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ORIGINAL PAPER

Self-assembled biotin-phenylalanine nanoparticles for the signal amplification of surface plasmon resonance biosensors

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Abstract

A strategy for amplifying the signal of surface plasmon resonance (SPR) biosensors is reported. Biotinylated phenylalanine (Biotin-Phe) monomers were rapidly self-assembled into nanoparticles in a mild environment. The self-assembled nanoparticles were then used as the carriers of streptavidin-antibody complexes by the streptavidin-biotin interaction. The signal was amplified because of the high molecular weight of the nanoparticle-streptavidin-antibody conjugate. With prostate-specific antigen as a model analyte, the target concentration as low as 1 pg mL^{-1} was readily measured. The results of the nanoparticle-enhanced SPR biosensor for analysis of serum samples are well consistent with those achieved by the enzyme-linked immunosorbent assays. This work is valuable for designing of various optical and electronic biosensors through the streptavidin-biotin interaction.

Keywords Surface plasmon resonance · Signal amplification · Self-assembly · Phenylalanine · Biotin · Prostate-specific antigen

Introduction

The increasing demands for early diagnosis of cancers promote the development of effective tools for sensitive detection of biomarkers [1, 2]. Surface plasmon resonance (SPR) is a powerful tool for real-time, online investigation and characterization of biomolecular physicochemical interaction [3]. The technique is very sensitive to monitor small changes in the surface quality or refractive index on noble metal surface. SPR biosensors have been extensively used in clinical diagnosis, drug research, food safety, and environmental monitoring [4–7]. Unfortunately, the target of interest is always very low in abundance and molecular weight, which leads to the weak change of refractive index in SPR detection. In order to overcome this problem, substantial efforts have been put into the development of nanomaterials as enhanced SPR-sensing substrates or tags for signal amplification, including metallic nanoparticles, magnetic nanoparticles, carbon-based nanomaterials, latex nanoparticles, and liposome nanoparticles [8–16]. The nanomaterial-based amplification tags can introduce external coupled surface plasmon wave with the sensing film, bring high molecular weight and refractive index change, or produce large evanescent field enhancement to the chip surface. Although satisfactory results have been achieved, these amplification methods always require time-consuming and laborious synthesis and tedious surface modification of nanomaterials. In addition, in heterogeneous bioassay, the non-specific adsorption of nanomaterials on solid surface or in the SPR channel is still a common but inevitable problem to be solved [11].

Besides nanomaterials, biomolecules with high molecular weight have also been used to amplify SPR signal [17–20]. For example, streptavidin (SA) with a molecular mass of ~ 60 KDa is a tetrameric protein, which can bind to four biotin molecules with high binding constant (K_d =

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10^{-15} M) [21]. The SA-DNA complexes have been applied to enhance SPR signal for sensitive detection of DNA and microRNAs [17, 18, 22]. Antibody (Ab) is a kind of high-molecular-weight biomacromolecule; we and others have reported the SPR detection of β-amyloid peptide and β-secretase by the signal amplification of Ab-SA conjugates [19, 20]. However, as far as we know, there are few reports on the signal amplification by using biological nanomaterials as the signal intensifiers.

Aromatic phenylalanine and its derivatives have good biocompatibility and excellent chemical properties. Phenylalanine-decorated molecules have been extensively designed and used to prepare various nanostructures by the rapid and simple self-assembly [23]. The building blocks have attracted great attention in the fields of drug delivery, tissue engineering, and biosensing [24]. By labeling phenylalanine with functional molecules and strictly controlling the assembly conditions, different nanostructures with specific feature and good morphology can be obtained. In the present work, the biotinylated phenylalanine (biotin-Phe) monomers were rapidly self-assembled into nanoparticles (denoted as biotin-FNPs) in a mild environment. Then, we proposed a versatile strategy to amplify the SPR signal by the "one-pot" prepared conjugates performed between Ab-SA and biotin-FNP through the strong SA-biotin interaction. The conjugate can be recruited on the gold chip surface through the specific antigen-antibody interaction. Biotin-FNP as the signal amplifier may exhibit a broad application prospect in designing of biosensors through the SA-biotin coupling chemistry.

