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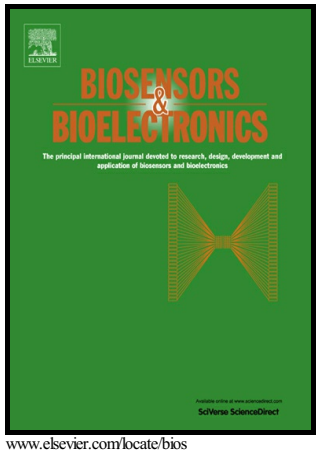

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Recent advances on aptamer-based biosensors to detection of platelet-derived growth factor

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Contents

Abstract

Platelet-derived growth factor (PDGF-BB), a significant serum cytokine, is an important protein biomarker in diagnosis and recognition of cancer, which straightly rolled in proceeding of various cell transformations, including tumor growth and its development. Fibrosis, atherosclerosis are certain appalling diseases, which PDGF-BB is near to them. Generally, the expression amount of PDGF-BB increases in human life-threatening tumors serving as an indicator for tumor angiogenesis. Thus, identification and quantification of PDGF-BB in biomedical fields are particularly important. Affinity chromatography, immunohistochemical methods and enzyme-linked immunosorbent assay (ELISA), conventional methods for PDGF-BB detection, requiring high-cost and complicated instrumentation, take too much time and offer deficient sensitivity and selectivity, which restrict their usage in real applications. Hence, it is essential to design and build enhanced systems and platforms for the recognition and quantification of protein biomarkers. In the past few years, biosensors especially aptasensors have been received noticeable attention for the detection of PDGF-BB owing to their high sensitivity, selectivity, accuracy, fast response, and low cost. Since the role and importance of developing aptasensors in cancer diagnosis is undeniable. In this review, optical and electrochemical aptasensors, which have been applied by many researchers for PDGF-BB cancer biomarker detection, have been mentioned and merits and demerits of them have been explained and compared. Efforts related to design and development of aptamer-based biosensors using nanoparticles for sensitive and selective detection of PDGF-BB have been reviewed considering: Aptamer importance as recognition elements, principal, application and the recent improvements and developments of aptamer based optical and electrochemical methods. In addition,

commercial biosensors and future perspectives for rapid and on-site detection of PDGF-BB have been summarized.

Key words: Platelet-derived growth factor, cancer biomarker, Aptamer, Biosensor, Biomedical analysis

1. Introduction

As a soluble extracellular signal proteins, growth factors, promulgate the growth, organization, and permanence of cells and tissues. Due to the binding of growth factors to their specific receptors on the surface of target molecules, they provide regulatory signals to stimulate or inhibit the proliferation, differentiation, adhesion, migration and gene expression of cells (Amsden 2015).

Human platelet-derived growth factor PDGF, a prominent disease-marker protein, is accumulated in platelet a-granules and while the platelet release event, released. Via its binding to the cell membrane, where the tyrosine receptors are located, it regulates the tumor growth and division (Yao et al. 2015).

The platelet-derived growth factors (PDGFAA, PDGFBB, PDGFCC, PDGF-DD, and PDGFAB) and their receptors (PDGFR-αα, PDGFR-ββ and PDGFR-αβ) compose a valuable system for illness diagnostics. The exertion of biological effects of these isoforms on their receptors via specific linking, results in their activation (Appiah-Kubi et al. 2016; Chen et al. 2013).

Through binding of the platelet-derived growth factors to their receptors on the cell membrane surface, they are differentially expressed in several cells and tissues. Among various isoforms of platelet-derived growth factors, PDGFBB has been straightly involved in the cell transformation process and the growth and progression of tumors (Fang et al. 2015; Lin et al. 2013). Moreover, it has been found that PDGF-BB expression often increase in cancers and plays as a new

effective lymphangiogenic agent. In normal cells, it is found to be expressed at down or undetectable levels, but the buildup of it in certain human tumors, such as sarcomas and gliboblastomas has seen. In other words, with the level of malignancy the autocrine and paracrine effects of PDGF–BB increase (Fang et al. 2015; Hong et al. 2017; Lin et al. 2013).

A significant role of platelet-derived growth factor-BB (PDGF-BB) in regulating the cell growth and division, has made it the most prominent serum cytokine. It is a vital protein in the treatment of certain human chronic dermal wounds. PDGF-BB is found in some drastic diseases, such as fibrosis and atherosclerosis and mostly overexpressed in human malignant tumors (Hong et al. 2017). PDGF-BB, as a latent protein biomarker, has increasing in biomedical diagnosis for early detection of renal function in diabetic nephropathy, breast cancer, prostate carcinoma, leukemia etc. It has been implicated in the pathogenesis of angiogenesis in liver cancer and gastrointestinal stromal tumors (Fang et al. 2015; He et al. 2016; Wang et al. 2013c).Thus a rapid, sensitive and accurate method for quantification of PDGF-BB is of importance for biomedical research and clinical diagnosis. Formerly, traditional antibody-based radio isotopic methods, molecular fluorescence and enzyme-linked immune-sorbent assay (ELISA) techniques were established for the detection of PDGF-BB, Although these techniques are very sensitive, however they suffer from certain restrictions such as time consuming method, high expensive instrumentation and insufficient specificity and selectivity, which limit their applications (Huang et al. 2015; Wang et al. 2015a; Yao et al. 2015). Recently, biosensors have become a crucial state of the art technology in laboratory medicine, particularly in point of care testing. Biosensors are analytical devices that employ biological/biochemical reactions for detecting target analytes and basically consist of a bio-element and a transducer (Ali et al. 2017; Murugaiyan et al. 2014). Aptamers, as a biocatalyst are artificial single-stranded DNA or RNA molecules which are able of binding to

small molecules, proteins and cells with high specificity and affinity. Unique features of aptamers over antibodies include shelf-life, flexibility in labeling, resistant to denaturation, stability and so on, it makes aptamers excellent candidates for biological analysis and biosensors (Nimjee et al. 2017; Zhou and Rossi 2017). This review gives a general overview of various aptamer-based biosensing methods, both, optical and electrochemical, for detection of PDGF-BB.

2. Aptamer-based biosensors(Aptasensors)

Aptasensors are biosensors which RNA or DNA aptamers are used as their recognition elements (Lai et al. 2007). The introduction of aptamers as recognition probes, led to the introducing of aptasensors in the early 1990‘s, offering a great alternative to the traditional analytical systems for detection of proteins (Lai et al. 2007; Zhou et al. 2014).

Aptamers are the most important kinds of “functional nucleic acids” (FNA) (the term origins from latin words aptus (to fit) and meros (part), which were described by Ellington and Szostak for the first time in 1990 (Jarczewska et al. 2016; Jun et al. 2014; Zhu et al. 2015). Short nucleic acids of single-stranded RNA or DNA molecules (approximately 12-80 nucleotides) are named aptamers. They have distinctive binding features to their targets of interests, such as high sensitivity, selectivity, specificity and capability to fold into several tertiary structures (Jun et al. 2014; Zhu et al. 2015). The SELEX method (Systematic Evolution of Ligands by Exponential Enrichment) is an in vitro procedure whereby numerous aptamers have been opted for a wide variety of targets containing proteins, drug molecules, ions, toxins, tissues and cells (Jun et al. 2014; Mokhtarzadeh et al. 2016; Mosafer et al. 2017).

A chemically synthesized pool of random oligonucleotides (up to 1015 diverse sequences) is the first stage of the onset of SELEX procedure. Continuous repetition of the main stages of the

selection process including binding, separation/division and amplification, leads to aquire nucleotides with enhanced binding potency against the interested target molecule. Following the 5 to 15 number of cycles, the sequences achieved are cloned, sequenced and then calculation and evaluation of their binding affinity, secondary structure and Gibbs energy with the purpose of selecting the aptamers with high specificity and affinity to the desired analyte, will be done (Jarczewska et al. 2016; Meirinho et al. 2016).

Compared with affinity receptor- based methods (*e.g.* antibodies), the design and development of biosensors using aptamers as bioreceptors or recognition elements provide several advantages including: **i)** easier artificial synthesis, **ii)** high sensitivity and selectivity, **iii**) reversible thermal denaturation, **iv)** suitability to numerous targets, **v)** chemical stability under a wide range of buffer conditions, **vi)** high resistance to severe treatments without loss of bioactivity, **vii)** versatility in labeling, immobilization, signaling and regeneration and **viii)** ease storage. Aptamers efficient immobilization at high densities in various surfaces, are certainly due to their miniature and short size (Fang et al. 2015; Meirinho et al. 2016; Zhang and Zhang 2012). Therefore, compared to antibodies, using aptamers as a bioreceptors leading to simply and effortlessly construction, integration, automation and miniaturization of biosensors. Moreover, facility of employing diverse detection approaches and different designs and feasibility of performing various analysis with slight changes of binding selectivity and affinity leading to easy and fast protein recognition and detection are further advantages of aptamers (Meirinho et al. 2016). Taken together these unique characteristics make aptamers an applicable and proper tool in the design and development of aptasensors for extremely sensitive and selective detection of proteins (Fang et al. 2015; Jarczewska et al. 2016). Studies on the applicability of aptamers for the detection of PDGF-BB are evaluated in this review.

2.1 Aptamer-based Optical PDGF-BB biosensors

During the last few years, optical biosensors had made great improvements and have been used in a variety of fields such as security, food safety, life science, environmental monitoring and medicine. In the field of medical and medicine, the optical transducer has been constructed for medical research and diagnostic purposes (Perumal and Hashim 2014). The word ‘‘optrode’’ created from the joining of ‘‘optical’’ and ‘‘electrode’’ words and is rarely used to describe optical based devices (Biran et al. 2008). During the last decade, combining the different optical transducers with the special features of aptamers, numerous sensing approaches such as fluorescence, surface-enhanced Raman spectroscopy (SERS), colorimetric, surface Plasmon resonance (SPR), electrochemiluminescence, and so on have been designed and developed (Wang et al. 2015a). Measuring various features of the target molecules is the main potential of these transduction strategies. Also providing real time, label free, and parallel detection of targets are additional advantages and capabilities of optical based biosensors (Perumal and Hashim 2014). During the past few decades, the recognition and detection of PDGF-BB protein using fluorescence, colorimetric, luminescent, surface-enhanced Raman spectroscopy and other aptamer based optical biosensors, involving fluorophore labeled aptamers or using of the redox species, have been reported (Penmatsa et al. 2013). Table 1 summarizes the studies made on the development and use of optical biosensors for the determination of PDGF-BB.

Table 1 Aptamer-based optical biosensors for the determination of PDGF-BB.

