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Recent advances in surface plasmon resonance biosensors for microRNAs detection

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ABSTRACT

miRNAs are a large family of non-coding RNAs which play important roles in translational and post-transcriptional regulation of gene expression and biological processes. Abnormal expression of miRNAs is related to the initiation and progression of different diseases which make them be promising candidates for early medical diagnostics. Thus, accurate detection of miRNAs has great significance for disorder diagnosis. Nevertheless, their intrinsic characteristics such as short sequence, low concentration and sequence homology challenge routine techniques. The detection assays need to be extremely sensitive and selective in small value of intricate RNA samples. Biosensor-based strategies have emerged as potential alternatives to conventional methods in miRNA quantification. The surface plasmon resonance (SPR), an optical biosensor, possessing various advantages including excellent reliability, selectivity and reproducibility represents a wide range of applications in real-time monitoring of biomolecular interactions and detection of biological and chemical analytes with label-based or label free form. Various signal amplification methods can overcome the limitation of SPR methods for detection of small molecules, making it suitable for clinical diagnosis. This review discusses main concepts and performance characteristics of SPR biosensor. Mainly, it focuses on newly emerged enhanced SPR biosensors towards high-throughput and ultrasensitive screening of miRNAs using labeling processes with focusing on the future application in biomedical research and clinical diagnosis. Actually, label-based signal amplification strategies of SPR platforms including nanoparticle enhancement, supersandwich assembly, streptavidin/biotin complex, antibody amplification, enzymatic reactions, triplex structure formation and catalytic hairpin assembly are discussed. Finally label free detection of miRNAs and advantages of SPR-based method was presented.

1. Introduction

Although protein-coding genes are the most well-studied sequences in the human genome, the coding exons and untranslated regions (UTRs) of mentioned genes account for only 2% of the human genome (Alexander et al., 2010). Because most of the human genome comprises of non-protein-coding regions, in recent years these DNA sequences are the focus of increasingly attention. The functional relevance of the non-protein-coding regions is particularly apparent for a several types of non-coding RNAs (ncRNAs) (Esteller, 2011). microRNAs (miRNAs), most widely studied group of endogenous ncRNAs, are short 20–22 nucleotide RNA molecules that mediate gene silencing by binding to the 3′ UTR of different target mRNAs and result in mRNA degradation or translation inhibition (Asadzadeh et al., 2019). miRNAs are known to be involved in multitude biological processes such as metabolism, proliferation, development, differentiation, apoptosis, drug resistance, homeostasis and stress response (Ghasabi et al., 2019; He and Hannon, 2004) and they can be found in a variety of tissue samples and body fluids in a wide range of eukaryotic organisms (Ferracin et al., 2010). The mechanism of miRNAs biogenesis is illustrated in Fig. 1. There is

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growing evidence that aberrant expression of specific miRNAs is closely contributed to many human disorders including cancers (Di Leva et al., 2014; Lujambio and Lowe, 2012; Mendell and Olson, 2012; Pasquinelli, 2012), neurological diseases (Eacker et al., 2009; Fiore et al., 2008) and cardiovascular diseases (Romaine et al., 2015; Small and Olson, 2011). The altered expression in miRNAs is mediated by several mechanisms such as mutations and polymorphisms, epigenetic changes, chromosomal abnormalities and defects in the miRNA biogenesis procedure (Visone and Croce, 2009).

Regarding to the importance of miRNAs in human diseases, they act as therapeutic targets and reliable molecular biomarkers for prediction of disease progression and clinical diagnostics. Therefore, developing a sensitive approach for miRNA detection in disease prognosis, diagnosis and treatment is an urgent demand. However, the precise detection of miRNA is challenging due to the inherent characteristics of miRNAs such as low level in the cell, extremely small size, easy to degrade by RNase, sequence homology among family members, the loss of universal internal references, the presence of miRNA isoforms or precursors in RNA samples along with variability in sample processing (Cissell et al., 2007; Fiammengo, 2017; Lv et al., 2016). There is, thereby, a need to develop novel, robust and technologically improved analytical assays for sensitive and accurate quantification of miRNAs. Conventional oligonucleotide detection techniques including northern blotting, microarray, multiplex ligation-dependent probe amplification, sequencing and quantitative real-time PCR suffer various limitations such as inadequate sensitivity, numerous operation cost, time-consuming, complex sample preparation and analysis, sophisticated tools and need to extrinsic labels like fluorophores or radiolabels (Abell et al., 2012; Hong et al., 2013). The biosensor-based methods hold many advantages including high sensitivity (from nM until even aM levels), fast measurements and minimal sample preparation that present great properties for fundamental research as well as clinical diagnosis (Cosnier and Mailley, 2008; Kilic et al., 2018). Several colorimetry (Bi et al., 2013), electrochemical (Yu et al., 2014), chemiluminescence (Bi et al., 2011), bioluminescence (Cissell et al., 2008), Raman spectroscopy (Driskell et al., 2009), fluorescence (Tu et al., 2013) biosensors are designed for oligonucleotide detection which commonly require additional tagging processes. Among these different sensing platforms available, surface plasmon resonance, as an optical and real-time biosensing method, has attracted excellent attention due to its unique privileges, such as high sensitivity, selectivity, and real-time monitoring of low molecular weight components (Homola, 2008; Liu et al., 2015b; Wijaya et al., 2011).

2. Surface plasmon resonance

Surface plasmon resonance (SPR), a widely used surface analytical

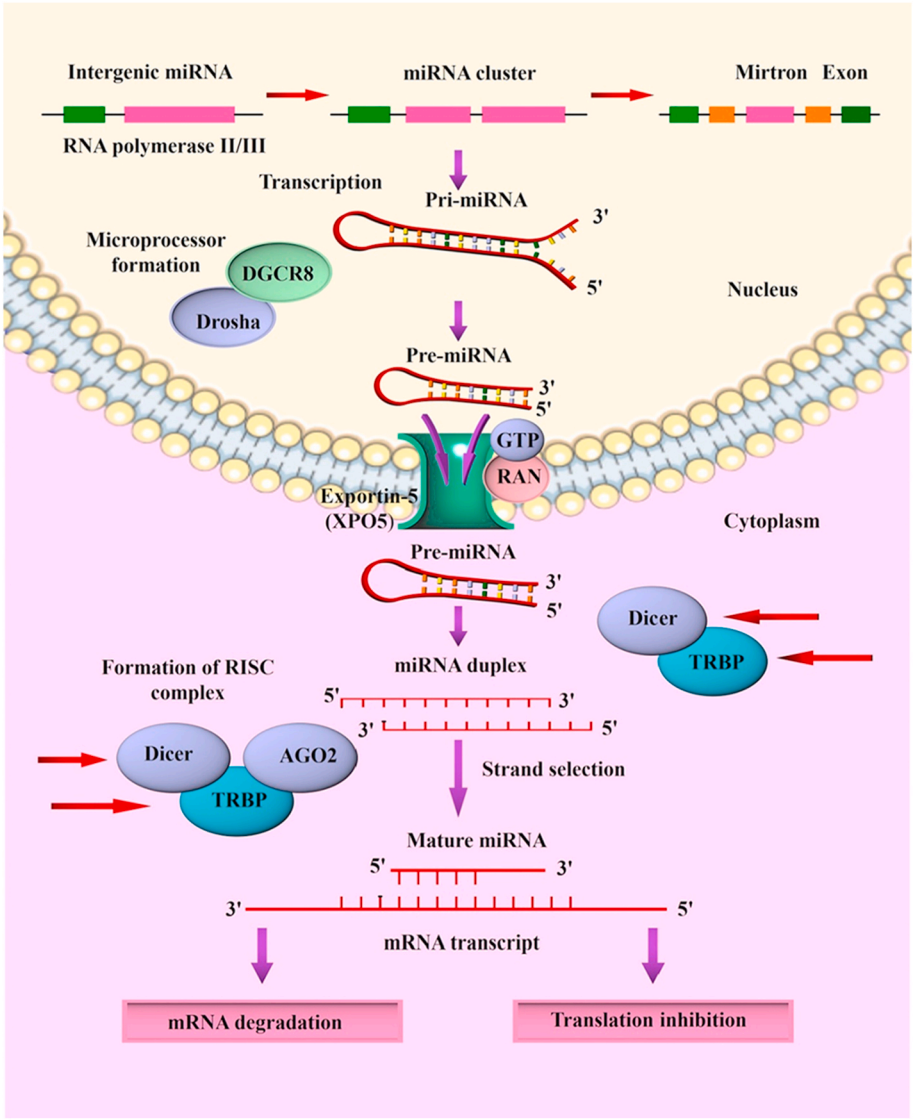

Fig. 1. The biogenesis of miRNAs. miRNA genes are typically located in clusters that transcribed as polycistrons. In addition, they can be organized between other genes (intergenic) or in the introns of the mRNA encoding genes (mirtron). Primary miRNA transcripts, known as pri-miRNAs, are transcribed by RNA polymerase II or III and then cleaved to 70-nt precursor miRNAs, called pre-miRNAs, via RNase III enzyme Drosha. Exportin-5 mediates the transport of pre-miRNAs from nucleus into cytoplasm in a RAN–GTP dependent manner. In cytoplasm, Dicer enzyme cleaves pre-miRNAs into short mature 20–22 nucleotide miRNAs. One strand of mature miRNAs is degraded and another strand is incorporated into RISC complex that contains a number of proteins and enzymes. The binding of miRNAs to the 3′ UTRs of different target mRNAs results in mRNA degradation or translation inhibition (Murchison and Hannon, 2004).

technique, has made a large contribution for immunoassay, multiple detection of biomolecules as well as real-time monitoring interactions of multiplexed chemical and biological analytes (Fathi et al., 2019b; Shalabney and Abdulhalim, 2011) including interactions between RNAs, DNAs or proteins and a wide variety of ligands or cofactors (Fig. 2) (Ritzefeld and Sewald, 2012). The unique abilities of SPR for quantifying low molecular weight make it suitable for wide applications in pharmaceutics, pharmaceutics, theranostics, environmental research and food safety (Fathi et al., 2019c; Rezabakhsh et al., 2020; Situ et al., 2010; Szunerits et al., 2013). Moreover, it exhibits various advantageous properties such as acceptable speed of analysis, relatively low cost, high specificity, high versatility, desirable reproducibility and repeatability, great precision, simple sample preparation and short response time (Homola, 2003).

SPR, as a solid support-based system, is a charge-density oscillation that exists at a two media interface with dielectric constants of opposite signs, for example, a dielectric (buffer, air or water) and a metal (commonly silver or gold), upon interaction with plane polarized light. This process leads to change the refractive index of the dielectric medium. The change in the refractive index of the dielectric gives rise to a modification of the propagation constant of the surface plasmons, altering the resonance condition between the interacting optical wave and the surface plasmons (Fathi et al., 2018; Homola et al., 1999; Wijaya et al., 2011). The majority of SPR biosensors function in prism-coupled configurations introduced by Kretschmann, (1972). These biosensors contain the following components: gold film, glass prism, light source and detector in which gold film is placed at the interface between two dielectric media, a glass prism with higher refractive index and the air or liquid sample with lower refractive index. Then, a laser beam overpasses the prism and excites the surface plasmons. The reflected light on the gold surface is measured by the detector to produce the SPR spectrum (Coutinho and Somoza, 2019; Tang et al., 2010). Gold films have been the most generally used in SPR biosensors, owe to its high density of conduction band electrons, the comfortable combination of optical wavelengths and reflectance angles, immovability in physiological buffer conditions and easy functionalization by thiolated biomolecules (Ferhan et al., 2018; Lakayan et al., 2018; Olaru et al., 2015).

SPR imaging (SPRi), SPR coupler and disperser (SPRCD) and surface plasmon resonance enhanced light scattering (SP-LS) are alternative forms of classical SPR platform. They not only preserve the advantages of classical SPR, but also develop an ultrasensitive biosensing scheme to detect low molecular weight biomarkers with dilute concentration. SPRi, also named SPR microscopy, is a highly versatile and promising affinity sensing approach for an array format which could simultaneously record and visualize up to hundreds interactions due to coupling the sensitivity of SPR measurements with the spatial capabilities of imaging by using a CCD camera (Scarano et al., 2010). SPRCD is a method of spectroscopy corresponding to surface plasmons which uses a specific diffraction grating structure. It simultaneously accompanies light into a surface plasmon and diffuses the diffracted light for spectral readout, allowing generating high-performance approach (Piliarik et al., 2009). The SP-LS platform uses combination of immunoassay and nanoparticles to improve SPR measurements. In this system, scattering from nanoparticle secondary probes is measured directly (see section 3.7) (Yang et al., 2016).

Sensitivity and limit of detection (LOD) are two main performance specifications of SPR platform. Sensitivity is defined as the ratio of the change in sensor output to the change in the quantity of sample that be measured (Homola and Piliarik, 2006). LOD is concentration of analyte that generates sensor output accordance with three standard deviations of sensor output evaluated for a blank sample (Thomsen et al., 2003). However, a typical SPR biosensor is unable to measure supremely small changes in refractive index and to analyze complex real-world samples. In addition, it may have the LOD at nanomolar level in direct detection of small molecules such as miRNA. The main restricted factor is the non-specific attachment of non-target substances to the biosensor surface which creates a false background signal diminishing biosensor sensitivity at low concentration of analytes. These problems hinder its widespread application in ultrasensitive detection, particularly for clinical diagnosis (He et al., 2000). To address this drawback, a variety of strategies have been incessantly investigated to further improve the SPR response and sensitivity.

