Y. Shan, J.-J. Xu, H.-Y. Chen, Distance-dependent quenching and enhancing of electrochemiluminescence from a CdS: Mn nanocrystal film by Au nanoparticles for highly sensitive detection of DNA, Chem. Commun. 8 (2009) 905–907.
[51] H. Zhou, J. Liu, J.-J. Xu, H.-Y. Chen, Highly sensitive electrochemiluminescence detection of single-nucleotide polymorphisms based on isothermal cycle-assisted triple-stem probe with dual-nanoparticle label, Anal. Chem. 83 (2011) 8320–8328.
[52] H. Zhou, J. Liu, J.-J. Xu, H.-Y. Chen, Ultrasensitive DNA detection based on Au nanoparticles and isothermal circular double-assisted electrochemiluminescence signal amplification, Chem. Commun. 47 (2011) 8358–8360.
[53] H. Zhou, Y. Zhang, J. Liu, J.-J. Xu, H.-Y. Chen, Electrochemiluminescence resonance energy transfer between CdS: Eu nancrystals and Au nanorods for sensitive DNA detection, J. Phys. Chem. C 116 (2012) 17773–17780.

[54] M.-S. Wu, L.-J. He, J.-J. Xu, H.-Y. Chen, RuSi@Ru(bpy)$_3^{2+}$/Au@Ag_2S nanoparticles electrochemiluminescence resonance energy transfer system for sensitive DNA detection, Anal. Chem. 86 (2014) 4559–4565.
[55] Y. Cheng, J. Lei, Y. Chen, H.X. Ju, Highly selective detection of microRNA based on distance-dependent electrochemiluminescence resonance energy transfer between CdTe nanocrystals and Au nanoclusters, Biosens. Bioelectron. 51 (2014) 431–436.
[56] M. Jiao, G. Jie, L. Tan, S. Niu, AgNPs-3D nanostructure enhanced electrochemiluminescence of CdSe quantum dot coupled with strand displacement amplification for sensitive biosensing of DNA, Anal. Chim. Acta 983 (2017) 166–172.
[57] Y.Y. Zhang, Q.M. Feng, J.J. Xu, H.Y. Chen, Silver nanoclusters for high-efficiency quenching of CdS nanocrystal electrochemiluminescence and sensitive detection of microRNA, ACS Appl. Mater. Interfaces 7 (2015) 26307–26314.
[58] A. Chen, S. Ma, Y. Zhuo, Y. Chai, R. Yuan, In situ electrochemical generation of electrochemiluminescent silver naonoclusters on target-cycling synchronized rolling circle amplification platform for microRNA detection, Anal. Chem. 88 (2016) 3203–3210.
[59] W.-W. Zhao, J.-J. Xu, H.-Y. Chen, Photoelectrochemical bioanalysis: the state of the art, Chem. Soc. Rev. 44 (2015) 729–741.
[60] L. Zhang, Y. Sun, Y.Y. Liang, J.P. He, W.-W. Zhao, J.-J. Xu, H.-Y. Chen, Ag nanoclusters could efficiently quench the photoresponse of CdS quantum dots for novel energy transfer-based photoelectrochemical bioanalysis, Biosens. Bioelectron. 85 (2016) 930–934.
[61] W.-W. Zhao, P.-P. Yu, Y. Shan, J. Wang, J.-J. Xu, H.-Y. Chen, Exciton-plasmon interactions between CdS quantum dots and Ag nanoparticles in photoelectrochemical system and its biosensing application, Anal. Chem. 84 (2012) 5892–5897.
[62] Z.Y. Ma, F. Xu, Y. Qin, W.-W. Zhao, J.-J. Xu, H.-Y. Chen, Invoking direct exciton-plasmon interactions by catalytic Ag deposition on Au nanoparticles: photoelectrochemical bioanalysis with high efficiency, Anal. Chem. 88 (2016) 4183–4187.
[63] W. Tu, H. Cao, L. Zhang, J. Bao, X. Liu, Z. Dai, Dual signal amplification using gold nanoparticles-enhanced zinc Selenide nanoflakes and P19 protein for ultrasensitive photoelectrochemical biosensing of microRNA in cell, Anal. Chem. 88 (2016) 10459–10465.
[64] G. Wen, W. Dong, B. Liu, Z. Li, L. Fan, A novel nonenzymatic cascade amplification for ultrasensitive photoelectrochemical DNA sensing based on target driven to initiate cyclic assembly of hairpins, Biosens. Bioelectron. 117 (2018) 91–96.
[65] M. Wang, H. Yin, N. Shen, Z. Xu, B. Sun, S. Ai, Signal-on photoelectrochemical biosensor for microRNA detection based on Bi2S3 nanorods and enzymatic amplification, Biosens. Bioelectron. 53 (2014) 232–237.
[66] G.L. Wang, K.L. Liu, J.X. Shu, T.T. Gu, X.M. Wu, Y.M. Dong, Z.J. Li, A novel photoelectrochemical sensor based on photocathode of PbS quantum dots utilizing catalase mimetics of bio-bar-coded platinum nanoparticles/G-quadruplex/hemin for signal amplification, Biosens. Bioelectron. 69 (2015) 106–112.
[67] Y.X. Dong, J.T. Cao, B. Wang, S.H. Ma, Y.M. Liu, Exciton–plasmon interactions between CdS@g-C3N4 heterojunction and Au@Ag nanoparticles coupled with DNAase-triggered signal amplification: toward highly sensitive photoelectrochemical bioanalysis of microRNA, ACS Sustainable Chem. Eng. 5 (2017) 10840–10848.
[68] J. Shu, Z. Qiu, S. Lv, K. Zhang, D. Tang, Plasmonic enhancement coupling with defect-engineered TiO2-x: a mode for sensitive photoelectrochemical biosensing, Anal. Chem. 90 (2018) 2425–2429.
[69] C. Li, H. Wang, J. Shen, B. Tang, Cyclometalated iridium complex-based label-free photoelectrochemical biosensor for DNA detection by hybridization chain reaction amplification, Anal. Chem. 87 (2015) 4283–4291.

[70] X.M. Shi, L.P. Mei, Q. Wang, W.W. Zhao, J.J. Xu, H.Y. Chen, Energy transfer between semiconducting polymer dots and gold nanoparticles in a photoelectrochemical system: a case application for cathodic bioanalysis, Anal. Chem. 90 (2018) 4277–4281.
[71] S. Lu, S. Wang, J. Zhao, J. Sun, X.R. Yang, Fluorescence light-up biosensor for microRNA based on the distance-dependent photoinduced electron transfer, Anal. Chem. 89 (2017) 8429–8436.
[72] C.I. Richards, S. Choi, J.-C. Hsiang, Y. Antoku, T. Vosch, A. Bongiorno, Y.-L. Tzeng, R.M. Dickson, Oligonucleotide-stabilized Ag nanocluster fluorophores, J. Am. Chem. Soc. 130 (2008) 5038–5039.
[73] P. Shah, A. Rørvig-Lund, S.B. Chaabane, P.W. Thulstrup, H.G. Kjaergaard, E. Fron, J. Hofkens, S.W. Yang, T. Vosch, Design aspects of bright red emissive silver nanoclusters/DNA probes for microRNA detection, ACS Nano 6 (2012) 8803–8814.
[74] J. Chen, Z. Luo, Y. Wang, Z. Huang, Y. Li, Y. Duan, DNA specificity detection with high discrimination performance in silver nanoparticle coupled directional fluorescence spectrometry, Sens. Actuators B 255 (2018) 2306–2313.
[75] G. Liu, J. Li, D.Q. Feng, J.J. Zhu, W. Wang, Silver nanoclusters beacon as stimuli-responsive versatile platform for multiplex DNAs detection and aptamer-substrate complexes sensing, Anal. Chem. 89 (2017) 1002–1008.
[76] H.-C. Yeh, J. Sharma, J.J. Han, J.S. Martinez, J.H. Werner, A DNA−silver nanocluster probe that fluoresces upon hybridization, Nano Lett. 10 (2010) 3106–3110.
[77] H.-C. Yeh, J. Sharma, I.-M. Shih, D.M. Vu, J.S. Martinez, J.H. Werner, A fluorescence light-up Ag nanocluster probe that discriminates single-nucleotide variants by emission color, J. Am. Chem. Soc. 134 (2012) 11550–11558.
[78] J. Zhang, C. Li, X. Zhi, G.A. Ramon, Y. Liu, C. Zhang, F. Pan, D. Cui, Hairpin DNA-templated silver nanoclusters as novel beacons in strand displacement amplification for microRNA detection, Anal. Chem. 88 (2016) 1294–1302.
[79] L. Ge, X. Sun, Q. Hong, F. Li, Ratiometric catalyzed-assembly of NanoCluster beacons: a nonenzymatic approach for amplified DNA detection, ACS Appl. Mater. Interfaces 9 (2017) 32089–32096.
[80] W. Zhou, J. Zhu, D. Fan, Y. Teng, X. Zhu, S. Dong, A multicolor chameleon DNA-templated silver nanocluster and its application for ratiometric fluorescence target detection with exponential signal response, Adv. Funct.Mater. 27 (2017) 1704092.
[81] C. Song, X. Yang, K. Wang, Q. Wang, J. Huang, J. Liu, W. Liu, P. Liu, Label-free and non-enzymatic detection of DNA based on hybridization chain reaction amplification and dsDNA-templated copper nanoparticles, Anal. Chim. Acta 827 (2014) 74–79.
[82] F. Xu, L. Luo, H. Shi, X. He, Y. Lei, J. Tang, D. He, Z. Qiao, K. Wang, Label-free and sensitive microRNA detection based on a target recycling amplification-integrated superlong poly(thymine)-hosted copper nanoparticle strategy, Anal. Chim. Acta 1010 (2018) 54–61.
[83] B.-Z. Chi, R.-P. Liang, W.-B. Qiu, Y.-H. Yuan, J.-D. Qiu, Direct fluorescence detection of microRNA based on enzymatically engineered primer extension polythymine (EPEPT) reaction using copper nanoparticles as nano-dye, Biosens. Bioelectron. 87 (2017) 216–221.
[84] D.S. Seferos, D.A. Giljohann, H.D. Hill, A.E. Prigodich, C.A. Mirkin, Nano-flares: probes for transfection and mRNA detection in living cells, J. Am. Chem. Soc. 129 (2007) 15477–15479.
[85] J. Liu, M. Cui, H. Zhou, W. Yang, DNAzyme based nanomachine for in situ detection of microRNA in living cells, ACS Sens. 2 (2017) 1847–1853.