Method	Assay Strategy	NPs	Linear range	LOD	Ref
Colorimetry	Strand displacement amplification	Au NPs	2.0-80 nM	1.1 nM	(Zhang et al. 2015a)
Colorimetry		Ag NPs			
Colorimetry	Silver decahedral nanoparticles	Au NPs	0.177-7.1 nM	177.5 pM	(Zhou et al. 2014)
Colorimetry	Competitive interactions	-			(Lin et al. 2011)
Colorimetry	Dual amplification system	Au NPs	0.5-20 nM	0.3 nM	(Tang et al. 2012)
	Target-mediated base stacking				(Chang et al. 2013)
Colorimetry	hybridization	-	0.04-4.1 pM	8.2 fM	
Colorimetry	Isothermal nucleic acids amplification	Au NPs		6 nM	
SERS		Au NPs/ Au PNNS	10-100 nM		(Lin et al. 2008)
	Aggregation-based Assay			0.32 nM	(Huang et al. 2005)
SERS	Electrostaic interaction				
Luminescence		Au NPs	0.32-1.74 nM	35 nM	(Wang and Chang 2014)
Luminescence	One- two- three- cascaded amplification	-		0.5 pM	
CL		-	35-400 nM		(Ye et al. 2016)
CL	Light switch complex $[Ru(phen)_2(dppz)]^{2+}$	Au NPs	1-50 pM	420 fM	(Jiang et al. 2004)
CL	Displacement of ruthenium (II) complex	-			(Babu et al. 2013)
CL		-	1 pM-10 nM	1 nM	(Sun et al. 2011)
CL	Sandwich type immuno complex	Au NPs		0.8	(Yao et al. 2015)

ECL	RCA	-	0-50 nM	pM	(Bi et al. 2014)
ECL	Cascade autocatalytic recycling	Au NPs	50-400	0.1	(Zhang et al.
ECL	Sandwich type LED-CL	-	pM	pM	2014b)
ECL	aptasensor	Au NPs	0.1-1000	0.06	(Wang et al.
ECL	Hidroxylamine amplification	Au NPs	pM	pM	2013b)
ECL	RCA	-	0.06-200	0.68	(Cao et al. 2011)
	Enzyme based sandwich type	-	pM	pM	(Zhang et al.
Fluorescent	Immunomagnetic sandwich		1-10000	50 pM	2015b)
	assay	Au NPs	pM	60 pM	(Zhu et al. 2010)
Fluorescent	Sandwich assay		0.1-100	10 fM	(Chai et al. 2011)
Fluorescent	A sandwich form layer- by-	Ag NCs	nM	0.017	(Liu et al. 2014)
Fluorescent	layer assembly	Cu NPs	0.06-6	pM	(Zhang et al.
	Sandwich format	-	nM	80 pM	2015c)
Fluorescent	Based on beta-		10 fM-	0.027	(Gao et al. 2018)
	cyclodextrine/graphitic carbon	-	1nM	pM	
Fluorescent	nitride composite		0.1-500	1.1 fM	(Liu et al. 2012)
Fluorescent	Target-induced silver	-	pM	0.13	
Fluorescent	nanoclusters formation	-	0.1-1000	pM	(Wang et al.
	Photo-induced electron transfer	-	nM	0.01	2015a)
Fluorescent	(PET)		0.1-10	pM	(Yang et al. 2014)
Fluorescent	Structure switching format	-	pM		(Jin et al. 2014)
Fluorescent	polarization assay based on	-	0.01-100	0.37	
Fluorescent	multiple protein-DNA-protein	-	pM	nM	(Penmatsa et al.
	structures	-	0.5 pM-1		2013)
Fluorescent	based on three-dimensional		nM	0.1	

Fluorescent	carbon microarrays	Au NPs	0.02pM-	pM	(Guo and Zhao
Fluorescent	Competitive thrombin-linked	-	20nM	4 nM	2016a)
	assay	-		68 pM	(Yang et al. 2007)
Fluorescent	Real time RCA		1-50 nM		(Fang et al. 2003)
Fluorescent	Real time assay	-		5 pM	
		Au NPs	0.5-10000		(Zhou et al. 2006)
Fluorescent	$[Ru(phen)_2(dppz)]^{2+}$ signaling		pM	125	(Jing et al. 2009)
Fluorescent	complex	-	0-0.5 nM	pM	(Ruslinda et al.
	Aptamer/plasmid complex	-	0.1-6 nM	0.4	2012b)
Fluorescent	amplification			nM	(Guo and Zhao
	Sandwich design	-	5 nM-100	110	2016b)
Fluorescent	Based on magnetic beads in a		nM	pM	
Fluorescent	sandwich format	Ag NPs			(Shukoor et al.
fluorescent	Bolean logic based detection	-	0.125-3	0.1	2012)
	Light switching excimer probe	-	nM	nM	(Yang et al. 2005)
fluorescent	Target-Triggering Two-Stage		-	0.1	(Zhang and Zhang
FRET	Amplification	-	110 pM-	ng/ml	2012)
	signal-off detection method	UC NPs/	150	4 pM	
FRET	single-step sensitive detection	Au NPs	nM	16 pM	(Ruslinda et al.
		-	-		2012a)
FRET	Diffractometric Detection		0.2-200	1 nM	(Zhu et al. 2016)
	Photochemical method	-	ng/ml	4 pM	
FRET			4-100 pM	904	(Lee et al. 2009)
FRET	target-triggered hybridization	-	0.25-8	fM	(Wang et al. 2012)
	chain reaction amplification	Ag NPs	nM		

	Sandwich assay			0.2	(Wang et al.
	Quantitative PCR		1-100 nM	nM	2015b)
	Isothermal circular strand		4 pM-45	10	
	displacement		nM	pg/ml	(Wang et al. 2016)
			16 pM-		(Xie and Walton
	Liquid crystal biosensor		50nM	10 pM	2010)
	Sandwich structure			1 pM	(Feng et al. 2011)
			0.01-100		
	based on the assembly of dye		nM	1.25	(Xia et al. 2014)
	labeled		10 pg/ml-	pM	(Lin et al. 2013)
	aptamer and graphene oxide		10μg/ml		
	(GO)		10pM-	625	(Liang et al. 2013)
	Molecular Beacon Aptamer-		100 nM	pM	
	based Bioaasay		1 pM-	10 nM	(Vicens et al.
	Decoupling of quencher-		1000 nM	0.87	2005)
	oligonucleotide		-	ng/ml	
	Strand displacement			5 nM	(Kim et al. 2009)
	amplification		-	10 nM	(Li et al. 2013)
			-		
			8-5000	167	
			ng/ml	pM	
			5-50 nM	10	
			0-850,	ng/μg	
			850-200		

			nM 0.167- 1.167 nM - 0.4-1.6 nM 6.2-50 ng/ml	0.4 nM 0.8 ng/ml	

2.1.1 Colorimetric based biosensors

Among aptamer-based optical techniques, colorimetric methodology is highly promising owing to the relatively low readout cost. Due to the AuNPs excellent extinction coefficients and greatly distance-dependent optical features, they have been applied as indicators in colorimetric technology (Zhang et al. 2015a). The use of a DNA aptamer along with gold nanoparticles (AuNPs) in chemical and biomedical analysis, can provide plain and direct colorimetric detection of desired analyte (Chang et al. 2013). Huang and coworkers designed a colorimetric biosensor for the sensitive and specific detection of PDGF-BB using GNPs from 13-nm and aptamer for observing the changes in the color and extinction of the specific aptamer and GNPs by cause of aggregation. The Apt-GNPs solutions changed color in the presence of PDGF-BB

due to the role of PDGF-BBs as bridges to linking Apt-GNPs together . At low concentrations, the color changed from red to purple, but at higher concentrations the change of the color was very slight. The proposed sensor provided analysis of PDGF-BB with a linear range from 35 nM to 400 nM and detection limit of 35 nM. Results of this study implied practical uses of Apt-GNPs in protein analysis and cancer diagnosis (Huang et al. 2005). In another study, Tang and coworkers reported an assay using aptamer for protein detection using colorimetric reaction and polymerase-mediated rolling-circle amplification (RCA). By primary aptamer-functionalized microbeads, the PDGF-BB was detected in a sandwich approach and a secondary aptamer was coupled to a RCA primer/circular template complex. As a result of the peroxidase-like DNAzyme activity, the second amplification produced a blue-green colorimetric signal. The limit of detection for this assay was 8.2 fM (Tang et al. 2012). Interestingly, Zhang and coworkers proposed a gold nano- particles labeled colorimetric sensor based on target-triggered strand displacement amplification for the quantification of platelet-derived growth factor-BB. When the target protein bound to the aptamer, the linear conformation of the probe was modified to a triple-helix structure. Then, the strand displacement amplification led to the production of a large number of reporter oligonucleotides. After detection of the reporter oligonucleotides, by using gold nanoparticle labels, the PDGF-BB protein was determined. The produced signal indicated a linear relationship for PDGF-BB within the concentration range from 2.0 to 80 nM with a detection limit of 1.1 nM. A distinct color change of gold nanoparticles was provided while the concentration of PDGF-BB was down to 4.0 nM (Zhang et al. 2015a).

2.1.2 Surface Enhanced Raman Scattering (SERS) based optical biosensors

SERS has become one of the most common sensing systems for biological analysis or molecular imaging, providing structural information and a high sensitivity. Sensitivity, easy operation and no detrimental effects are the advantages of The SERS technique (Wang and Chang 2014). Ye and coworkers proposed a new and simple one-two-three signal amplification surface-enhanced Raman scattering assay for the PDGF-BB detection by using label-free aptamer (Fig 1). The one–two–three cascade DNA amplification includes, target-aptamer binding interaction, hairpin DNA switches and DNA amplification reactions. Compared to traditional signal amplification methods, this assay had some significant properties: **(i)** For appropriate hybridization without interfering the affinity of the aptamer toward PDGF-BB, a probe conjugating a label-free aptamer was constructed. **(ii)** A novel three step amplification mode was constructed to amplify the SERS signal using the unique conformation switch of the aptamer and supporter. The linear range was from 1 pM to 10 nM and the detection limit of PDGF-BB was down to 0.42 pM (Ye et al. 2016).