Experimental

Chemicals and reagents

Prostate-specific antigen (PSA), anti-PSA (Ab_1), and biotinylated anti-PSA (biotin-Ab_2) were provided by Linc-Bio Science Co. Ltd. (Shanghai, China, http://lzhenyul.biogo.net/). PSA ELISA kits, SA, human serum albumin (HSA), IgG, alpha-fetoprotein (AFP), thrombin, TCEP, l-ethyl-3(3-(dimethylamino)propyl) carbodiimide (EDC), N-hydroxysulfosuccinimide (NHS), and 11-mercaptoundecanoic acid (MUA) were purchased from Sigma-Aldrich (Shanghai, China, www.sigmaaldrich.com/china-mainland.html). Other analytical-grade regents were supplied by Aladdin Industrial Corporation (Shanghai, China, https://www.aladdin-e.com/) and used without further purification. Biotin-Phe was synthesized and purified by China Peptides Co., Ltd. (Shanghai, China, http://chinapeptides.itrademarket.com/). Three male serums were provided by the People's Hospital of Anyang City (Anyang, China). Millipore water was used throughout all the experiments.

Instruments

The morphology of biotin-FNP was characterized by SU8010 scanning electron microscope (SEM) (Hitachi, Japan) and atomic force microscopy (AFM) (Bruker Nano Inc., Santa Barbara, CA). The average size of the nanoparticles was measured by ZetaPALS laser-scattering particle-size analyzer (Brookhaven Instruments Corporation, USA). All SPR measurements were performed on a BI-SPR 3000 instrument (Biosensing Instrument Inc., Tempe, AZ).

Preparation of Ab_2-SA-biotin-FNP conjugate

The lyophilized biotin-Phe was dissolved to 20 mg mL^{-1} by DMSO and diluted to 2 mg mL^{-1} by phosphate buffer (10 mM, pH 8.4). After shaking gently for 10 min, the unassembled biotin-Phe monomers were filtered by a 30 KD filter membrane. The resulting biotin-FNP was diluted to 0.2 mg mL^{-1} by SPR detection buffer (10 mM phosphate, pH 7.4) and stored at 4 °C for use. The Ab_2-SA complex was prepared by mixing 0.5 μg mL^{-1} biotin-Ab_2 and 0.02 μg mL^{-1} SA in the SPR detection buffer. Before use, the complex was diluted to a desired concentration. The conjugate of Ab_2-SA-biotin-FNP was prepared by adding 1 mL of 10 ng mL^{-1} Ab_2-SA (equivalent biotin-Ab_2) to 1 mL of the as-prepared biotin-FNP suspension. Since each SA molecule contains four biotin-binding sites, the free biotin-binding sites in the Ab_2-SA complex allow for the anchor of Ab_2-SA on the surface of biotin-FNP.

Preparation of SPR chips

Before the SPR experiment, the MUA-covered SPR chips were fabricated by self-assembly [25, 26]. Briefly, the cleaned gold chip was immersed in a 10 mM MUA solution in the dark for 24 h, and the MUA self-assembled monolayers (SAMs) are formed on the chip surface through the Au–S interaction. Next, the modified chip was cleaned with ethanol and water. The mixture of 0.4 M EDC and 0.1 M NHS was used to activate the carboxyl groups in the MUA SAMs for 15 min. After washing with water, the activated chips were incubated with phosphate buffer containing 0.5 mg mL^{-1} capture antibody of Ab_1 for 2 h. To block the unreacted activated carboxyl group, the Ab_1-modified chips were incubated with 1 mM ethanolamine solution for 20 min. Then, the prepared sensor chip was washed thoroughly with water, dried under nitrogen flow, and kept at 4 °C for use.