In this overview, remarkable attention has been focused on the current state of development of SPR technology to facilitate research

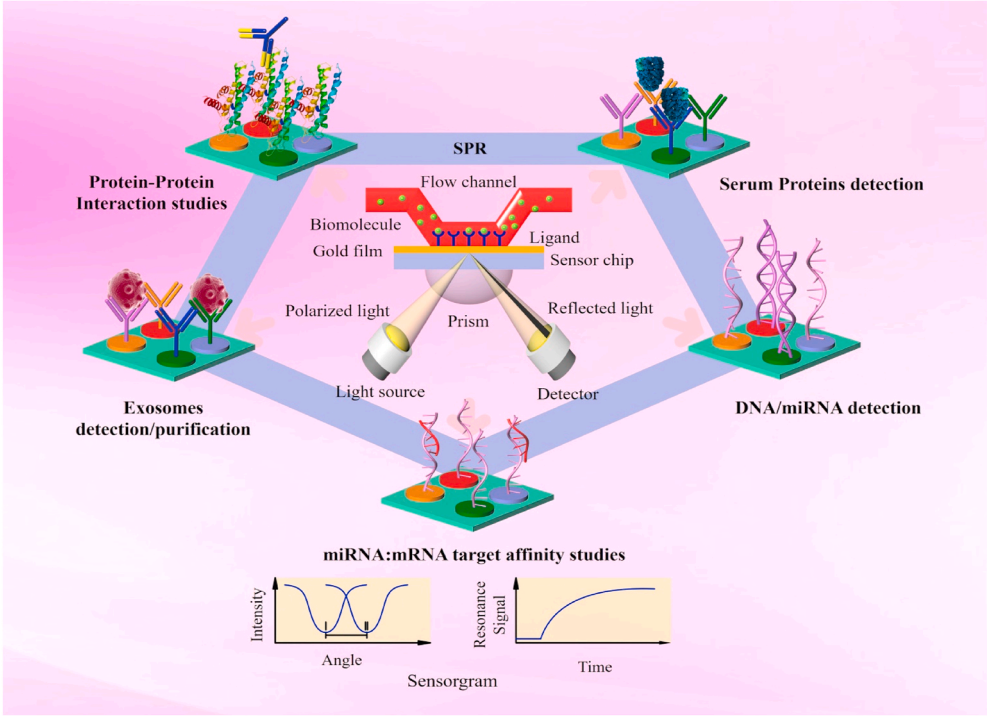

Fig. 2. Schematic diagram of a SPR biosensor, indicating its ability to monitor interactions between DNAs, RNAs, proteins and other ligands or cofactors.

into the on-site detection of miRNAs, underling its future use in clinical and practical diagnosis. Further, SPR surface functionalization and signal amplification based on label free and label-based detection approaches including nanoparticle enhancement, sandwich assembly, streptavidin/biotin complex, antibody amplification, enzymatic reactions, triplex structure formation and catalytic hairpin assembly are covered in the review. Publications, pointing on recently reported examples with rely on their advantages and drawbacks, were reviewed and compared to recognize the different strategies and modifications of SPR biosensors in the detection of miRNAs. The characteristics of different strategies in miRNA detection using SPR were discussed in Table 1.

3. Label-based SPR biosensors for miRNA detection

The unique features of metallic nanoparticles (NPs) such as controlled shape and size, great surface energy, high surface area to volume ratio, adjustable absorption and emission attributes, large dielectric constant, high density and stability, biocompatibility and easy preparation have made them ideal for designing good efficiency biosensors (Das et al., 2013; Fathi et al., 2019a; Hasanzadeh et al., 2018b). Gold-NPs (AuNPs), also called plasmonic NPs, are one of the most typically used metallic NPs in the field of biosensors (Hasanzadeh et al., 2018c). The main advantages of AuNPs are the supreme catalytic and electrical properties, potent absorption in the near-infrared and visible wavelength regions, enhancement of the SPR electromagnetic field as well as improvement of signal amplification for analytes with especially low concentration (Hasanzadeh et al., 2018d; Saha et al., 2012; Su et al., 2017; Zeng et al., 2014). In addition, low cytotoxicity, intrinsic biocompatibility, high affinity for thiolated substrates and excellent stability in biological fluids candidate AuNPs as potential materials and labels for biomedical applications such as miRNA detection in biological fluids or cancer tissues and cells (Giljohann et al., 2010). In term of the similar features to AuNPs, gold nanorods (AuNRs) possessing strong SPR properties, high refractive index sensitivity, adjustable longitudinal plasmon band, flexibility for functionalization, and excellent absorption cross section have ability for enhancing the detectability of SPR signal (Cao et al., 2014; Mansouri et al., 2020). The companionship of AuNPs and AuNRs, as the primary amplification elements, with other supporting strategies, as the secondary amplification elements, could considerably improve the sensitivity and specificity of sensing platforms. In the following sections, different types of AuNPs and AuNRs based SPR biosensors in a solid support-based system for the detection of miRNA will be discussed.

3.1. Graphene oxide-AuNPs based SPR biosensors

Atomically thin two-dimensional (2D) substances with a layered structure have been attracting increasing consideration, owing to their unique attributes. Graphene is a monolayer of sp2-bonded carbon atoms firmly wrapped into a 2D honeycomb lattice (Geim and Novoselov, 2010; Hasanzadeh et al., 2016). It is stable under ambient situations and has unusual electronic features like wonderful high carrier mobility at partly high charge carrier concentrations as well as at room temperature (Bolotin et al., 2008). Other interesting electronical, mechanical and thermal properties of graphene such as electrical conductivity, high optical transmittance, large surface area, strong mechanical rigidity and excellent thermal make it superior to traditional materials (Erogul et al., 2015). Following this trend, graphene oxide (GO), a graphene derivative, re-appeared as an intensive research interest (Pei and Cheng, 2012). GO has resembling atomically thin structural lattice, but consists reactive oxygen functional groups. Therefore, it can covalently attach to small molecules and polymers. Besides, the presence of functional groups in GO nanosheet (epoxide and hydroxyl groups on the basal planes along with carboxyl and carbonyl groups at the edges) makes it strongly hydrophilic, which allows GO to readily dissolve in water and several other common polar solvents and also form large-scale uniform films. These properties of GO nanosheet offer it a good candidate for use in the various applications including field-effect transistors, polymer composites, biomedical usage, sensors and biosensors (Dreyer et al., 2010; Stankovich et al., 2006). GO exhibits advantageous specifications to be used in biosensing platforms due to the accessibility to be tuned as a semi-metal, semiconductor or insulator, heterogeneous electronic and chemical structure, the supreme abilities for direct wiring with biomolecules, and the feasibility to be processed in solution (Morales-Narváez and Merkoçi, 2012).

New composite materials were manufactured by the combination of NPs and GO to ameliorate their existing attributes with a synergistic effect. The use of the these composites displays highly selective and sensitive response to target substrate in measuring medium (Erogul et al., 2015). Benefiting from this features, a GO-AuNPs hybrids-based SPR was developed as a new technique to detect miRNA-141, extracted from human cancer cell lines (prostate, hepatocellular and colon) (Wang et al., 2016a). miRNA-141 plays important role in tumorigenesis and acts as both oncogene and tumor suppressor (Zhao et al., 2013). The LOD for this GOAu-SPR was achieved as low as 1 fM that was 10^3 (1 pM) and 10^5 (100 pM) times lower than for AuNPs amplified SPR and direct hybridization measurement, respectively. Meanwhile, GOAu-SPR provided great selectivity for discriminating diversities between miRNA family members and high efficiency in a complex biological matrix. However, the time consuming procurement of GO-AuNPs hybrids and the reaction of miRNAs with hybrids restricted the clinical application of this sensor. The GOAu-SPR was accomplished in only a facile two-step assay. First, DNA-linked GO-AuNPs hybrid was created by the binding of assistant and helper DNA to GO-AuNPs hybrid. Second, thiolated DNA probes covalently attached to the Au surface and incubated with miRNA solution. Finally, DNA-linked GO-AuNPs hybrid was captured with Au surface via interaction between the terminus of capture DNA and miRNA (Fig. 3A). The tremendous signal enhancement in this SPR was attained by large surface area of GO, increased quantity of DNA-linked GO-AuNPs hybrids captured on Au film, the electronic coupling between localized plasmon of AuNPs and the surface plasmon wave correlated with Au film as well as the high mass-density and dielectric constant of the AuNPs on the surface of GO nanosheets. On the other hand, the simple generation of thiolated single strand DNA (ssDNA) provided the property of reproducibility (Wang et al., 2016a).

An ultrasensitive and alternative method used two layers of GO-AuNPs composites as both sensing substance and signal amplification element. Firstly, thiolated capture DNA was bound to the GO-AuNPs covered Au surface. Secondly, miRNA-141 and DNA functionalized GO-AuNPs mixtures were introduced to form a complex structure (Fig. 3B). The small shift of the resonance angle 0.0119° after miRNA injection was promoted to 0.1744° following adding of DNA-GO-AuNPs (Li et al., 2017). Comparing with the previous study (Wang et al., 2016a), the two-layer nature of this sensing approach improved LOD as low as 0.1 fM. Three reasons for this signal amplification including: 1) producing strong local electromagnetic field due to the surface plasmon, dielectric constant and high mass-density of AuNPs on the GO sheet, 2) the electromagnetic coupling between Au film and the AuNPs on the upper layer of GO-AuNPs, 3) immobilizing more capture DNA because of high specific surface area of bottom GO-AuNPs. The detection time using this two-layer biosensor, also, was decreased until 60 min. Moreover, excellent selectivity of this SPR could successfully detect miRNA-141 from other members of the miRNA-200 family and also in biological samples. More importantly, small molecules like adenosine could also be detected using this assay, providing it as a promising strategy for biosensing and bioanalysis (Li et al., 2017).

3.2. Molybdenum sulfide-AuNPs based SPR biosensors

Molybdenum disulfide (MoS2), a 2D layered chalcogenide nanomaterial, is an inorganic graphene analog with hexagonal crystal structure. The high surface area, 2D ultrathin atomic layer structure

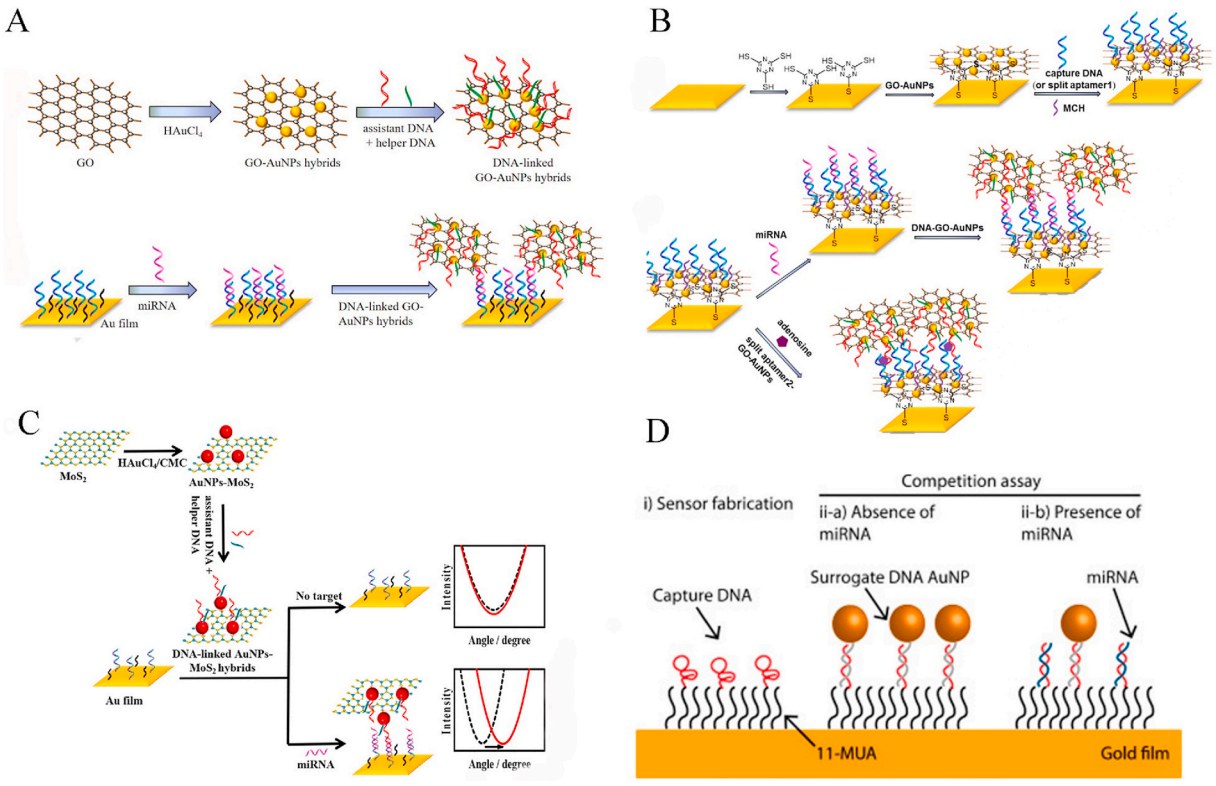

Fig. 3. Schematic representation of designing SPR biosensors using NPs based on: A) One layer graphene oxide (Wang et al., 2016a), B) Two layers graphene oxide (Li et al., 2017), C) Molybdenum disulfide (Nie et al., 2017), D) Oligodeoxynucleotides (Hong et al., 2018).

along with novel optoelectronic and nanoelectronic properties introduced MoS2 nanosheet as a promising supporting material in optoelectronics, nanoelectronics, and energy harvesting. To better MoS2 functionalizing, the defective or edge sites of MoS2 nanosheets are selectively decorated with AuNPs by non-covalent bonds to form AuNPs-decorated MoS2 (AuNPs-MoS2) nanocomposites (Shi et al., 2013; Su et al., 2014). These nanocomposites render novel magnetic, catalytic and optoelectronic activity as well as outstanding electrochemical properties such as fast mass transport, high current density, electron mobility and great faradic-to-capacitive current ratios (Parlak et al., 2017). Meanwhile, AuNPs-MoS2 composites supply high surface area for capture DNA probes. Due to these unique properties of the AuNPs-MoS2 nanocomposites, they were broadly employed in many sensors, such as photoluminescence sensor (Bhanu et al., 2014), electrochemistry sensor (Yang et al., 2017b), surface-enhanced Raman scattering biosensor (Zhou et al., 2015) and chemiluminescence biosensor (Wang et al., 2015b). Further, AuNPs-MoS2 nanocomposites could produce localized SPR which directed potent plasmon-exciton coupling (Miao et al., 2015). It highlights the application of AuNPs-MoS2 nanocomposites in the construction of a high sensitive SPR biosensor.

