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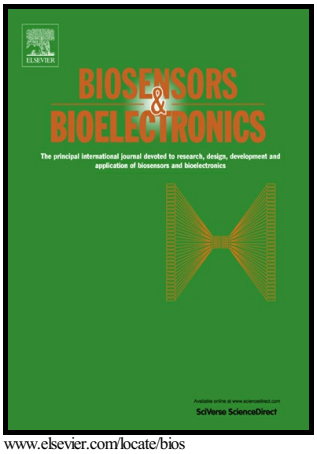

www.elsevier.com/locate/bios

PII: S0956-5663(18)30494-9
DOI: https://doi.org/10.1016/j.bios.2018.06.062
Reference: BIOS10582

To appear in: *Biosensors and Bioelectronic*

Received date: 27 April 2018
Revised date: 21 June 2018
Accepted date: 28 June 2018

Cite this article as: Chen Zhou, Haimin Zou, Chengjun Su, Dongxia Ren, Jing Chen and Yongxin Li, Signal Amplification Strategies for DNA-based Surface Plasmon Resonance Biosensors, *Biosensors and Bioelectronic,* https://doi.org/10.1016/j.bios.2018.06.062

Signal Amplification Strategies for DNA-based Surface Plasmon Resonance Biosensors

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Abstract: DNA has well-defined ability to recognize a wide variety of targets, such as small biological molecules, proteins, inorganic ions and small organic molecules. As molecular recognition elements, DNA can be used to build simple, rapid and sensitive biosensors for detection of these targets. DNA-based SPR sensors are considered to be a real-time and label-free tool. We present a systematical and critical review on DNA-based SPR biosensors and their signal amplification via various strategies, focusing on recent advances in nanomaterials, novel DNA amplifications, redox reactions on surface, enzyme amplifications, as well as promising multiplex amplification strategies.

Keywords: Surface plasmon resonance biosensor; Nanomaterial; Electrically neutral DNA probe; DNA amplification; Redox reactions; Enzyme amplification

1. Introduction

Deoxyribonucleic acids (DNA) has well-defined ability to recognize many targets, such as small biological molecules, proteins, inorganic ions and some small organic molecules. Therefore, DNA, as a molecular recognition element, can be utilized to build DNA-based biosensor for detection of a specific target. Aptamers, collectively referred to as functional nucleic acids, are RNA or DNA fragments. They have sequence-specific folds that achieve their tertiary structures and activities through a combination of different molecular interactions and motifs. Specific properties of artificial nucleosides have contributed to the development of more efficient tools for biosensors. In fact, artificial DNA probes have been utilized together with a number of different transduction platforms in order to achieve more sensitive and selective detection of nucleic acids, proteins and other compounds. The currently available transduction platforms mainly include colorimetric assay (Xia et al. 2017), surface plasmon resonance (SPR) (Yuan et al. 2017a) and electrochemical analysis (Zhang et al. 2017b). Other techniques, such as fluorescence sensors

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(Alhadrami et al. 2017) and phosphorescent resonance energy transfersensors (Lv et al. 2017), have also been reported.

SPR biosensor is a flow-through biosensor technique measuring very small changes in refractive index (RI) on noble metal surface when analytes bond to the surface. SPR has become a powerful real-time and label-free tool to probe the biomolecular interactions (Zhou et al. 2008). This technique has been widely utilized to study the interactions between drug–protein, DNA–protein, antibody–microorganism, protein–receptor, low molecular substance–protein, antibody–antigen and so on. When compared with ELISA method, SPR method has the advantages of simple operation, rapid detection, and low consumption of samples. Due to these advantages, over the past decades, SPR biosensors have been extensively applied to environmental monitoring, drug screening, food analysis and clinical diagnosis (Mohammadzadeh-Asl et al. 2018). In recent years, DNA-based SPR biosensors have received particular attention in the field of analytical chemistry, and achieved the analysis of a wide range of analytes including DNA (Daems et al. 2016), Micro RNA (Vaisocherova et al. 2015), peptides (Zhang et al. 2017a), proteins (Liu and Cheng 2012) and even small molecules and metal ions (Piriya et al. 2017). Up to now, several strategies have been developed for signal amplification of DNA-based SPR biosensors, such as nanomaterials, electrically neutral DNA probe, DNA amplification, enzyme amplification and other strategies.

A few authors have summarized the signal amplification strategies for SPR biosensors, mainly focusing on plasmonic nanomaterials (Piriya et al. 2017; Zhang et al. 2017a) and nucleic acids detection (Fong and Yung 2013; Sipova and Homola 2013). However, a systematical and comprehensive overview of the signal amplification strategies for DNA-based SPR biosensors is still needed. Consequently, we have made an in-depth summary of the signal amplification strategies of DNA-based SPR biosensors for detection of various molecules (Scheme 1). Meantime, we also discussed their future trends and perspectives.

2. Signal amplification strategy based on nanomaterials

SPR has become a leading technique for *in situ* bioaffinity assay of diverse targets. A key edge of SPR lies in on-line measurement of biomolecules without fluorescent or enzymatic labeling. However, the detection limits of such label-free SPR sensors generally remain at nanomolar level. A variety of nanomaterials were employed in signal amplification of SPR sensors, which have been well reviewed. Here, we mainly focused on the nanomaterials reported recently, especially silver nanomaterials and gold nanomaterials with various shapes that were

rarely reviewed before, for signal amplification of DNA-based SPR biosensors. Nanomaterials could give rise to great mass accumulation and consequent changes in the refractive index near the bioconjugated interface. Metal nanoparticles, such as AuNPs and AgNPs, exhibit good SPR-related optical phenomena that can be linked to the presence or absence of target biomolecules.

2.1 Gold nanomaterials

It is well known that SPR are ultra-sensitive to particle size, shape, inter-particle space and dielectric constant of the surrounding dielectric materials. Therefore, gold nanomaterials with various shapes seem attractive for SPR sensors (Fig. 1).

2.1.1 Gold nanoparticles

Gold nanoparticle (AuNPs) has shown a remarkable sensitivity improvement for small molecule detection based on SPR sensors (Springer et al. 2017). There are two main factors to change the SPR condition and cause signal enhancement, including localized surface plasmon resonance (LSPR)-SPR coupling effect and size/mass-material properties associated with AuNPs. Hong et al. (Hong and Hall 2012) examined the two factors in the context of a classical SPR bio-interaction assay format, and found the coupling effect was a distance dependent factor. The dominant enhancement associated with coupling effect only occurred within 8 nm distance for 20 nm AuNPs, and caused a change of 7 nm wavelength shift/nm distance from the Au SPR thin film. Beyond this distance, the size/mass-material properties associated with AuNPs were the major factors in signal enhancement. The properties of DNA functionalized AuNPs were so unique that a new terminology, namely spherical nucleic acids (SNA), was introduced (Cutler et al. 2012). Knez et al. (Knez et al. 2013) found that SNA could theoretically allow identification of the exact mutation of DNA in combination with more sensitive detectors. Such signal enhancement could result in identifying single nucleotide polymorphisms (SNPs) even when they were part of a cluster of mutations, rendering DNA melting in a complete standalone SNP detection platform. Lee et al. (Lee et al. 2013a) also adopted circularly shaped highly ordered Au nanopattern to enhance the sensitivity and selectivity of SPR sensor. The detection limit of the method for HIV-1 particles was estimated to be 200 fg/mL with a correlated coefficient (R^2) of 0.9990, which was 10 folds higher than those of previously reported virus detection method based on LSPR (Park et al. 2012). However, this method still requires large improvement in recognition of different binding events regarding of multiple analytes. Vaisocherová et al. (Vaisocherova et al. 2015) presented a label-free optical biosensor based on SPR image (SPRi) for rapid and multiple detection of miRNAs in erythrocyte lysate (EL) samples, which utilized sandwich-type hybridization in EL in