PSA detection

The Ab_1-modified chip was fixed on the SPR instrument with a 200-μL sample ring. PSA sample was loaded into the sample circuit on the injection valve and delivered into the fluidic

channel by a syringe pump (model fusion 710, Chemyx Inc., Stafford). When the sample had entered the channel, the solution flow was stopped to retain the sample at the channel for a given time. The residual sample was washed away by rinsing the channel with the buffer solution. When the baseline was stable, the Ab_2-SA-biotin-FNP suspension was injected into the channel and the signal was recorded.

For PSA determination in real samples, three fresh male bloods were collected, stored at room temperature for 2 h, and then centrifuged at 2000 rpm for 5 min. After that, 50 μL of serums were taken out, diluted 100 times with the buffer solution, and then analyzed with the same procedures as those for the analysis of PSA standard samples.

Results and discussion

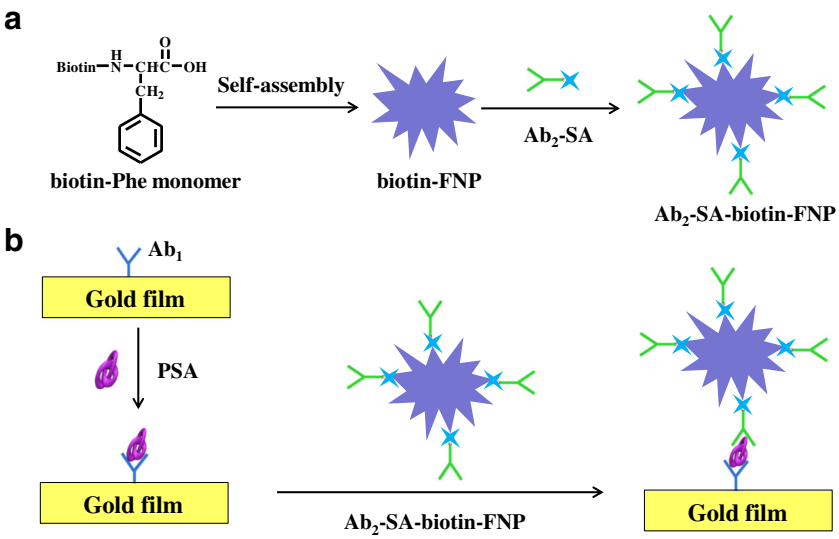
Principle of this method

Tetrameric SA protein can capture four biotin molecules with high-binding constant and thus has been commonly used to prepare amplification tags as the linker of recognition element and nanomaterial. In this work, the biotin-FNP nanoparticles were synthesized by the self-assembly of biotin-Phe monomers (Scheme 1a). The AFM and SEM images indicate that the biotin-FNPs are monodisperse (Fig. S1). The nanostructures keep an excellent stability even after storage for 1 month. After modification of Ab_2-SA, the average size of the nanoparticles increased from ~43 to ~82 nm observed by laser-scattering particle-size analyzer. Thus, the biotin-FNP can be used as the carrier to load the Ab_2-SA complex by the strong SA-biotin interaction. Taking PSA as a model analyst, the SPR biosensor was carried out with a classic sandwich-like detection model. Scheme 1b illustrates the detection strategy based on the signal amplification of Ab_2-SA-biotin-FNP. The capture antibody of Ab_1 was covalently fixed on the MUA-covered gold chip surface by the standard amine coupling reaction. After the capture of PSA, the Ab_2-SA-biotin-FNP conjugate was recruited on the gold chip surface through the specific antigen-antibody interaction.