[86] X. He, T. Zeng, Z. Li, G. Wang, P.N. Ma, Catalytic molecular imaging of microRNA in living cells by DNAProgrammed nanoparticle disassembly, Angew. Chem. Int. Ed. 55 (2016) 3073–3076.
[87] C. Wang, H. Zhang, D. Zeng, W. Sun, H. Zhang, A. Aldalbahi, Y. Wang, L. San, C. Fan, X. Zuo, X. Mi, Elaborately designed diblock nanoprobes for simultaneous multicolor detection of microRNAs, Nanoscale 7 (2015) 15822–15829.
[88] J. Shi, M. Zhou, A. Gong, Q. Li, Q. Wu, G.J. Cheng, M. Yang, Y. Sun, Fluorescence lifetime imaging of nanoflares for mRNA detection in living cells, Anal. Chem. 88 (2016) 1979–1983.
[89] H. Peng, X.F. Li, H. Zhang, X.C. Le, A microRNA-initiated DNAzyme motor operating in living cells, Nat. Commun. 8 (2017) 14378.
[90] X. Yang, Y. Tang, S.D. Mason, J. Chen, F. Li, Enzyme-powered three-dimensional DNA nanomachine for DNA walking, payload release, and biosensing, ACS Nano 10 (2016) 2324–2330.
[91] Y. Li, G.A. Wang, S.D. Mason, X. Yang, Z. Yu, Y. Tang, F. Li, Simulation-guided engineering of an enzyme-powered three dimensional DNA nanomachine for discriminating single nucleotide variants, Chem. Sci. 9 (2018) 6434–6439.
[92] Y. Yang, J. Huang, X. Yang, X. He, K. Quan, N. Xie, M. Ou, K. Wang, Gold nanoparticle based hairpin-locked-DNAzyme probe for amplified miRNA imaging in living cells, Anal. Chem. 89 (2017) 5850–5856.
[93] Y. Yang, J. Huang, X. Yang, K. Quan, H. Wang, L. Ying, N. Xie, M. Ou, K. Wang, FRET nanoflares for intracellular mRNA detection: avoiding false positive signals and minimizing effects of system fluctuations, J. Am. Chem. Soc. 137 (2015) 8340–8343.
[94] Y. Wu, J. Huang, X. Yang, Y. Yang, K. Quan, N. Xie, J. Li, C. Ma, K. Wang, Gold nanoparticle loaded split-DNAzyme probe for amplified miRNA detection in living cells, Anal. Chem. 89 (2017) 8377–8383.
[95] C.P. Liang, P.Q. Ma, H. Liu, X. Guo, B.C. Yin, B.C. Ye, Rational engineering of a dynamic, entropy-driven DNA nanomachine for intracellular microRNA imaging, Angew. Chem. Int. Ed. 56 (2017) 9077–9081.
[96] D. Li, W. Zhou, R. Yuan, Y. Xiang, A DNA-fueled and catalytic molecule machine lights up trace under-expressed microRNAs in living cells, Anal. Chem. 89 (2017) 9934–9940.
[97] N. Li, C. Chang, W. Pan, B. Tang, A multicolor nanoprobe for detection and imaging of tumor-related mRNAs in living cells, Angew. Chem. Int. Ed. 51 (2012) 7426–7430.
[98] W. Pan, H. Yang, N. Li, L. Yang, B. Tang, Simultaneous visualization of multiple mRNAs and matrix metalloproteinases in living cells using a fluorescence nanoprobe, Chem. A Eur. J. 21 (2015) 6070–6073.
[99] W. Pan, Y. Li, M. Wang, H. Yang, N. Li, B. Tang, FRET-based nanoprobes for simultaneous monitoring of multiple mRNAs in living cells using single wavelength excitation, Chem. Commun. 52 (2016) 4569–4572.
[100] S. Ye, X. Li, M. Wang, B. Tang, Fluorescence and SERS imaging for the simultaneous absolute quantification of multiple miRNAs in living cells, Anal. Chem. 89 (2017) 5124–5130.
[101] J. Sun, F. Pi, J. Ji, H. Lei, Z. Gao, Y. Zhang, J.D. Habimana, Z. Li, X. Sun, Ultrasensitive "FRET-SEF" probe for sensing and imaging microRNAs in living cells based on gold nanoconjugates, Anal. Chem. 90 (2018) 3099–3108.
[102] H. Ma, N. Xue, Z. Li, K. Xing, X. Miao, Ultrasensitive detection of miRNA-155 using multi-walled carbon nanotube-gold nanocomposites as a novel fluorescence quenching platform, Sens. Actuators B 266 (2018) 221–227.

[103] L. Zhang, S.R. Jean, X. Li, T. Sack, Z. Wang, S. Ahmed, G. Chan, J. Das, A. Zaragoza, E.H. Sargent, S.O. Kelley, Programmable metal/semiconductor nanostructures for mRNA-modulated molecular delivery, Nano Lett. 18 (2018) 6222–6228.
[104] K. Zhang, L. Yang, F. Lu, X. Wu, J.J. Zhu, A Universal upconversion sensing platform for the sensitive detection of tumour-related ncRNA through an Exo III-assisted cycling amplification strategy, Small 14 (2018). 1703858.
[105] C. Zong, M. Xu, L.-J. Xu, T. Wei, X. Ma, X.-S. Zheng, R. Hu, B. Ren, Surface-enhanced Raman spectroscopy for bioanalysis: reliability and challenges, Chem. Rev. 118 (2018) 4946–4980.
[106] F. Gao, J. Lei, H. Ju, Label-free surface-enhanced Raman spectroscopy for sensitive DNA detection by DNA-mediated silver nanoparticle growth, Anal. Chem. 85 (2013) 11788–11793.
[107] Y. Qian, T. Fan, Y. Yao, X. Shi, X. Liao, F. Zhou, F. Gao, Label-free and Raman dyes-free surface-enhanced Raman spectroscopy for detection of DNA, Sens. Actuators B 254 (2018) 483–489.
[108] J. Zheng, A. Jiao, R. Yang, H. Li, J. Li, M. Shi, C. Ma, Y. Jiang, L. Deng, W. Tan, Fabricating a reversible and regenerable Raman-active substrate with a biomolecule-controlled DNA nanomachine, J. Am. Chem. Soc. 134 (2012) 19957–19960.
[109] M. Liu, Z. Wang, S. Zong, R. Zhang, D. Zhu, S. Xu, C. Wang, Y. Cui, SERS-based DNA detection in aqueous solutions using oligonucleotide-modified Ag nanoprisms and gold nanoparticles, Anal. Bioanal. Chem. 405 (2013) 6131–6136.
[110] L.-J. Xu, Z.-C. Lei, J. Li, C. Zong, C.J. Yang, B. Ren, Label-free surface-enhanced Raman spectroscopy detection of DNA with single-base sensitivity, J. Am. Chem. Soc. 137 (2015) 5149–5154.
[111] J. Shen, J. Su, J.Y.B. Zhao, D. Wang, S. Wang, K. Li, M. Liu, Y. He, S. Mathur, C. Fan, S. Song, Email author, Bimetallic nano-mushrooms with DNA-mediated interior nanogaps for high-efficiency SERS signal amplification, Nano Res. 8 (2015) 731–742.
[112] J. Su, D. Wang, L. Norbel, J. Shen, Z. Zhao, Y. Dou, T. Peng, J. Shi, S. Mathur, C. Fan, S. Song, Multicolor gold-silver nano-mushrooms as ready-to-use SERS probes for ultrasensitive and multiplex DNA/miRNA detection, Anal. Chem. 89 (2017) 2531–2538.
[113] R. Guo, F. Yin, Y. Sun, L. Mi, L. Shi, Z. Tian, T. Li, Ultrasensitive simultaneous detection of multiplex disease-related nucleic acids using double-enhanced surface-enhanced Raman scattering nanosensors, ACS Appl. Mater. Interfaces 10 (2018) 25770–25778.
[114] Q. Zhou, J. Zheng, Z. Qing, M. Zheng, J. Yang, S. Yang, L. Ying, R. Yang, Detection of circulating tumor DNA in human blood via DNA-mediated surface-enhanced Raman spectroscopy of single-walled carbon nanotubes, Anal. Chem. 88 (2016) 4759–4765.
[115] O. Tian, M.J. Neumann, X. McClain, L. Yang, C. Zhou, P. Zhang, N.J. Nordlander, Halas, aluminum nanocrystals: a sustainable substrate for quantitative SERS-based DNA detection, Nano Lett. 17 (2017) 5071–5077.
[116] X. Li, F. Zheng, R. Ren, Detecting miRNA by producing RNA: a sensitive assay that combines rolling-circle DNA polymerization and rolling circle transcription, Chem. Commun. 51 (2015) 11976–11979.
[117] B. Guven, I.H. Boyaci, U. Tamer, E. Acar-Soykut, U. Dogan, Development of rolling circle amplification based surface-enhanced Raman spectroscopy method for 35S promoter gene detection, Talanta 136 (2015) 68–74.