addition to signal amplification by streptavidin-functionalized AuNPs. The limits of detection (LODs) were 0.35~0.95 pM, comparable to those recently obtained by using the electrochemical and lateral-flow biosensors for single miRNA detection in miRNA buffered extracts and serum (Gao et al. 2013; Ren et al. 2013). Liu et al. (Liu et al. 2017) designed DNA-linked AuNPs that could initiate the formation of DNA super sandwich structure through addition of two reporter DNA sequences, and developed a novel, sensitive and versatile SPR sensor for the detection of miRNA and cancer cell. Due to the electronic coupling between localized plasmon of AuNPs and the surface plasmon wave associated with gold film, as well as the enhancement of the refractive index of the medium next to the gold film caused by DNA super-sandwich structure, the shift of resonance angle was enhanced obviously, and as low as 0.6 fM miRNA-21 could be detected. In addition, numerous positively charged silver nanoparticles (AgNPs) were attached to the long-range negatively charged DNA super sandwich, resulting in a further increase of resonance angle shift. The self-assembly gold nanoislands was also reported to enhance the response of LSPR biosensor for detection of microvesicles isolated from A-549 cells, SH-SY5Y cells, blood serum and urine. The LOD was as low as 0.194 μg/mL (Thakur et al. 2017).

2.1.2 Gold-core nanoparticles

A nanogold seeded nucleation colored sensor was reported in detail (Luo et al. 2012). Based on the uranyl-specific DNAzyme reaction as a model by using nanogold aggregation, nanoparticle-seeded nucleation and silver deposition process, a novel spectrophotometric method was established for analysis of trace amount of UO_2^{2+}. In this assay, 0.083~0.67 nmol/L UO_2^{2+} could be quantified rapidly with a detection limit of 0.04 nmol/L. Moon et al. (Moon et al. 2012) investigated improved SPR detection for DNA hybridization using gold core–silica shell nanoparticles. The measurement results of 24-mer single-stranded DNA oligomers hybridization suggested that core-shell nanoparticles (CSNPs) on gratings of 400 nm period could provide enhanced optical signals by 36 times over the conventional thin film-based SPR detection. CSNP-mediated DNA hybridization produced 3 times larger angular shift than AuNPs with the same core size. Compared with traditional detection limit of 1 pg/mm^2, their detection limit was decreased to the order of tens of fg/mm^2. Li et al. (Li et al. 2013) established a novel label-free LSPR method for the detection of mercury ions, which could be performed via core–satellite assembly (gold nanoplates surrounded by gold nanorods).

2.1.3 Gold nanorods and nanostars

Gold nanorods (AuNRs) have recently been considered as a new class of photostable and highly sensitive optical transducers for labeling antibody and nucleic acid of biological specimens.

Wang et al. (Wang et al. 2012b) established a reliable, broad-range and easy-to-perform bacterial genomic DNA detection platform. It was confirmed to quantify artificial target sequences with high sensitivity and excellent specificity by using a pair of universal AuNRs-based nanoprobes and reading the decrease in its sensitive longitudinal absorption band. It could give a Yes or No diagnostic result in analyzing various known or unknown bacteria-spiked platelet concentrates, although it could not identify the bacterial species. Recently, star-shaped nanoparticles, namely gold nanostars, were applied to signal amplification. The employment of gold nanostars in the labeled sandwich-like SPR assay led to the decreased detection limits of about three orders of magnitude (from 6.1 nM to 10 pM) for the synthetic DNA target (84 mer) (Mariani et al. 2015).

2.1.4 Gold nanotriangles

Triangular nanoparticles and SPR have been applied to the development of methods for label-free detection of peptide nucleic acid (PNA)–DNA and DNA–DNA hybridization. Gold nanotriangles (AuNTs) showed a remarkable sensitivity of 468 nm per RIU and allowed to detect 20-mer targets. The study of Soares and coworkers (Soares et al. 2014) demonstrated that, even at room temperature, hybridization with complementary PCR products of 345 bp caused remarkably high LSPR shift of 22 nm in their platform. However, there was only 3 nm shift in a similar platform using gold nanospheres. Therefore, it would be highly desirable to explore the application and new properties of anisotropic AuNPs, including AuNTs, for improved functionalization and bio-conjugation as well as detection sensitivity.

2.1.5 Gold nanoprisms and nanobipyramids

Recently, a molecular sensor fabricated with gold nanoprisms with a 35 nm average edge length has displayed an unprecedentedly large reversible shift of 21 nm upon a minor increase of 0.6 nm in the thickness of local dielectric environment (Joshi et al. 2014a). Therefore, gold nanoprisms with this size and geometry have unique properties, and could provide extremely high sensitivity in plasmonic biosensors. Joshi et al. (Joshi et al. 2014b) designed a regenerative and highly sensitive solid-state LSPR sensor based on gold nanoprisms without labels or amplification for the detection of miRNAs. The LSPR-based assays could detect miRNAs in plasma directly, and showed at least 2-fold higher sensitivity than those following RNA extraction and quantification by reverse transcriptase-polymerase chain reaction.

Previous work has proved that, compared with spherical AuNPs, the anisotropic AuNRs with an intense electromagnetic field can generate much stronger SPR signals. Interestingly enough, theoretical calculations further disclosed that many NPs with unusual shapes like Au nanostars (Hao et al. 2007), Au nanotriangles (Walker et al. 2010) and Ag or Au nanobipyramids (AuNBPs)

(Le Ru et al. 2011; Lombardi et al. 2012) possessed even stronger SPR properties than AuNRs, owing to the increased electromagnetic field originating from the sharp tips or the antenna effect (Ghosh et al. 2017). Liu et al. (Liu et al. 2014) reported a plasmonic circular dichroism (CD) response of highly purified AuNBPs induced by the helical DNA. Higher concentration of cDNA resulted in larger scale assembly of AuNBPs, thus generating stronger plasmonic CD response and a lower detection limit of 5 nM for cDNA. This result indicated that SPR signal of AuNBPs based on plasmonic CD was about 7 times higher than that of AuNRs assembly, which should be attributed to the intense electromagnetic field and large LSPR intensity at the sharp tips of the AuNBPs (Lombardi et al. 2012).

2.2 Silver Nanoparticles

Silver nanoparticles (AgNPs) has an advantage over other noble metals, because its SPR energy is removed from inter-band transitions, and AgNPs results in a narrow band of SPR (Christopher et al. 2011). In turn, this narrower band exhibits much stronger shift upon an increase of local dielectric constant when compared with the shift observed in AuNPs. On the other hand, AgNPs are more reactive than AuNPs, thereby losing their original morphology and decreasing subsequently their sensitivity. However, AgNPs have gained particular attention in SPR biosensor recently due to their unique optical and electronic properties (Fig. 2).

Chu and coworkers (Chu et al. 2014) successfully prepared a new type of AgNPs -like “dioscorea batatas bean” with enhanced LSPR property. The results suggested that these AgNPs with unique structure could be readily adaptable to LSPR enhancement compared with a range of other nanomaterials. Silver nanotriangles are widely used in biosensors based on SPR detection, and have been successfully applied to DNA detection and even gene mutation detection (Duan et al. 2012). Besides, triangular silver nanoprisms with three-dimensional nanostructures also exhibit exquisite features in LSPR owing to an extreme degree of anisotropy in their structures (Zhang et al. 2011). Yang et al. (Yang et al. 2014) developed a facile DNA detection assay based on triangular silver nanoprisms etching process. Meanwhile, the enzyme and hybridization chain reaction were integrated into this system, and the results indicated that this plasmonic DNA assay could detect as low as 6.0 fM target DNA by simple mixture and magnetic separation.