Feasibility of this method

As shown in Fig. 1A, a direct injection of 2-ng-mL^{-1} PSA into the Ab_1-covered channel caused a small signal change. No significant increase in the SPR signal was observed even if injecting 10-ng-mL^{-1} PSA into the channel (data not shown), which is indicative of the "saturated" coverage of the sensor surface by PSA. A net change of 80.62 mDeg was obtained after injecting Ab_2-SA-biotin-FNP suspension to the PSA-covered channel. The signal enhancement is originated from the capture of Ab_2-SA-biotin-FNP whose size is much bigger than that of PSA. By increasing the reaction time between PSA and Ab_1, we found that the SPR signal change was intensified by almost 1.5-fold (Fig. S2). Thus, when PSA had entered the channel, the solution flow was stopped to make the sample keep at the channel for 30 min (the optimized time) in the following detection assays.

In order to verify the feasibility of the signal amplification strategy, the solutions of Ab_2-SA, SA-biotin-FNP, and Ab_2-SA-biotin-FNP were injected into the PSA-treated fluidic channels, respectively. The corresponding SRP sensorgrams were collected, as shown in Fig. 1B. When Ab_2-SA was injected into the channel, a small SPR dip shift was observed (curve a), which should be attributed to the binding of Ab_2-SA and the captured PSA. When injecting Ab_2-SA-biotin-FNP into another channel, the SPR dip shift increased to 121.39 mDeg (curve b). This enhancement indicated that the



Scheme 1 **a** Chemical structure and self-assembly process of biotin-Phe monomers. **b** Schematic representation for the design of SPR biosensor with Ab_2-SA-biotin-FNP as the signal enhancer.

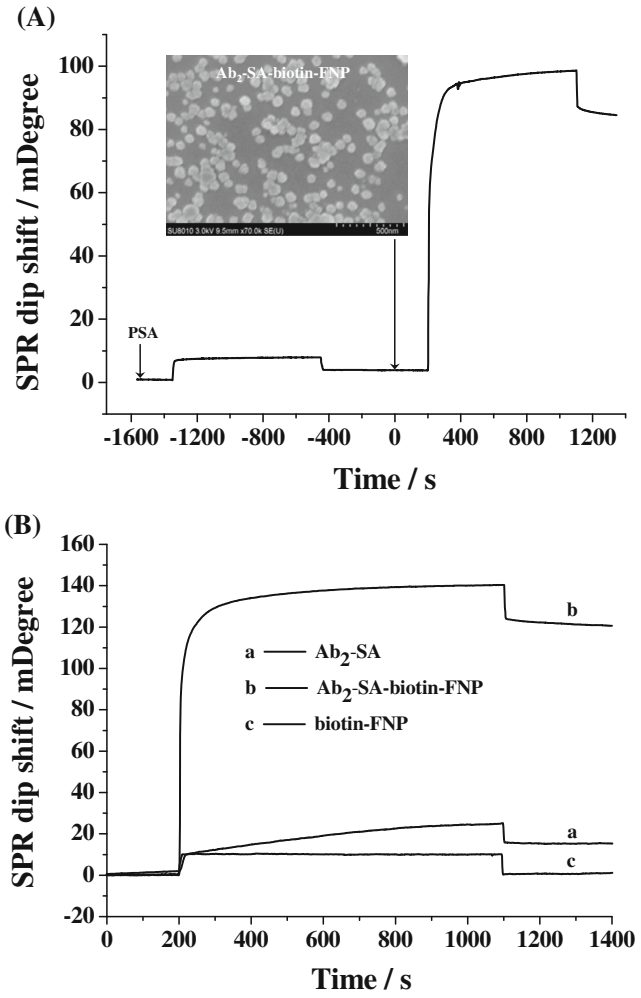


Fig. 1 **A** SPR sensorgram for injecting PSA and Ab_2-SA-biotin-FNP into the Ab_1-modified channel. The arrow is indicative of the time when the injection was made. The concentration of PSA was 2 ng mL^{-1}. **B** SPR sensorgrams for injecting Ab_2-SA (curve a), Ab_2-SA-biotin-FNP (curve b), and biotin-FNP (curve c) into the Ab_1/PSA-modified channels

signal was amplified by the biotin-FNP. When injecting biotin-FNP only into the chip surface (curve c), no obvious signal change was observed, indicating that the biotin-FNP had no non-specific adsorption on the sensor surface. These results suggested that the Ab_2-SA-biotin-FNP can serve as an excellent candidate to amplify the SPR-sensing signal.