[118] M. Shi, J. Zheng, Y. Tan, G. Tan, J. Li, Y. Li, X. Li, Z. Zhou, R. Yang, Ultrasensitive detection of single nucleotide polymorphism in human mitochondrial DNA utilizing ion-mediated cascade surface-enhanced Raman spectroscopy amplification, Anal. Chem. 87 (2015) 2734–2740.
[119] L.P. Ye, J. Hu, L. Liang, C.Y. Zhang, Surface-enhanced Raman spectroscopy for simultaneous sensitive detection of multiple microRNAs in lung cancer cells, Chem. Commun. 50 (2014) 11883–11886.
[120] Y. He, X. Yang, R. Yuan, Y. Chai, Switchable target-responsive 3D DNA hydrogels as a signal amplification strategy combining with SERS technique for ultrasensitive detection of miRNA 155, Anal. Chem. 89 (2017) 8538–8544.
[121] V.V. Thacker, L.O. Herrmann, D.O. Sigle, T. Zhang, T. Liedl, J.J. Baumberg, U.F. Keyser, DNA origami based assembly of gold nanoparticle dimers for surface-enhanced Raman scattering, Nat. Commun. 5 (2014) 3448.
[122] H. Di, H. Liu, M. Li, J. Li, D. Liu, High-precision profiling of sialic acid expression in cancer cells and tissues using background-free surface-enhanced Raman scattering tags, Anal. Chem. 89 (2017) 5874–5881.
[123] J. Guo, Y. Chen, Y. Jiang, H. Ju, Polyadenine-modulated DNA conformation monitored by surface-enhanced Raman scattering (SERS) on multibranched gold nanoparticles and its sensing application, polyadenine-modulated DNA conformation monitored by surface-enhanced Raman scattering (SERS) on multibranched gold nanoparticles and its sensing application, Chem. A Eur. J. 23 (2017) 9332–9337.
[124] S. Tanwar, K.K. Haldar, T. Sen, DNA origami directed Au nanostar dimers for single-molecule surface-enhanced Raman scattering, J. Am. Chem. Soc. 139 (2017) 17639–17648.
[125] Y. Zheng, A.H. Soeriyadi, S.H.N. Rosa, U. Bach, J.J. Gooding, Reversible gating of smart plasmonic molecular traps using thermoresponsive polymers for single-molecule detection, Nat. Commun. 6 (2015) 8797.
[126] Y. Chen, L. Ding, W. Song, M. Yang, H. Ju, Protein-specific Raman imaging of glycosylation on single cells with zone-controllable SERS effect, Chem. Sci. 7 (2016) 569–574.
[127] X. Wu, C. Hao, J. Kumar, H. Kuang, N.A. Kotov, L.M. Liz-Marzán, C. Xu, Environmentally responsive plasmonic nanoassemblies for biosensing, Chem. Soc. Rev. 47 (2018) 4677–4696.
[128] C. Zhou, H. Zou, C. Sun, D. Ren, J. Chen, Y. Li, Signal amplification strategies for DNA-based surface plasmon resonance biosensors, Biosens. Bioelectron. 117 (2018) 678–689.
[129] P. Liu, X. Yang, S. Sun, Q. Wang, K. Wang, J. Huang, J. Liu, L. He, Enzyme-free colorimetric detection of DNA by using gold nanoparticles and hybridization chain reaction amplification, Anal. Chem. 85 (2013) 7689–7695.
[130] W. Xu, X. Xue, T. Li, H. Zeng, X. Liu, Ultrasensitive and selective colorimetric DNA detection by nicking endonuclease assisted nanoparticle amplification, Angew. Chem. Int. Ed. 48 (2009) 6849–6852.
[131] Q. Liu, L. Li, Y. Zhao, Z. Chen, Colorimetric detection of DNA at the nanomolar level based on enzyme-induced gold nanoparticle de-aggregation, Mikrochim. Acta 185 (2018) 3.
[132] H. Ravan, Isothermal RNA detection through the formation of DNA concatemers containing HRP-mimicking DNAzymes on the surface of gold nanoparticles, Biosens. Bioelectron. 80 (2016) 67–73.
[133] M. Liu, C.Y. Hui, Q. Zhang, J. Gu, B. Kannan, S. Jahanshahi-Anbuhi, C.D. Filipe, J.D. Brennan, Y. Li, Target-induced and equipment-free DNA amplification with a simple paper device, Angew. Chem. Int. Ed. 55 (2016) 2709–2713.

[134] X.L. Li, Z.L. Zhang, W. Zhao, X.H. Xia, J.J. Xu, H.Y. Chen, Oriented assembly of invisible probes: towards single mRNA imaging in living cells, Chem. Sci. 7 (2016) 3256–3263.
[135] Y. Gu, J. Song, M.X. Li, T.T. Zhang, W. Zhao, J.J. Xu, M. Liu, H.Y. Chen, Ultrasensitive microRNA assay via surface plasmon resonance responses of Au@Ag nanorods etching, Anal. Chem. 89 (2017) 10585–10591.
[136] Z. Chen, Y. Peng, Y. Cao, H. Wang, J.-R. Zhang, H.-Y. Chen, J.-J. Zhu, Light-driven nano-oscillators for label-free single-molecule monitoring of microRNA, Nano Lett. 18 (2018) 3759–3765.
[137] G.-S. Qian, B. Kang, Z.-L. Zhang, X.-L. Li, W. Zhao, J.-J. Xu, H.-Y. Chen, Plasmonic nanohalo optical probes for highly sensitive imaging of survivin mRNA in living cells, Chem. Commun. 52 (2016) 11052–11055.
[138] T. Zhang, H. Li, S. Hou, Y. Dong, G. Pang, Y. Zhang, Construction of plasmonic core-satellite nanostructures on substrates based on DNA-directed self-assembly as a sensitive and reproducible biosensor, ACS Appl. Mater. Interfaces 7 (2015) 27131–27139.
[139] M.X. Li, C.H. Xu, N. Zhang, G.S. Qian, W. Zhao, J.J. Xu, H.Y. Chen, Exploration of the kinetics of toehold-mediated strand displacement via plasmon rulers, ACS Nano 12 (2018) 3341–3350.
[140] J. Li, Q. Liu, H. Xi, X. Wei, Z. Chen, Y-Shaped DNA duplex structure-triggered gold nanoparticle dimers for ultrasensitive colorimetric detection of nucleic acid with the dark-field microscope, Anal. Chem. 89 (2017) 12850–12856.
[141] K. Kim, J.W. Oh, Y.K. Lee, J. Son, J.M. Nam, Associating and dissociating nanodimer analysis for quantifying ultrasmall amounts of DNA, Angew. Chem. Int. Ed. 56 (2017) 9877–9880.
[142] T. Xie, M. Li, Y.T. Long, Dual-channel signals for intracellular mRNA detection via a PRET nanosensor, Chem. Commun. 53 (2017) 7768–7771.
[143] J. Yu, J. Jeon, N. Choi, J.O. Lee, Y.P. Kim, J. Choo, SERS-based genetic assay for amplification-free detection of prostate cancer specific PCA3 mimic DNA, Sens. Actuators B 251 (2017) 302–309.
[144] J. Zhou, Q.X. Wang, C.Y. Zhang, Liposome-quantum dot complexes enable multiplexed detection of attomolar DNAs without target amplification, J. Am. Chem. Soc. 135 (2013) 2056–2059.
[145] S. Bi, T. Zhao, B. Luo, J.J. Zhu, Hybridization chain reaction-based branched rolling circle amplification for chemiluminescence detection of DNA methylation, Chem. Commun. 49 (2013) 6906–6908.
[146] Y. Zhang, L. Wang, F. Luo, B. Qiu, L. Guo, Z. Weng, Z. Lin, G. Chen, An electrochemiluminescence biosensor for Kras mutations based on locked nucleic acid functionalized DNA walkers and hyperbranched rolling circle amplification, Chem. Commun. 53 (2017) 2910–2913.
[147] W.B. Zheng, C.Y. Liang, Y. Xiong, Y.Q. Zhuo, R. Chai, Yuan, universal ratiometric photoelectrochemical bioassay with target-nucleotide transduction-amplification and electron-transfer tunneling distance regulation strategies for ultrasensitive determination of microRNA in cells, Anal. Chem. 89 (2017) 9445–9451.
[148] X. Li, Y. Wang, L. Wang, Q. Wei, A surface plasmon resonance assay coupled with a hybridization chain reaction for amplified detection of DNA and small molecules, Chem. Commun. 50 (2014) 5049–5052.
[149] W. Sun, W. Song, X. Guo, Z. Wang, Ultrasensitive detection of nucleic acids and proteins using quartz crystal microbalance and surface plasmon resonance sensors based on target-triggering multiple signal amplification strategy, Anal. Chim. Acta 978 (2017) 42–47.

[150] R. Tavallaie, J. McCarroll, M. Le Grand, N. Ariotti, W. Schuhmann, E. Bakker, R.D. Tilley, D.B. Hibbert, M. Kavallaris, J.J. Gooding, Nucleic acid hybridization on an electrically reconfigurable network of gold-coated magnetic nanoparticles enables microRNA detection in blood, Nat. Nanotechnol. 13 (2018) 1066–1071.
[151] H. Zhang, Y. Liu, J. Gao, J. Zhen, A sensitive SERS detection of miRNA using a label-free multifunctional probe, Chem. Commun. 51 (2015) 16836–16839.
[152] S. Ye, Y. Wu, X. Zhai, B. Tang, Asymmetric signal amplification for simultaneous SERS detection of multiple cancer markers with significantly different levels, Anal. Chem. 87 (2015) 8242–8249.
[153] E.J.H. Wee, Y. Wang, S.C.H. Tsao, M. Trau, Simple, sensitive and accurate multiplex detection of clinically important melanoma DNA mutations in circulating tumour DNA with SERS nanotags, Theranostics 6 (2016) 1506–1513.
[154] Y. He, X. Yang, R. Yuan, Y. Chai, "Off" to "On" surface-enhanced Raman spectroscopy platform with padlock probe-based exponential rolling circle amplification for ultrasensitive detection of microRNA 155, Anal. Chem. 89 (2017) 2866–2872.
[155] Y. Liu, M. Luo, J. Yan, X. Xiang, X. Ji, G. Zhou, Z. He, An ultrasensitive biosensor for DNA detection based on hybridization chain reaction coupled with the efficient quenching of a ruthenium complex to CdTe quantum dots, Chem. Commun. 49 (2013) 7424–7426.
[156] X. Li, J. Song, Q. Xue, H. Zhao, M. Liu, B. Chen, Y. Liu, W. Jiang, C.Z. Li, Sensitive and selective detection of the p53 gene based on a triple-helix magnetic probe coupled to a fluorescent liposome hybridization assembly via rolling circle amplification, Analyst 142 (2017) 3598–3604.
[157] H. Fang, N. Xie, M. Ou, J. Huang, W. Li, Q. Wang, J. Liu, X. Yang, K. Wang, Detection of nucleic acids in complex samples via magnetic microbead-assisted catalyzed hairpin assembly and "DD-A" FRET, Anal. Chem. 90 (2018) 7164–7170.
[158] S. Yue, T. Zhao, S. Bi, Z. Zhang, Programmable strand displacement-based magnetic separation for simultaneous amplified detection of multiplex microRNAs by chemiluminescence imaging array, Biosens. Bioelectron. 98 (2017) 234–239.
[159] L. Yang, Y. Tao, G. Yue, R. Li, B. Qiu, L. Guo, Z. Lin, H.H. Yang, Highly selective and sensitive electrochemiluminescence biosensor for p53 DNA sequence based on nicking endonuclease assisted target recycling and hyperbranched rolling circle amplification, Anal. Chem. 88 (2016) 5097–5103.
[160] P. He, W. Qiao, L. Liu, S. Zhang, A highly sensitive surface plasmon resonance sensor for the detection of DNA and cancer cells by a target-triggered multiple signal amplification strategy, Chem. Commun. 50 (2014) 10718–10721.
[161] Y. Li, Y. Chang, R. Yuan, Y. Chai, Highly efficient target recycling-based netlike Y-DNA for regulation of electrocatalysis toward methylene blue for sensitive DNA detection, ACS Appl. Mater. Interfaces 10 (2018) 25213–25218.
[162] Y.H. Yuan, Y.D. Wu, B.Z. Chi, S.H. Wen, R.P. Liang, J.D. Qiu, Simultaneously electrochemical detection of microRNAs based on multifunctional magnetic nanoparticles probe coupling with hybridization chain reaction, Biosens. Bioelectron. 97 (2017) 325–331.
[163] V. R.-Valdepeñas Montiel, E. Povedano, E. Vargas, R.M. Torrente-RodrĺGuez, M. Pedrero, A.J. Reviejo, S. Campuzano, J.M. Pingarrón, Comparison of different strategies for the development of highly sensitive electrochemical nucleic acid biosensors using neither nanomaterials nor nucleic acid amplification, ACS Sens. 3 (2018) 211–221.
[164] F. Li, Y. Dong, Z. Zhang, M. Lv, Z. Wang, X. Ruan, D. Yang, A recyclable biointerface based on cross-linked branched DNA nanostructures for ultrasensitive nucleic acid detection, Biosens. Bioelectron. 117 (2018) 562–566.