Wang’s group (Wang et al. 2014) prepared reliable DNA-conjugated Au@Ag core–shell nanoparticles (Au@AgNPs). Based on the outstanding properties of DNA embedded Au@AgNPs, they proposed a facile and sensitive SPR approach to colorimetrically detect glucose in water and fetal bovine serum with LOD of 10 nM (Kang et al. 2015). Compared with previously reported

colorimetric sensing based on silver materials, this method was superior to single color fading in the two responsive phenomena, including SPR band decline and red-shift.

2.3 Graphene Nanomaterials

Graphene has been becoming more and more popular in the development of sensors because of its special properties. Islam et al. (Islam and Kouzani 2013) elaborated that a graphene-based SPR (G-SPR) structure could improve the sensitivity of SPR sensor. The G-SPR exhibited a larger shift and eight times higher sensitivity of RI than conventional SPR sensors. The interactions of DNA with graphene oxide (GO) play a role of key importance in materials science, nanotechnology, biosensoring, and biomedicine. GO has been extensively used as quencher in single-stranded DNA (ssDNA) sensing (Huang et al. 2012; Wang et al. 2012a). A previous study showed that SPR signal was very sensitive to the assembly and change of oxide state of GO nanosheets. Xue et al. (Xue et al. 2014) reported a SPR assay based on GO for ultra-sensitive ssDNA detection with a LOD of 10 fM. The assay showed highly stable detection performance even after repeated regeneration.

In a search for widening the access to graphene-based SPR, Zagorodko et al. (Zagorodko et al. 2014) exhibited great interest in graphene-on-metal SPR interfaces for the detection of DNA hybridization events at attomolar level. The strategy consisted of noncovalent functionalization of graphene-coated SPR interfaces and gold nanostars carrying ssDNA. The DNA sensor exhibited a LOD of ca. 500 aM for complementary DNA and a linear dynamic range up to 10^{-8} M. The performances of four types of graphene doped ZnO nanostructures, including nanocomposites, nanoflowers, nanotubes and nanofibers, was investigated by Gupta's group(Tabassum and Gupta 2017). It was confirmed that comparatively better optical properties existed in the ZnO: graphene nanofibers, and the calculated value of LOD of the nicotine SPR sensor fabricated with nanofibers was found to be 0.074 μM.

In view of increasing the available surface area for analyte binding as well as improving their electrical conductivity and electron mobility, GO–AuNPs hybrids have hold the greatest promise for implementation in a wide array of biosensors (Hu et al. 2014; Li et al. 2015). Recently, the GO–AuNPs hybrids have been used as solid support for the immobilization of recognition molecules in some works for the detection of IgG (Zhang et al. 2013) and ractopamine (Yao et al. 2016). Afterward, a novel and simple SPR biosensor utilizing GO–AuNPs hybrids as signal tags was designed for the detection of miRNA-141 (Wang et al. 2016). DNA-linked GO–AuNPs hybrids as signal tags were used to form a sandwich complex on the SPR sensing surface. On the one hand, the SPR signal was enhanced by electronic coupling between localized plasmon of

AuNPs and surface plasmon wave associated with gold film (Liu and Cheng 2012; Wang et al. 2011). On the other hand, GO possessed large specific surface area and loaded a large amount of AuNPs, thus SPR signal could be further enhanced. With GO–AuNPs hybrids assisting signal amplification, a low LOD of 1 fM for miRNA-141 was achieved, which was 3 orders of magnitude lower than that of AuNPs amplified SPR sensor, and 5 orders of magnitude lower than that of direct hybridization measurement. For prospective development, it is worthwhile to improve the sample injection system in order to shorten the analytical time.

2.4 Other Nanoparticles

2.4.1 Silica Nanoparticles

Since silica nanoparticles (SiNPs) possesses only one real refractive index (no absorption) in the visible and NIR spectral regions, the enhancement degree of SPR response by the SiNPs is independent of wavelength, and should be simply associated with nanoparticle size. In addition to gold core–silica shell nanoparticles mentioned above, Zhou et al. (Zhou et al. 2012) employed DNA-modified SiNPs for simultaneous detection of two 38-mer ssDNA oligonucleotides at concentrations down to 25 fM, which was approximately 20 times more sensitive than those observed previously with nanoparticle-enhanced SPR sensor. What's more, the use of SiNPs to improve the sensitivity of SPR sensor also avoided the interference caused by the coupling of local plasma field of AuNPs on the surface of gold film.

2.4.2 Magnetic Nanoparticles

Magnetic nanoparticles (MNPs) have been subjected to extensive studies in the past few decades owing to their promising potentials in biomedical applications. The versatile intrinsic properties enable the use of MNPs in many biomedical applications (Lee et al. 2014). Recently, MNPs have been utilized in signal amplification in SPR biosensor. A novel and versatile SPR sensor was developed for sensitive detection of DNA by integrating multiple signal amplification strategies (He et al. 2014b). It was found that the angular shift was about 16 times higher than that of Au-Rolling circle amplification (Au-RCA) format. This enhancement was attributed to the employment of MNPs bio-bar-code probe as the signal amplification intermediary, since they could increase the coverage of RCA product on the sensing surface.

In recent years, more and more study employed the sandwich hybridization of probes functionalized with various nanoparticles to further achieve the signal amplification of nucleic acid (Cheng et al. 2014; Xiang et al. 2013).

3. Signal Amplification Based on DNA Techniques

In DNA-based SPR assay, the DNA was adopted as recognition element. To improve significantly the sensitivity of SPR biosensors, the optimized hybridization conditions and electrically neutral DNA probe are often employed. Additionally, the target DNA is also amplified with various strategies, such as DNA amplifications with or without enzyme.

3.1 Electrically Neutral DNA Probe

In addition to the technological advances in biosensor instrumentation, the optimizations of hybridization conditions (ionic strength of buffer, composition of sensor surface) and sensing probe sequence have critical influences on the sensitivity and specificity of SPR based methods. Due to the strong electrostatic repulsion, the efficiencies of DNA immobilization on the probe surface and hybridization are hampered. The most common strategy for improvement of DNA detection is to increase the concentrations of divalent or monovalent cations in the buffer solution. Petrovykh et al. (Petrovykh et al. 2003) elucidated that the concentrations of divalent cations higher than monovalent cations in the buffer solution were able to improve the surface coverage of DNA probes on the chips. Kick et al. (Kick et al. 2009) reported that an increasing salt concentration or replacement of Na^{+} with Mg^{2+} in the solution could shield the charge of DNA fragments and improve the efficiency of DNA hybridization. Various neutralized nucleic acids also have been demonstrated as alternative and attractive probes for the design of DNA chips. However, the mechanism has not been clearly revealed. Chen et al. (Chen et al. 2013) newly developed neutral ethylated DNA (E-DNA), a DNA analog with the ‘‘RO-P-O’’ backbone (where R could be methyl, ethyl, aryl, or alkyl group) obtained from synthetic procedures, and a silicon nanowire (SiNW) field-effect transistor (FET). They also compared its performance as probes with that of common DNA for DNA detection. The results demonstrated that E-DNA probe in the FET measurement had significantly enhanced sensitivity. Though the sequence design of E-DNA probe is very simple, special chemical modification of E-DNA is required.

3.2 DNA Amplification with Enzyme

Polymerase chain reaction based thermal cycle is the most common DNA amplification strategy with enzyme in biochemical analysis. With the development of molecular biotechnology, various isothermal amplification methods, such as loop-mediated isothermal amplification, exponential amplification reaction and so on, have also been applied to SPR biosensors for signal amplification and on-site detection. The DNA amplification with enzyme has the advantages of rapidness and high specificity, while requiring expensive enzymes and strict temperatures.