Optimization of experimental conditions

In this work, Ab_2-SA was responsible for recognizing the captured target and linking with biotin-FNP. When injecting various concentrations of Ab_2-SA into the PSA-saturated SPR channel, the signal increased with the increase of Ab_2-SA concentration and began to level off beyond 5 ng mL^{-1} (equivalent biotin-Ab_2) (Fig. S3). In the following assays, a large amount of Ab_2-SA (50 ng mL^{-1}) was used for the preparation of Ab_2-SA-biotin-FNP and the detection of PSA. The concentration of biotin-FNP used for loading of Ab_2-SA has also been optimized. As shown in Fig. S4, the SPR signal was intensified with the increase of biotin-FNP concentration below 20 μg mL^{-1}. The result indicated that increasing the concentration of biotin-FNP facilitated the formation of more Ab_2-SA-biotin-FNP conjugates. However, when the concentration was higher than 20 μg mL^{-1}, the signal began to decrease. The result is understandable since high concentration of biotin-FNP may decrease the loading number of Ab_2-SA per biotin-FNP. Therefore, 20 μg mL^{-1} of biotin-FNP was used as the optimal concentration for the preparation of Ab_2-SA-biotin-FNP conjugate. We also studied the regeneration of the biosensor and found that the sensor chip can be regenerated easily by consecutively injecting 10 mM NaOH solution (i.e., desorption PSA and Ab_2-SA-biotin-FNP). There was no significant change in the SPR dip shift after 7 regeneration/assay cycles (Fig. S5). The good regenerations suggested that the captured antibody of Ab_1 attached onto the chip surface by amino covalent coupling reaction remained high stability and activity. The result is in agreement with that reported in the previous studies [20, 27, 28].

Sensitivity

Under the optimized conditions, Ab_2-SA-biotin-FNP was injected into the SPR channels treated by different concentrations of PSA. Figure 2A shows the SPR sensorgrams at

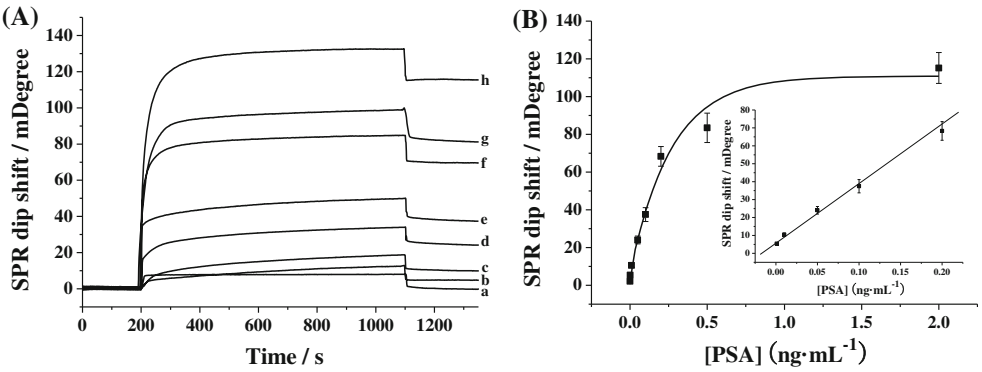


Fig. 2 **A** SPR sensorgrams for analysis of PSA at various concentrations (a~h: 0, 0.001, 0.01, 0.05, 0.1, 0.2, 0.5, and 2 ng mL^{-1}). **B** Plots of SPR dip shift against PSA concentration. The inset shows the linear part of the curve in the range of 0.001~0.2 ng mL^{-1}