[165] P. Hu, S. Zhang, T. Wu, D. Ni, W. Fan, Y. Zhu, R. Qian, J. Shi, Fe-Au nanoparticle-coupling for ultrasensitive detections of circulating tumor DNA, Adv. Mater. 30 (2018) 1801690.
[166] W. Lu, Y. Chen, Z. Liu, W. Tang, Q. Feng, J. Sun, X. Jiang, Quantitative detection of microRNA in one step via next generation magnetic relaxation switch sensing, ACS Nano 10 (2016) 6685–6692.
[167] B. Tian, Z. Qiu, J. Ma, M. Donolato, M.F. Hansen, P. Svedlindh, M. Stromberg, On-particle rolling circle amplification-based core-satellite magnetic superstructures for microRNA detection, ACS Appl. Mater. Interfaces 10 (2018) 2957–2964.
[168] F. Ma, C.C. Li, C.Y. Zhang, Development of quantum dot-based biosensors: principles and applications, J. Mater. Chem. B 6 (2018) 6173–6190.
[169] W. Tang, G. Zhu, L. Liang, C.Y. Zhang, A single quantum dot-based biosensor for DNA point mutation assay, Analyst 140 (2015) 5936–5943.
[170] O. Zavoiura, U. Resch-Genger, O. Seitz, Quantum dot-PNA conjugates for target-catalyzed RNA detection, Bioconjug. Chem. 29 (2018) 1690–1702.
[171] J. Hu, M.H. Liu, C.Y. Zhang, Integration of isothermal amplification with quantum dot-based fluorescence resonance energy transfer for simultaneous detection of multiple microRNAs, Chem. Sci. 9 (2018) 4258–4267.
[172] M. Shanehsaz, A. Mohsenifar, S. Hasannia, N. Pirooznia, Y. Samaei, M. Shamsipur, Detection of helicobacter pylori with a nanobiosensor based on fluorescence resonance energy transfer using CdTe quantum dots, Microchim. Acta. 180 (2012) 195–202.
[173] Y. Wang, P.D. Howes, E. Kim, C.D. Spicer, M.R. Thomas, Y. Lin, S.W. Crowder, I.J. Pence, M.M. Stevens, Duplex-specific nuclease-amplified detection of microRNA using compact quantum dot-DNA conjugates, ACS Appl. Mater. Interfaces 10 (2018) 28290–28300.
[174] A.F. Jou, C.H. Lu, Y.C. Ou, S.S. Wang, S.L. Hsu, I. Willner, J.A. Ho, Diagnosing the miR-141 prostate cancer biomarker using nucleic acid-functionalized CdSe/ZnS QDs and telomerase, Chem. Sci. 6 (2015) 659–665.
[175] S. Su, J. Fan, B. Xue, L. Yuwen, X. Liu, D. Pan, C. Fan, L. Wang, DNA-conjugated quantum dot nanoprobe for high-sensitivity fluorescent detection of DNA and microRNA, ACS Appl. Mater. Interfaces 6 (2014) 1152–1157.
[176] Y. Liu, A. Kannegulla, B. Wu, L.J. Cheng, Quantum dot Fullerene-Based molecular beacon nanosensors for rapid, highly sensitive nucleic acid detection, ACS Appl. Mater. Interfaces 10 (2018) 18524–18531.
[177] Y. Shen, N. Zhang, Y. Sun, W.W. Zhao, D. Ye, J.J. Xu, H.Y. Chen, Activatable QD-based near-infrared fluorescence probe for sensitive detection and imaging of DNA, ACS Appl. Mater. Interfaces 9 (2017) 25107–25113.
[178] X. Qiu, N. Hildebrandt, Rapid and multiplexed microRNA diagnostic assay using quantum dot-based förster resonance energy transfer, ACS Nano 9 (2015) 8449–8457.
[179] Z. Li, Z. Lin, X. Wu, H. Chen, Y. Chai, R. Yuan, Highly efficient electrochemiluminescence resonance energy transfer system in one nanostructure: its application for ultrasensitive detection of microRNA in cancer cells, Anal. Chem. 89 (2017) 6029–6035.
[180] W.W. Zhao, J.J. Xu, H.Y. Chen, Photoelectrochemical DNA biosensors, Chem. Rev. 114 (2014) 7421–7441.
[181] G.L. Wang, J.X. Shu, Y.M. Dong, X.M. Wu, W.W. Zhao, J.J. Xu, H.Y. Chen, Using G-quadruplex/hemin to "Switch-On" the cathodic photocurrent of p-type PbS quantum dots: toward a versatile platform for photoelectrochemical aptasensing, Anal. Chem. 87 (2015) 2892–2900.
[182] G.C. Fan, L. Han, J.R. Zhang, J.J. Zhu, Enhanced photoelectrochemical strategy for ultrasensitive DNA detection based on two different sizes of CdTe quantum dots cosensitized TiO2/CdS:Mn hybrid structure, Anal. Chem. 86 (2014) 10877–10884.

[183] Y. Zang, J. Lei, P. Ling, H. Ju, Catalytic hairpin assembly-programmed porphyrin–DNA complex as photoelectrochemical initiator for DNA biosensing, Anal. Chem. 87 (2015) 5430–5436.
[184] Y. Zang, J. Lei, Q. Hao, H. Ju, CdS/MoS 2 heterojunction-based photoelectrochemical DNA biosensor via enhanced chemiluminescence excitation, Biosens. Bioelectron. 77 (2016) 557–564.
[185] H. Cao, S. Liu, W. Tu, J. Bao, Z. Dai, A carbon nanotube/quantum dot based photoelectrochemical biosensing platform for the direct detection of microRNAs, Chem. Commun. 50 (2014) 13315–13318.
[186] X.M. Shi, G.C. Fan, Q. Shen, J.J. Zhu, 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 (2016) 35091–35098.
[187] W. Wang, Q. Hao, W. Wang, L. Bao, J. Lei, Q. Wang, H. Ju, Quantum dot-functionalized porous ZnO nanosheets as a visible light induced photoelectrochemical platform for DNA detection, Nanoscale 6 (2014) 2710–2717.
[188] K.S. Novoselov, A.K. Geim, S.V. Morozov, D. Jiang, Y. Zhang, S.V. Dubonos, I.V. Grigorieva, A.A. Firsov, Electric field effect in atomically thin carbon films, Science 306 (2004) 666–669.
[189] F. Li, J. Chao, Z. Li, S. Xing, S. Su, X. Li, S. Song, X. Zuo, C. Fan, B. Liu, W. Huang, L. Wang, L. Wang, Graphene oxide-assisted nucleic acids assays using conjugated polyelectrolytes-based fluorescent signal transduction, Anal. Chem. 87 (2015) 3877–3883.
[190] S.J. Zhen, X. Xiao, C.H. Li, C.Z. Huang, An enzyme-free DNA circuit-assisted graphene oxide enhanced fluorescence anisotropy assay for microRNA detection with improved sensitivity and selectivity, Anal. Chem. 89 (2017) 8766–8771.
[191] W. Pan, B. Liu, X. Gao, Z. Yu, X. Liu, N. Li, B. Tang, A graphene-based fluorescent nanoprobe for simultaneous monitoring of miRNA and mRNA in living cells, Nanoscale 10 (2018) 14264–14271.
[192] L. Yang, J. Li, W. Pan, H. Wang, N. Li, B. Tang, Fluorescence and photoacoustic dual-mode imaging of tumor-related mRNA with a covalent linkage-based DNA nanoprobe, Chem. Commun. 54 (2018) 3656–3659.
[193] X. Zhu, Y. Shen, J. Cao, L. Yin, F. Ban, Y. Shu, G. Li, Detection of microRNA SNPs with ultrahigh specificity by using reduced graphene oxide-assisted rolling circle amplification, Chem. Commun. 51 (2015) 10002–10005.
[194] H. Yan, Y. Xu, Y. Lu, W. Xing, Reduced graphene oxide-based solid-phase extraction for the enrichment and detection of microRNA, Anal. Chem. 89 (2017) 10137–10140.
[195] X. Fan, Y. Qi, Z. Shi, Y. Lv, Y. Guo, A graphene-based biosensor for detecting microRNA with augmented sensitivity through helicase-assisted signal amplification of hybridization chain reaction, Sens. Actuators B 255 (2018) 1582–1586.
[196] C. Hong, A. Baek, S.S. Hah, W. Jung, D.E. Kim, Fluorometric detection of microRNA using isothermal gene amplification and graphene oxide, Anal. Chem. 88 (2016) 2999–3003.
[197] Z. Zhang, Y. Wang, N. Zhang, S. Zhang, Self-assembly of nucleic acid molecular aggregates catalyzed by a triple-helix probe for miRNA detection and single cell imaging, Chem. Sci. 7 (2016) 4184–4189.
[198] L. Li, J. Feng, H. Liu, Q. Li, L. Tong, B. Tang, Two-color imaging of microRNA with enzyme-free signal amplification via hybridization chain reactions in living cells, Chem. Sci. 7 (2016) 1940–1945.