3.2.1 Polymerase Chain Reaction

Polymerase chain reaction (PCR) is a useful technique for DNA amplification *in vitro*. Zhang et al. (Zhang et al. 2012) developed a SPR-based DNA biosensor for Salmonella detection, and the target gene was amplified by using a modified semi-nested asymmetric PCR. The use of PCR allows a highly sensitive and specific detection within 4.5 h, and 10^2 CFU Salmonella in 1mL sample could be detected. Yang et al. (Yang et al. 2013) employed an array chip method based on PCR technique and a homebuilt spectral SPR imaging system for identification of HLA-Bn27 gene for clinical diagnosis with a LOD of 5 nM.

Previously, a fiber optic SPR (FO-SPR) melting assay was established as liable post-PCR analysis method to distinguish SNPs in short DNA strands. The target DNA could form complexes between two hybridization probes, each complementary to one half of the target molecule and immobilized either on AuNPs or on the sensor surface (Knez et al. 2013; Knez et al. 2015). However, it could not monitor specific nucleic acid sequences in real time during the PCR reaction. To cope with the aforementioned drawbacks, Daems et al. (Daems et al. 2016) established a robust, rapid and highly sensitive FO-SPR bioassay on a compact biosensor platform that could identify and quantify bacterial DNA in a multiplex way. The concept was further developed in a fiber optic PCR melting assay (FO-PCR-MA) to achieve both quantification and cycle-to-cycle identification of multiple DNA targets on the same FO-SPR sensor. Here, the increase of DNA amount during the PCR amplification resulted in a yield increase of hybridization complexes binding to the sensor surface through hybridization probes. During each heating phase, the target DNA strands disconnected from the hybridization probes, thereby releasing AuNPs from the FO-SPR sensor surface. This caused mass changes on the sensor and subsequently refractive index changes, which could be used to determine the characteristic melting temperature of the target sequence and hence its identification. This threshold corresponded to a DNA concentration of 0.3 µM for MAP and 0.4 µM for *M. bovis*. However, considerably lower peak heights were obtained compared with the previous experiments. Since PCR-based method needs thermal cycle instrument, it can't meet the requirements of on-site detection.

3.2.2 Loop-Mediated Isothermal Amplification

As a contrast, isothermal amplification methods have been reported to achieve higher efficiency and shorter amplification time for on-site measurement without thermal cycling procedure. Loop-mediated isothermal amplification (LAMP), a classical isothermal amplification method, has become the preferred method for on-site screening because of its advantages in isothermal condition, amplification efficiency and specificity. Chuang et al. (Chuang et al. 2012)

reported a simple, low-cost SPR method based on LAMP for on-site detection of hepatitis B virus (HBV) with a detection limit of 2 fg/mL. However, more research should be carried out to improve the precision of SPR system based on isothermal amplification for analysis of other viruses in complicated real samples. Nawattanapaiboon et al. (Nawattanapaiboon et al. 2015) combined SPR with LAMP to identify *S. aureus* by the detection of femB and to detect antibiotic resistance by the detection of mecA in methicillin-resistant *S. aureus* at a low level of 10 copies/mL in clinical samples. Therefore, the requirement of complex primer design makes this method quite limited for LAMP application.

3.2.3 Exponential Amplification Reaction

Galas and co-workers devised an exponential amplification reaction (EXPAR) for short oligonucleotides (called triggers) by a combination of polymerase strand extension and single-strand nicking (Van Ness et al. 2003). The reaction provided 10^6~10^9-fold amplification under isothermal conditions within minutes. Compared with other signal amplification methods, the EXPAR method has many distinct advantages such as isothermal nature, high amplification efficiency, and rapid amplification kinetics. A novel and versatile SPR sensor was developed for sensitive detection of DNA by integrating multiple signal amplification strategies reported by He and co-works (He et al. 2014b). As shown in Fig. 3-I, the proposed strategies for DNA assay included EXPAR, RCA, and AuNPs. On the basis of amplification reaction in cycles I and II, the target DNA triggers could be exponentially produced, and eventually leading to a large amount of MNP bio-bar-code probe labeled DNA duplex on the Au chip. The results demonstrated that with the EXPAR assistance, the SPR response was enhanced about 1.7 times. Although the EXPAR method has been applied to virus detection, the generation of the trigger from a genomic target is limited in the sequences within the genomic DNA that contain adjacent nicking-enzyme recognition sites. This hampers the wide application of EXPAR for nucleic acid detection.

3.2.4 Rolling Circle Amplification

Rolling circle amplification (RCA) has shown its attraction due to the specificity and multiplexing besides simplicity. The typical ligation-rolling circle amplification (L-RCA) based on ligase relies on base pairing principle which requires perfect complementarity on the ligation nick. It can forbid the mismatch, and the occurrence rate of false positive results was low when compared with PCR. When used as a signal amplification method, RCA can directly amplify signal on solid phase and enable high multiplexing without interference. Moreover, RCA amplifies the circular probe only, without accumulation of target templates over time, which minimizes the risk of contamination and the potential biohazard (Petryayeva and Krull 2011).

However, this method cannot solve the problem of multiplex mutations parallel detection including the design and selection of specific probes, precise localization of multiplexing probes and unbiased signal amplification.

Xiang et al. (Xiang et al. 2013) presented a new strategy of multi-channel SPR biosensor array combined with surface-anchored RCA and Au nanoparticles signal amplification technique to identify five point mutations in parallel. The LOD of the method was 5×10^{-12} M. In their assay, RCA amplified the SPR signal by almost 10-fold before addition of AuNPs, which enhanced the signal for another approximately 2.1-fold compared with the previous RCA methods. Therefore, how to improve the multiplexing capabilities of the biosensor array should be further studied. A SPR biosensor based on RCA and AuNPs was also reported by Shi and coworkers (Shi et al. 2014) for isothermal identification of DNA. In this study, the probes included a specific padlock probe, a capture probe bound to biotin, and an AuNPs-modified probe which hybridized with the RCA products. The sensitivity of this assay (0.5 pM) was higher than those of SPR biosensors for DNA hybridization detection (10 pM) (Ananthanawat et al. 2009). When the concentration was higher than 5×10^{-7} M, however, the SPR signal no longer increased. He et al. (He et al. 2014a) developed a SPR aptasensor combined with RCA and bio-bar-coded AuNP enhancement for protein detection (Fig. 3-II). The strategy showed ultra-high sensitivity and excellent specificity. However, for the sandwich assay format, not all the target proteins had two or more aptamers. This greatly hampered its universal application.

3.2.5 Polymerization Extension Reaction

Polymerization extension reaction (PER), like PCR, is also based on DNA polymerase for nucleic acid amplification. The analysis process can be completed within 15 min. Li et al. (Li et al. 2014c) presented a novel biosensor that combined highly specific PER analysis with the label-free SPR detection to discriminate single-base mutation. The basic principle of PER was shown in Fig. 3-III. In this study, the detection limit of 100 pM can be achieved. Compared with other works of point mutation detection by SPR biosensor, this method showed a competitive sensitivity for standard solutions containing synthetic oligonucleotides.