In this way, Nie et al., (2017) fabricated a SPR biosensing approach with structural principles similar to those mentioned in GO-AuNPs SPR biosensor (Wang et al., 2016a). However, they used AuNPs-MoS2, instead of GO-AuNPs, as a great sensing substrate due to providing high surface area for DNA probes and inducing potent plasmon-exciton coupling. The principle of AuNPs-MoS2-based SPR biosensor was illustrated in Fig. 3C. The great sensitivity and high selectivity of this assay allowed the detection of miRNA-141 with LOD 0.5 fM. The binding of miRNA to probes resulted in resonance angle shift 0.0126° that improved to 0.2632° after adding of DNA-linked AuNPs-MoS2 nanocomposites. The largest the shift of resonance angle was observed for AuNPs/MoS2-SPR in increasing miRNA-141 concentrations from 0 to 50 pM compared to direct hybridization measurement and AuNPs amplified SPR. Further, a good reproducibility until 6 cycles was determined for this proposed biosensor. The acceptable process time and feasibility of detection of various contents of miRNA-141 in serum and different human cancer cell lines including hepatocellular carcinoma, prostate carcinoma, colon cancer and cervical cancer cell lines makes biosensor suitable for clinical diagnosis (Nie et al., 2017).

3.3. Oligodeoxynucleotide modified-AuNPs based SPR biosensors

Since the gold surface of SPR biosensor allows good compatibility for the biological substances, competition assays with SPR sensing provide the advantage of raised sensitivity for the detection of various types of small biomolecules like miRNAs. The principle of this assay is based on the competition of single strand surrogate oligodeoxynucleotide (ODN)-conjugated AuNPs and miRNA for selective hybridization with capture DNA (immobilized on the gold surface of the SPR chip) via sequence-specific hybridization. The detection sensitivity has been considerably meliorated with the use of ODN-capped AuNPs for their high dielectric constant and density (He et al., 2000). Particularly, the difficulty for miRNA to dominate ODN-modified AuNPs for the binding of DNA probes is problematic, since the predominance of ODN will have a negative effect on the detection sensitivity. Although it seems that few ODN on AuNPs improve the signal in competition strategy, a low number of ODN attached to AuNPs induces the risk of AuNPs collapse (Hong et al., 2018). In addition to ODN concentration on the surface of AuNPs, other critical experimental parameters involving AuNP size and hybridization buffer are also fundamental to better optimize a competition method for miRNA sensing. The radius of curvature which is extremely dependent upon the dimensions of the AuNPs affects ODN surface coverage. Previous reports also indicated that polyethylene glycol (PEG) could be used as a potential hybridization buffer for competition assays, since it remarkably increases the efficient concentration of the interacting biomolecules, improves the attachment of complementary DNA or RNA and stabilizes AuNPs in solution (Hill et al.,

2009; Manson et al., 2011; Zhang et al., 2012).

In order to use this technique, Hong et al., (2018) designed a competition sensing assay for detection of miRNA-200 b, an indicator of tumors invasion and epithelial-to-mesenchymal transition (Feng et al., 2012). As shown in Fig. 3D, the gold surface was modified with 11-MUA as a linker to promote the binding efficiency of probe through amide bond and arise probe density on the chip surface as well as increase hybridization signal. While 32 nm DNA/AuNPs revealed the stronger SPR response among different sizes of AuNPs, the colloidal instability was observed for these 32 nm AuNPs. Accordingly, 28 nm DNA/Au NPs at a ratio of 20:1 was optimized to detect miRNA-200 b with LOD 500 pM. Importantly, the use of PEG in hybridization buffer inhibited DNA/AuNPs aggregation and increased the SPR response following promotion in the hybridization of ODN-functionalized AuNPs to the probes. The sensor selectivity was confirmed by the response absence with a non-complementary let-7a miRNA (Hong et al., 2018).

3.4. Antimonene and AuNRs based SPR biosensors

Apart from different well-known 2D materials, such as graphene and MoS2, antimonene has received notable attention in last years. Antimonene is a monolayer composed of bulk antimony (Sb) (Gibaja et al., 2016) and like to graphene materials has an sp2-bonded honeycomb lattice. However, antimonene has premier physicochemical properties that distinguish it from other similar common 2D materials. These properties include potent spin–orbit coupling, more delocalized 5s/5p orbitals, great stability, better hydrophilicity, stronger charge transfer and electronic orbital hybridization (Pumera and Sofer, 2017). Antimonene quantum dots and nanosheets have been widely used in field effect transistors (Wang et al., 2017), photothermal therapy (Tao et al., 2017) and nonlinear optics (Lu et al., 2017). Applications of antimonene as an optic substance achieved from its specific absorption, dielectric function, refractivity, reflectivity and energy loss spectra (Singh et al., 2016).

According to the aforementioned matters, the interaction between antimonene and DNA for usage in optical sensing was investigated by Xue et al., (2019). The superior sensitivity of antimonene for nucleic acid sensing was obtained by its high adsorption energies (Ead) and work function (ΔW) for ssDNA. In this biosensor, a gold chip surface was covered with antimonene nanosheets. For amplification of SPR signal, ssDNA was conjugated to AuNRs. Then, ssDNA-AuNRs complex was employed to adsorb onto the antimonene. Because of the potent interaction between antimonene and ssDNA, the ΔW extremely increased following DNA absorption. In comparison, the flow of miRNA solution through the surface of antimonene nanosheet and miRNA binding to ssDNA-AuNRs complex decreased the Ead due to low affinity of dsDNA to antimonene. It led to release of miRNA-ssDNA-AuNRs complex from antimonene surface and created negative shift in the SPR resonance angle. Schematic illustration of antimonene-based miRNA sensing strategy was indicated in Fig. 4. The AuNR-based SPR could quantify attomolar-level of miRNA-21 and had profoundly low LOD of 10 aM that is 10^5 times lower than for non-AuNR modified SPR. In beside of miRNA detection, this SPR has been shown that assess miRNA-21 and miRNA-155 (two candidate biomarkers for cancer diagnosis (Dudda et al., 2013; Kumarswamy et al., 2011)) by only one nucleobase mutation. Because mismatched miRNAs are bound the antimonene nanosheets instead of ssDNA- AuNR complex, the addition of mismatched miRNA resulted in a slightly right shift in the SPR angle. Meanwhile, maximum sensitivity 171°RIU^{-1} for antimonene was achieved when the number of layer was four. These results introduce this antimonene-based SPR as ultrasensitive DNA and RNA sensor device for early cancer diagnosis (Xue et al., 2019).

3.5. Streptavidin functionalized-AuNPs based SPR biosensors

Streptavidin is a homotetramer protein from the Streptomyces

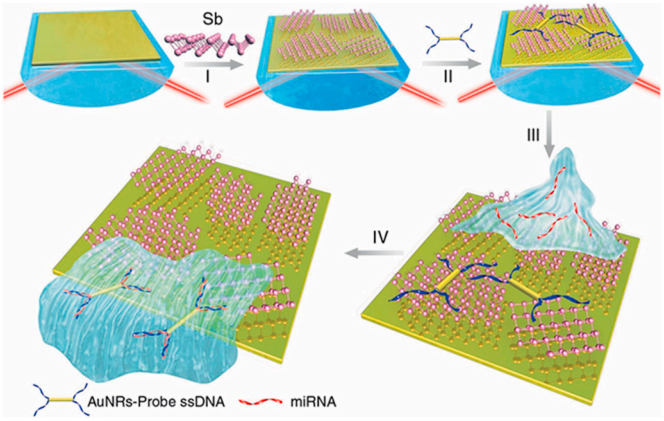

Fig. 4. Fabrication of a miRNA sensing assay integrated with antimonene nanosheet. I) The surface of gold film is covered by the antimonene nanosheets. II) ssDNA-AuNR is adsorbed on the antimonene sheets. III) miRNA is added on the surface of antimonene and attached to ssDNA-AuNR complex. IV) The interaction between AuNR-ssDNA and miRNA lead to release of the ssDNA-AuNR from the antimonene nanosheets. It causes to decrease of the SPR angle. Sb = antimony (Xue et al., 2019). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

avidinii bacterium that binds to four biotin molecules. The important traits of streptavidin comprising high thermostability and resistance against enzymatic degradation, denaturing agents and extreme pH make it useful for a large number of applications in bioassays, drug delivery, imaging protocols, purification procedures and sensors. The majority of streptavidin-based applications are in need of biotinylation of the target molecules via chemical or enzymatic reactions. Since streptavidin gene can tolerate vast mutations, it establish a good platform for engineering researches (Dundas et al., 2013). A wide range of macromolecules like polysaccharides, proteins and nucleic acids can be readily bound to biotin without critical effect on their physical, biological and chemical characteristics (Orth et al., 2003). Further, the binding of biotinylated molecules to streptavidin is accomplished at physiological conditions without exposure to toxic chemicals, harmful UV light, high salinity and extreme pH (Orth et al., 2003). Streptavidin-biotin based detection is a simple and biologically valuable method to pattern substrate on SPR sensor surface. By functionalization of various type of AuNPs like Au-nanorods or Au-nanostars with streptavidin, any biotinylated miRNA is detectable. Using this system, simple, fast, very sensitive and selective streptavidin heightened SPR based biosensors has been developed for sensing of miRNA profiling. Benefiting from the features of both AuNRs and streptavidin/biotin system, a facile SPR detection strategy for miRNA sensing was developed by applying biotinylated thiolated molecular beacon (MB) probes and strepavidinylated AuNRs (Stre-AuNRs). MB probes possess remarkable advantages compared with the linear probes due to competitive dynamics along with their stable and strong stem-loop structure. In this study, miRNA hybridization to MB probes immobilized on the gold film unfolded the loop sequence of MB and formed a rigid hybrid. This process activated the biotin terminal from MB for readily availability to the Stre-AuNRs detection probes. The presentation of detection probes to a sensor surface increased mass and refractive index as well as electronic coupling of the AuNRs plasmon and surface and thereby resulted in a substantially amplified signal response (Fig. 5A). The sensor sensitivity in the presence of Stre-AuNRs probes was 1000-folds higher than that without Stre-AuNRs that determined as LOD 0.045 pM versus 0.056 nM. Moreover, a good linear relationship was achieved between the signal response and miRNA concentration ranging from 0.1 to 100 pM. The SPR response value for the complementary target sequences was 2.96 times more than the three-base mismatch sequence, indicating acceptable specificity of this sensing

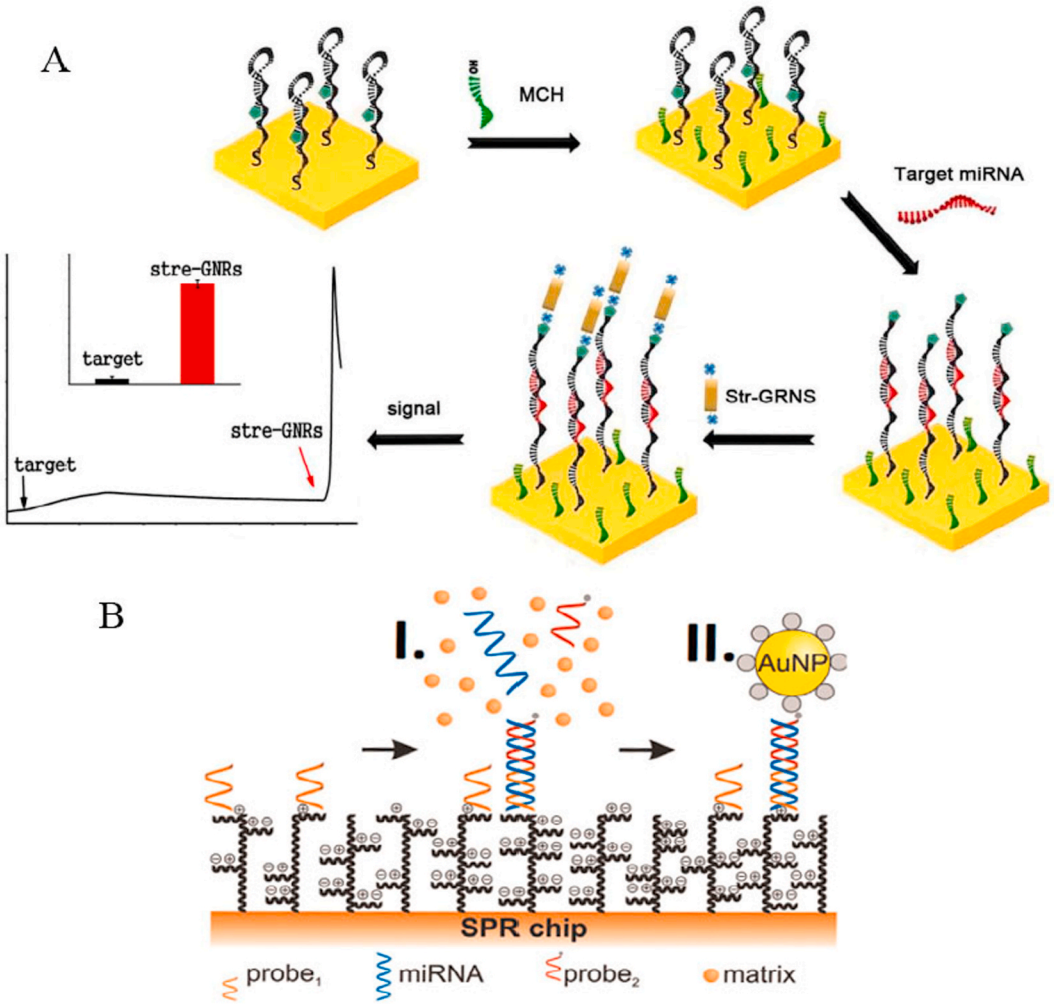

Fig. 5. Schematic illustration of designing strepavidin/biotin-based SPR sensing platforms using: A) strepavidinylated AuNRs (Hao et al., 2017), B) strepavidinylated-AuNPs with ultra-low fouling poly carboxybetaine acrylamide (Vaisocherová et al., 2015).

assay. Although, this approach requires more complex optimizing processes, detection process takes only 45 min (Hao et al., 2017).