[199] X.M. Shi, G.C. Fan, X. Tang, Q. Shen, J.J. Zhu, Ultrasensitive photoelectrochemical biosensor for the detection of HTLV-I DNA: a cascade signal amplification strategy integrating λ-exonuclease aided target recycling with hybridization chain reaction and enzyme catalysis, Biosens. Bioelectron. 109 (2018) 190–196.
[200] Z. Gao, H. Xia, J. Zauberman, M. Tomaiuolo, J. Ping, Q. Zhang, P. Ducos, H. Ye, S. Wang, X. Yang, F. Lubna, Z. Luo, L. Ren, A.T.C. Johnson, Detection of sub-fM DNA with target recycling and self-assembly amplification on graphene field-effect biosensors, Nano Lett. 18 (2018) 3509–3515.
[201] C. Chen, B. Li, Graphene oxide-based homogenous biosensing platform for ultrasensitive DNA detection based on chemiluminescence resonance energy transfer and exonuclease III-assisted target recycling amplification, J. Mater. Chem. B 1 (2013) 2476.
[202] H. Zhou, Y.Y. Zhang, J. Liu, J.J. Xu, H.Y. Chen, Efficient quenching of electrochemiluminescence from K-doped graphene-CdS: Eu NCs by G-quadruplex-hemin and target recycling-assisted amplification for ultrasensitive DNA biosensing, Chem. Commun. 49 (2013) 2246–2248.
[203] S. Barua, H.S. Dutta, S. Gogoi, R. Devi, R. Khan, Nanostructured MoS2-based advanced biosensors: a review, ACS Appl. Nano Mater. 1 (2018) 2–25.
[204] F. Chen, M. Bai, K. Cao, Y. Zhao, X. Cao, J. Wei, N. Wu, J. Li, L. Wang, C. Fan, Y. Zhao, Programming enzyme-initiated autonomous DNAzyme nanodevices in living cells, ACS Nano 11 (2017) 11908–11914.
[205] Q. Xi, D.M. Zhou, Y.Y. Kan, J. Ge, Z.K. Wu, R.Q. Yu, J.H. Jiang, Highly sensitive and selective Strategy for MicroRNA detection based on WS2 nanosheet mediated fluorescence quenching and duplex-specific nuclease signal amplification, Anal. Chem. 86 (2014) 1361–1365.
[206] Y. Song, X. Yan, G. Ostermeyer, S. Li, L. Qu, D. Du, Z. Li, Y. Lin, Direct cytosolic microRNA detection using single-layer perfluorinated tungsten diselenide nanoplatform, Anal. Chem. 90 (2018) 10369–10376.
[207] C. Tan, P. Yu, Y. Hu, J. Chen, Y. Huang, Y. Cai, Z. Luo, B. Li, Q. Lu, L. Wang, Z. Liu, H. Zhang, High-yield exfoliation of ultrathin two-dimensional ternary chalcogenide nanosheets for highly sensitive and selective fluorescence DNA sensors, J. Am. Chem. Soc. 137 (2015) 10430–10436.
[208] C. Zhu, Z. Zeng, H. Li, F. Li, C. Fan, H. Zhang, Single-layer MoS2-based nanoprobes for homogeneous detection of biomolecules, J. Am. Chem. Soc. 135 (2013) 5998–6001.
[209] M. Xiao, T. Man, C. Zhu, H. Pei, J. Shi, L. Li, X. Qu, X. Shen, J. Li, MoS2 nanoprobe for MicroRNA quantification based on duplex-specific nuclease signal amplification, ACS Appl. Mater. Interfaces 10 (2018) 7852–7858.
[210] M. Xiao, A.R. Chandrasekaran, W. Ji, F. Li, T. Man, C. Zhu, X. Shen, H. Pei, Q. Li, L. Li, Affinity-modulated molecular beacons on MoS2 nanosheets for MicroRNA detection, ACS Appl. Mater. Interfaces 10 (2018) 35794–35800.
[211] G. Oudeng, M. Au, J. Shi, C. Wen, M. Yang, One-Step in situ detection of miRNA-21 expression in single cancer cells based on biofunctionalized MoS2 nanosheets, ACS Appl. Mater. Interfaces 10 (2018) 350–360.
[212] H. Fan, Z. Zhao, G. Yan, X. Zhang, C. Yang, H. Meng, Z. Chen, H. Liu, W. Tan, A smart DNAzyme-MnO(2) nanosystem for efficient gene silencing, Angew. Chem. Int. Ed. 54 (2015) 4801–4805.
[213] J. Li, D. Li, R. Yuan, Y. Xiang, Biodegradable MnO_2 nanosheet-mediated signal amplification in living cells enables sensitive detection of down-regulated intracellular microRNA, ACS Appl. Mater. Interfaces 9 (2017) 5717–5724.

[214] F. Chen, M. Bai, K. Cao, Y. Zhao, J. Wei, Y. Zhao, Fabricating MnO2 nanozymes as intracellular catalytic DNA circuit generators for versatile imaging of base-excision repair in living cells, Adv. Funct. Mater. 27 (2017) 1702748.
[215] M.S. Hizir, N. Nandu, M.V. Yigit, Homologous miRNA analyses using a combinatorial nanosensor array with two-dimensional nanoparticles, Anal. Chem. 90 (2018) 6300–6306.
[216] H. Furukawa, K.E. Cordova, M. O'Keeffe, O.M. Yaghi, The chemistry and applications of metal-organic frameworks, Science 341 (2013) 1230444.
[217] M. Zhao, Y. Wang, Q. Ma, Y. Huang, X. Zhang, J. Ping, Z. Zhang, Q. Lu, Y. Yu, H. Xu, Y. Zhao, H. Zhang, Ultrathin 2D metal-organic framework nanosheets, Adv. Mater. 27 (2015) 7372–7378.
[218] L. Qin, L.X. Lin, Z.P. Fang, S.P. Yang, G.H. Qiu, J.X. Chen, W.H. Chen, A water-stable metal-organic framework of a zwitterionic carboxylate with dysprosium: a sensing platform for Ebolavirus RNA sequences, Chem. Commun. 52 (2016) 132–135.
[219] H.T. Zhang, J.W. Zhang, G. Huang, Z.Y. Du, H.L. Jiang, An amine- functionalized metal-organic framework as a sensing platform for DNA detection, Chem. Commun. 50 (2014) 12069–12072.
[220] T. Ye, Y. Liu, M. Luo, X. Xiang, X. Ji, G. Zhou, Z. He, Metal-organic framework-based molecular beacons for multiplexed DNA detection by synchronous fluorescence analysis, Analyst 139 (2014) 1721–1725.
[221] J.F. Guo, R.M. Fang, C.Z. Huang, Y.F. Li, Dual amplifying fluorescence anisotropy for detection of respiratory syncytial virus DNA fragments with size- control synthesized metal-organic framework MIL-101, RSC Adv. 5 (2015) 46301–46306.
[222] H.S. Wang, H.L. Liu, K. Wang, Y. Ding, J.J. Xu, X.H. Xia, H.Y. Chen, Insight into the unique fluorescence quenching property of metal-organic frameworks upon DNA binding, Anal. Chem. 89 (2017) 11366–11371.
[223] J. Tian, Q. Liu, J. Shi, J. Hu, A.M. Asiri, X. Sun, Y. He, Rapid, sensitive, and selective fluorescent DNA detection using iron-basedmetal-organic framework nanorods: Synergies of the metal center and organiclinker, Biosens. Bioelectron. 71 (2015) 1–6.
[224] L. Xu, P. Zhang, Y. Liu, X. Fang, Z. Zhang, Y. Liu, L. Peng, J. Liu, Continuously tunable nucleotide/lanthanide coordination nanoparticles for DNA adsorption and sensing, ACS Omega. 3 (2018) 9043–9051.
[225] S. Wu, C. Li, H. Shi, Y. Huang, G. Li, Design of metal-organic framework- based nanoprobes for multicolor detection of DNA targets with improved sensitivity, Anal. Chem. 90 (2018) 9929–9935.
[226] P. Ling, J. Lei, L. Zhang, H. Ju, Porphyrin-encapsulated metal – organic frameworks as mimetic catalysts for electrochemical DNA sensing via allosteric switch of hairpin DNA, Anal. Chem. 87 (2015) 3957–3963.
[227] J. Zheng, D. Ma, M. Shi, J. Bai, Y. Li, J. Yang, R. Yang, A new enzyme-free quadratic SERS signal amplification approach for circulating microRNA detection in human serum, Chem. Commun. 51 (2015) 16271–16274.
[228] F. Gao, J. Lei, H. Ju, Sensitive fluorescence detection of DNA using isothermal exponential amplification coupled quantum dots coated silica nanospheres as label3, RSC Adv. 3 (2013) 13163–13168.
[229] P. Zhang, F. Cheng, R. Zhou, J. Cao, J. Li, C. Burda, Q. Min, J.J. Zhu, DNA-hybrid-gated multifunctional mesoporous silica nanocarriers for dual-targeted and microRNA-responsive controlled drug delivery, Angew. Chem. 53 (2014) 2371–2375.
[230] Z. Zhang, D. Balogh, F. Wang, S.Y. Sung, R. Nechushtai, I. Willner, Biocatalytic release of an anti-cancer drug from nucleic-acids-capped mesoporous SiO2 using DNA or molecular biomarkers as triggering stimuli, ACS Nano 7 (2013) 8455–8468.