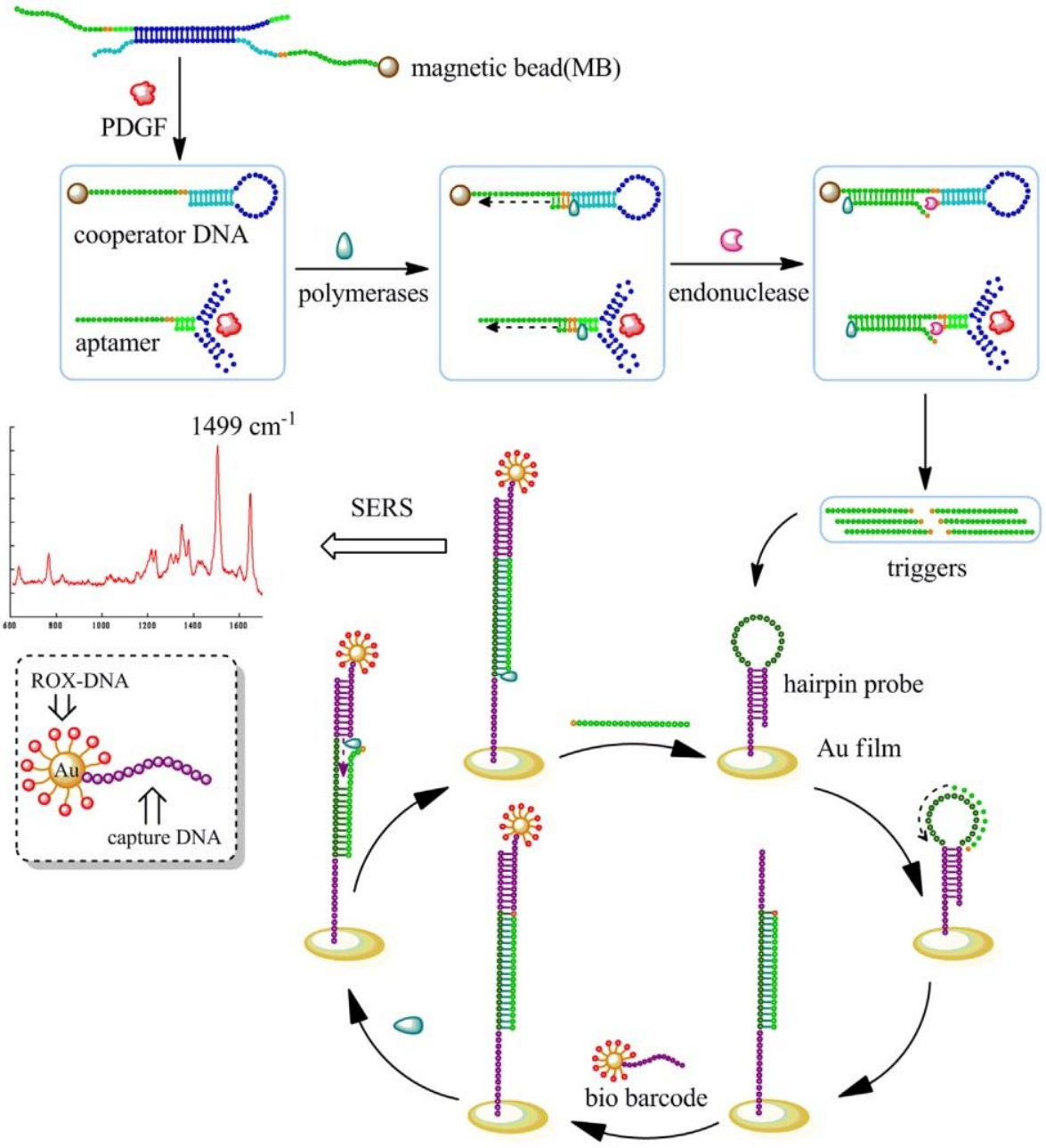

Fig. 1. A label free dual-primer self-generation SERS signal amplification aptasensor for protein detection. This figure was obtained with permission from (Ye et al. 2016).

2.1.3 Luminescent based optical biosensors

Among current methods towards the protein detection by a signal transducer from the interaction between aptamer and target into measurable electrochemical, fluorescence, colorimetric, and

Raman scattering readout, fluorescence method is simply strong strategy owing to its high sensitivity, selectivity and facility of detection. Labeling of the aptamers with fluorophores and quenchers employing modified base sequence are the main drawbacks of the existing approaches, which are time consuming, expensive, and usually have design difficulties (Babu et al. 2013; Jiang et al. 2004). Jiang and colleagues developed an assay for detection of protein, using the aptamer and $[Ru(phen)_2(dppz)]^{2+}$ molecular light switch. By taking advantage of the sensitive luminescence change when binding of the protein and aptamer accomplish. The low limit of detection of this assay was 1 nM (Jiang et al. 2004). To overcome the above mentioned drawbacks Babu and coworkers reported a label-free detection strategy, including a platelet-derived growth factor conjugated to aptamer and hydrophobic Ru(II) complex as sensor system for PDGF (Fig 2). In the presence of aptamer, due to the hydrophobic interaction, a noticeable enhancement of Ru(II) complex luminescence was observed. In the presence of PDGF, the luminescence intensity was diminished, due to the interaction of PDGF and aptamer resulting in the displacement of Ru(II) complex to the solution. This strategy successfully could detect a target protein in a mixture of proteins, down to 0.8 pM (Babu et al. 2013).

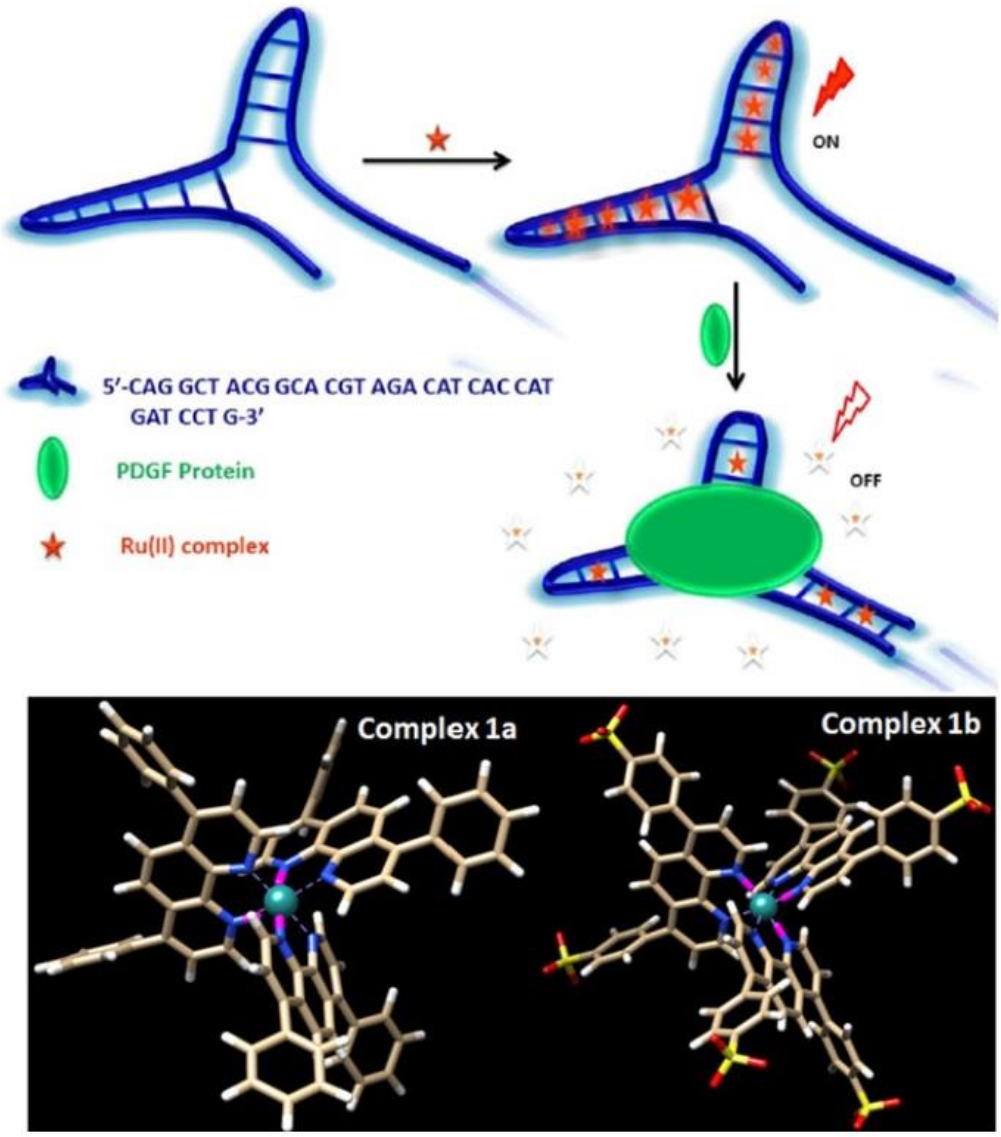

Fig. 2. Schematic illustration of aptamer–$[Ru(dpsphen)_3]^{4-}$ system and signaling mechanism for PDGF quantification. This figure was obtained with permission from (Babu et al. 2013).

2.1.4 Chemiluminescence based optical biosensors

Chemiluminescence is an optical strategy in which the luminescence energy resulted from a chemical reaction is used. In fact, producing the luminescence as a side output of the reaction is because of the relaxation of the excited state of the molecules or atoms to their ground state after a chemical reaction. Therefore, chemiluminescence can be used to detect specific biochemical

reactions and this important feature has led to the design and development of the chemiluminescence based biosensor (Perumal and Hashim 2014). Interestingly, Cao et al. reported a powerful chemiluminescent platform for sensitive and selective detection of protein by using rolling circle amplification for signal enhancement and 96-well plate for immobilization and separation carrier. The sandwich of the antibody immobilized on the surface of 96-well plate with the protein target and the aptamer was made. This aptamer–primer sequence was then employed as the primer of RCA. A number of the biotinylated probes and streptavidin–horseradish peroxidase (SA–HRP) were captured on the plate, and the CL signal was amplified. The detection limit of the proposed sensor was down to 10 fM and the concentration range of PDGF-BB was linear from 10 fM to 1 nM (Cao et al. 2011). In another study Bi and coworkers developed a label free chemiluminescent assay for platelet-derived growth factor BB determination. They used an exonuclease III aided cascade autocatalytic recycling amplification (Exo-CARA) method and take the advantage of recognition feature of cleavage function of Exo III and aptamer (Fig 3). A duplex DNA (aptamer–blockerhybrid), the hairpin structures, and Exo III were the components of the fabricated assay. The fabricated strategy had some advantages compared to other CL strategies such as, simplicity of the assay, inexpensive instrumentation without requiring labels, high amplification efficiency, isothermal conditions and homogeneous reaction without washing steps and separation with a linear range of 1 to 10000 pM and low limit of detection of 0.68 pM for PDGF-BB (Bi et al. 2014).