The combination of strepavidinylated-AuNPs with ultra-low fouling poly (carboxybetaine acrylamide) (pCBAA) has opened a new perspective in the design of SPR biosensor. pCBAA brushes constituting three-dimensional like structures in solution provide a maximum loading capacity for probe immobilization. Hence, pCBAA brushes are promising candidates for biosensing in complex biological fluids like blood plasma (Vaisocherová et al., 2014). So, the study of Vaisocherova et al. can be a noteworthy effort in this field (Vaisocherová et al., 2015). They designed a SPRi biosensor based on strepavidinylated-AuNPs and pCBAA to detect miRNA-16, miRNA-181, miRNA-34a, and miRNA-125 b in erythrocyte lysate (EL) obtained from human peripheral blood. As illustrated in Fig. 5B, SPR chips were coated by the pCBAA that its surface functionalization was achieved by two main reactions including activation of the carboxyl groups and covalently attached amino-modified probes called probe1. Then, EL samples containing miRNAs that mixed with complementary probe2 (biotin-terminated probes) were flowed along the probe1-pCBAA-coated surface to form stable miRNA-probe1-probe2 complexes. The enhancement of sensor response to miRNA detection was performed with streptavidin-coated AuNPs that bind to probe2. The surface loading capacity of probes was enhanced about 9.8×10^{12} probes/cm^2 with increasing brush thickness of pCBAA in the range of 13–40 nm. Besides, high immobilization levels of probe1 was detected that it was compatible with data obtained from other studies (Lahiri et al., 1999; Vaisocherova et al., 2008) which used standard ethyleneglycol-based mixed alkanethiolate monolayers functionalized with probes by the biotin streptavidin interaction. This SPR assay could screen clinical EL samples in around 45 min for concentrations as low as sub-pM of different miRNAs. Although LOD of this biosensor is more than that achieved by new generation of biosensors, as fM and aM, this sensor provides rapid simultaneous and multiplex detection of several miRNAs in cell lysate with high resistance to fouling from 90% EL samples. Another advantage of this method is no need for miRNA extraction or pre-amplification steps. Moreover, the related LODs was improved by reducing the sensor operating temperature to less than 15 °C to promote the hybridization of oligonucleotides (Vaisocherová et al., 2015).

3.6. *Supersandwich-based SPR biosensors*

The common supersandwich assembly, as an amplification strategy, is mediated by introducing a signal probe that hybridizes to two regions of a target DNA. However, since extreme target DNA should participate in the formation of the supersandwich, the LOD of this protocol would be limited. Hence, the novel supersandwich based assay has developed by using of two auxiliary probes. The self-assembly of these probes forms one dimensional DNA concatamers, which act as vehicles for signal amplification. Even a single target DNA can conduct the linkage of a long concatamer to a capture probe on the sensor surface, instead of taking part in the concatamers. Importantly, the sensing assays based on DNA concatamers can remarkably enhance the LOD relative to the traditional

sandwich assays. Under optimized conditions, the length of the DNA concatamers can attain around μm level (Chen et al., 2011). Interestingly, the formation of concatamers was also used in ultrasensitive electrochemical biosensor for direct recognition of circulating miRNAs in human serum (Hong et al., 2013).

For the first time, Wang et al., (2016b) coupled AuNPs with supersandwich assembly, as a secondary amplification procedure, to design a SPR platform for detection of miRNA-21 which is a potential cancer biomarker upregulated in multiple tumor tissues (Zhu et al., 2008). Thiol-modified hairpin probe targeting miRNA-21 was captured by gold film. The binding of miRNA-21 to probe unfolded its stem-loop structure. Then, DNA-linked AuNPs were added to miRNA-probe hybrid (Fig. 6A). The electronic coupling between AuNPs plasmon and surface plasmon wave of gold film clearly enhanced the shift of resonance angle and thereby, increasing the sensor sensitivity. Further sensitivity was achieved by hybridizing two DNA reporters, as auxiliary probes, to complementary sequences in AuNP surface and producing a DNA supersandwich structure. The change of resonance shift was reported from 0.0030° (only hairpin probe) to 0.1695° (supersandwich structure). Increasing in miRNA-21 concentration from 0 to 150 pM let to gradually increment in the resonance angle. The LOD of this biosensor was estimated as 8 fM that is more less than LOD of AuNPs amplified SPR, supersandwich amplified SPR and direct hybridization measurement as 1 pM, 10 pM and 100 pM, respectively. Moreover, this biosensor could successfully distinguish miRNA-21 from single-base and three-base mismatch RNAs. More selectivity of biosensor was observed for discrimination between miRNA-21 and other non-specific miRNAs, let-7c and let-7i. Interestingly, signal of miRNA-21 detection in serum was similar to that in buffer and not affected by other components of the serum, indicating its potentials for practical and clinical applications. Moreover, no signal reduction was reported at least for 9 cycles. These properties made this sensor superior to enzyme-based biosensors in which enzyme may result in irreversible damage to the structure of miRNA biosensors (Wang et al., 2016b).

The silver nanoparticles (AgNPs) are catalytically and electrochemically active. They display Raman enhancement properties, particle size dependent surface plasmon resonance and higher extinction coefficients relative to AuNPs of the same size. Thus, these particles generate notable technological and scientific interest in photographic, electrode and catalysis processes (Hasanzadeh et al., 2018a; Lee et al., 2007). To get monodisperse NPs and to make the stable suspension of NPs, surfactants are employed as good stabilizers for AgNPs. Cetyltrimethylammonium bromide (CTAB) is a common cationic surfactant that forms a self-assembly monolayer on the surface of AgNPs to generate the positive zeta potential and spherical shape for the AgNPs. Accordingly, CTAB-AgNPs are usually used for the analysis of biomedical sample and pharmaceutical preparations (Walekar et al., 2014). Owing to the aforementioned advantages, the combination of CTAB-AgNPs with AuNPs and supersandwich assembly was recently performed for miRNA sensing assay. In this research, AgNPs were also used for multiple signal amplification. Thereby, further increment in resonance angle shift was mediated by attachment of positively charged and CTAB-capped AgNPs to negatively charged DNA surpersandwich. Although the detection process in this assay was too complicated, expensive and time-consuming, especially for practical applications, these multiple strategy amplifications significantly enhanced sensor sensitivity to provide LOD as 0.6 fM that is comparable to other previous works. The excellent selectivity of this SPR for mismatch and non-specific miRNAs was similar to previous study (Wang et al., 2016b). However, its reproducibility with same condition was seen for 6 cycles. Of specific importance, this modified sensing system could also detect cancer cells. In this way, magnetic bead-attached cell-specific aptamers were used for cell detection (Liu et al., 2017). Aptamers are artificial single stranded oligonucleotides (DNA or RNA) which derived from an in vitro evolution process called SELEX. They have high affinity and specificity to target molecules such as proteins, peptides, nucleic acids, viruses, bacteria and even cells and tissues (Eivazzadeh-Keihan et al., 2018; Hasanzadeh et al., 2018e; Mokhtarzadeh et al., 2016; Yousefi et al., 2019).

The cascade signal amplification based on both DNA supersandwich assembly and streptavidin/biotin system was successfully introduced by designing a versatile and enzyme-free SPR sensor for miRNA-21 detection (Ding et al., 2015) that distinguish it from common streptavidin/biotin assays. Gold sensor chips functionalized with thiolated hairpin capture probe that hybridizing with miRNA-21 changed its hairpin conformation to bind to biotin-labeled auxiliary probe AP1. Addition of second auxiliary probe, AP2, formed DNA supersandwich assembly and generated an amplified SPR signal. More signal enhancement is achieved by binding of streptavidin to biotinylated AP1. The LOD was reported as low as 9 pM that is a much lower compared to traditional RNA detection assays like Northern blotting. Although the process was a bit complicated, this SPR sensor provided extremely selective and sensitive detection of miRNA in real biological samples for clinical diagnostics. It is estimated this biosensor could detect 1.2 fM of miRNA-21 in the 4 μg total RNA sample extracted from MCF-7 cells. This new generation DNA supersandwich assembly is comparable to traditional sandwich assays that use only AP1 with ratio 1:1 of AP1 to miRNA. It produces a much smaller SPR signal. The excellent specificity of this SPR biosensor was achieved by discriminating target miRNA from single base mismatched and double-base mismatch target miRNAs. Besides, the signals for another miRNA, miRNA-222, and non-complementary sequence was reported as small as that of the blank. The high specificity of biosensor could be attributed to the high affinity of hairpin probe. In addition to great specificity, two other advantages of this method were reusability and high speed of detection. The same chip could be reused at least 20 times and miRNA detection process took only 30 min (Ding et al., 2015). The typical supersandwich and streptavidin/biotin system-based SPR sensorgram is depicted in Fig. 6B.

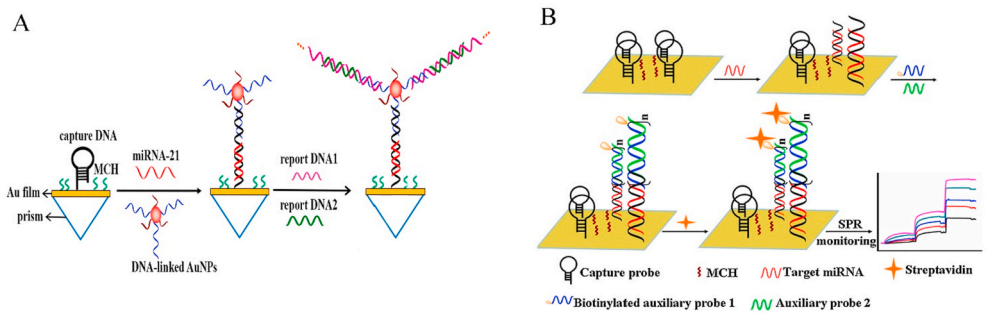

Fig. 6. Schematic representation of supersandwich-based SPR biosensors using A) DNA-linked AuNPs (Wang et al., 2016b), B) streptavidin/biotin system (Ding et al., 2015).

3.7. Antibody-based SPR biosensors

Antibodies (Abs), the main substance of animal immune system, are glycoproteins with a well-known structure that bind to their associated targets, called antigens (Ags). In fact, Abs are defined as "reporters" of many infections or other health diseases. Two main advantages of Abs, high stability and strong affinity to Ag, recommend them as suitable tools to improve the performance of bioanalytical techniques through the promotion of specific binding and the inhibition of non-specific binding (Trilling et al., 2013). The predominant Ab forms used in these techniques are monoclonal and polyclonal Abs. Monoclonal Abs are evolved from a single clonal hybridoma and polyclonal Abs are derived from several plasma cells. These Abs have finally differentiated in response to an Ag (Conroy et al., 2009). Importantly, immunosensors, a type of bioaffinity biosensors, are analytical devices in which the binding event between Ab and Ag (any analyte such as viruses, bacteria, toxins, proteins and acid nucleics) forms a stable complex, highlighting the advantages of immunosensors for different applications (environmental matrices, food analysis and medical diagnosis) (Eivazzadeh-Keihan et al., 2017; Hasanzadeh et al., 2017a; Mokhtarzadeh et al., 2017). Either Ag or Ab immobilizes on the surface of different transducers to produce a potential new immunosensor classified as electrochemical, optical, calorimetric and mass variation. The binding of Ab to Ag with high affinity leads to the detection of Ag in the presence of other substrates and produces a measurable signal. These biosensors combine the advantages of high selectivity and good sensitivity. Furthermore, they allow following of immunoreactions in real time (Felix and Angnes, 2018; Hasanzadeh et al., 2018c; Mokhtarzadeh et al., 2017).

Given that early diagnosis of disorders, especially cancers, can improve the prognosis and therapeutic effects, a one simple step SPR biosensing was developed for the simultaneous detection of miRNA-125 b and Alpha Fetoprotein (AFP) in Hepatocellular Carcinoma (HCC). The detection of miRNA-125 b was achieved by the combination of Ab and streptavidin/biotin system and the detection of AFP was mediated by Double Antibody Sandwich Method (DASM) (Yu et al., 2020). It is necessary to mention that both miRNA-125 b and AFP are serum markers and can use for early detection of HCC. miRNA-125 b acts as a tumor suppressor and its downregulation results in cell invasion and migration of HCC (Li et al., 2015). AFP functions as a transport molecule for numerous distinct ligands such as retinoids, steroids, heavy metals, fatty acids, dyes, bilirubin and various drugs. The serum AFP is still the golden standard diagnostic biomarker amongst others for HCC (Debruyne and Delanghe, 2008). In this multi-marker detection system, parallel channels of a single chip could measure clinical detection range of AFP and low concentration of miRNA-125 b. The surface of a four-channel chip was modified with a layer of carboxymethyl dextran matrix and then activated by amine coupling. In the direct measurement of AFP, monoclonal Abs bound to second channel of chip to detect concentrations 25–400 ng/mL of AFP. The detection sensitivity of AFP and SPR response signal was improved by DASM that formed a sandwich structure of monoclonal Ab, AFP, and polyclonal Ab. Although both the direct measurement and DASM showed acceptable linearity, DASM provided better linear correlation and more sensitivity in AFP detection. For miRNA-125 b detection, streptavidin/biotin system was applied in third channel of chip for binding of the biotinylated DNA probe to surface-fixed streptavidin (Fig. 7A). DNA/miRNA-125 b hybrid changed the refractive index and SPR response signal. This signal was enhanced by the binding of Ab to DNA/miRNA-125 b hybrid. While Ab led to higher SPR response signal compared to direct measurement in concentration ranges 6.25–100 nM of miRNA-125 b, signal fluctuation observed for Abs applied system was more drastic. A possible reason may be due to binding of Abs to DNA/miRNA hybrids one-to-one in high concentration of miRNA-125 b. Importantly despite to direct measurement method, Ab enhanced method has exhibited sensitive enough to

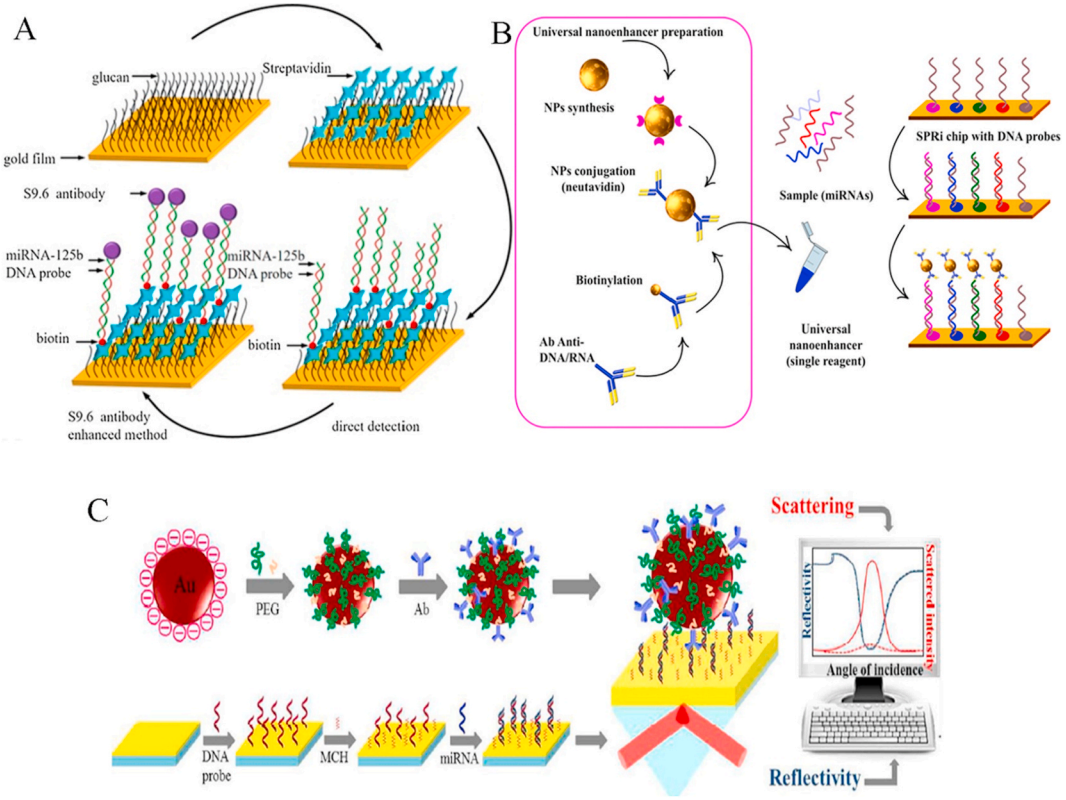

Fig. 7. Schematic representation of the strategies used for SPR biosensors based on Abs. A) simultaneous detection of miRNA-125 b and Alpha Fetoprotein by the combination of Ab and streptavidin/biotin system (Yu et al., 2020), B) by the combination neutravidin AuNPs and Ab (Sguassero et al., 2019), C) using SP-LS and Ab-conjugated AuNPs (Yang et al., 2017a).

detect low concentration ranges of 0–8 nM and 0–1000 pM of miRNA-125 b and provided the LOD as123.044 pM. Although this sensing strategy provides a little more LOD compared with other similar sensing schemes, its main advantage is ability of multi-marker detection (Yu et al., 2020).