[231] X. Wang, M. Cui, H. Zhou, S. Zhang, DNA-hybrid-gated functional mesoporous silica for sensitive DNA methyltransferase SERS detection, Chem. Commun. 51 (2015) 13983–13985.
[232] P. Gai, C. Gu, H. Li, X. Sun, F. Li, Ultrasensitive ratiometric homogeneous electrochemical microRNA biosensing via target-triggered Ru(III) release and redox recycling, Anal. Chem. 89 (2017) 12293–12298.
[233] P. Gai, C. Gu, T. Hou, F. Li, Integration of biofuel cell-based self-powered biosensing and homogeneous electrochemical strategy for ultrasensitive and easy- to-use bioassays of microRNA, ACS Appl. Mater. Interfaces 10 (2018) 9325–9331.
[234] J. Wang, X.L. Li, J.D. Zhang, N. Hao, J.J. Xu, H.Y. Chen, Integrati on of DNA bio-gates and duplex-specific nuclease signal amplification: towards electrochemiluminescence detection of surviving mRNA, Chem. Commun. 51 (2015) 11673–11676.
[235] P. Zhang, Z. He, C. Wang, J. Chen, J. Zhao, X. Zhu, C.Z. Li, Q. Min, J.J. Zhu, In situ amplification of intracellular microRNA with MN azyme nanodevices for multiplexed imaging, logic operation, and controlled drug release, ACS Nano 9 (2015) 789–798.
[236] X. Meng, W. Dai, K. Zhang, H. Dong, X. Zhang, Imaging multiple microRNAs in living cells using ATP self-powered strand-displacement cascade amplification, Chem. Sci. 9 (2018) 1184–1190.
[237] D. MendezGonzalez, M. Laurenti, A. Latorre, Á. Somoza, A. Vazquez, A.I. Negredo, E. LopezCabarcos, O.G. Calderón, S. Melle, J. RubioRetama, Oligonucleotide sensor based on selective capture of upconversion nanoparticles triggered by target-induced DNA inter-strand ligand reaction, ACS Appl. Mater. Interfaces 9 (2017) 12272–12281.
[238] M.K. Tsang, W.W. Ye, G. Wang, J. Li, M. Yang, J. Hao, Ultrasensitive detection of ebola virus oligonucleotide based on upconversion nanoprobe/nanoporous membrane system, ACS Nano 10 (2016) 598–605.
[239] W.W. Ye, M.K. Tsang, X. Liu, M. Yang, J. Hao, Upconversion luminescence resonance energy transfer (LRET)-based biosensor for rapid and ultrasensitive detection of Avian Infl uenza virus H7 subtype, Small 10 (2014) 2390–2397.
[240] P. AlonsoCristobal, P. Vilela, A. ElSagheer, E. LopezCabarcos, T. Brown, O.L. Muskens, J. RubioRetama, A.G. Kanaras, Highly sensitive DNA sensor based on upconversion nanoparticles and graphene oxide, ACS Appl. Mater. Interfaces 7 (2015) 12422–12429.
[241] D. Zhu, Z.Y. Miao, Y. Hu, X.J. Zhang, Single-step, homogeneous and sensitive detection for microRNAs with dual-recognition steps based on luminescence resonance energy transfer (LRET) using upconversion nanoparticles, Biosens. Bioelectron. 100 (2018) 475–481.
[242] Y. Chen, H.T.T. Duong, S. Wen, C. Mi, Y. Zhou, O. Shimoni, S.M. Valenzuela, D. Jin, Exonuclease III-assisted upconversion resonance energy transfer in a wash-free suspension DNA assay, Anal. Chem. 90 (2018) 663–668.
[243] Y. Wang, Z. Wu, Z. Liu, Upconversion fluorescence resonance energy transfer biosensor with aromatic polymer nanospheres as the lable-free energy acceptor, Anal. Chem. 85 (2013) 258–264.
[244] J.G.J. Raj, M. Quintanilla, K.A. Mahmoud, A. Ng, F. Vetrone, M. Zourob, Sensitive detection of ssDNA using an LRET-based upconverting nanohybrid material, ACS Appl. Mater. Interfaces 7 (2015) 18257–18265.
[245] Q. Ding, Q. Zhan, X. Zhou, T. Zhang, D. Xing, Theranostic upconversion nanobeacons for tumor mRNA ratiometric fluorescence detection and imaging- monitored drug delivery, Small 12 (2016) 5944–5953.
[246] R. Gao, C. Hao, L. Xu, C. Xu, H. Kuang, Spiny nanorod and upconversion nanoparticle satellite assemblies for ultrasensitive detection of messenger RNA in living cells, Anal. Chem. 90 (2018) 5414–5421.

[247] K. Zhang, S. Song, S. Huang, L. Yang, Q. Min, X. Wu, F. Lu, J.J. Zhu, Lighting up microRNA in living cells by the disassembly of lock-like DNA-programmed UCNPs-AuNPs through the target cycling amplification strategy, Small 14 (2018) 1802292.
[248] H. Ren, Z. Long, X. Shen, Y. Zhang, J. Sun, J. Ouyang, N. Na, Sandwich DNA hybridization fluorescence resonance energy-transfer strategy for miR-122 detection by core-shell upconversion nanoparticles, ACS Appl. Mater. Interfaces 10 (2018) 25621–25628.
[249] Y. Cen, W.J. Deng, Y. Yang, R.Q. Yu, X. Chu, A core-shell-shell multifunctional nanoplatform for intracellular tumor-related mRNAs imaging and near-infrared light triggered photodynamic-photothermal synergistic therapy, Anal. Chem. 89 (2017) 10321–10328.
[250] W. Qiang, W. Li, X. Li, X. Chen, D. Xu, Bioinspired polydopamine nanospheres: a superquencher for fluorescence sensing of biomolecules, Chem. Sci. 5 (2014) 3018–3024.
[251] Y. Meng, P. Liu, W. Zhou, J. Ding, J. Liu, Bioorthogonal DNA adsorption on polydopamine nanoparticles mediated by metal coordination for highly robust sensing in serum and living cells, ACS Nano 12 (2018) 9070–9080.
[252] S. Xu, Y. Nie, L. Jiang, J. Wang, G. Xu, W. Wang, X. Luo, Polydopamine nanosphere/gold nanocluster (Au NC)-based nanoplatform for dual color simultaneous detection of multiple tumor-related microRNAs with DNase- I-assisted target recycling amplification, Anal. Chem. 90 (2018) 4039–4045.
[253] C.K. Choi, J. Li, Y.J. Xu, L.W. Ho, M. Zhu, K.K. To, C.H.J. Choi, L. Bian, A gold@polydopamine core-shell nanoprobe for long-term intracellular detection of microRNAs in differentiating stem cells, J. Am. Chem. Soc. 137 (2015) 7337–7346.
[254] D. He, X. He, X. Yang, H.W. Li, A smart ZnO@polydopamine-nucleic acid nanosystem for ultrasensitive live cell mRNA imaging by the target-triggered intracellular selfassembly of active DNAzyme nanostructures, Chem. Sci. 8 (2017) 2832–2840.
[255] Q. Wang, B.C. Yin, B.C. Ye, A novelpolydopamine-based chemiluminescence resonanceenergy transfer method for microRNA detection coupling duplex-specific nuclease-aided target recycling strategy, Biosens. Bioelectron. 80 (2016) 366–372.
[256] M. Mayer, S. Takegami, M. Neumeier, S. Rink, A.J. Wangelin, S. Schulte, M. Vollmer, A.G. Griesbeck, A. Duerkop, A.J. Baeumner, Electrochemiluminescence bioassays with a water-soluble luminol derivative can outperform fluorescence assays, Angew. Chem. Int. Ed. 57 (2018) 408–411.
[257] Y. Gao, B. Li, G-Quadruplex DNAzyme-based chemiluminescence biosensing strategy for ultrasensitive DNA detection: combination of exonuclease III-assisted signal amplification and carbon nanotubes-assisted background reducing, Anal. Chem. 85 (2013) 11494–11500.
[258] Y. Xia, L. Wang, J. Li, X. Chen, J. Lan, A. Yan, Y. Lei, S. Yang, H. Yang, J. Chen, A ratiometric fluorescent bioprobe based on carbon dots and acridone derivate for signal amplification detection exosomal microRNA, Anal. Chem. 90 (2018) 8969–8976.
[259] Y. Feng, F. Sun, N. Wang, J. Lei, H. Ju, $Ru(bpy)_3^{2+}$ incorporated luminescent polymer dots: double-enhanced electrochemiluminescence for detection of single-nucleotide polymorphism, Anal. Chem. 89 (2017) 7659–7666.
[260] R.H. Fei, C. Tan, Y. Huang, H.C. Chen, A.Z. Guo, H.L. Wang, Y.G. Hu, Self-Assembled Ti^{4+}@Biospore microspheres for sensitive DNA analysis, ACS Appl. Mater. Interfaces 9 (2017) 34696–34705.
[261] N.C. Seeman, H.F. Sleiman, DNA nanotechnology, Nat. Rev. Mater. 3 (2017) 17068.
[262] F. Yang, Q. Li, L. Wang, G.-J. Zhang, C.H. Fan, Framework-nucleic-acid-enabled biosensor development, ACS Sens. 3 (2018) 903–919.