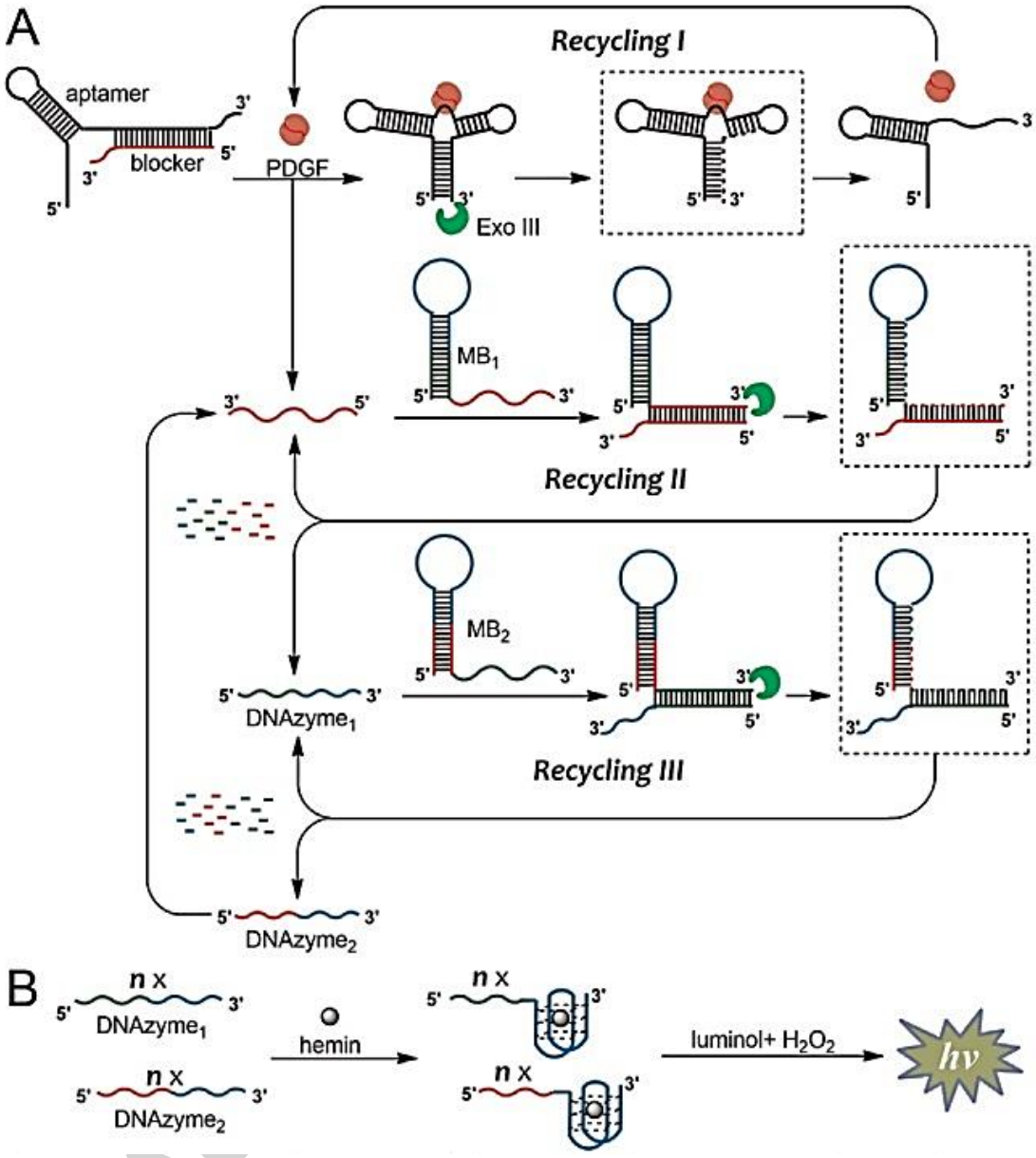

Fig. 3. A label-free Chemiluminescense assay using ExoIII-aided cascade autocatalytic recycling amplification for PDGF-BB determination. This figure was obtained with permission from (Bi et al. 2014).

2.1.5 Electrochemiluminescence based optical biosensors

Owing to the simplicity, high sensitivity, rapidity and easy controllability electrochemiluminescence method has become a robust and attractive detection method. Because

of above mentioned features, it has been extensively applied in biosensor and bioassay. Electrochemiluminescense method covers advantages of manageability from electrochemisty and slight background from chemluminescence, resulting in easy, high sensitivity, cost-effective and simple instrumentation and sensitive detection (Liu et al. 2014; Zhang et al. 2015c). Zhu and colleagues proposed an aptamer based immunomagnetic electrochemiluminescence assay for sensitive protein detection (Fig 4). A sandwich type assay used two kind of aptamers including an aptamer labeled with biotin for sensitive and rapid capture of analyte and a $[Ru(bpy)_3]^{2+}$ (TBR)-labeled aptamer for signal amplification ECL detection of platelet-derived growth factor BB. According to the experimental results, the detection limit of the proposed bioassay was 80 pM of PDGF-BB with a concentration range from 0.1 to 1000 nM. Also, application of the fabricated strategy for PDGF-BB quantification in fetal calf serum resulted low background interference (Zhu et al. 2010). In another study Zhang and coworkers reported an ECL based aptasensor for detection of platelet-derived growth factor BB. As a probe, CdS quantum dots–polyamidoamine and aptamer (CdSQDs–PAMAM–Apt) were used. Integration of the NH_2–aptamer 2 with nanocomposites, via glutaraldehyde as coupling reagent, formed the CdSQDs–PAMAM–Apt2 probe. For sensitive detection of PDGF-BB, MWCNTs–chitosan composites and two kinds of aptamers, including NH_2–aptamer1 with the same base sequence as Aptamer2, were immobilized on the surface of the electrode. Upon addition of PDGF-BB, the CdS QDs–PAMAM–Apt2 probe and aptamer1 provided the sandwich, leading in relative enhancement of ECL emission. The linear range of PDGF-BB was from 0.5 pM to 1 nM and the detection limit of 0.13 pM was obtained (Zhang et al. 2015c).

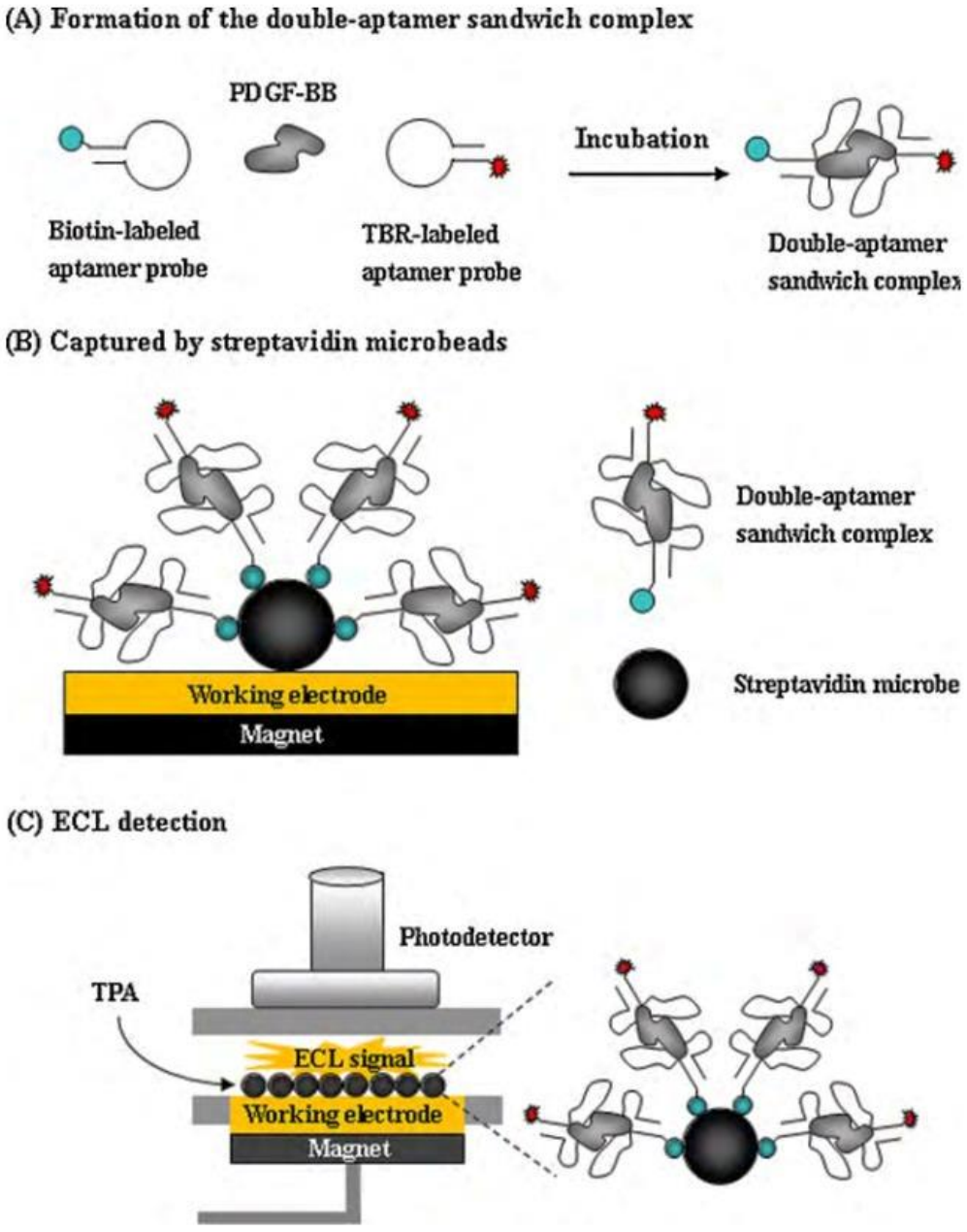

Fig. 4. Schematic presentation of the immunomagnetic electrochemiluminescense aptasensor. This figure was obtained with permission from (Zhu et al. 2010).