Table 1 An overview on nanomaterials-based SPR methods for the determination of PSA

Chip modifier	Signal label	Linear range (pg mL^{-1})	LOD (pg mL^{-1})	Ref.
AuNPs/SiO_2	Direct detection	Not reported	100	[29]
MIP	Direct detection	$1 \times 10^2 \sim 5 \times 10^4$	91	[28]
CMD	Direct detection	$1 \times 10^3 \sim 4.5 \times 10^5$	1000	[30]
SAM	20 nm Ab-AuNPs	10~400	5	[27]
SAM	40 nm Ab-AuNPs	$1.17 \times 10^3 \sim 1.5 \times 10^5$	290	[31]
Protein G	20 nm Ab-AuNPs	$1.7 \times 10^3 \sim 1.7 \times 10^7$	1700	[32]
Mixed SAM	20 nm Ab-SA-AuNPs	Not reported	73	[33]
SAM	10 nm Ab-SA-AuNPs	Not reported	150	[34]
SAM	Ab-SA-biotin-FNP	1~200	1	This work

different PSA concentrations. It can be observed that the SPR signal increased with the increase of PSA concentration. Figure 2B depicts the relationship between SPR dip shift (θ) and PSA concentration. The plateau exhibited by the curve is indicative of "saturated" coverage of the chip by PSA and Ab_2-SA-biotin-FNP conjugate. In the concentration range of 1~200 pg mL^{-1}, a linear regression equation of $\theta = 332.4$ [PSA] (ng mL^{-1}) + 5.7 was obtained. The relative standard deviations (RSDs) obtained at three chips are all below 10%, suggesting an acceptable reproducibility. The limit of detection (LOD) was estimated to be 1 pg mL^{-1} by determining the target smallest concentration at which the SPR dip shift is clearly distinguishable from the response to the blank control ($n = 3$). The value is lower than that achieved by direct injection of PSA onto the SPR chip modified with gold nanoparticles (AuNPs) [29], PSA-templated microcontact imprinting (MIP) [28], or carboxymethylated dextran (CMD) [30] and is preferable to that by competitive assay with the amplification tags of antibody-AuNPs [27] or sandwich-like assays with antibody-conjugated tags of 40 nm AuNPs [31], 20 nm AuNPs [32] or SA-AuNPs [33], and 10 nm SA-AuNPs (Table 1) [34]. The sensitivity is also comparable to or even better than that for the detection of other biomarkers with the amplification tags of metallic, magnetic nanoparticles, or carbon-based nanomaterials [11]. The high sensitivity should be attributed to the large size and high molecular weight of Ab_2-SA-biotin-FNP conjugate. Moreover, in contrast to other amplification tags, the signal label of biotin-FNP exhibits no non-specific adsorption on the sensor surface and can be prepared without additional modification and purification steps. Although the accuracy and reproducibility have to be improved, the work proposed a novel strategy to amplify SPR signal and prepare hybrid colloidal nanomaterials.

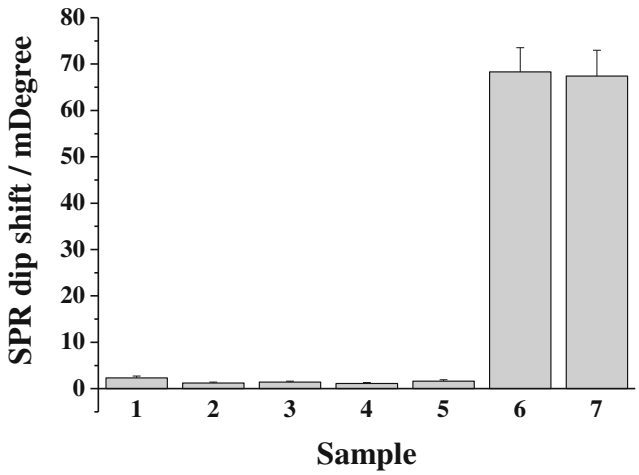


Fig. 3 Selectivity of this method to various proteins: sample 1, blank control; sample 2, HSA; sample 3, IgG; sample 4, AFP; sample 5, thrombin; sample 6, PSA; sample 7, the mixture of HAS, IgG, AFP, thrombin, and PSA. The concentration of PSA was 0.2 ng mL^{-1} and that of other proteins was 20 ng•mL^{-1}