[263] Y. Zhang, J. Tu, D. Wang, H. Zhu, S.K. Maity, X. Qu, B. Bogaert, H. Pei, H. Zhang, Programmable and multifunctional DNA-based materials for biomedical applications, Adv. Mater. 1703658 (2018).
[264] Q. Hu, H. Li, L. Wang, H. Gu, C.H. Fan, DNA nanotechnology-enabled drug delivery systems. Chem. Rev. (2018). https://doi.org/10.1021/acs.chemrev.7b00663.
[265] R.P. Goodman, R.M. Berrya, A.J. Turberfielda, The single-step synthesis of a DNA tetrahedron, Chem. Commun. (2004) 1372–1373.
[266] X. Zhou, M. Zhao, X. Duan, B. Guo, W. Cheng, S. Ding, H. Ju, Collapse of DNA tetrahedron nanostructure for "Off−On" fluorescence detection of DNA methyltransferase activity, ACS Appl. Mater. Interfaces 9 (2017) 40087–40093.
[267] X. Yang, Y. Wen, L. Wang, C. Zhou, Q. Li, L. Xu, L. Li, J. Shi, R. Lal, S. Ren, J. Li, N. Jia, G. Liu, PCR-free colorimetric DNA hybridization detection using a 3D DNA nanostructured reporter probe, ACS Appl. Mater. Interfaces 9 (2017) 38281–38287.
[268] F. Xu, H. Dong, Y. Cao, H. Lu, X. Meng, W. Dai, X. Zhang, K.A. Al-Ghanim, S. Mahboob, Ultrasensitive and multiple disease-related microRNA detection based on tetrahedral DNA nanostructures and duplex-specific nuclease-assisted signal amplification, ACS Appl. Mater. Interfaces 8 (2016) 33499–33505.
[269] D. Ye, X. Zuo, C. Fan, DNA nanotechnology-enabled interfacial engineering for biosensor development, Annu. Rev. Anal. Chem. 11 (2018) 171–195.
[270] H. Pei, X. Zuo, D. Pan, J. Shi, Q. Huang, C. Fan, Scaffolded biosensors with designed DNA nanostructures, NPG Asia Mater. 5 (2013) e51.
[271] S. Dong, R. Zhao, J. Zhu, X. Lu, Y. Li, S. Qiu, L. Jia, X. Jiao, S. Song, C. Fan, R. Hao, H. Song, Electrochemical DNA biosensor based on a tetrahedral nanostructure probe for the detection of avian influenza A (H7N9) virus, ACS Appl. Mater. Interfaces 7 (2015) 8834–8842.
[272] M. Lin, J. Wang, G. Zhou, J. Wang, N. Wu, J. Lu, J. Gao, X. Chen, J. Shi, X. Zuo, C. Fan, Programmable engineering of a biosensing interface with tetrahedral DNA nanostructures for ultrasensitive DNA detection, Angewandte Chemie. 54 (2015) 2151–2155.
[273] Z. Ge, M. Lin, P. Wang, H. Pei, J. Yan, J. Shi, Q. Huang, D. He, C. Fan, X. Zuo, Hybridization chain reaction amplification of microRNA detection with a tetrahedral DNA nanostructure-based electrochemical biosensor, Anal. Chem. 86 (2014) 2124–2130.
[274] X. Wang, F. Chen, D. Zhang, Y. Zhao, J. Wei, L. Wang, S. Song, C. Fan, Y. Zhao, Single copy-sensitive electrochemical assay for circulating methylated DNA in clinical samples with ultrahigh specificity based on a sequential discrimination-amplification strategy, Chem. Sci. 8 (2017) 4764–4770.
[275] Y. Wena, G. Liu, H. Pei, L. Li, Q. Xu, W. Liang, Y. Li, L. Xu, S. Ren, C. Fan, DNA nanostructure-based ultrasensitive electrochemical microRNA Biosensor, Methods 64 (2013) 276–282.
[276] Y.L. Huang, S. Mo, Z.F. Gao, J.R. Chen, J.L. Lei, H.Q. Luo, N.B. Li, Amperometric biosensor for microRNA based on the use of tetrahedral DNA nanostructure probes and guanine nanowire amplification, Microchim. Acta 184 (2017) 2597–2604.
[277] M. Lin, Y. Wen, L. Li, H. Pei, G. Liu, H. Song, X. Zuo, C. Fan, Q. Huang, Target-responsive, DNA nanostructure-based E-DNA sensor for microRNA analysis, Anal. Chem. 86 (2014) 2285–2288.
[278] P. Miao, Y. Tang, J. Yina, MicroRNA detection based on analyte triggered nanoparticle localization on a tetrahedral DNA modified electrode followed by hybridization chain reaction dual amplification, Chem. Commun. 51 (2015) 15603–15740.
[279] P. Miao, B. Wang, X. Chen, X. Li, Y. Tang, Tetrahedral DNA nanostructure-based microRNA biosensor coupled with catalytic recycling of the analyte, ACS Appl. Mater. Interfaces 7 (2015) 6238–6243.

[280] P. Miao, B. Wang, F. Meng, J. Yin, Y. Tang, Ultrasensitive detection of microRNA through rolling circle amplification on a DNA tetrahedron decorated electrode, Bioconjug. Chem. 26 (2015) 602–607.
[281] D. Zeng, Z. Wang, Z. Meng, P. Wang, L. San, W. Wang, A. Aldalbahi, L. Li, J. Shen, X. Mi, DNA tetrahedral nanostructure-based electrochemical miRNA biosensor for simultaneous detection of multiple miRNAs in pancreatic carcinoma, ACS Appl. Mater. Interfaces 9 (2017) 24118–24125.
[282] Q.M. Feng, Y.H. Guo, J.J. Xu, H.Y. Chen, A surface-confined DNA assembly amplification strategy on DNA nanostructural scaffold for electrochemiluminescence biosensing, Biosens. Bioelectron. 100 (2018) 571–576.
[283] Q.M. Feng, Y.H. Guo, J.J. Xu, H.Y. Chen, Self-assembled DNA tetrahedral scaffolds for the construction of electrochemiluminescence biosensor with programmable DNA cyclic amplification, ACS Appl. Mater. Interfaces 9 (2017) 17637–17644.
[284] M.X. Li, Q.M. Feng, Z. Zhou, W. Zhao, J.J. Xu, H.Y. Chen, Plasmon-enhanced electrochemiluminescence for nucleic acid detection based on gold nanodendrites, Anal. Chem. 90 (2018) 1340–1347.
[285] H. Lu, J. Pan, Y. Wang, S.Y. Ji, W. Zhao, X. Luo, J.J. Xu, H.Y. Chen, Electrochemiluminescence energy resonance transfer system between RuSi nanoparticles and hollow Au nanocages for nucleic acid detection, Anal. Chem. 90 (2018) 10434–10441.
[286] Y. Zhou, H. Wang, H. Zhang, Y. Chai, R. Yuan, Programmable modulation of copper nanoclusters electrochemiluminescence via DNA nanocranes for ultrasensitive detection of microRNA, Anal. Chem. 90 (2018) 3543–3549.
[287] W. Li, W. Jiang, Y. Ding, L. Wang, Highly selective and sensitive detection of miRNA based on toehold-mediated strand displacement reaction and DNA tetrahedron substrate, Biosens. Bioelectron. 71 (2015) 401–406.
[288] Y. Zhang, Z. Shuai, H. Zhou, Z. Luo, B. Liu, Y. Zhang, L. Zhang, S. Chen, J. Chao, L. Weng, Q. Fan, C. Fan, W. Huang, L. Wang, Single-molecule analysis of MicroRNA and logic operations using a smart plasmonic nanobiosensor, J. Am. Chem. Soc. 140 (2018) 3988–3993.
[289] Z. Li, B. Zhao, D. Wang, Y. Wen, G. Liu, H. Dong, S. Song, C. Fan, DNA nanostructure-based universal microarray platform for high-efficiency multiplex bioanalysis in biofluids, ACS Appl. Mater. Interfaces 6 (2014) 17944–17953.
[290] D. Zeng, H. Zhang, D. Zhu, J. Li, L. San, Z. Wang, C. Wang, Y. Wang, L. Wang, X. Zuo, X. Mi, A novel ultrasensitive electrochemical DNA sensor based on double tetrahedral nanostructures, Biosens. Bioelectron. 71 (2015) 434–438.
[291] W. Diao, M. Tang, S. Ding, X. Li, W. Cheng, F. Mo, X. Yan, H. Ma, Y. Yan, Highly sensitive surface plasmon resonance biosensor for the detection of HIV-related DNA based on dynamic and structural DNA nanodevices, Biosens. Bioelectron. 100 (2018) 228–234.
[292] K. Wang, M.Q. He, F.H. Zhai, J. Wang, R.H. He, Y.L. Yu, Autonomous DNA nanomachine based on cascade amplification of strand displacement and DNA walker for detection of multiple DNAs, Biosens. Bioelectron. 105 (2018) 159–165.
[293] S. Liu, L. Fang, Y. Wang, L. Wang, Universal dynamic DNA assembly- programmed surface hybridization effect for single-step, reusable, and amplified electrochemical nucleic acid biosensing, Anal. Chem. 89 (2017) 3108–3115.
[294] P. Zhang, J. Jiang, R. Yuan, Y. Zhuo, Y. Chai, Highly ordered and field-free 3D DNA nanostructure: the next generation of DNA nanomachine for rapid single- step sensing, J. Am. Chem. Soc. 140 (2018) 9361–9364.
[295] L. Zhu, Q. Liu, B. Yang, H. Ju, J. Lei, Pixel counting of fluorescence spots triggered by DNA walkers for ultrasensitive quantification of nucleic acid, Anal. Chem. 90 (2018) 6357–6361.