3.2.6 Ligation Chain Reaction

Recently, it was shown that AuNPs could be combined with DNA amplification through the ligation chain reaction (LCR). Shen and coworkers (Shen et al. 2012) developed a simple and ultrasensitive colorimetric DNA assay based on LCR and AuNPs as signal generators. This colorimetric assay had a linear range spanning 6 orders of magnitude and a detection limit of 50 aM. Reported by Knez and coworkers (Knez et al. 2015), the AuNPs-LCR was further improved

by replacing the colorimetric read-out of the assay, in which SPR sensor could be directly used to measure AuNPs binding. A considerable increase of the assay sensitivity was obtained. In this regard, the original assay was redesigned by ligating probes in free solution instead of on AuNPs, which were then bound to complementary probes immobilized on both AuNPs surface and FO-SPR sensor surface (Fig. 3-IV). This LCR assay had a LOD of 13.75 fM. Optimal ligation probe and ligation conditions could decrease the LOD further to a similar level as PCR.

3.3 Enzyme-free DNA Amplification

Target DNA could also be amplified without enzyme by introducing other DNA fragments, thereby achieved significantly improved sensitivity in DNA-based SPR assay. The enzyme-free DNA amplification strategy could avoid the limitations of unstable and expensive protein enzymes, and could be performed at room temperature, which made the system more simple, stable and low-cost. While, it involved complex design of DNA sequence and required much longer amplification time.

3.3.1 Hybridization Chain Reaction

Hybridization chain reaction (HCR) is another type of nucleic acid amplification reaction, which suggests the possibility of constructing biosensors solely from unmodified single-stranded DNA. Li et al. (Li et al. 2014b) introduced a simple and highly sensitive biosensor for the detection of DNA and small molecules by coupling DNA-based HCR with the SPR strategy. The SPR signal could be amplified with the introduction of long duplex sequence in the presence of initiator strands. The LOD of 0.3 fM was 6 orders lower than that of a LSPR amplified with AuNPs (Spadavecchia et al. 2013). The scheme of HCR was illustrated in Fig. 4-I. Yao et al. (Yao et al. 2015) utilized HCR to improve the sensitivity of nicking enzyme signal amplification, and designed a SPR platform for ultrasensitive detection of adenosine based on the cascade of multiple DNA cycle amplification strategy and AuNPs assisted SPR signal amplification with a detection limit of 4 fM. The sensitivity of this method was much higher than that of the aptamer and AuNPs amplification–based SPR assay (1 nM) (Wang and Zhou 2008).

The HCR strategy showed high sensitivity and selectivity without participation of enzyme molecules, thereby avoiding the limitations of thermo unstable protein enzymes and the requirements of specific recognition site for nicking endonuclease. Significantly, due to the universality of aptamers, the method can be generalized to a wide variety of targets such as proteins, cells, and other small molecules relevant to medical diagnostics and environmental monitoring.

3.3.2 Catalytic Hairpin Assembly

In last decade, catalytic hairpin assembly (CHA), as an enzyme-free amplification method, has been developed from DNA nanotechnology, and proven powerful in amplifying and transducing signals at the terminus of nucleic acid amplification reactions. CHA can be utilized for the development of nonenzyme-based isothermal amplification strategies. However, traditional CHA has high background signal due to the nonspecific products in the absence of targets (Jiang et al. 2014). Fortunately, mismatched CHA can decrease the product yields of uncatalyzed background reactions, which makes CHA a more fascinating strategy in signal amplification.

In 2016, a novel and simple strategy was developed for miRNA detection by coupling the enzyme-free DNA nanotechnology with the label-free SPR biosensing platform for the first time (Li et al. 2016a). For the sake of decreasing background signal and improving analytical performance of CHA amplification strategy, mismatched base pairs of the breathing site in the hairpin-2 (H2) were introduced in this work (Fig. 4-II). The designed strategy provided excellent analytical performance in miRNA detection and could detect target miRNA as low as 1 pM with a wide linear range. The analytical performances were much better when compared with those of other biosensors based on CHA amplification, such as fluorescence (10 pM) (Li et al. 2011) and colorimetry (1 nM) (Li et al. 2014a). It also revealed that the mismatched CHA strategy proposed in this work had a feature of lower detection limit. Li et al. (Li et al. 2016b) designed a mismatched CHA for further improving the analytical performance of multi component nucleic acid enzyme (MNAzyme)-based biosensing strategies to integrate with SPR biosensor for highly sensitive detection of miRNA. The limit of detection for miRNA was calculated to be 1 pM, which was much lower than those of MNAzyme-based biosensing (Jie et al. 2015) and SPR biosensing using protein enzymes (Zeng et al. 2015). The cascade signal amplification of MNAzyme catalysis, CHA cycle and streptavidin enhancement endues the developed SPR biosensor with high sensitivity. Strand displacement reactions (SDR), similar to CHA, is also an enzyme-free and label-free signal amplification circuit, and can be specifically triggered by target DNA, leading to the cyclic utilization of target DNA and the formation of plentiful double-stranded DNA (dsDNA) products. Recently, an innovative surface plasmon resonance (SPR) biosensing strategy has been developed for highly sensitive detection of HIV-related DNA based on entropy-driven strand displacement reactions and double-layer DNA tetrahedrons (DDTs) (Diao et al. 2018). Due to the high efficiency of ESDRs and large molecular weight of DDTs, the SPR response signal was enhanced dramatically. The proposed SPR biosensor could detect target DNA sensitively and specifically in a linear range from 1 pM to 150 nM with a detection limit of 48 fM.

4. Signal amplification strategy based on redox reactions

Precipitation in redox reaction could change the refractive index near the bioconjugated interface, and consequently enhance the sensitivity of SPR biosensors. Recently, a few research groups have reported that biomimetic catalysis-induced precipitation and nano-effect deposition could significantly improve the detection limit of SPR biosensors.

As a kind of metalloporphyrins, Fe(III)tetrakis (1-methyl-4-pyridyl) porphyrin pentachlorideporphyrin pentachlorid (FeTMPyP) plays a prominent role in the peroxidase-like catalysis, and its activity prevails over other irons, manganese and cobalt derivatives and even competes against those of natural enzymes. By making full use of highly symmetric stereochemistry, dsDNA has been discovered accommodating individual FeTMPyP automatically and tightly within its intrinsic groove regardless of sequence. While it happens to have no interaction between porphyrin and the ssDNA. An HCR-assisted biomimetic catalysis-induced precipitation was tailored to SPR-based DNA assay (Fig. 5-I) (Yuan et al. 2015). As a proton provider, 4-Chloro-1-naphthol can be oxidized quickly into hydrophobic diquinones by H_2O_2 under the catalysis of FeTMPyP–dsDNA, and precipitated on the surface of SPR chip, thereby causing considerable shifts. A detection limit of 0.73 fM was achieved, which was superior to most reported DNA biosensors (Manzanares-Palenzuela et al. 2015), testifying the ultra-sensitive method for DNA detection. Yuan et al. (Yuan et al. 2017b) also developed a sensitive SPR sensor of femtomolar-level DNA detection (Fig 5-II).

5. Enzyme Digestion Technique

Enzyme digestion technique could not only be utilized to digest non-target DNA and improve consequently the sensitivity of SPR assay, but also be adopted to reuse the target DNA through repeated cycles of hybridization, cleavage, and dissociation, thereby resulting in obvious signal amplification. The most common enzymes include Enzyme exonuclease III, Ribonuclease H and DNA nicking endonuclease. Since different enzymes have different activity and reaction conditions, enzymes could be chosen according to the actual requirement.

Enzyme exonuclease III (ExoIII) exhibits 3′→5′ exodeoxyribonuclease activity, which involves specific binding to dsDNA followed by selective hydrolysis of one strand from the DNA duplex. Lee et al. (Lee et al. 2013b) reported a novel enzyme-linked antibody aptamer sandwich (ELAAS) method for the detection of VR-2332 of PRRSV type II. The detection limit was 4.8

$TCID_{50}$/mL, comparable to some of the previous reports of PCR-based detection. Moreover, this study did not require any complicated equipment or extra costs.