2.1.6 Fluorescent based optical biosensors

Fluorescence method is the most commonly used method for detection of proteins, because it is sensitive, rapid, simple and comparatively cost-less (Wang et al. 2016). Using of the

fluorochrome molecules combined with the fluorescence based biosensor result in the production of light during the biorecognition interaction and leading to the detection of target molecule. By combining fluorescent technique in to the sensing probes, the biological recognition procces is transduced to an optical signal, as many of targets and biological sensing elements does not have intrinsic spectral features (Perumal and Hashim 2014). Due to the non-destructiveness, reproducibility, simplicity and high signal production, the fluorescent strategy have attracted remarkable consideration during the past few years (Wang et al. 2015a). Taking advantages of fluorescent techniques and aptamers, various aptamer-based fluorescent methods have been developed for PDGF-BB detection. For example, Wang et al presented a label-free and enzyme-free aptasensor for protein quantification using target-triggered hybridization chain reaction amplification strategy and grapheme oxide (GO)-based selective fluorescence quenching, for the first time (Fig 5). The costructed aptasensor showed a fluorescence detection of PDGF-BB with a detection limit of 1.25 pM. As the fabricated aptasensor did not require any fluorescent label or enzyme thus the approach is more simple, suitable and inexpensive. Using the target aptamer to trigger the HCR, covers the limitations of the sandwich format, circumventing the requisite of two binding sites per target protein (Wang et al. 2015b). Wang et al reported another label-free fluorescent aptasensor for detection of PDGF-BB by photo-induced electron transfer between DNA and Ag fluorescent nano-clusters and G-quadruplex/hemin complexes. In the presence of PDGF-BB, the linkage between PDGF-BB and its aptamer resulted in the conformational change of DNA and led to the release of G-quadruplex sequence part. After formation of HRP-DNA zyme, and electron transfer between DNA-Ag NCs to the hemin center of HRP-DNA zyme the PET occurred with a reduction of fluorescence intensity of DNA-Ag NCs. The prepared assay provided a low detection limit of 0.1 pM for PDGF-BB with a concentration range from 0.5 to

10000 pM. The constructed assay was the first aptamer-based DNA-AgNCs logic gate reported for the PDGF-BB quantification (Wang et al. 2015a). Zhu et al proposed a sensitive and single-step aptamer macroarray on a strong nano-plasmonic substrate using fluorescent technique (Fig 6). The developed aptamer macroarrays by these researchers, achieved a detection of target protein in one step and provided a wide range of linear detection from 10 pg/mL to 10 μg/mL with low limit of detection down to 10 pg/mL. Also the prepared assay can be applicable to the detection of other protein biomarkers owing to its inexpensiveness and easily adaptable into presently available strategies (Zhu et al. 2016).

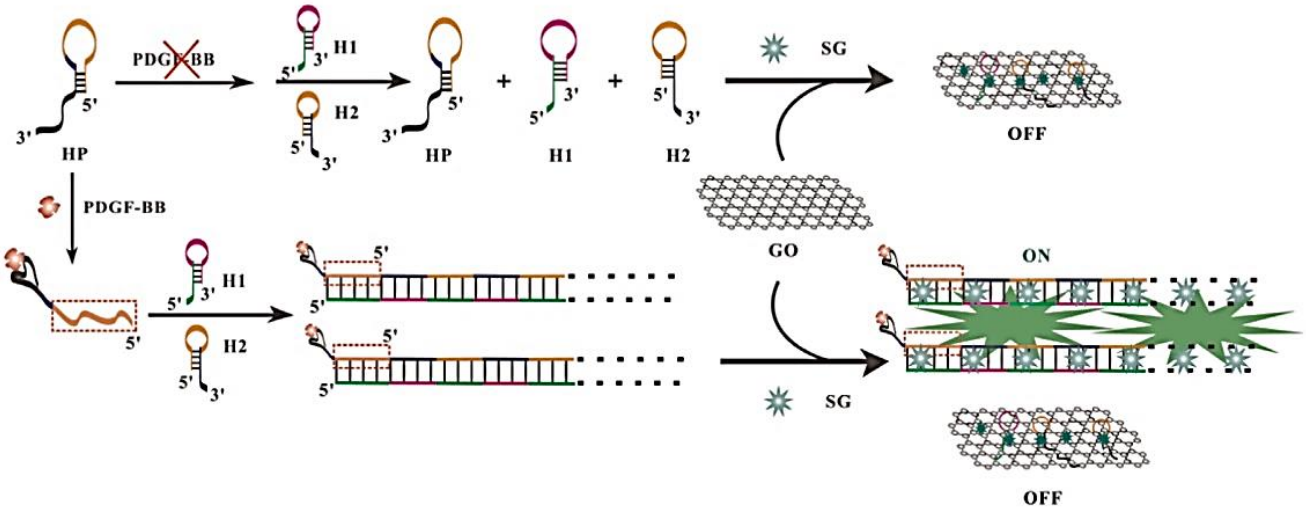

Fig. 5. Representation of the fluorescent strategy for the detection of PDGF-BB based on the target-triggered hybridization chain reaction amplification. This figure was obtained with permission from (Wang et al. 2015b).

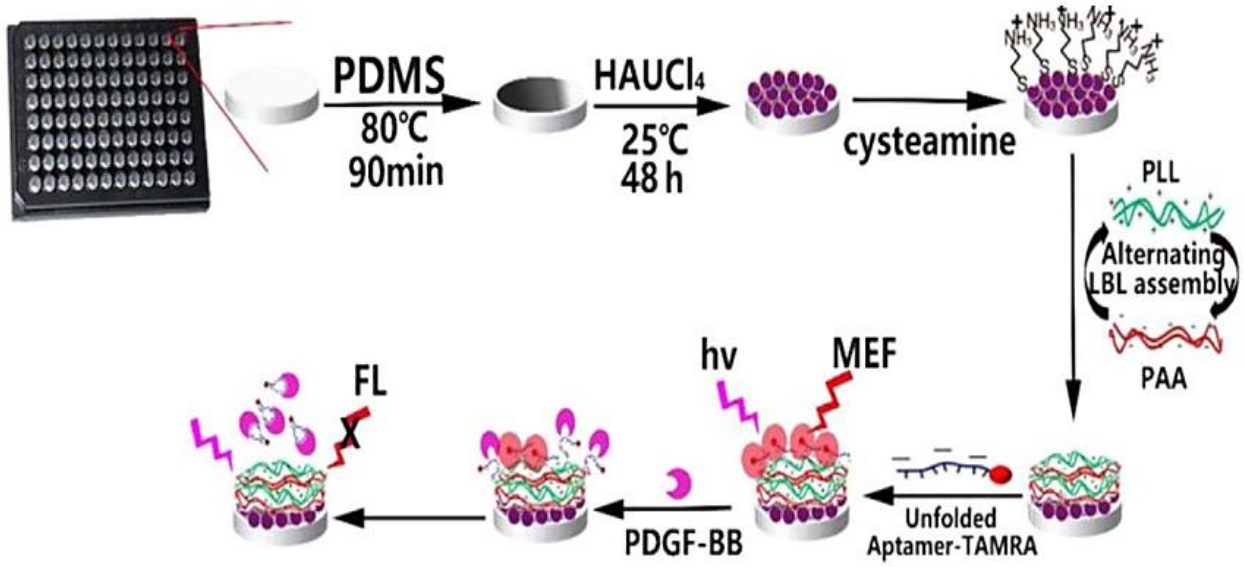

Fig. 6. Schematic illustration of PDGF-BB detection mechanism using MEF aptamer macroarray. This figure was obtained with permission from (Zhu et al. 2016).

2.1.6.1 Fluorescence resonance energy transfer (FRET) based optical biosensors

Fluorescence resonance energy transfer technique is a kind of fluorescence optical method that can be used for high-sensitivity and high-specificity detection of DNA, target proteins and other specific analytes (Kim et al. 2009). The basic role of this technique is the nanoradiative transition of excitation energy to a proximal ground state receiver from an excited state donor (Li et al. 2013). FRET technique have been widely used in sensors (Li et al. 2013) and few studies using fluorescence resonance energy transfer have been reported for PDGF-BB detection. For example, Lin et al. developed a FRET based aptasensor using UCNPs as donor and gold nanoparticles as acceptor for the PDGF–BB quantification in 30% blood serum. In the presence of PDGF–BB, the fluorescence signal of PUCNPs in the sandwich assay decreased. The constructed aptasensor could detect the PDGF–BB protein with a low detection limit of 10 nM, high specificity, stability and anti-interference capability. Also the proposed assay exhibits high ability in the observing of other target proteins and in diseases diagnosis (Chang et al. 2013). Li

and colleagues reported a FRET based sensor for the detection of PDGF-BB by using Ag NPs (Fig 7). Aptamers were functionalized with fluorophore and then along with quencher-carrying strands, were joined to the nanoparticles, functionalized with streptavidin to construct a FRET assay based on silver nanoparticles. Comparing to the FRET assays based on gold nanoparticles and bare FRET sensors, the new FRET sensor exhibited considerable increase in fluorescence intensity, sensitivity and target specificity. A linear ranges of PDGF-BB was in concentrations of 100−500 and 6.2−50 ng/mL with the detection limit of 0.8 ng/mL. Due to reported studies for PDGF-BB detection using FRET technique, FRET is simple and easy assay only requiring a fluorescent labeled aptamer (Li et al. 2013).

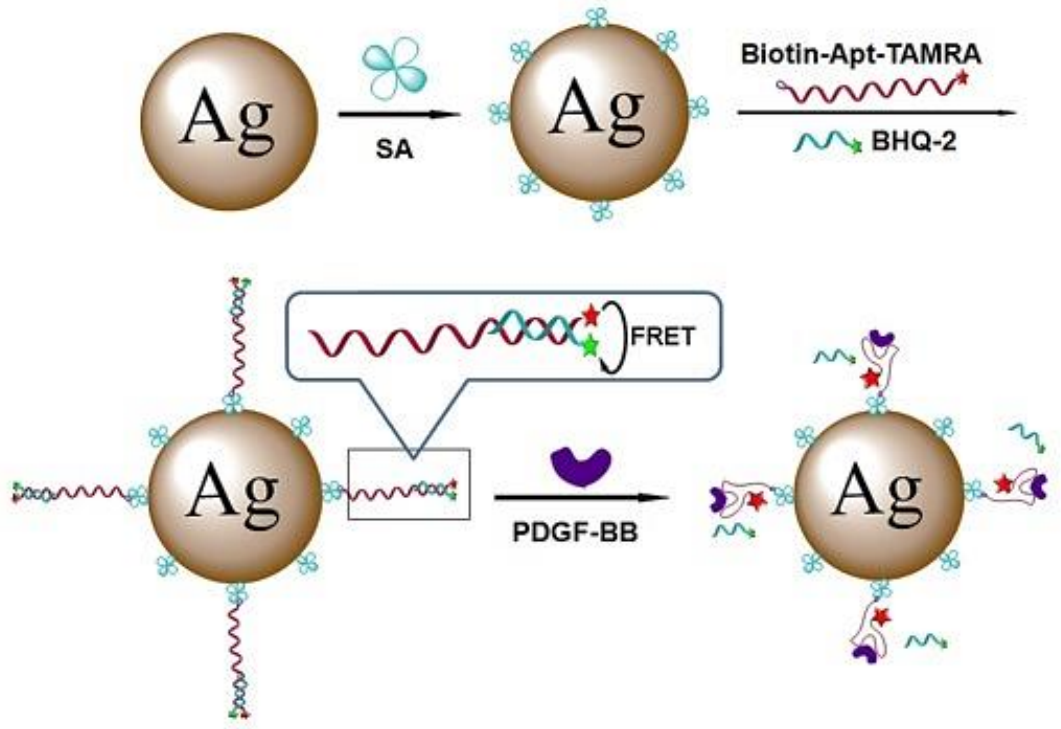

Fig. 7. Preparation of the FRET Sensor based on Ag nanoparticles for Human PDGF-BB detection. This figure was obtained with permission from (Li et al. 2013).