Although the streptavidin/biotin system is extensively used in bio-nanotechnology and molecular biology, neutravidin/biotin system also provides a potential ability for analytical approaches. Neutravidin, a modified form of avidin, does not comprise carbohydrate, thus removing the potential of lectin binding. Yet, the strong affinity of biotin binding is retained. Neutravidin renders the lowermost nonspecific binding among the well-known biotin binding proteins at least to some extent due to a neutral isoelectric point that minimize nonspecific adsorption. Besides, it is a low expensive alternative to streptavidin (Vermette et al., 2003). Owing to the aforementioned advantages, a single universal SPRi was established using nanoenhancer composed from neutravidin AuNPs (nAuNPs) functionalized with the biotinylated-Ab mab 0105-P against DNA/RNA hybrids. This strategy was applied for simultaneous detection of Multiple Sclerosis-related miRNAs (miRNA-23a,-126,-422 and −223). As represented in Fig. 7B, the addition of nanoenhancer to the miRNA/probes duplex captured on the gold chip greatly enhanced SPRi signal. Ab:biotin molar ratio 1:25 resulted in about 900-fold enhancement for miRNA detection which was comparable with nAuNPs alone or non-biotinylated Abs. The estimated LOD for four miRNAs was in range from 0.55 pM to 1.79 pM. Using of nanoenhancer allow SPRi to distinguish the mutated sequence probably due to the 3D changes arising from the base-base mismatch. While the proposed method is practical for clinical purposes, the spotting process for immobilizing thiolated probes on a chip surface and production of the nanoenhancer needs to be complex optimization procedures (Sguassero et al., 2019).

The combination of AuNPs and Ab for further signal enhancement was also used for development of a rapid and ultrasensitive scheme based on SP-LS to detect miRNA-122 with the LOD of 60 fM within 30 min (Yang et al., 2017a). In this study, miRNA-122 was injected for hybridization with gold-surface immobilized DNA probes. The DNA-RNA hybridization signal was amplified up to 5 times with D5H6 Ab-conjugated AuNPs. For further signal amplification, AuNPs with 55 nm was selected, as the power scattered from 55 nm AuNPs was 20-fold higher than that from 36 nm. Only negligible changes were observed in the reflectivity and scattering intensity for non-specific miRNA-192, indicating high affinity and specificity of the Ab to DNA-miRNA-122 duplex. Besides, LOD of 300 fM was attained for miRNA-122 in a high concentration background of non-specific miRNA-192, confirming the specificity and sensitivity of the assay. The sensitivity provided by SP-LS showed 283-fold improvements than previous study for the miRNA-122 detection (Sipova et al., 2010). However, note that this sensitivity is obtained in ideal measurement conditions regardless of the biological noise in clinical samples (Yang et al., 2017a). Schematic representation of the Ab-conjugated AuNPs strategy is illustrated in Fig. 7C.

3.8. Enzyme-based SPR biosensors

Enzyme-based biosensors have emerged as a noteworthy strategy for quantitative and qualitative analysis of a various analytes in food quality control, biomedicine, as well as environmental, pharmaceutical and agricultural industry. These biosensors have been designed on immobilization methods, such as adsorption of enzymes by ionic bonding, covalent bonding or van der Waals forces. Enzyme-based optical biosensors have also been expanded over nearly half-century. In clinical section, these biosensors present advantages of fast and extra-laboratory analysis with considerable reduction of cost per sample. Furthermore, the generally excellent turnover rates of biocatalysts and the high specificity of substrate-enzyme interactions have attracted an extensive interest to make specific and sensitive enzyme-based biosensors (Choi, 2004; Hasanzadeh et al., 2017b; Ispas et al., 2012; Mehrotra, 2016). Nevertheless, the enzymes have some disadvantages, including instability, specific reaction conditions, and difficulties in storage. Additionally, as the enzymatic activity is sensitive to be affected by the environmental media, the enzyme-based amplification assays require partly clean samples for miRNAs detection (Yang et al., 2012). Recently, some modifications have been provided an interesting development in the present enzyme-based optical biosensors research. In following sections, some useful examples of enzyme-based SPR biosensors are introduced.

3.8.1. Locked nucleic acid and poly a polymerase-based SPR biosensors

The critical challenges for miRNAs analysis are their innate small size and low fraction in a total RNA sample. The short length of miRNAs supplies very little sequence for designing probes or labeling. The low fraction of miRNAs makes serious to label them with the highest specific activity feasible. Furthermore, miRNAs exist in three various forms (pri-miRNA, pre-miRNA and mature miRNA) that only the mature miRNA is functional. Therefore, it is important to remove signals from the pri- and pre-miRNAs (Shingara et al., 2005). The enzymatic or chemical modifications such as ligation, polymerase reactions and biotinylation of the target miRNA are generally used to overcome these limitations (Babak et al., 2004; Liang et al., 2005; Nelson et al., 2004). Direct enzymatic tailing of miRNA in which the polyadenylation of the 3^{-}-end of miRNA is mediated by the poly A polymerase (PAP) enzyme provided a successful strategy for labeling and hybridization of active miRNAs down to a concentration of 10 pM (Shingara et al., 2005).

Locked nucleic acid (LNA) is a synthetic DNA/RNA analog that has a methylene bridge that connects the 4′-carbon of ribose with the 2′-oxygen. This structure changes LNA configuration, providing it great advantages such as high affinities for complementary sequences, low toxicity, thermostability, nuclease resistance and the ability to make RNA/DNA-LNA chimeras. Besides, LNA could be synthesized by standard methods and be available through a commercial supplier. Possessing these advantages, LNA has the potential to be used for in vivo suppression of gene expression, oligonucleotide arrays and nucleic acid recognition (Braasch and Corey, 2001; Saadati et al., 2019). Importantly, LNA is largely used for the development of high-performance affinity biosensors for nucleic acid detection (Chen et al., 2008; Lin et al. 2009, 2011; Martinez et al., 2009; Wang et al., 2011).

According to the aforementioned advantages, Fang et al., (2006) combined the surface reaction of PAP, the surface bound LNAs, the adsorption of DNA-modified AuNPs on the poly A tails and finally the detection of the hybridization points by AuNP-amplified SPRi. The synthetic or mouse liver extracted miRNAs (miRNA-16, miRNA-23 b and miRNA-122 b) were adsorbed onto an 11-Mercaptoundecylamine (MUAM)-coated LNA microarray and then poly A tails were added to the miRNAs via PAP. The poly A tails efficiently overcame the binding challenge of AuNPs to the small miRNAs. Finally, the signal amplification was achieved by attachment of poly thymine-coated AuNPs (T30-coated AuNPs) to poly A tails (Fig. 8A). This method could successfully detect different concentrations of three miRNAs since percent reflectivity was reported as 9.7% for most abundant miRNA-122 b as well as 0.8% and 0.4% for low level miRNA-23 b and miRNA-16, respectively. No nonspecific adsorption was seen at LNA arrays, indicating excellent specificity of this SPR platform. LOD of this study reported as 10 fM that is around 50 times more sensitive compared to similar fluorescence-based microarray detection method (Shingara et al., 2005). However, complex protocol of this approach and its emphasis on a surface initiated enzymatic amplification restrict its practical applicability (Fang et al., 2006).

3.8.2. Organic compound and poly a polymerase-based SPR biosensors

3,3′,5,5′-Tetramethylbenzidine (TMB) is a much less hazardous but more sensitive derivation of benzidine. The oxidation of TMB by horseradish peroxidase (HRP) enzyme yields blue products (Josephy et al., 1982). Therefore, TMB can be used as an analytical reagent in surface biosensor microarrays with great spatial resolution. TMB

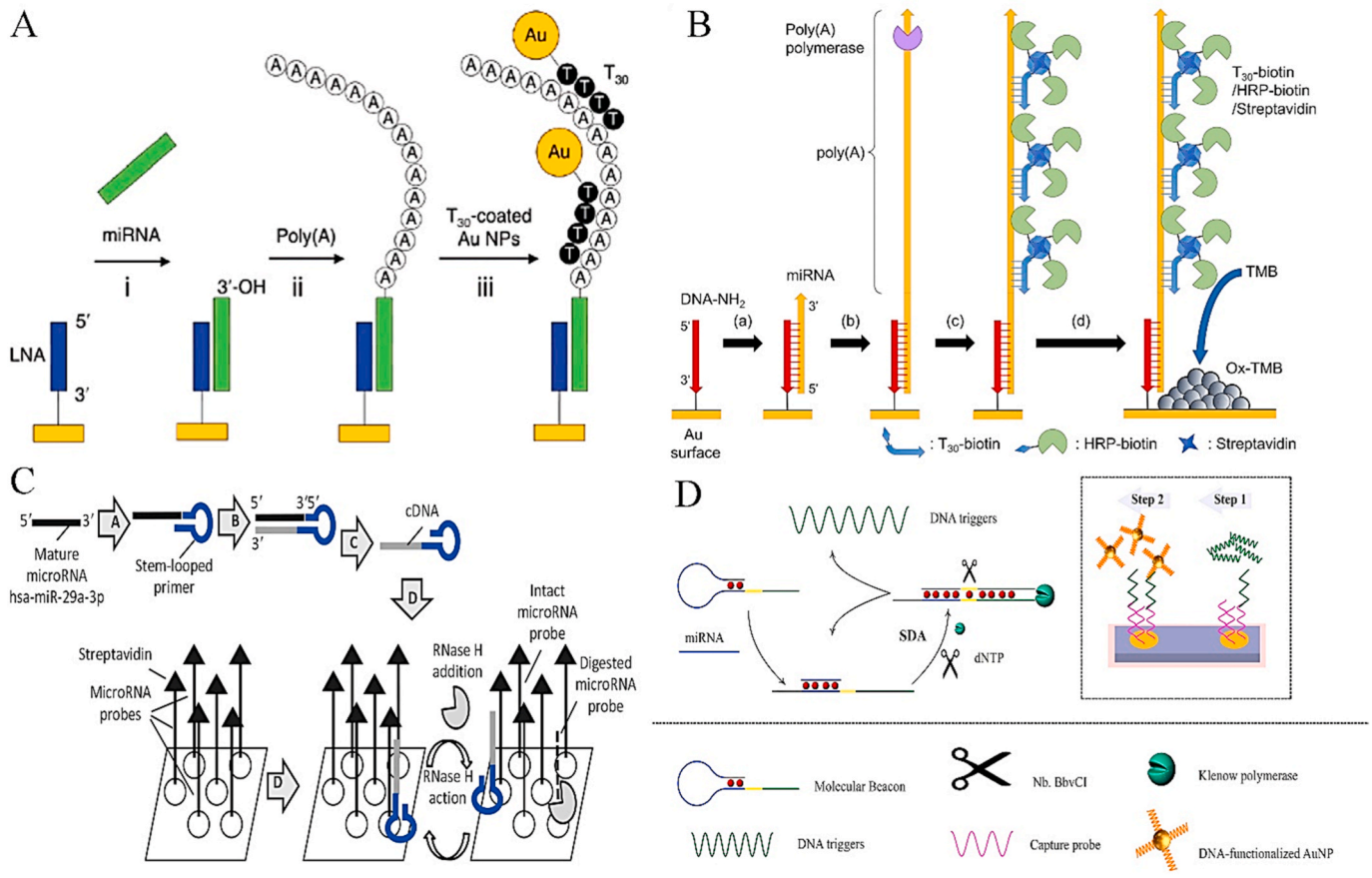

Fig. 8. The detailed scheme of enzyme-based SPR biosensors using A) LNA and poly A polymerase (Fang et al., 2006), B) TMB and poly A polymerase (Aoki et al., 2019), C) RNase H in non-PCR MARS strategy (Ho et al., 2017; Loo et al., 2015), D) strand displacement amplification (Zeng et al., 2017).

produces a localized surface precipitation reaction that is detectable with either electrochemical or optical methods (Frey et al., 2000). For this reason, TMB is largely used in electrochemical techniques (Akter et al., 2017; Fanjul-Bolado et al., 2005; Shen et al., 2014) and SPR (Li et al., 2007; Linman et al., 2010) for signal enhancement. TMB-based signal amplification is also used in biochemical staining processes, such as immunohistochemistry and ELISA as a visualizing reagent (Frey et al., 2000).