Ribonuclease H (RNase H) is a sequence of non-specific endonuclease found in HIV-1 and some other prokaryotes and eukaryotes. During HIV-1 infection, the RNA from the virus is reversibly transcribed into cDNA, and the retroviral RNase H degrades the RNA in the RNA–DNA hybrid, leaving the cDNA in host cells for viral replication. Loo et al. (Loo et al. 2015) introduced a new method called MARS (MicroRNA-RNase-SPR) assay using RNase H and SPR sensor for the detection of miRNA in virus H1N1 infection, with a LOD of 1 nM. The process can be completed within 1 h without PCR thermal cycles.

DNA nicking endonuclease has attracted increasing interest in applications of biological detection, because of its strong recognition capability for DNA sequences. It is notable that the target can be reused through repeated cycles of hybridization, cleavage, and dissociation, thereby resulting in exponential amplification of the signal. In addition, taking advantage of the nicking enzyme, the reactions can be performed under isothermal condition without specialized instrumentation, which has the potential for routine analysis. A novel cascade cycle amplified device combined with AuNPs SPR assay based on DNA nicking endonuclease was designed for adenosine detection (Yao et al. 2015). The SPR angle shift showed a good linear correlation with adenosine concentration ranging from 0.005 to 0.5 pM, with a detection limit as low as 4 fM. The detection limit of this method was much lower than that of fluorescent aptasensor for adenosine assay based on Exo III assisted signal amplification (1 nM) (Hu et al. 2012).

6. Other signal amplification strategies (see in supplementary materials)

7. Conclusion and perspectives

Regarding recent advances in synthesis of noble metal nanomaterials, the anisotropic nanoparticles (e.g., Au nanostars, Au nanobipyramids, Au nanotriangles) have been substituting for spherical nanoparticles, and becoming the dominant signal amplification materials in SPR biosensors. We expect more promising nanocomposites such as AuNPs -rGOs will combine with SPR biosensors. As more and more aptamers for different targets are found, DNA-based SPR sensors will have wider range of applications. With regard to the detection property of DNA-based SPR biosensors, complicate sample matrices show certain degree of signal suppression in many studies. Furthermore, quite a large number of DNA-based SPR biosensors have not been applied in real samples. So the development of signal amplification strategies for detection of analytes in

different matrices with SPR biosensors should be emphasized in the future. For commercial use, though ELISA is a quite mature technique, DNA analogs, such as aptamers and DNAzymes, have many advantages over antibodies to make DNA-based SPR biosensor kits promising. In addition, to some extent, development of multiplex amplification strategies, combining with DNA amplification technology, nanocomposites, enzyme amplification and so on, would be a trend in the future.

In recent years, the novel SPR sensors combined with other sensor techniques have gradually become a research hotspot since it has the advantages of two sensor techniques. The SPR sensor, in combination with electrochemical analysis techniques (Zhang et al. 2017a), can simultaneously detect two different physicochemical signals, which would broaden the application fields and reduce the detection limit. The SPRi microarray microfluidic integrated system can achieve batch rapid detection when combined with microfluidics technique. Coupled with optical techniques such as fluorescence spectroscopy (Khakbaz and Mahani 2017), interferometry, and surface-enhanced Raman scattering, the sensitivity and resolution of SPR sensor in some specific usage environments can be improved. Due to the non-destructiveness of SPR sensor technique, it can also be combined with mass spectrometry to achieve qualitative and ultrasensitive quantitative analysis for biological macromolecules such as proteins and peptides. In addition, for real-time and *in situ* detection of important biomolecules and related information in complex life system, SPR sensor technique and other analytical techniques should also be combined to achieve this goal, which will also be the focus of future research. The development trend of SPR sensor is versatility, integration, and the necessity of its technological progress. In the future, more and more sensors will be connected with SPR sensors to achieve more sensitive and specific detection.

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Figure captions:

Scheme 1 Signal amplification strategies of DNA-based SPR biosensors.

Fig. 1 Schematic diagram of SPR biosensor fabricated with various gold nanomaterials. (Reprinted with permission from Ref. (Joshi et al. 2014b; Mariani et al. 2015) (Liu et al. 2014)).

Fig. 2 Schematic diagram of SPR biosensor fabricated with various silver nanomaterials. (Reprinted with permission from Ref. (Chu et al. 2014) (Duan et al. 2012) (Yang et al. 2014) (Wang et al. 2014)).

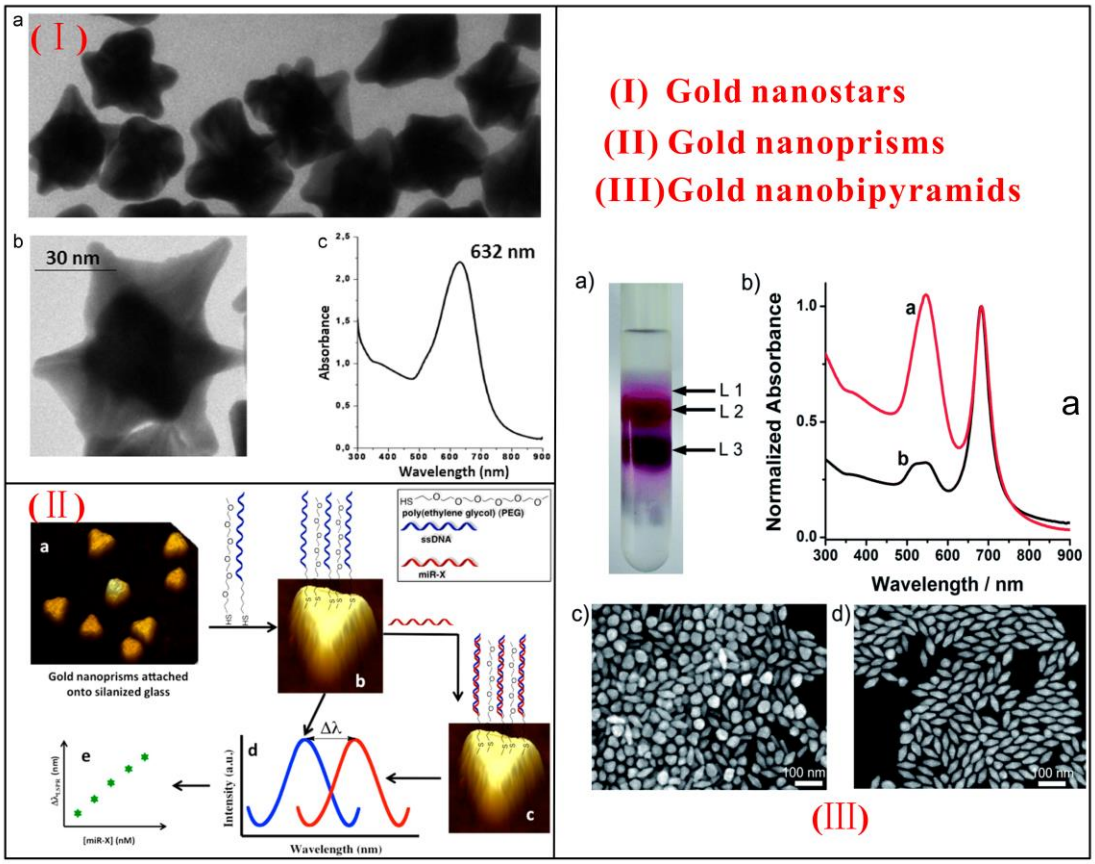
Fig. 3 Schematic representations of the SPR biosensors based on DNA amplification with enzyme (Reprinted with permission from Ref. (He et al. 2014b) (He et al. 2014a) (Knez et al. 2015; Li et al. 2014c)).