[296] L. Peng, P. Zhang, Y. Chai, R. Yuan, Bi-directional DNA walking machine and Its application in an enzyme-free electrochemiluminescence biosensor for sensitive detection of microRNAs, Anal. Chem. 89 (2017) 5036–5042.
[297] D. Wang, C. Vietz, T. Schröder, G. Acuna, B. Lalkens, P. Tinnefeld, A DNA walker as a fluorescence signal amplifier, Nano Lett. 17 (2017) 5368–5374.
[298] Y. Zhao, S. Hu, H. Wang, K. Yu, Y. Guan, X. Liu, N. Li, F. Liu, DNA dendrimer-streptavidin nanocomplex: an efficient signal amplifier for construction of biosensing platforms, Anal. Chem. 89 (2017) 6907–6914.
[299] H. He, J. Dai, Y. Meng, Z. Duan, C. Zhou, B. Zheng, J. Du, Y. Gu, D. Xiao, Self-assembly of DNA nanoparticles through multiple catalyzed hairpin assembly for enzyme-free nucleic acid amplified detection, Talanta 179 (2018) 641–645.
[300] N. Xie, J. Huang, X. Yang, Y. Yang, K. Quan, H. Wang, L. Ying, M. Ou, K. Wang, A DNA tetrahedron-based molecular beacon for tumor-related mRNA detection in living cells, Chem. Commun. 52 (2016) 2346–2349.
[301] L. He, D.Q. Lu, H. Liang, S. Xie, C. Luo, M. Hu, L. Xu, X. Zhang, W. Tan, Fluorescence resonance energy transfer-based DNA tetrahedron nanotweezer for highly reliable detection of tumor-related mRNA in living cells, ACS Nano 11 (2017) 4060–4066.
[302] L. He, D. Lu, H. Liang, S. Xie, X. Zhang, Q. Liu, Q. Yuan, W. Tan, mRNA- initiated, three-dimensional DNA amplifier able to function inside living cells, J. Am. Chem. Soc. 140 (2018) 258–263.
[303] C.Y. Tay, L. Yuan, D.T. Leong, Nature-inspired DNA nanosensor for real-time in situ detection of mRNA in living cells, ACS Nano 9 (2015) 5609–5617.
[304] W. Zhou, D. Li, C. Xiong, R. Yuan, Y. Xiang, Multicolor-encoded reconfigurable DNA nanostructures enable multiplexed sensing of intracellular MicroRNAs in living cells, ACS Appl. Mater. Interfaces 8 (2016) 13303–13308.
[305] S. Wang, M. Xia, J. Liu, S. Zhang, X. Zhang, Simultaneous imaging of three tumor-related mRNAs in living cells with a DNA tetrahedron-based multicolor nanoprobe, ACS Sens. 2 (2017) 735–739.
[306] S. Li, L. Xu, M. Sun, X. Wu, L. Liu, H. Kuang, C. Xu, Hybrid nanoparticle pyramids for intracellular dual microRNAs biosensing and bioimaging, Adv. Mater. 29 (2017) 1606086.
[307] S. Li, L. Xu, W. Ma, X. Wu, M. Sun, H. Kuang, L. Wang, N.A. Kotov, C. Xu, Dual-mode ultrasensitive quantification of microRNA in living cells by chiroplasmonic nanopyramids self-assembled from gold and upconversion nanoparticles, J. Am. Chem. Soc. 138 (2016) 306–312.
[308] K. Ren, Y. Xu, Y. Liu, M. Yang, H. Ju, A responsive "nano string light" for highly efficient mRNA imaging in living cells via accelerated DNA cascade reaction, ACS Nano 12 (2018) 263–271.
[309] Q. Wei, J. Huang, J. Li, J. Wang, X. Yang, J. Liu, K. Wang, A DNA nanowire based localized catalytic hairpin assembly reaction for microRNA imaging in live cells, Chem. Sci. 9 (2018) 7802–7808.
[310] C. Xue, S.X. Zhang, C. He Ouyang, D. Chang, B.J. Salena, Y. Li, Z.S. Wu, Target-induced catalytic assembly of Y-shaped DNA and its application for in situ imaging of microRNAs, Angew. Chem. Int. Ed. 57 (2018) 9739–9743.
[311] L. Syedmoradi, M. Daneshpour, M. Alvandipour, F.A. Gomez, H. Hajghassem, K. Omidfar, Point of care testing: theimpactofnanotechnology, Biosens. Bioelectron. 87 (2017) 373–387.
[312] J. Hu, S. Wang, L. Wang, F. Li, B. Pingguan-Murphy, T.J. Lu, F. Xu, Advances in paper-based point-of-care diagnostics, Biosens. Bioelectron. 54 (2014) 585–597.
[313] M. Wu, Q. Lai, Q. Ju, L. Li, H.-D. Yu, W. Huang, Paper-based fluorogenic devices for in vitro diagnostics, Biosens. Bioelectron. 102 (2018) 256–266.

[314] M. Safavieh, M.K. Kanakasabapathy, F. Tarlan, M.U. Ahmed, M. Zourob, W. Asghar, H. Shafiee, Emerging loop-mediated isothermal amplification-based microchip and microdevice technologies for nucleic acid detection, ACS Biomater Sci. Eng. 2 (2016) 278–294.
[315] C. Jung, A.D. Ellington, Diagnostic applications of nucleic acid circuits, Acc. Chem. Res. 47 (2014) 1825–1835.
[316] J. Hu, L. Wang, F. Li, Y.L. Han, M. Lin, T.J. Lu, F. Xu, Oligonucleotide-linked gold nanoparticle aggregates for enhanced sensitivity in lateral flow assays, Lab Chip 13 (2013) 4352–4357.
[317] X. Gao, H. Xu, M. Baloda, A.S. Gurung, L.P. Xu, T. Wang, X. Zhang, G. Liu, Visual detection of microRNA with lateral flow nucleic acid biosensor, Biosens. Bioelectron. 54 (2014) 578–584.
[318] Y. Chen, N. Cheng, Y. Xu, K. Huang, Y. Luo, W. Xu, Point-of-care and visual detection of Paeruginosa and its toxin genes by multiple LAMP and lateral flow nucleic acid biosensor, Biosens. Bioelectron. 81 (2016) 317–323.
[319] Y. Wang, D. Liu, J. Deng, Y. Wang, J. Xu, C. Ye, Loop-mediated isothermal amplification using self-avoiding molecular recognition systems and antarctic thermal sensitive uracil-DNA-glycosylase for detection of nucleic acid with prevention of carryover contamination, Anal. Chim. Acta 996 (2017) 74–87.
[320] J.R. Choi, J. Hu, Y. Gong, S. Feng, W.A. Wan Abas, B. PingguanMurphy, F. Xu, An integrated lateral flow assay for effective DNA amplification and detection at the point of care, Analyst 141 (2016) 2930–2939.
[321] C. Feng, X. Mao, H. Shi, B. Bo, X. Chen, T. Chen, X. Zhu, G. Li, Detection of microRNA: a point-of-Care testing method based on a pH-responsive and highly efficient isothermal amplification, Anal. Chem. 89 (2017) 6631–6636.
[322] Y. Wang, Y. Wang, L. Zhang, J. Xu, C. Ye, Visual and multiplex detection of nucleic acid sequence by multiple cross displacement amplification coupled with gold nanoparticle-based lateral flow biosensor, Sens. Actuators B 241 (2017) 1283–1293.
[323] X. Fu, Z. Cheng, J. Yu, P. Choo, L. Chen, J. Choo, A SERS-based lateral flow assay biosensor for highly sensitive detection of HIV-1 DNA, Biosens. Bioelectron. 78 (2016) 530–537.
[324] M.O. Noor, A. Shahmuradyan, U.J. Krull, Paper-based solid-phase nucleic acid hybridization assay using immobilized quantum dots as donors in fluorescence resonance energy transfer, Anal. Chem. 85 (2013) 1860–1867.
[325] M.O. Noor, U.J. Krull, Paper-based solid-phase multiplexed nucleic acid hybridization assay with tunable dynamic range using immobilized quantum dots as donors in fluorescence resonance energy transfer, Anal. Chem. 85 (2013) 7502–7511.
[326] M.O. Noor, D. Hrovat, M. Moazami-Goudarzi, S.G.U. Espie, J. Krull, Ratiometric fluorescence transduction by hybridization after isothermal amplification for determination of zeptomole quantities of oligonucleotide biomarkers with a paper-based platform and camera-based detection, Anal. Chim. Acta 885 (2015) 156–165.
[327] M.O. Noor, U.J. Krull, Camera-based ratiometric fluorescence transduction of nucleic acid hybridization with reagentless signal amplification on a paper-based platform using immobilized quantum dots as donors, Anal. Chem. 86 (2014) 10331–10339.
[328] X. Deng, C. Wang, Y. Gao, J. Li, W. Wen, X. Zhang, S. Wang, Applying strand displacement amplification to quantum dots-based fluorescent lateral flow assay strips for HIV-DNA detection, Biosens. Bioelectron. 105 (2018) 211–217.
[329] H. Deng, X. Zhou, Q. Liu, B. Li, H. Liu, R. Huang, D. Xing, Paperfluidic chip device for small RNA extraction, amplification, and multiplexed analysis, ACS Appl. Mater. Interfaces 9 (2017) 41151–41158.

[330] S. Takalkar, K. Baryeh, G. Liu, Fluorescent carbon nanoparticle-based lateral flow biosensor for ultrasensitive detection of DNA, Biosens. Bioelectron. 98 (2017) 147–154.
[331] W. Qiu, H. Xu, S. Takalkar, A.S. Gurung, B. Liu, Y. Zheng, Z. Guo, M. Baloda, K. Baryeh, G. Liu, Carbon nanotube-based lateral flow biosensor for sensitive and rapid detection of DNA sequence, Biosens. Bioelectron. 64 (2015) 367–372.
[332] Q. Ju, U. Uddayasankar, U. Krull, Paper-based DNA detection using lanthanide-doped LiYF4 upconversion nanocrystals as bioprobe, Small 10 (2014) 3912–3917.
[333] L. Zhang, B. Ding, Q. Chen, Q. Feng, L. Lin, J. Sun, Point-of-care-testing of nucleic acids by microfluidics, Trends Anal. Chem. 94 (2017) 106–116.
[334] Z. Cheng, K. Wang, Z. Wu, L. Zhou, Z. Wang, Y. Bai, J. Zhao, H. Mao, Low-cost quantitative detection of nucleic acid using microbeads and microcolumn array chip, Sens. Actuators B 258 (2018) 1302–1308.
[335] A.S. Ghrera, C.M. Pandey, B.D. Malhotra, Multiwalled carbon nanotube modified microfluidic-based biosensor chip for nucleic acid detection, Sens. Actuators B 266 (2018) 329–336.
[336] R.M. Mohamadi, I. Ivanov, J. Stojcic, R.K. Nam, E.H. Sargent, S.O. Kelley, Sample-to-answer isolation and mRNA profiling of circulating tumor cells, Anal. Chem. 87 (2015) 6258–6264.
[337] J. Das, I. Ivanov, E.H. Sargent, S.O. Kelley, DNA clutch probes for circulating tumor DNA analysis, J. Am. Chem. Soc. 138 (2016) 11009–11016.
[338] J. Das, I. Ivanov, L. Montermini, J. Rak, E.H. Sargent, S.O. Kelley, An electrochemical clamp assay for direct, rapid analysis of circulating nucleic acids in serum, Nat. Chem. 7 (2015) 569–575.
[339] J.D. Besant, J. Das, I.B. Burgess, W. Liu, E.H. Sargent, S.O. Kelley, Ultrasensitive visual read-out of nucleic acids using electrocatalytic fluid displacement, Nat. Commun. 6 (2015) 6978.
[340] J. Das, I. Ivanov, T.S. Safaei, E.H. Sargent, S.O. Kelley, Combinatorial probes for high-throughput electrochemical analysis of circulating nucleic acids in clinical samples, Angew. Chem. Int. Ed. 57 (2018) 3711–3716.
[341] L. Shi, J. Lei, B. Zhang, B. Li, C.J. Yang, Y. Jin, Ultrasensitive and facile detection of microRNA via a portable pressure meter, ACS Appl. Mater. Interfaces 10 (2018) 12526–12533.
[342] J. Fang, Y. Guo, Y. Yang, W. Yu, Y. Tao, T. Dai, C. Yuan, G. Xie, Portable and sensitive detection of DNA based on personal glucose meters and nanogold-functionalized PAMAM dendrimer, Sens. Actuators B (2018) 118–126.