2.2 Aptamer-based Electrochemical PDGF-BB biosensors

As a significant sub-group of sensors, the electrochemical sensors use an element called electrode as a transduction part (Meirinho et al. 2016). According to a IUPAC recommendation in 1999, an electrochemical biosensor is an independently integrated system, that uses a bioreceptor through contacting with electrochemical transduction part to allow specific quantitative or semi quantitative analytical information (Perumal and Hashim 2014; Thévenot et al. 2001). In fact, the current produced from the reduction and oxidation reactions measured by electrochemical biosensors and can be related to either the concentration of the electroactive species present or its rate of production/consumption. When an interaction between analyte and target take place, the measurable output signal is produced which is symmetrical to the concentration of the target molecule (Perumal and Hashim 2014). Compared to other transduction methods such as optical, piezoelectric or thermal detection, and owing to its high sensitivity and selectivity, simplicity, the ability to work with turbid samples, disposability and accuracy, easy control, compatibility with new microfabrication technologies, inherent miniaturization, robustness, rapid response, possibility of usage for online control, and inexpensiveness; the electrochemical aptasensors are highly applicable and attractive for diagnosis purposes and use in point-of-care tools, in addition to simultaneous multi-analyte detection (Meirinho et al. 2016). Electrochemical biosensors classified into four categories including: amperometric, surface charge using Field-Effect Transistors (FETs), impedance and voltammetric sensors based on electrochemical transduction (Perumal and Hashim 2014; Thévenot et al. 2001). Food industry, environmental observing, therapeutic purposes, clinical diagnostic, detection of protein biomarkers, cells, pathogens and small molecules are the fields

for which the electrochemical atasensors are highly used (Meirinho et al. 2016). The application of electrochemical aptasensors for the detection of PDGFBB protein is summarized in Table 2.

Table 2 Aptamer-based electrochemical biosensors for the determination of PDGF-BB

Method	**Assay Strategy**	**Technique**	**Linear range**	**LOD**	**Ref**
Amperometric	CAT–PtNPs–DNA dendrimer-based sensing system	DPV	0.00005-35 nM	0.02 pM	(Zhang et al. 2014a)
Amperometric	Sandwich sensing system	EIS- i-t	0.1pg/ml-10ng/ml	0.03pg/ml	(Zhao et al. 2017)
Amperometric	Dual signal amplification strategy using hydroxyapatite NPs	SWV	0.1pg/ml-10ng/ml	50 fg/ml	(Jiang et al. 2017)
FET	CPMCNFs-aptamer (CPB-Abt) FET snsor	-	5-50000 fM	5 fM	(Jun et al. 2014)
FET	Aptamer based EGFET sensor	RCA	1.78 fM-178 pM	8.8 pM	(Lin et al. 2016)
FET	A-MHCPP FET sensor	-	50-1 µg/ml	1.78 fM	(SeopáLee and HeeáCho 2016)
EIS	Reagent less aptamer based impedance biosensor	NIS	-	40 nM	(Liao and Cui 2007)
EIS	Reagentless polypyrrole and aptamer based probe	EIS	1µg/ml-10ng/ml	1µg/ml	(Liao et al. 2007)
Voltammetric	Co_3 $(po_4)_2$ BSA- based aptasensor	DPV	0.01-100 ng/ml	1pg/ml	
EIS		EIS		3.7pg/ml	
EIS		EIS		20 fM	
EIS		EIS		26.5 fM	

Voltammetric	Exo III- aided signal amplification strategy	LSV	0.0001-1 nM	10 fM	(He et al. 2016)
Voltammetric		DPV		50 pM	(Huang et al. 2016)
Voltammetric	Carbon- based nanocomposites with aptamer- templated silver nanoclusters	DPV-EIS	32.3fM-1.61 pM	1 nM	(Zhang et al. 2017)
Voltammetric		SWV		18 pg/ml	
Voltammetric	Proximity-dependent surface hybridization assay	CV	1pg/ml-1ng/ml	0.01 pM	(Zhang et al. 2007)
Voltammetric		ACV		63 pM	
Voltammetric	Aptamer-RCA immunoassay	DPV	- -	8 pM	(Zhou et al. 2007)
Voltammetric	E-AB sensor	SWV	1-40 nM	0.42 pM	(Lai et al. 2007)
Voltammetric	A label-free aptasensor using SAMs	DPV	50-500 ng//ml	1.8 pM	(Degefa and Kwak 2008)
Voltammetric	Electrochemical immunosensor	DPV	0-0.001 nM	1.6 fm/l	(Huang et al. 2008)
Voltammetric	Electrochemical sandwich sensor based on AuNPs	CV	0.084-8.4 nM	1.7 pM	(Wang et al. 2009)
Voltammetric	Target-binding induced Sandwich sensor based on single-walled carbon nanotubes and graphen sheets	CV	0.01-35 nM	0.6 pM	
Voltammetric		CV		0.17 pM	(Wu et al. 2010) (Bai et al. 2012)
Voltammetric	Immunosensor based on GO initiated sandwich protocol	ACV	0.00083-8.3 nM	10 pg/ml	(Qu et al. 2011)
Voltammetric		DPSV		1.6 pg/ml	

	Aptasensor based on the		4 pM-4.69		(Yu et al. 2012)
Voltammetric	Klenow Fragment	DPV	nM	0.03 pM	
					(Wang et al.
Voltammetric	polymerase induced	DPV	-	0.3 pM	2013c)
	reaction				
Voltammetric	Aptasensor based on HRCA	DPV	0.005-60	0.4 pM	(Deng et al.
	label-frptasensor based on		nM		2013)
Voltammetric	direct electrochemistry	CV		0.08ng/ml	
Voltammetric	A sandwich assay based on	DPV	0.002-40	52 fM	(Han et al.
	multi-labeled FC_{60}		nM		2013)
Voltammetric	nanohybrid	SWV		0.52 nM	
	Immunosensor based on		0.00042-		(Wang et al.
	silver mediated electron		0.83 nM		2013a)
	transfer		20 pg/ml-		
	A background current-		200ng/ml		(Zhang et al.
	eliminated aptameric		0-1000		2015d)
	sensing platform		ng/ml		
	Aptasensor array using in				(Song et al.
	Situ DNA Hybridization		0.001-1		2014)
	inducing AgNPs		nM		
	Aptasensor based on VS_2-				(Huang et al.
	GR coupled with Exo III-		0.001-10		2015)
	aided signal amplification		nM		
	Sandwich assay based on				(Fang et al.
	MOS_2/carbon aerogel		0.001-1		2015)

	composites Aptasensor assay based on leaf like VS_2 nanosheets Structure-switching hairpin probe Proximity hybridization-induced isothermal EXPAR Aptasensor based on new structure of GNPs containing α-CD		nM 0.1-500 ng/ml 0.1 pM-1nM 0.52-1.52 nM		 (Liu et al. 2015) (Hu et al. 2015) (Yu et al. 2017) (Hasanzadeh et al. 2018)

2.2.1 Amperometric electrochemical biosensors

Amperometric sensors measure the produced current from the reduction and oxidation reactions of an electroactive components in a biochemical reaction which principally associated with the target concentration with a fixed potential (Perumal and Hashim 2014). The amperometric transduction can be conjugated with enzymes, nucleic acids and antibody bioreceptors and are applicable for glucose detection, protein detection, disease, environmental monitoring and *etc.* (Jarczewska et al. 2016; Perumal and Hashim 2014). Recently, Jiang and coworkers made a dual signal amplification for electrochemical aptasensing of PDGF-BB. Hydroxyapatite nanoparticles (HAP-NPs) were used as support for deposition of the aptamer. To form a redox-active molybdophosphate precipitate, on the surface of a carbon electrode, phosphate groups of both aptamer and HAP-NPs react with molybdate. Intensity current, related to the concentration of the analyte, was generated by applying a voltage of 0.21 V (Fig 8). The linear range of the prepared

assay was 0.1 pg/m to 10 ng/mL of PDGF-BB, with a detection limit of 50 fg/mL. Anyway, further trials are required to simplify the surface functionalization of hydroxyapatite (HAP) nanoparticles and enhance the HAP nanoparticles resistance in buffers and aqueous solution (Jiang et al. 2017).

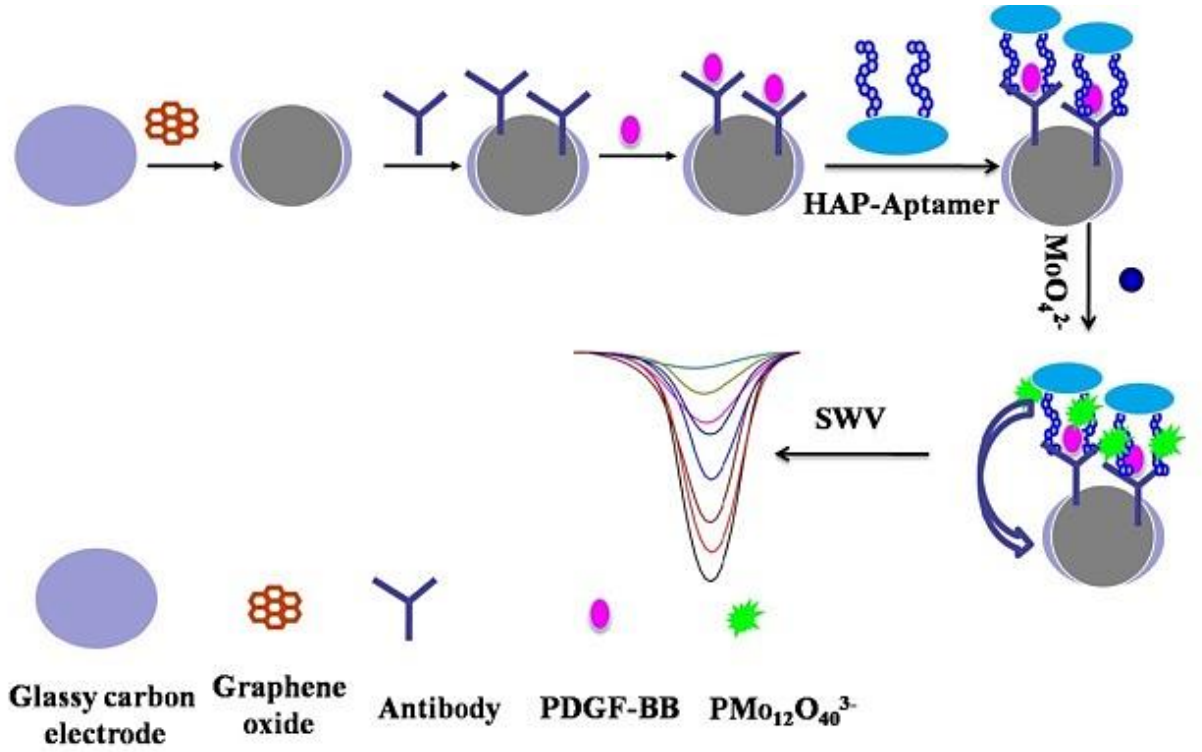

Fig. 8. Schematic illustration and preparation of the dual signal amplification based electrochemical aptasensor. This figure was obtained with permission from (Jiang et al. 2017).