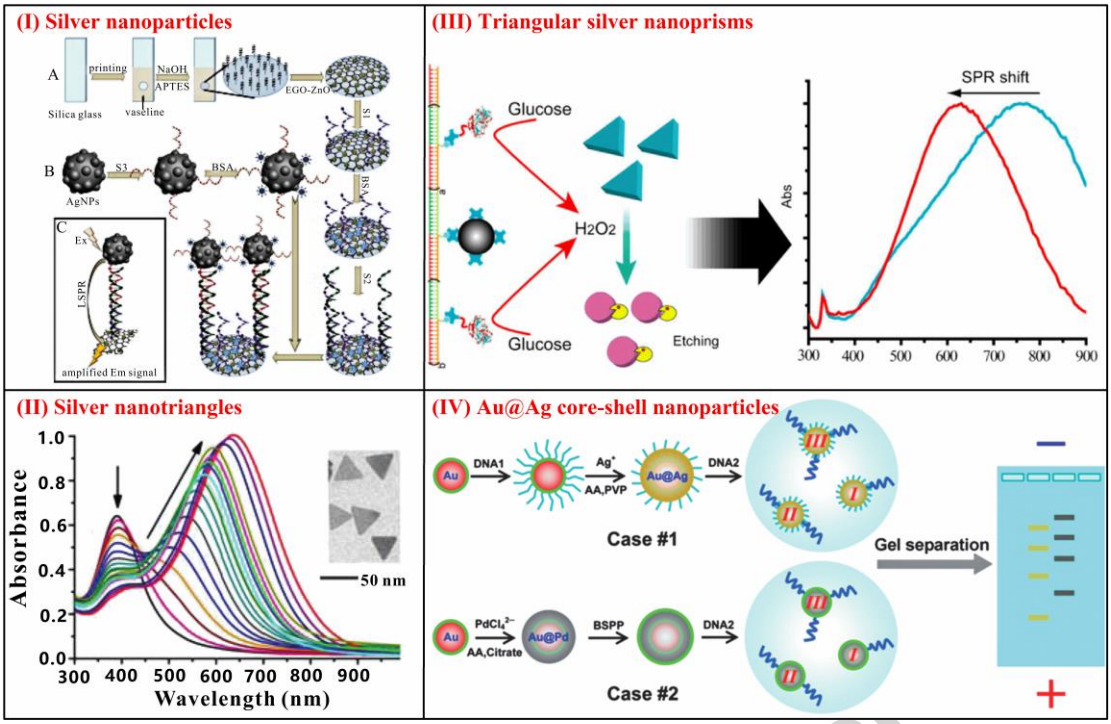
Fig. 4 Schematic representations of the SPR biosensors based on enzyme-free DNA amplification. (Reprinted with permission from Ref. (Li et al. 2014b) (Li et al. 2016a)).

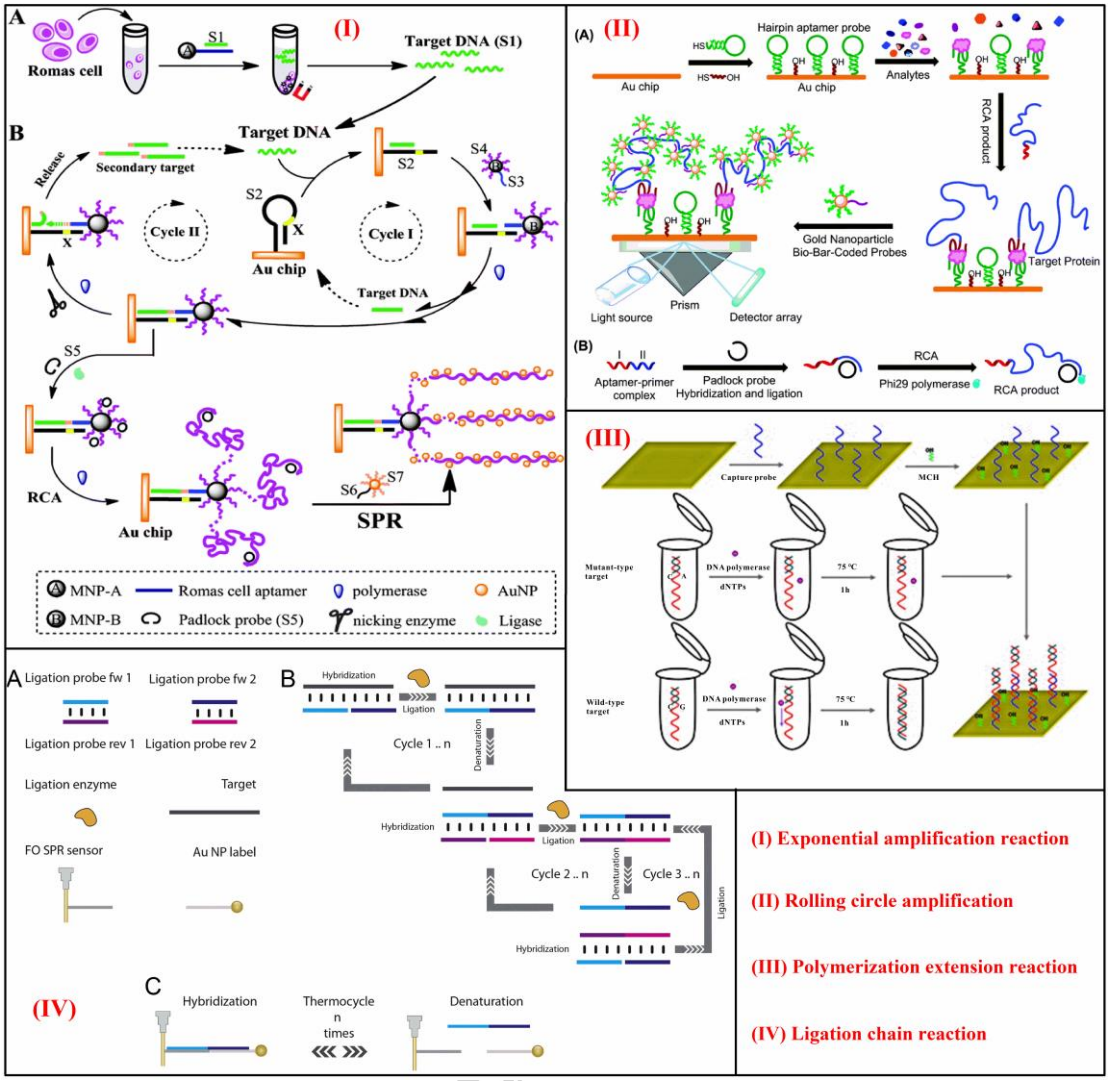
Fig. 5 Schematic representations of the SPR biosensors based on redox reactions. (Reprinted with permission from Ref. (Yuan et al. 2015) (Yuan et al. 2017b)).