Selectivity and anti-interference

Selectivity and anti-interference are two important parameters to evaluate the practical application of biosensors. In order to verify the specificity of the method for PSA detection, we challenged the biosensor with other proteins. The SPR dip

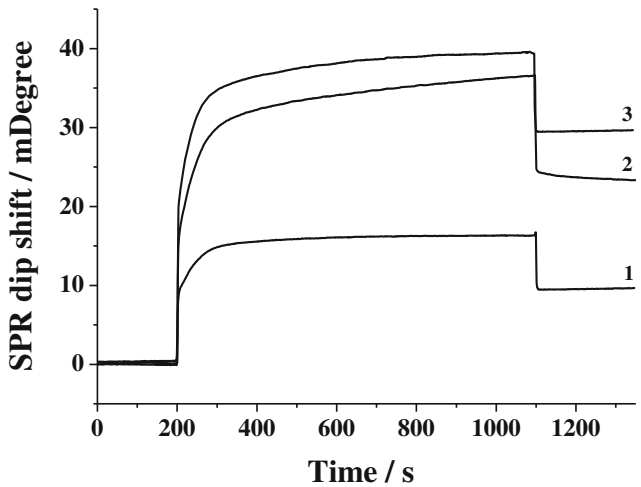


Fig. 4 SPR sensorgrams for injecting Ab_2-SA-biotin-FNP into the three serum-treated channels

Table 2 Results for analysis of PSA in serum samples by this method and ELISA kit

Sample	This method (ng mL^{-1})	ELISA (ng mL^{-1})
1	1.26 ± 0.1	1.68 ± 0.1
2	5.32 ± 0.5	5.87 ± 0.4
3	7.26 ± 0.6	7. 14 ± 0.5

shifts for HSA, IgG, AFP, and thrombin (bar 2–5) were closed to the blank control (bar 1) (Fig. 3) although the concentration of the four interfering proteins was almost 100 times higher than that of PSA. In order to ensure the anti-interference of biosensor, the mixture of PSA and other proteins was used to deal with the chip. The results suggested that there is no significant difference in SPR signal change when the chip was treated with the mixture or PSA only (cf. bar 6 and bar 7). This suggested that these interferences had nearly no influence on PSA detection. Note that the biosensor is very sensitive; therefore, the interference from biological matrix can be eliminated by diluting the real sample if other interfering components can adsorb on the chip surface.

Real sample assays

To indicate the amenability of our strategy for clinical applications, three human serum samples were analyzed. Figure 4 depicts the SPR sensorgrams for analysis of different samples. According to the established standard curve aforementioned, the PSA concentrations were calculated to be 1.26, 5.32, and 7.26 ng mL^{-1} in the original serums. The results are well consistent with those found by the commercial ELISA kit (Table 2), indicating that the method is suitable for the quantitative detection of PSA in real samples.

Conclusion

In conclusion, the self-assembled biotin-FNP was fabricated in a mild environment. The nanoparticle exhibits excellent stability and can be readily conjugated with recognition elements such as SA and antibody. The Ab_2-SA-biotin-FNP conjugate was then used as the label to develop a SPR biosensor. Thanks to the large size and high molecular weight of the conjugate, the SPR signal was greatly amplified. In our preception, this method provides a powerful tool for determining ultralow concentration of biomarkers. Moreover, this work proposes an interesting strategy to create hybrid colloidal nanomaterials by self-assembly.

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Compliance with ethical standards

Conflict of interest The author(s) declare that they have no competing interests.

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