2.2.2 Field-effect transistors (FETs) based biosensors

Recently, field-effect transistors (FETs) have been attracted many attentions because of their ability in transforming the biological signals into electrical output (Thévenot et al. 2001). In order to being sensitive to their target biomolecules, surface modification of FET-based biosensors is essential (Lin et al. 2016). In the last two decades, for providing an accurate and reliable sensing systems, incorporating the CMOS biosensors with aptamers due to their

compatibility is considered an efficient method. All of the CMOS sensing systems, the extended-gate field-effect transistors (EGFETs) are of particular interests because no post-CMOS action is needed (Jun et al. 2014; Lin et al. 2016; Thévenot et al. 2001). Lin et al. proposed an assay based on triggering rolling circle amplification of DNAs on extended-gate field-effect transistors to improve the sensitivity. The standard CMOS technology was used to form the EGFETs. The fabricated EGFET assay could detect the target protein of 8.8 pM, better than that achieved by traditional EGFETs (Lin et al. 2016). Lee et al. reported another field-effect transistor aptasensor for a platelet-derived growth factor detection (Fig 9). They immobilized the aptamers functionalized with amine on the surface of carboxylated polypyrrole. The fabricated FET aptasensors showed high sensing ability toward PDGF-BB with a concentration ranges from 1.78 fM to 178 pM and low limit detection as low as 1.78 fM among interfering biomolecules at room temperature. Regarding to the reusability of the prepared aptasensor and due to the covalent bonding used in the procedure of immobilization for recognition process, prepared assay exhibited high selectivity toward its target and 4 weeks long life time (SeopáLee and HeeáCho 2016).

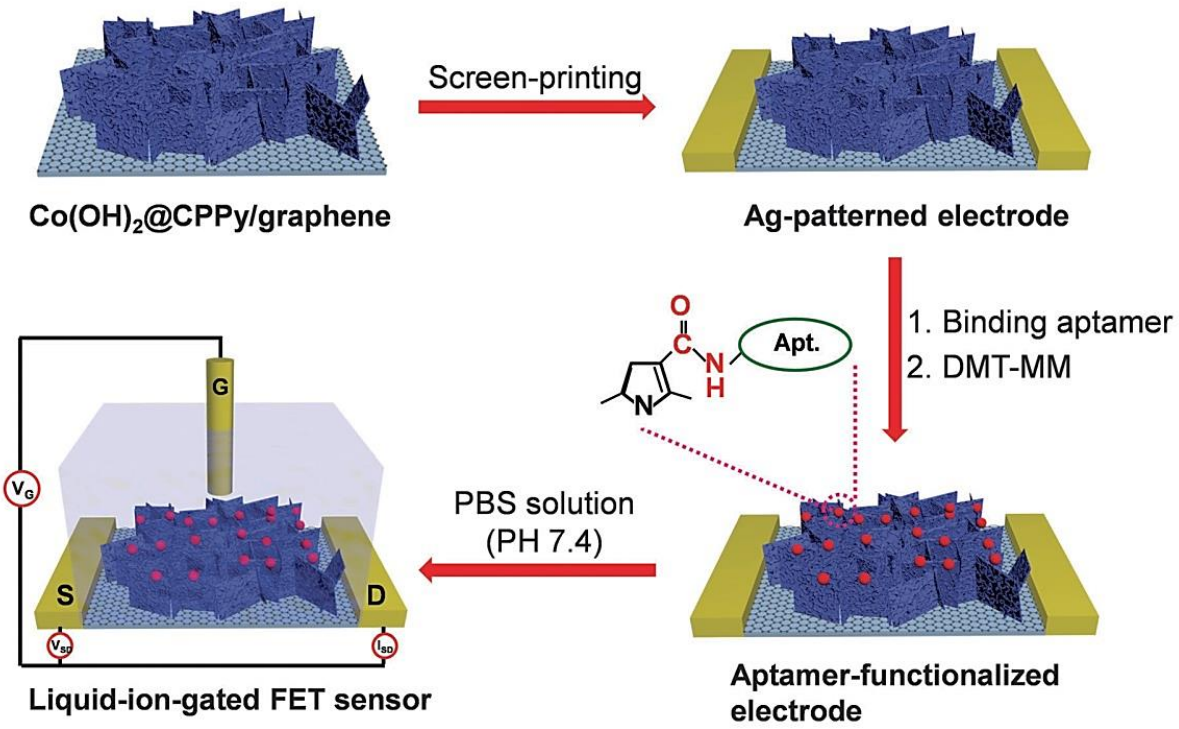

Fig. 9. Schematic illustration of the electrolyte-gated aptasensor electrode with the immobilized PDGF-B aptamers on the MHCPPs signal transducer. This figure was obtained with permission from (SeopáLee and HeeáCho 2016).

2.2.3 Electrical impedance spectroscopy biosensors

Also, among all the electrochemical methods, the electrical impedance spectroscopy (EIS) is not a common recognition method of sensing systems; however, recently this technique has become very popular for bioreceptor transduction. The obvious difference of this method compared with other electrochemical detection devices is a conductivity detection that scans the detection volume with an electrical frequency sweep in the range of 10 kHz and 10 MHz. Typically, impedance spectroscopy has many advantages over lower concentration detection methods such as simplicity, ease of operation, low-cost, fast response and so on (Huang et al. 2016; Perumal and Hashim 2014). A study by Liao al. shows that EIS based transduction has been employed in PDGF-BB detection in concentration range of 50–1µg/ml and the detection limit about 40 nM

(Liao and Cui 2007). Also, He and coworkers used nanomaterials as a sensing probe for construction of an EIS electrochemical aptasensor for the determination of PGDF-BB. They synthesized $Co_3(PO4)_2$-based nanocomposite via a simple self-assembly strategy aided by aptamer and BSA. The conducted aptasensor by exhibiting large surface active areas, good biocompatibility, high functionality could detect PDGF- BB concentrations as low as 3.7 pg/mL (He et al. 2016). In addition zhang and coworkers developed an EIS biosensor based on carbon-based nanocomposites of AgNPs and aptamer for the sensitive detection of PGDF-BB. Results of this report showed that the linear range of 32.3 fM- 1.61 pM, with detection limit of 26.5 fM (Zhang et al. 2017).

2.2.4 Voltammetric biosensors

The unique advantages of electrochemical aptasensors such as simplicity, sensitivity, specificity and suitability have made them particularly attracting for the quantification of the protein disease biomarkers in a very low levels. Voltammetric techniques which are highly sensitive, selective and have remarkable advantages, such as possibility of simultaneous measurements of a variety of targets, low cost, fast response and so on are the most popular method available for electrochemical biosensing of PDGF-BB. Currently different techniques such as, differential pulse voltammetry (DPV), cyclic voltammetry (CV) and square-wave voltammetry (SWV) are available for the sensitive and specific detection of proteins via electrochemical aptasensors (Perumal and Hashim 2014). Among these techniques, Square wave voltammetry (SWV) is considered as one of the most advanced voltammetric techniques. The current sampling process in SWV and the specific shape of the potential modulation provide an improved sensitivity and high quality voltammetric information, enabling efficient discrimination toward charging currents (Hasanzadeh et al. 2018; Meirinho et al. 2016; Perumal and Hashim 2014). In this part,

a special emphasis is given to the use of electrochemical aptasensors for a sensitive and selective detection of PDGF-BB using voltammetry techniques. Fang and coworkers prepared (Fig 10) a sandwich assay by means of Apt2 and Au NPs labeled Fc as tracer. Via a facile hydrothermal route assisted by L-cystein, carbon aerogel incorporated molybdenum disulfide was synthesized and applied to modified electrode. The Fc-AuNPs-Apt2 was a promising redox probe to generate amperometric response and therefore enhance detection signals. Based on the sandwich approach, a dual signal amplification strategy was established with a wide linear response in the range of 0.001–10 nM and a limit of detection of 0.3 pM (Fang et al. 2015). Recently Hasanzadeh et al. developed an aptasensor based on a novel structure of AuNPs supporting alpha-cyclodextrin, for detection of PDGF-BB using SWV technique. In this report, the fabricated aptasensor exhibited good biocompatibility, and specificity for protein detection. In this work, the linear rage was 0.52–1.52 nM with low limit of quantification of 0.52 nM for the detection of PDGF-BB. Also, the electrochemical aptasensor was able to detect cancer-related targets in unprocessed human plasma samples. By changing the aptamer sequences toward the specific targets, the conducted platform can be extended for sensitive detection of various target proteins (Hasanzadeh et al. 2018).