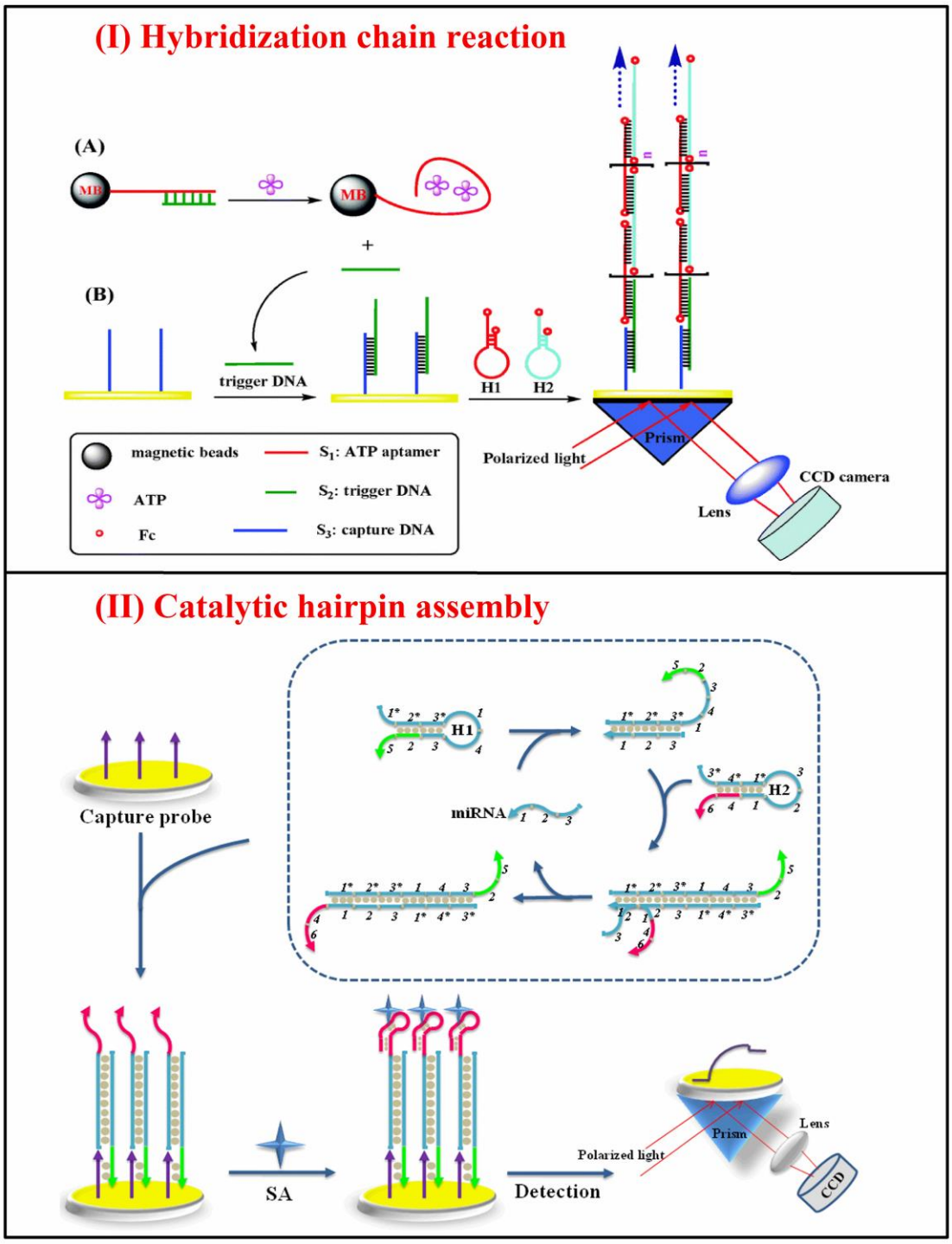
Highlights

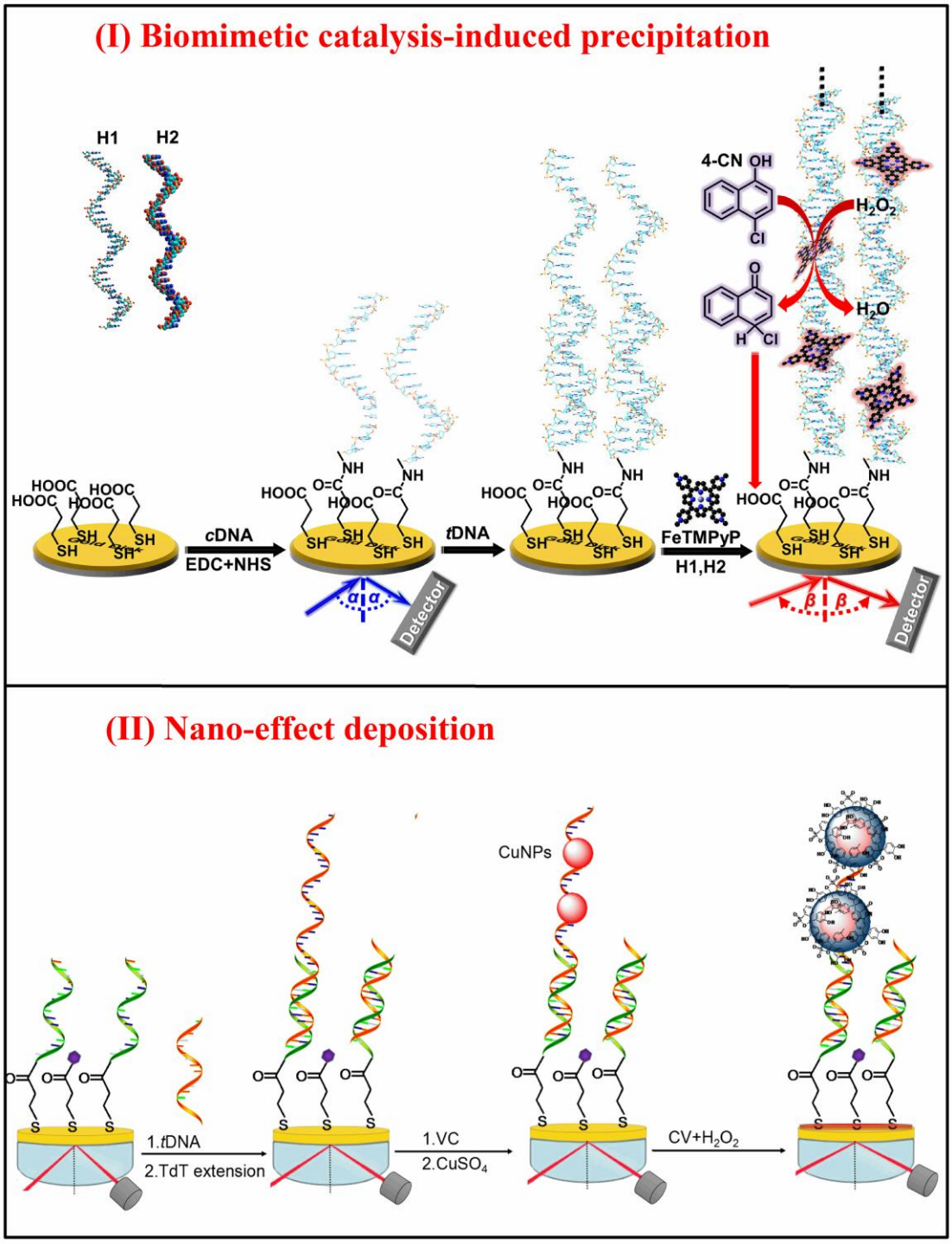
- DNA has well-defined ability to recognize many targets and could be utilized to build DNA-based biosensor.
- SPR sensor is a powerful real-time and label-free tool to probe the biomolecular interactions.
- In this review, we covered the recent signal amplification strategies of DNA-based SPR biosensors for detection of various molecules and discussed future trends and perspectives of SPR biosensor.










(I) Biomimetic catalysis-induced precipitation
H1
H2
4-CN
OH
Cl
H_2O_2
H_2O
H
Cl
cDNA
EDC+NHS
tDNA
FeTMPyP
H1,H2
Detector
Detector
(II) Nano-effect deposition
CuNPs
1.tDNA
2.TdT extension
1.VC
2.$CuSO_4$
CV+H_2O_2