In this regard, a simple, practical and cost-effective SRPi method using organic compound TMB, instead of metal NPs as a common signal enhancer, was established for sequence-specific detection of miRNA-21 at the attomole level (Aoki et al., 2019). Schematic exhibition of the TMB-based strategy is illustrated in Fig. 8B. SRPi chips were modified with two types of DNA-NH2 probes: DNA-NH2-A, complementary probe to miRNA-21, and DNA-NH2-B, non-complementary probe to miRNA-21. After miRNA-21 hybridization, PAP extended poly A tail at the 3′-terminal of the miRNA. T30-biotin/HRP-biotin/streptavidin ternary complex was tethered to poly A tail. The DNA-NH2-A sensor revealed larger responses than those for the DNA-NH2-B sensor due to reaction of the ternary complex with the poly A tails. It seems that low SPR responses for DNA-NH2-B sensor were mediated by non-specific adsorption of the ternary complex to the SPR sensor surface. Moreover, treatment of the ternary complex with TMB could result in oxidizing of TMB to Ox-TMB and generating a blue precipitate. Similarly, the SPR response for DNA-NH2-A sensor was significantly enlarged compared to that for DNA-NH2-B. This method could detect miRNA at the aM level means that its sensitivity was similar to or greater than that metal NPs based methods. However, the limitation of this method was the lack of effective washing out Ox-TMB in the presence of air bubbles, resulting in nonlinearity between SPR response and miRNA concentration (Aoki et al., 2019).

3.8.3. *RNase H enzymatic reaction-based two-dimensional SPR biosensors*

Ribonuclease H or simply RNase H hydrolyzes the RNA part in RNA–DNA hybrids. Therefore it is required for removal of RNA primers, after they acts as starters for the DNA polymerases in DNA synthesis. RNase H also removes the RNA in DNA-RNA duplexes during viral DNA synthesis to finally a solely double-stranded DNA (dsDNA) is generated. In retroviruses with RNA genome like influenza and HIV virus, RNase H degrading the RNA in the DNA-RNA hybrid leaves the dsDNA in host cells for viral replication. RNase H is not limited to retroviruses but it found in some prokaryotes and eukaryotes (Cerritelli and Crouch, 2009; Moelling, 2012). This enzyme could be used in some surface enzymatic amplification procedures to greatly improve nucleic acid detection through RNA microarrays (Goodrich et al., 2004b). The conjunction of RNA microarrays and RNase H sufficiently improved the sensitivity of SPRi for the detection of DNA fragments down to a concentration of 1 fM (Goodrich et al., 2004a).

For the first time, non-PCR miRNA-RNase-SPR (non-PCR MARS) was developed as a sensing method to detect hsa-miRNA-29a-3p (Ho et al., 2017; Loo et al., 2015), a marker associated with influenza A H1N1 viral infection (Peng et al., 2016). In this study, using RNase H enzymatic reaction in a two-dimensional SPR (2D-SPR) improved SPR signal amplification. Firstly, hsa-miRNA-29a-3p extracted from throat swab samples of influenza patient was converted into cDNA by stem-loop primers. Second, cDNA was hybridized to the biotinylated-miRNA probe that immobilized on the sensing surface and attached to streptavidin. Then, RNase H digested the RNA probe to release cDNA from the RNA–cDNA hybrid. The unbound cDNA could repeatedly anneal to the new probes for subsequent RNase H digestion and thereby signal

amplification (Fig. 8C). The using biotin–streptavidin in non-PCR MARS platform notably ameliorated the signal-to-noise ratio and assay sensitivity. High specificity was observed for precise hybridization of hsa-miRNA-29a-3p probes to its corresponding target cDNA. The concentration of miRNA in a patient sample could be determined from the standard curve of known cDNA concentration of related miRNA. The LOD of this MARS assay for miRNA-29a-3p was found to be 1 nM and this assay could be completed in less than 1 h without thermal cycling. To avoid erroneous results, the pH and concentrations of glycerol could be carefully optimized for the RNase H reaction (Ho et al., 2017; Loo et al., 2015).

3.8.4. Strand displacement amplification-based SPR biosensors

The strand displacement amplification (SDA) is a DNA amplification strategy that does not need temperature cycling and utilize readily available enzymes. This strategy is based upon the capability of a restriction enzyme (RE) to nick the unmodified strand of a specific hemimodified DNA recognition site, then the ability of a DNA polymerase to expand the 3′ end at the nick and finally displace the downstream strand. Repeat cycles of nicking, polymerization, and displacement reactions amplify the target DNA exponentially and produce detectable dsDNA (Walker et al., 1992). SDA was used in some fluorescent sensor-based assays for detection of DNA (Guo et al., 2009) and cocaine (He et al., 2010; Shlyahovsky et al., 2007). Also, exponential SDA provided the sensitive and direct detection of miRNAs in a complex biological matrix, offering it as a high potential for clinical applications, point-of-care diagnosis and basic research (Shi et al., 2014).

So, the study of Zeng et al., (2017) can be a valuable attempt in this area. They devised a home-made SPRi platform relied on a practicable nucleic acid-based amplification method by applying SDA, and AuNP enhancement sandwich assembly for detection of miRNA-155 (Zeng et al., 2017). miRNA-155 is a typical multifunctional miRNA participated in multiple biological processes including immunity, inflammation and hematopoiesis. Deregulation of miRNA-155 is associated with viral infections, cardiovascular diseases and cancers (Jurkovicova et al., 2014). A MB consisting three areas (miRNA-binding area, amplification area for generating DNA triggers and recognition area for Nb. *Bbv*CI RE enzyme) were used for established SDA reaction. miRNA-155 hybridization to corresponding area opened the MB template and produced a duplex structure that extended by Klenow DNA polymerase to form a complete duplex. Subsequently, the Nb. *Bbv*CI cleaved the upper DNA strand to subject a new replication site for Klenow. The continuous cycle of extension, cleavage, and SDA led to production of DNA triggers that on one side could bind to probes immobilized on the gold island microchips of SPRi and on the other bind to DNA-functionalized AuNPs. This process mediated sandwich formation and significantly amplified detection signal (Fig. 8D). The LOD was estimated to be 45.45 pM that is about 36 times higher than that observed for the conventional triple-stranded hybridization. This biosensing strategy did not represent any improvement in the analytical performance compared with the previous reported colorimetric methods for miRNA detection (Liu et al. 2014, 2015a; Wang et al., 2015a). But, this method exhibited acceptable reproducibility and also technical support for high-throughput miRNA investigation by using dual signal amplifications of MB mediated SDA and AuNPs amplification. Besides, the method outlined here displayed an excellent selectivity to discriminate perfectly complementary miRNA-155, single-base or double-base mismatched miRNA-155 and non-complementary miRNA-21. Although this assay requires complex protocol with multiple preparation step, the efficiency of biosensor was not affected in complex mixtures of serum, introducing it as potential tool for miRNA sensing and clinical diagnostics in real biological samples within 75 min (Zeng et al., 2017).

3.9. Catalytic hairpin assembly-based SPR biosensors

The catalytic hairpin assembly (CHA) is an enzyme-free signal amplification strategy based on hairpin probes that has been widely exerted for detection of different biomarkers (Li et al., 2011). It is a powerful method to transduce and amplify signals until hundred-fold at the terminal of nucleic acid amplification reactions (Jiang et al., 2013). The fast turnover rates of CHA results in high sensitivity and negligible background in target-specific reactions (Zhuang et al., 2014). Thereby, CHA-based biosensing strategies could be introduced as potential alternative methods for detection of miRNAs in clinical diagnosis and biomedical research (Zhang et al., 2015).

Wei et al., (2020) used a rapid technology with more sensitivity (much lower LOD as 53.7 fM) for let-7a miRNA sensing within 50 min. They combined CHA amplification circuit with spherical nucleic acid to significantly enhance sensitivity. The spherical nucleic acid are typically composed of spherical NPs densely functionalized with either RNA or DNA, and they enhance nucleic acid stability in complex environments by restricting the extent of degradation mediated by endogenous nucleases (Mokhtarzadeh et al., 2019). The two hairpin probes (H1 and H2) were utilized to tether with spherical nucleic acid, resulting in a substantially amplified SPR signal. Consistent with findings of previous study (Li et al., 2016), this technology could discern members of homologous let-7a miRNA families, even with 1–2 nucleotide differences due to stable stem-loop structure of probes which only unfolded by the target miRNA to generate the H1–H2 hybrid. The efficient changes in SPR signal response was attained in concentrations 0.1–1500 pM of target let-7a with a good linearity. Moreover, it was qualified to detect let-7a miRNA in complicated biological sample, fetal bovine serum, suggesting a miRNA analysis assay for early clinical diagnosis (Wei et al., 2020). The linear range of the proposed method was wider than that of SRP based on streptavidin functionalized AuNR-assisted signal amplification strategy (0.1 pM–100 pM) (Hao et al., 2017).

4. Label-free SPR biosensors for miRNA detection

Label-free detection in SPR introduces an effective method compared with common label-based techniques like fluorescence. Although, using AuNPs as a label for enhancing the SPR response units causes the loose of label-free detection system, it makes the sensitive diagnosis in SPR biosensors. Label free detection presents a preference for removing molecular labels when practical information is wanted. This is particularly accurate for specific targets where labels can change the protein function.

In this regard, a label free SPR biosensor by streptavidin oligonucleotide (SON) complex based strepavidin/biotin system was designed for miRNA-122 expression profiling detection (Zhang et al., 2013a). miRNA-122 is a tissue-specific miRNA with high expression in liver cancerous cells that mediates metastasis of hepatocellular carcinoma (Jopling, 2012). This miRNA, also, implicates in hepatitis C virus pathogenesis and cholesterol biosynthesis (Esau et al., 2006; Jangra et al., 2010). In this sensing assay, SON complex was established ex situ by mixing of biotinylated DNA probe and streptavidin. The gold chip was functionalized with the thiolated DNA capture probe complementary to miRNA-122. After injection of miRNA, SON complex was added to bind to a part of the target miRNA-122 (Fig. 9A). This process remarkably increased the assay sensitivity owing to the enhanced mass. The maximum signal response was observed in a concentration of 5 μgmL^{-1} of streptavidin. Also, the signal amplification by SON was reported as a 5-fold increase in response change for SON complex compared to direct measurement (without enhancement). The assay selectivity was investigated by the introduction of single nucleotide mismatches on the DNA capture probes. Besides, response signal for non-specific miRNA-29 was as small as the background. The LOD of this sensor was 17 pM for miRNA-122 and was measured as 1.7 fM in sample volume of 100 μL. This number is much lower than that of Northern blot, enzyme-based electrochemical sensors and some antibody enhanced SPR. While more sensitive assays for miRNA detection has been established upon hairpin probe based, nanoparticle based and

Table 1
Characteristics of different SPR-based methods in miRNA detection.

RU enhancer in SPR	Immobilized capture sequence on Au sensor surface	Analytical performance	Detected miRNA sequence	Detection steps and related time (min)	miRNA Samples	target discrimination from different miRNAs (or mismatched miRNAs [a])	pros and cons	Ref
Label-based SPR biosensors								
GO-AuNPs	5′-AGA CAG TGT TAT TTT TTT TTT–SH–3’	LOD: 1 fM Reproducibility: 1% n = 5	5′-UAACACUGUCUGGUAAAGAUGG-3′	Two steps 110	miRNA-141→ extracted from human cancer cell lines: prostate carcinoma (22Rv1), hepatocellular carcinoma (SMMC-7721), colon cancer (LoVo), and cervical cancer (HeLa)	Different miRNAs including miRNA family members including miRNA-429, miRNA-200a, miRNA-21 and random miRNA	Pros: •great selectivity for discriminating miRNA family members, •high efficiency in a complex biological matrix Cons: • time consuming	(Wang et al., 2016a)
GO-AuNPs hybrids	5′-AGA CAG TGT TAT TTT TTT TTT–SH–3’	LOD: 0.1 fM Linear range: 0.1 pM - 2.0 nM.	5′-UAACACUGUCUGGUAAAGAUGG-3′	Two steps 60	miRNA-141→ extracted from human cancer cell lines: prostate carcinoma (22Rv1), hepatocellular carcinoma (SMMC 7721), and colon cancer (LoVo)	miRNA-200a, miRNA-429, miRNA-21 and random miRNA	Pros: • excellent selectivity • time-effective	(Li et al., 2017)
AuNPs/MoS2 hybrids	5′-AGACAGTGTTATTTTTTTTTT–SH–3’	LOD:0.5 fM Reproducibility: 1.2% (n = 6)	5′-UAACACUGUCUGGUAAAGAUGG-3′	Two steps 50	miRNA-141→ extracted from human cancer cell lines: prostate carcinoma (22Rv1), hepatocellular carcinoma (SMMC 7721), colon cancer (LoVo) and cervical cancer (HeLa)	miRNA-141, miRNA-200a, miRNA-429, let-7d and random miRNA	Pros: • great sensitivity, selectivity and reproducibility • time-effective	(Nie et al., 2017)
ODN-capped Au NPs	5′- TCATCATTACCAGGCAGTATTA-NH2-3’	LOD: 500 pM (3 times the noise)	5′-UAAUACUGCCUGGUAAUGAUGA-3′	One step 60	miRNA-200 b → synthetic	let-7a	Pros: • great selectivity •time-effective	Hong et al. (2018)
AuNRs	Antimonene and AuNRs-Probe-ssDNA (SH - TCA ACA TCA GTC TGA TAA GCT A)	LOD: 10 aM (3:1 signal to noise ratio)	5′-UAG CUU AUC AGA CUG AUG UUG A-3′	One step 20	miRNA-21→ synthetic	mismatched miRNA-21 +++	Pros: •ultra-sensitivity •time-effective	(Xue et al., 2019)
Streptavidinylated AuNRs	Biotinylated thiolated MB: 5′–SH–TTA GCA C CGC CAA TAT TTA CGT GCT GCT A TGC TAA-biotin-3’	LOD: 45 fM (4 times the standard deviation of the control) Linear range: 0.1–100 pM	5′-UAGCAGCACGUAAAUAUUGGCG-3′	Two steps 45	miRNA→ synthetic	+++ +	Pros: •great specificity •time-effective Cons:	(Hao et al., 2017)

(*continued on next page*)

Table 1 (*continued*)