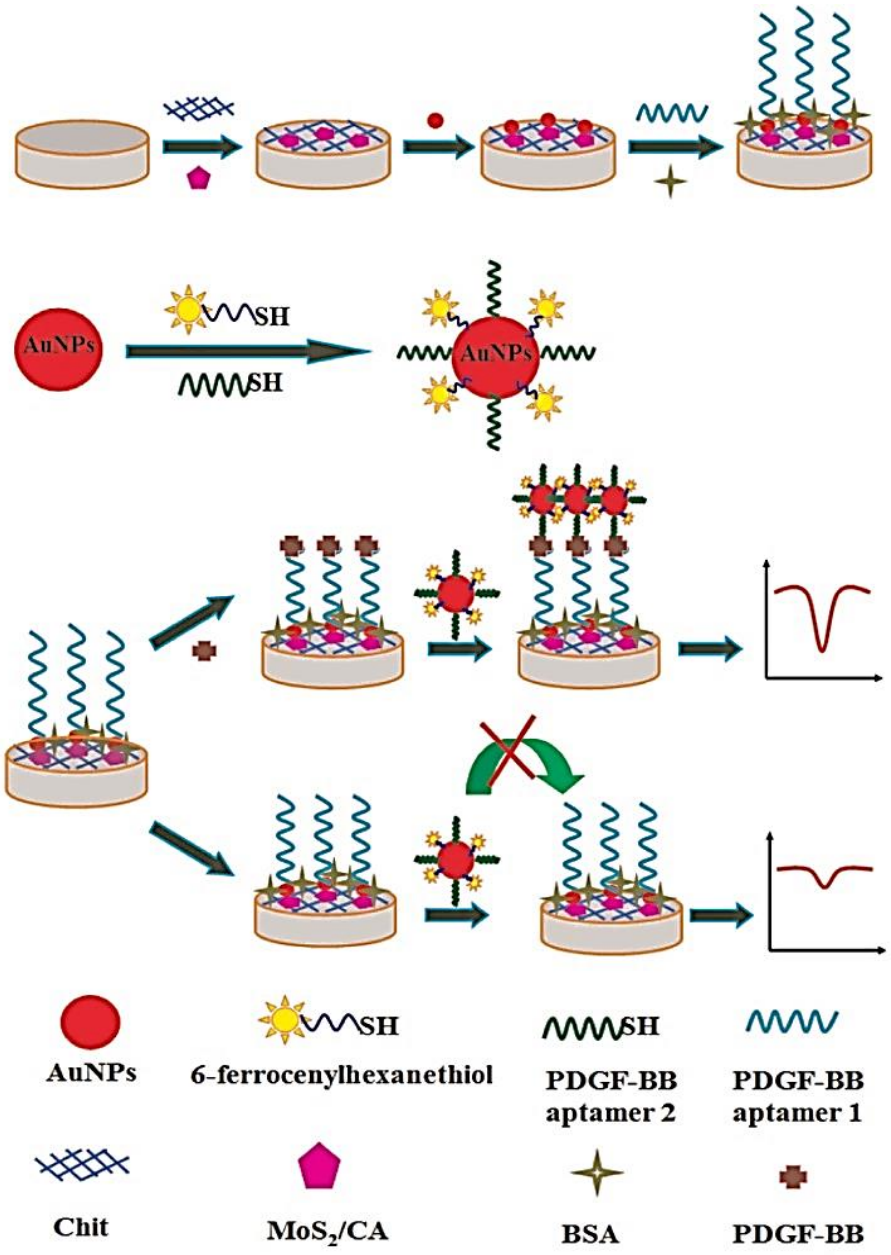

Fig. 10. Preparation of the electrochemical aptasensor based on MoS2/CA and AuNPs signal amplification for the PDGF-BB detection. This figure was obtained with permission from (Fang et al. 2015).

2.3 Aptamer-based portable PGM PDGF-BB biosensors

The development and use of portable sensors for cost-less, on-site and fast determination of a various analytes has long been sought, due to their promise in environmental observing, personal

health care and scientific researches (Hong et al. 2017; Ma et al. 2014). Although these kind of sensors had been investigated many years ago, currently, only a few of sensors are marketably accessible to the public. Personal glucose meter (PGM) which is extensively accessible and improved or saved many of diabetic patients lives, is the best successful example of the portable sensors (Clark and Lyons 1962). The portable "pocket" size, accurate and reliable quantitative results, low cost, controllability and easy operation are the great advantages of personal glucose meters which are the main reasons of their broad success. Recently, different approaches have been developed to expand the application of PGM (Hong et al. 2017; Ma et al. 2014). For example, Ma et al. by introducing invertase conjugates to secondary aptamer, applied a portable PGM for PDGF-BB detection. The quantification of PGDF- BB was relevant to the improved signal of the PGM and the color change in test strips. 2.9 fM of PGDF-BB analyzed by using this platform. Also, by using the designed biosensor in biological samples such as clinical human saliva samples to PDGF-BB detection, acceptable results obtained (Ma et al. 2014). Recently, Hong and coworkers proposed a new triply amplified DNAzyme-based portable aptasensor including aptamer payload on nanoparticles, cation exchange reaction releasing of many Zn^{2+} and the step by catalyzing cleavage of 8-17 DNA zyme for sensitive and rapid detection of PDGF-BB (Fig 11). The formation of glucose from sucrose by the cleaved DNA fragment labeled with invertas permitted the detection and quantification of PDGF-BB. by PGM accompanied with the change of color from yellow to green. The PDGF-BB quantification was relevant to the improved signal of the personal glucose and the color change in test strips. 0.11 fM PDGF-BB could determinate via prepared triply amplified assay. The prepared portable sensing platform provide great promising for applicability in clinical diagnostics and allow the real time, online and fast detection owing to its vast accessibility, easy operation, cost-

effectiveness and small size. Additionally the fabricated portable sensing system has the capacity to be used in personal families (Hong et al. 2017).

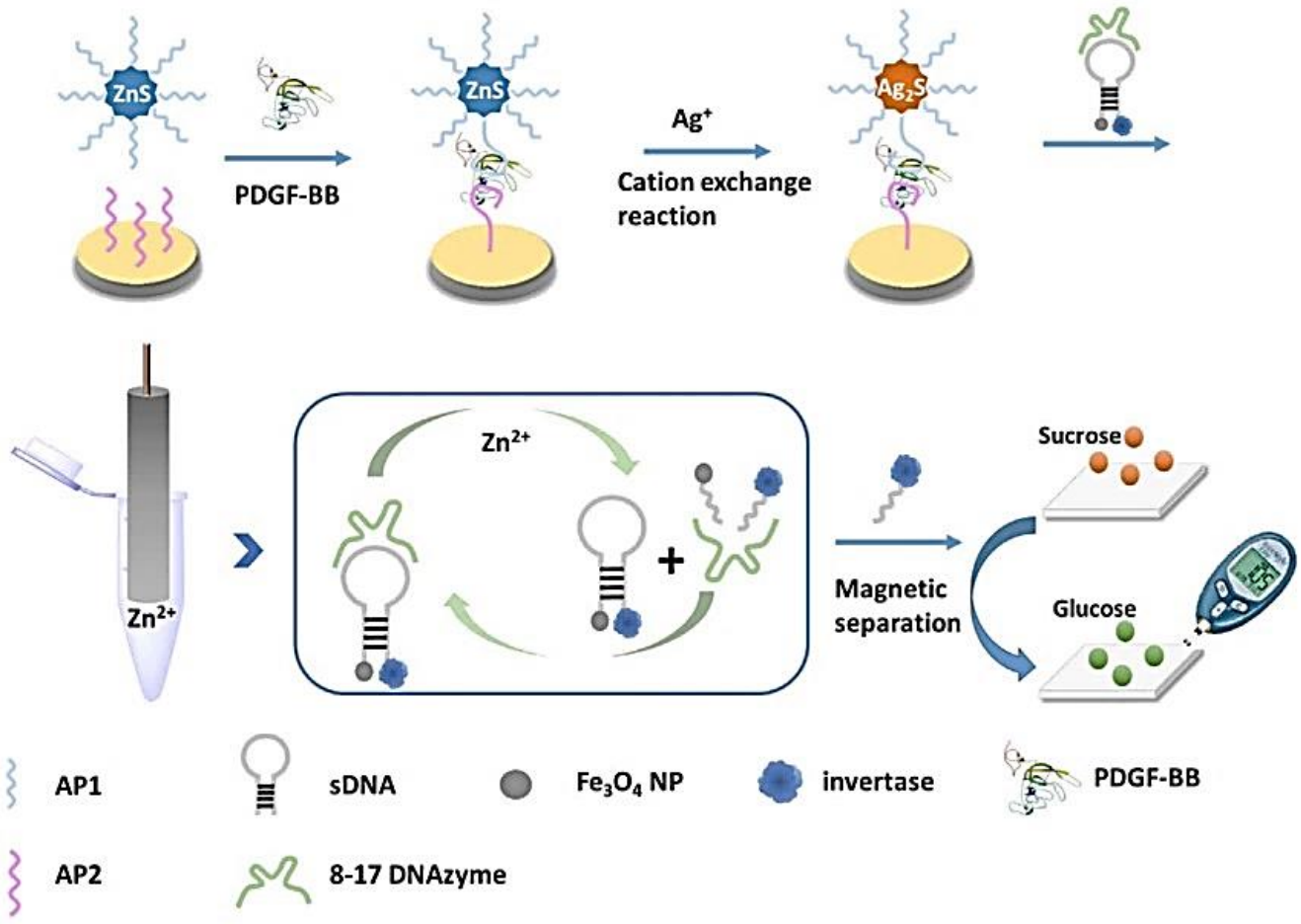

Fig.11. preparation of the PGM portable aptasensor based on a triply amplification for the detection of PDGF-BB. This figure was obtained with permission from (Hong et al. 2017).

3. Conclusion and further perspective

Rapid and sensitive determination of PDGF-BB, is particularly essential as a potential protein marker in early diagnosis of cancer, therapeutic purposes and cancer prognosis. During the last decade, biosensor technology has attracted many attentions due to being suitable for the detection of interested targets in low levels with inexpensive instrumentation and rapid analysis

time. Fabrication and establishment of aptamers as strong bioanalytical systems is the latest active trend in the biosensing technology. Aptamers are short and single stranded RNA or DNA oligonucleotides with the specific binding potential to various of analytes, carrying more advantages than antibodies. They are amenable to chemicaly modifications and compared to antibodies are more robust. Providing the feasibility of simultaneous quantification, decreasing the cost of the determination procces and requiring only a few minutes for the analysis, have made aptasensors an appropriate alternative. Herein PDGF-BB aptamer based biosensing methods have been discussed including optical and electrochemical aptasensors. Owing to the low sample volume, simple pretreatment process, high sensitivity, automated and short detection time and cost-effective instrumentation, the electrochemical aptasensors based on the specific interaction between aptamer and target molecule, have received considerable attention. An overview shows that the large specific surface area of the nanomaterials and nanoparticles, which provides immobilizing of more signal molecules on the surface of the sensory electrode and excellent electronic conductivity, have made them a useful alternative for signal amplification. Also in this review the efforts related to design and development of personal glucose meter portable sensors for the detection of PDGF-BB have been summarized. Owing to their easy operation, wide availability, effective-cost and small size, the PDGF-BB portable aptasensors may have lots of applications in clinical diagnostics and may allow the on-site, real time and fast detection and also could be used in personal families. To sum up, the design and development of in vivo solutions should be a priority, as many of the sensing platforms have been designed and improved for in vitro quantification of PDGF-BB. For medical application, the advantages of inexpensive instrumentation would provide the designing of easy, very low cost and disposable sensors for in-home use. However, further efforts are still needed to facilitate and improve their

use for a fast, direct and accurate PDGF-BB detection. As more than one protein biomarker is involved in the great number of cancers, therefore, next developments on the aptasensors must be made toward the design of multiple detection sensing systems for same or different biomarkers, as most of these biomarkers can be found in very low amounts in biological fluids.

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Highlights:

- Merits and demerits of conventional Platelet-derived growth factor (PDGF-BB) detection methods have been compared.
- Aptamers provided highly sensitive and selective bioreceptors for detection of PDGF Principles and different types of Aptasensors such as optical, and electrochemical, aptasensors have been explained.
- Emerging of nanotechnology has opened a novel window for aptasensors fabrication with improved figures of merit.