RU enhancer in SPR	Immobilized capture sequence on Au sensor surface	Analytical performance	Detected miRNA sequence	Detection steps and related time (min)	miRNA Samples	target discrimination from different miRNAs (or mismatched miRNAs [a])	pros and cons	Ref
							• more complex optimizing processes	
Sandwich-type hybridization and streptavidin-functionalized AuNPs	Probe 1 and 2 for miRNA-16: NH2-(CH2)12–5′- CGC CAA TAT TTA C -3′, 5′-GTG CTG CTA-3′-TEG-Biotin Probe 1 and 2 for miRNA-181: NH2-(CH2)12–5′- ACT CAC CGA CA-3′, 5′-GCG TTG AAT GTT-3′-TEG-Biotin Probe 1 and 2 for miRNA-34a: NH2-(CH2)12–5′- ACA ACC AGC TAA-3′, 5′-GAC ACT GCC A-3′-TEG-Biotin Probe 1 and 2 for miRNA-125 b: NH2-(CH2)12–5′- TCA CAA GTT AGG -3′, 5′-GTC TCA GGG A-3′-TEG-Biotin	LOD miRNA-16: 0.35 pM, LOD miRNA-181: 0.39 pM, LOD miRNA-34a: 0.50 pM, (LOD was calculated based on Blank+3 × SD)	miRNA-16: 5′-UAG CAG CAC GUA AAU AUU GGC G-3′ miRNA-181: 5′-AAC AUU CAA CGC UGU CGG UGA GU-3′ miRNA-34a: 5′-UGG CAG UGU CUU AGC UGG UUG U-3′ miRNA-125 b: 5′-UCC CUG AGA CCC UAA CUU GUG A-3′	Two steps 45	miRNA-16 miRNA-181 miRNA-34a miRNA-125 b → extracted from Erythrocyte lysate	Control experiments	Pros: • excellent loading capacity for probe immobilization • multiplex detection of miRNAs • time-effective • no need for miRNA extraction or pre-amplification steps	(Vaisocherová et al., 2015)
DNA supersandwich and AuNPs	5′–SH–C6H12-GGCCGTCAACATCAGTCTGATAAGCT AAACATGATGACGGCC-3’	LOD: 8 fM Reproducibility: 1% (n = 9)	5′-UAGCUUAUCAGACUGAUGUUGA-3′	Three steps 180	miRNA-21 → synthetic	let-7c and let-7i +++ +	Pros: •great reproducibility • useable for biological samples Cons: • time consuming	(Wang et al., 2016b)
Multiple amplification strategy (DNA super-sandwich, AuNPs and AgNPs amplification)	5′–SH–C6H12-GGCCGTCAACATCAGTCTGATAAGCTAAACA TGATGACGGCC-3′	LOD: 0.6 fM	5′-UAGCUUAUCAGACUGAUGUUGA-3′	Three steps 205	miRNA-21 → Synthetic Human hepatocellular carcinoma cell line SMMC-7721	let-7c and let-7i +++ +	Pros: • excellent selectivity • detection of cancer cells Cons: • time consuming • complicated detection process • expensive	(Liu et al., 2017)
DNA super-sandwich	5′–SH–(CH2)6-GGCCGTCAACATCAGTCTGATAAGCTAAACATGATGACGGCC-3’	LOD: 9 pM Reproducibility: 6.3% (n = 5)	5′-UAGCUUAUCAGACUGAUGUUGA-3′	Two steps 30	miRNA-21 → Both synthetic and extracted from human breast adenocarcinoma MCF-7 cell	miRNA-222 +++ ++	Pros: • great sensitivity, selectivity • time-effective • useable for real biological samples • reusability Cons: • complicated	(Ding et al., 2015)

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Table 1 (*continued*)

RU enhancer in SPR	Immobilized capture sequence on Au sensor surface	Analytical performance	Detected miRNA sequence	Detection steps and related time (min)	miRNA Samples	target discrimination from different miRNAs (or mismatched miRNAs [a])	pros and cons	Ref
							detection process	
DASM and streptavidin	No mentioned	LOD: 123.044 pM LOD = 3 (SD/S)	No mentioned	One step	miRNA-125 b → extracted from serum of patient with Hepatocellular Carcinoma	–	Pros: • multi-marker detection system • useable for real biological samples Cons: • more LOD compared with other similar sensing schemes	Yu et al. (2020)
AuNPs and antibody	Capture probe for miRNA-23a: 5′–SH–C6-TTTTTTTTTGGAAATCCCTGGCAATGTGAT-3’ Capture probe for miRNA-126: 5′–SH–C6-TTTTTTTTTCGCATTATTACTCACGGTACGA-3’ Capture probe for miRNA-422: 5′–SH–C6-TTTTTTTTTGCCTTCTGACCCTAAGTCCAGT-3’ Capture probe for miRNA-223: 5′–SH–C6-TTTTTTTTTTGGGGTATTTGACAAACTGACA-3’	LOD: Average 1pM (LOD: the average of three replicated blank injections + 3 SD)	miRNA-23a 5′-AUCACAUUGCCAGGGAUUUCC-3′ miRNA-126 5′-UCGUACCGUGAGUAAUAAUGCG-3′ miRNA-422> 5′-ACUGGACUUAGGGUCAGAAGGC-3′ miRNA-223 5′-UGUCAGUUUGUCAAAUACCCCA-3′	Two steps <60	miRNA-23a miRNA-126 miRNA-422 miRNA-223 → Both synthetic and extracted from the serum of healthy control subjects	mutated miRNA or miRNA isomers +++ +	Pros: • time-effective • useable for real biological samples Cons: • complicated optimization process	(Sguassero et al., 2019)
Ab conjugated AuNP	Capture probe: 5′–HS–(CH2)6-CAA ACA CCA TTG TCA CAC TCC A-3’	LOD: 60 fM (3 times the standard deviation of the reflectivity/ scattered intensity baseline noise)	5′-UGG AGU GUG ACA AUG GUG UUU G-3′	One step 30	miRNA-122 → synthetic	high concentration of non-target miRNA (1.0 nM of miRNA-192)	Pros: • time-effective • great specificity and sensitivity	Yang et al. (2017a)
AuNPs and polymerase amplification	miRNA-23 b-LNA: 5′-TCCCTGGCAATGTGAT(C)15(CH2)3–S–S-3′ miRNA-122 b-LNA: 5′-CCA TTGTCACACTCCA(C)15(CH2)3–S–S-3′ miRNA-16-LNA: 5′-TATTTACGT TATTTACGTGCTGCTA(C)15(CH2)3–S–S-3′	LOD:10 fM Linear range: 10 to 500 fM.	miRNA-23 b 5′-AUCACAUUGCCAGGGAUUACCAC-3′ miRNA-122 b 5′-UGGAGUGUGACAAUGGUG UUUGA-3′ miRNA-16 5′-UAGCAGCACGUAAAUAUUGGCG-3′	Three steps >90	miRNA-23 b miRNA-122 b miRNA-16→ Both synthetic and extracted from mouse liver	–	Pros: • excellent specificity • detection of different concentrations of miRNAs Cons: • complex protocol	Fang et al. (2006)
Enzymatic amplification based on extension of poly A tail, T30-biotin/ HRP-biotin/ streptavidin complex	DNA-NH2_A: 5′-TCA GTC TGA TAA GCT A-NH2-3’ DNA-NH2_B: 5′-GTG CCT TCA CTG CAG T-NH2-3’	LOD: attomole level	5′-UAG CUU AUC AGA CUG AUG UUG A-3′	Three steps >180	miRNA-21→ synthetic	Different target miRNA concentrations.	Pros: • cost-effective • sensitivity Cons: • time consuming nonlinearity between SPR response and	Aoki et al. (2019)

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Table 1 (*continued*)

RU enhancer in SPR	Immobilized capture sequence on Au sensor surface	Analytical performance	Detected miRNA sequence	Detection steps and related time (min)	miRNA Samples	target discrimination from different miRNAs (or mismatched miRNAs [a])	pros and cons	Ref
RNase H enzymatic reaction	RNA probe: 5'- (biotin)-uagcaccaucugaaaucgguuauuuuuuuu-(C6)-SH-3'	LOD: 1 nM (signal at blank plus 3 times of standard deviation)	cDNA sequence: 5′-TAACCGATTTCAGATGGTGCTA-3′	Three steps 60	hsa-miRNA-29a-3p → extracted from secretions of patient with influenza virus infection	hsa-miRNA-181–5p	miRNA concentration Pros: • high specificity • time-effective Cons: • need for precise optimization	(Ho et al., 2017; Loo et al., 2015)
DNA-AuNP	5′–SH–(CH2)6-TTTTTGTCAGATGAATTCG-3'	LOD: 45.45 pM linear range; 0.02–10 nM. Reproducibility:5.37% N = 6	5′-UUAAUGCUAAUCGUGAUAGGGGU-3′	Two steps 100	miRNA-155 → synthetic	miRNA-21 +++ ++	Pros: • excellent selectivity • useable for real biological samples Cons: • complex protocol	(Zeng et al., 2017)
CHA and spherical nucleic acid	No mentioned	LOD: 53.7 fM Linear range: 0.1 pM-1.5 nM reproducibility: 8.71% n = 5	No mentioned	Three steps 50	let-7a miRNA→ synthetic	number of let-7 family members +++	Pros: • great sensitivity • time-effective • useable for real biological samples	Wei et al. (2020)
Label free SPR biosensors								
Sandwich hybrids	5′-TGT CAC ACT CCA AAA AAA-(CH2)6-SH 3′	LOD: 17 pM Reproducibility: 5.7% (n = 30)	5′- UGG AGU GUG ACA AUG GUG UUU G -3′	One step 30	miRNA-122 → synthetic	miRNA-29 +++	Pros: • simplicity • time-effective • high reproducibility • useable for complex mixtures	Zhang et al. (2013a)
Triplex formation	3′-AAAAG*G × G*TCCTTAGGGAT15SH-5' G* = 8-aminoG	LOD: 1 nM (3 times the baseline noise standard deviation)	5′-GUCCAGUUUUCCCAGGAAUCCCU-3′	One Step >20	miRNA-145→ synthetic	Different bioreceptor variants	Pros: • simplicity • high specificity • time-effective Cons: • large LOD compared with other SPR platforms	(Aviñó et al., 2016)
CHA	No mentioned	LOD: 1pM (blank injections + 3 SD) Linear range: 5pM to 100 nM reproducibility: 1–1.1% n = 5	No mentioned	Two steps >60	miRNA-21→ Both synthetic and extracted from human breast	five different miRNA sequences	Pros: • good specificity • high reproducibility	(Li et al., 2016)

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Table 1 (*continued*)

RU enhancer in SPR	Immobilized capture sequence on Au sensor surface	Analytical performance	Detected miRNA sequence	Detection steps and related time (min)	miRNA Samples	target discrimination from different miRNAs (or mismatched miRNAs [a])	pros and cons	Ref
					adenocarcinoma MCF-7 cells		• useable for real biological samples Cons: • complexity of designing two complex hairpin probes and optimizing hybridization conditions	
Antibody based	Capture probe: SH-5′-(CAA ACA CCA TTG TCA CAC TCC A-3′	LOD:2 pM (three standard deviations of the baseline noise)	5′-UGG AGU GUG ACA AUG GUG UUU G-3′	Two steps 30	miRNA-122 → Both synthetic and extracted from mice liver samples	No mentioned	Pros: • simplicity • time-effective Cons: • expensive	(Sipova et al., 2010)
Protein p19 amplification	5′-CAA ACA CCA UUG UCA CAC UGU CCG AUA AGG GUC AG-3’	LOD: 4 nM	5′-UGG AGU GUG ACA AUG GUG UUU G-3′	Three Steps >40	miRNA-122 → Both synthetic and extracted from Human hepatoma cells (Huh 7.5)	No mentioned	Pros: • time-effective Cons: • high LOD • need to the precise design of the probe	(Nasheri et al., 2011a)

RU: Response unit; LOD: Limit of detection; SH: Thiol group; GO-AuNPs: Graphene oxide-gold nanoparticles; AuNPs-MoS2: gold nanoparticles-decorated molybdenum sulfide; ODN: oligonucleotide; AuNRs: gold nanorods; MB: molecular beacon; DASM: Double Antibody Sandwich Method; CHA: catalytic hairpin assembly.

[a] Selective distinguish is indicated as:+++ Single base mismatch, ++Two bases mismatch, +Three bases mismatch

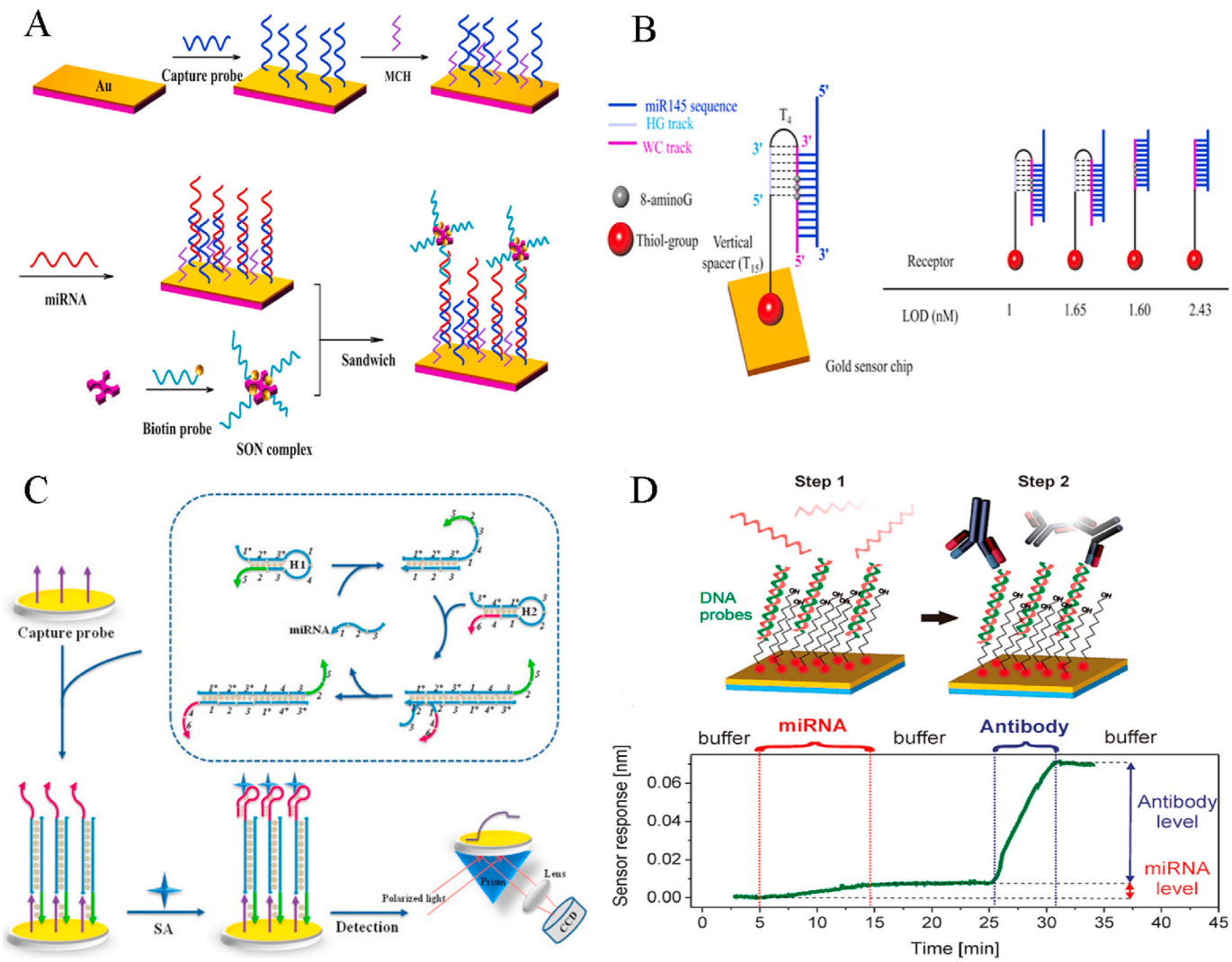

Fig. 9. Schematic illustration of label free detections A) designing streptavidin oligonucleotide/biotin-based SPR sensing platforms (Zhang et al., 2013a). B) SPR approach using triple-helix formation. The estimated LODs for triplex structures with 8-aminoG, triplex structures without 8-aminoG, duplex structures with 8-aminoG and duplex structures without 8-aminoG were reported as 1, 1.65, 1.6 and 2.43 nM, respectively. HG: Hoogsteen hydrogen bond, WC: Watson and Crick hydrogen bond (Aviñó et al., 2016). C) The principle of SPR sensing method using mismatched CHA circuit strategy (Li et al., 2016). D) strategy used for SPR biosensors based on Abs using SPRCD and typical Ab (Wang et al., 2009).

super-sandwich based biosensors, main advantages of this biosensor are simplicity, high speed of process (30 min) and high reproducibility up to 30 cycles. Moreover, feasible applicability was confirmed by this evidence that analytical performance of this biosensor was not disturbed in complex mixtures like human total RNA samples (Zhang et al., 2013a).

The common recognition event for miRNA detection is based on the hybridization of miRNA with a typical DNA probe and the formation of duplex structure. However, alternative formats like triple-helix formation can also be utilized to detect miRNA. Triplexes are formed at special polypyrimidine-polypurine sequences based on Hoogsteen base pairing to the Watson-Crick duplex. These triple helix sites are pervasive within the human genome, particularly at promoter regions (Goñi et al., 2004). Replacement of guanine by 8-aminoguanine (8-aminoG) immensely stabilized the triple helix (Aviñó et al., 2002) and the presence of parallel and antiparallel tail-clamps enhanced the efficiency of triplex formation (Nadal et al., 2005). Accordingly, tail-clamps triplexes carrying 8-aminoG was applied to establish an affinity capture technique for the detection of Listeria mRNA through a SPR biosensor (Carrascosa et al., 2012). In order to use this technique, an alternative label-free approach using triple-helix formation was described to measure miRNA-145, a tumor suppressor reduced in several human cancers. As shown in Fig. 9B, parallel clamps captured on gold chips of home-made SPR targeted a seven-homopyrimidine sequence of miRNA-145 with Watson-Crick interactions. On the other hand, Hoogsteen base pairing was formed between homopurine and inverted homopyrimidine portion of the clamps. The formation of triplex structures was stabilized by adding 8-aminoG to clamps. Thereby, this platform showed the maximum response as LOD 1 nM that is lower as compared to LOD 1.65, 1.6 and 2.43 for triplex structures without 8-aminoG, duplex structures with 8-aminoG and without 8-aminoG, respectively. Nevertheless, this platform provides the large LOD compared with other SPR platforms mentioned in this review that provide the LOD as low as pM, fM and even aM. Although high specificity and simplicity with only requirement to seven pyrimidines in the miRNA sequence are two enormous privilege of this approach, detection of small number of polypyrimidine sequences or having discontinuity in the polypurine-polypyrimidine sequences of miRNA are needed further research (Aviñó et al., 2016).

Also, a label free SPR biosensing platform was developed using two hairpin probes (H1 and H2) in a CHA circuit for detection of miRNA-21. In order to improve the analytical performance and reduce the background signal, mismatched base pairs were introduced in H2. Furthermore, a programmable streptavidin aptamer was applied into the CHA

amplification circuit for enhancing the detection signal. Thereby, system LOD was calculated to be 1 pM (0.1 fM in 100 μL detection volume) with a large linear range from 5 pM to 100 nM of miRNA concentrations. In this method, the binding of miRNA-21 to H1 resulted in its unfolding by a strand displacement reaction and concealed part of H1 was exposed to H2. Interaction of H1 and H2 displaced target miRNA, released it to the next amplification cycle for producing plentiful amounts of CHA products and finally exposed the aptamer sequence of H2 to streptavidin. Subsequently, H1–H2 complex was captured by the DNA probes on the SRP chip (Fig. 9C). The good specificity for this method was evaluated by successful detecting of miRNA-21 from mismatch and non-complementary target miRNAs. Meanwhile, The SPR chip could be regenerated 100 times while the signal response merely reduced less than 10%. Finally, this biosensor showed potential to analyze miRNAs in real human samples. However, the assay efficiency was strongly dependent to design two complex hairpin probes and optimize hybridization conditions (Li et al., 2016).

Also, for the first time Sipova et al. (Š; ípová et al., 2010) developed a label free and high-performance portable SPRCD biosensor along with Abs to detect miRNA-122, a marker for drug-induced liver injury (Wang et al., 2009). SPRCD surface was functionalized with thiolated DNA probes to capture miRNA. On the other hand, special Abs used for the specific detection of the DNA × miRNA duplex and substantial increasing of sensor sensitivity (Fig. 9D). The LOD for direct detection of synthetic miRNA-122 and Ab amplified detection was reported as 100 and 2 pM, respectively. The great sensor response to miRNA-122 binding was observed for TrisMg solution compared to TrisNa and PBS solution. Moreover, nonspecific hybridization to the sensing surface was not identified in the TrisMg solution and the regeneration protocol maintained probes activity for at least 5 detection cycles. On the other hand, SPRCD technology could detect concentrations higher than 100 pM of miRNA-122 isolated from mouse liver tissue. This result represented a high agreement with that achieved by the qPCR. Regardless of the high cost of Abs, the simplicity and high speed (less than 30 min) of this technology makes it suitable for selected miRNA profiling (Sipova et al., 2010).

In another work for label free detection of miRNA, Nasheri et al., (2011a) used SPRi system based on p19 in developing of SPR biosensor. P19 is a 19-kDa protein encoded by tombusvirus, a plant RNA virus, and plays a role in defense against host defense systems. This protein functions as a suppressor of RNA interference with size-selective and sequence-independent affinity toward 21–23 -bp RNA duplexes. The affinity of p19 reduces remarkably for shorter or longer double strand RNA species. The base for this specificity is the presence of two pairs of tryptophan amino acids that render end-capping interactions to stabilize a 21-nt RNA (Silhavy et al., 2002). In this sensing assay, thiolated probes against miRNA-122 were bound to the surface of gold chip (Nasheri et al., 2011b). Following miRNA-122 hybridization onto the probes, p19 was capped onto the miRNA-122/probe duplexes on the chip in order to amplification of signal response. The estimated LOD of miRNA-122 target through direct binding to the probe was 40 nM, while it was reduced by a factor of 10 following use of p19 to cap the miRNA-122/probe duplexes. However, its sensitivity was estimated to be at least 500 times less than the bead-based enzyme-linked immunoassay that performed in the same study. In this luminescence method, His-tagged p19 protein capped onto miRNA-122/probe duplex on the magnetic-bead surface. A monoclonal anti-His-tag Ab conjugated with HRP was attached to the His tag of the immobilized p19. The addition of HRP substrate then produced bioluminescence signal detected in a multi well plate format. The LOD of this method was 1 fM. Since the estimated LOD for this p19-based SPR biosensor is the highest among other sensing platforms introduced in this article, this SPR assay do not provide any improvement in the sensitivity of miRNA detection compared with similar assays. Further, this SPR approach need to the precise and complex design of the probe.

5. Advantages of miRNA SPR biosensors

Some of molecular assays and sensing methods can be applied to identify miRNA such as PCR and biosensors. The pros and cons of these methods were shown in Table 2. The advent of novel biosensor-based tools like electrochemical and optical biosensors contributes to a specific diagnosis in miRNA detection. In comparison with usual diagnostic methods like northern blotting, microarray and real-time PCR, SPR-based diagnosis is postulated as an accurate, non-invasive, and rapid detection of a large number of samples in a single test (Gleerup et al., 2019). Conventional oligonucleotide detection techniques suffer various limitations such as inadequate sensitivity, numerous operation cost, time-consuming, complex sample preparation and analysis, sophisticated tools and need to extrinsic labels like fluorophores or radiolabels. In recent years, various electrochemical or optical based biosensors have been used for the ultrasensitive detection of miRNA (Han et al., 2019; Shabaninejad et al., 2019). According to some works in developing of electrochemical-based biosensors for miRNA detection, application of numerous enzymes which participate in the oxidation-reduction reactions is inevitable. These enzymes which generate the final electrochemical response in sensing process require completely to keep the

Table 2
The pros and cons of current miRNA diagnosis techniques.

Method	pros and cons	Ref
Fluorescence	Pros: Exhibit good signal-to-noise ratios, Detection of target miRNAs within complex RNA mixtures Cons: Having the fluorescent property in molecules, Low specify, Large sample volume,	Aw et al. (2016)
PCR	Pros: Fairly simple to understand and to use, Broader quantification range Cons: High risk of contamination, False-positive anxiety, Difficulty in primer design	(Hajia, 2017; Ye et al., 2019)
QCM biosensors	Pros:Real-time, Short cycle detection, Quantified detection, Unique detection mechanism consisting of hybrid duplexes formation of miRNA and DNA probe, Not affected by other miRNAs Cons: Non-mass frequency changes, Nonspecific adsorption, Limitations in high and low temperatures which led to produce undesirable frequency shifts in the crystals	(Li et al., 2019; Park and Lee, 2019)
Electrochemical biosensors	Pros: High sensitivity, Simple use, Small sample size, Rapid response, and Compatibility Cons: Narrow or limited temperature range; having major challenge in making these systems portable for POC, Limited lifespan	Shabaninejad et al. (2019)
SPR biosensors	Pros: Rapid simultaneous detection of multiple miRNAs, Determination of target miRNA spiked into human total RNA samples, Label-free detection, Real-time monitoring, Small sample volume, Amplification-free biosensing platform, Availability of sensors, Rapid detection, Reusable sensor chips, Repeatable measurements, Sensitive, Specific, Cost-effective. Cons: Mass transport effect, Heterogeneity of the surface sites, Non-specific binding to sensor surface	(Wang et al., 2016c; Zhang et al., 2013b)

POC: point of care; QCM: quartz crystal microbalance; PCR: polymerase chain reaction; SPR: surface plasmon resonance.

stability and activity until biosensor fabrication (Hu et al., 2016; Peng et al., 2014). But in SPR based biosensors, obtained response units are related to the absorbing of any biological molecules on gold sensor surface and it is not depending on the red/ox agents like enzymes. In SPR biosensors, the absorption of molecules led to the change in refractive index and mass shift on gold surface which it is dateable in produced evanescent filed of gold surface plasmons. SPR based biosensors with having multi-channel measurements from 2 channels in the usual SPR device to 1000 channels in SPR imaging systems provide real-time and selective detection based on refractive index and mass changing on gold sensor surface. Application of NPs for enhancing the SPR response units leads to improve the sensitivity and selectivity in oligonucleotide detection and DNA microarray analysis. Using SPR optical based methods, researchers are able to develop the precise and sensitive analytical approaches for femto-molar concentration detection of miRNA in samples. In SPR methods using different modified surface chemistry, the high ratio immobilization of thiolated or biotinylated capture probes on the SPR gold chips is possible for absorbing of small sequences of RNA. Also, using the nanostructures on the developing of enhanced SPR biosensors leads to the decrease of signal-to-noise ratio compared with usual microtiter plate analyses in miRNA detection.

6. Conclusion

The use of miRNAs as early biomarkers for clinical diagnosis of different types of disease has become a research hotspot in recent years. Therefore, specific, sensible and quantitative technologies for measuring the expression levels of miRNAs are in urgent need. Biosensor-based techniques such as those based on SPR provide an attractive alternative to conventional methods. SPR is an advanced technology for sensitive, rapid, real-time, label-free, and in-situ detection of miRNAs. Nevertheless, in the direct analysis of miRNA, the sensitivity of SPR is not satisfying for detection of trace substance in complex biological samples. Thus, some surface functionalization and signal amplification strategies have been adopted to promote the sensitivity and response of SPR biosensing. Among the different strategies discussed in this article, using NPs provides the most improvement in the SPR sensitivity for miRNA analysis. The combination of NPs with 2D materials, especially antimonene, is one of the most active research areas in providing the high efficiency of signal amplification. Although, some enzyme-based amplification assays suffer disadvantages such as high cost of testing, poor reproducibility and strict control of reaction conditions, the emerging integration of NPs with suitable enzyme-based sensing platforms reveals a big leap towards the large reduction in the LOD as 10 fM. Even lower LOD could be achieved by novel modifications in the process optimisation of miRNA detection in enzyme-based SPR systems. The accompanying of NPs with other strategies such as supersandwich assembly, streptavidin/biotin system, antibody and CHA could significantly enhance the sensitivity and applicability of these approaches particularly in complex samples. However, the SPR biosensor-based method is not suitable for universal profiling, but with selected and specific target miRNAs. Further, commercial SPR devices, for instance Biacore, are expensive and need consumable sensor chips that fit certain characteristics of thickness, size, and so forth. The design of homemade SPR instrument could overcome this problem. They usually are small and inexpensive and also all portions are accessible for visualization and manipulations. While, further studies are needed to overcome the various limitations of different SPR-based biosensors, they will be promising and potential assays for miRNA sensing in biomedical research and clinical diagnosis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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