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A recyclable electrochemical sensing platform for breast cancer diagnosis based on homogeneous DNA hybridization and host-guest interaction between cucurbit [7]uril and ferrocene-nanosphere with signal amplification

Shuai Yang [a], Min You [a], Lizhu Yang [b], Fan Zhang [a,*], Qingjiang Wang [a], Pingang He [a]

[a] School of Chemistry and Molecular Engineering, East China Normal University, Shanghai 200241, PR China
[b] School of Pharmaceutical Sciences, Wenzhou Medical University, Zhejiang, 325035, PR China

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ABSTRACT

Recently, many strategies have been developed to trace the breast cancer susceptibility gene (BRCA), which is closely related to the occurrence of breast cancer. In this work, a novel recyclable electrochemical sensing platform was constructed to detect BRCA DNA based on the homogeneous hybridization of this target sequence with ferrocene-labeled DNA/Au nanospheres (FcNS) and horseradish peroxidase-labeled DNA/Au nanospheres (HRPNS) concatamers, and the host-guest interaction between cucurbit [7]uril (CB [7]) adsorbed on the electrode and Fc on the hybridization complex. With the optimization of experimental conditions, the fabricated sensing platform showed improved sensitivity with a low detection limit of 25 pM (S/N = 3), contributed by the dual amplification of signal using FcNS and HRPNS concatamers, and high specificity for BRCA DNA. The captured complex was dissociated from CB [7]-modified electrode with the rise of pH value to recycle the sensing platform. Furthermore, this detection strategy displayed the reliability and applicability in the analysis of human serum samples, indicating great potential for applications in early diagnosis of breast cancer.

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1. Introduction

Nowadays, cancers have been considered as one of the greatest threats in human life, among which the breast cancer causes a high risk to women health [1]. Therefore, the early diagnosis of breast cancer is in great demand. Accumulated evidences have demonstrated that the mutations of breast cancer susceptibility gene (BRCA) can significantly increase the incidence of breast cancer. Therefore, BRCA gene has become a clinically important biomarker for early diagnosis of breast cancer. Recently, in order to achieve the determination of sequence-specific DNA, a lot of methods have been developed, such as electrochemistry, fluorescence (FL), nuclear magnetic resonance (NMR), chromatography [2–5]. Among them, electrochemical DNA detection has attracted increasing attentions due to its advantages, such as quick response, high sensitivity, simple fabrication [6–8]. In the conventional electrochemical biosensing strategies, DNA probes were usually immobilized on the sensing platform [9–11], which could cause relatively low hybridization efficiency [12,13], and thus limit the detection sensitivity. Moreover, the immobilization process was irreversible, leading to the poor renewability of the sensing platform.

Homogeneous DNA hybridization is an immobilization-free and easy-operating technique to be appropriately applied to the fabrication of DNA sensing platform with the improved sensitivity [14–17], contributed by the increased DNA hybridization efficiency in liquid phase. Moreover, it can reduce the cross-contamination of nucleic acid on the sensing platform, enhancing the reliability of DNA detection [18]. Thus, it is highly desirable to develop the facile and sensitive electrochemical sensing platform combined with homogeneous hybridization for the detection of sequence-specific DNA.

To improve the renewability of sensing platform, host-guest interaction has been exploited in the development of a recyclable DNA detection strategy, which was firstly reported by our group [19]. As we know that the interaction between host and guest molecules relies on non-covalent bond, which can be easily dissociated with the variation of some specific conditions, such as pH, light and temperature, thus realizing the recyclability of sensing platform. Cucurbit[*n*]urils, a new-type cage-like macromolecule with high symmetry, is increasingly utilized as host molecule in supramolecular chemistry after the blossom of crown ether, cyclodextrin and calixarene [20–25]. It is composed of glycoluril units and has a hydrophobic cavity [26,27], which can bond with various kinds of guests, including ferrocene (Fc), adamantane and organic cations, through hydrogen bonds, hydrophobic and ion-dipole interactions. It has been reported that Fc presents the special affinity to cucurbit [7]uril (CB [7]), since their binding constant reaches up

* Corresponding author.
E-mail address: fzhang@chem.ecnu.edu.cn (F. Zhang).

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to 10^9 M^{-1} [28]. Moreover, the complex of CB [7] and Fc can be dissociated by simple pH control [29].

In this paper, a novel recyclable electrochemical sensing platform is constructed with the combination of homogeneous DNA hybridization and host-guest interaction (Scheme 1) for the determination of BRCA DNA. With the existence of the target DNA, horseradish peroxidase-labeled DNA/Au nanospheres (which can be denoted as HRPNS) concatamers could be linked to ferrocene-labeled DNA/Au nanospheres (which can be denoted as FcNS) through homogeneous hybridization to increase the hybridization efficiency. The formed complex is further captured on the electrode through host-guest interaction between CB [7] and Fc, which brings a great deal of HRP labeled on the concatamers to the electrode. The complex can be also released from the electrode through the dissociation between CB [7] and Fc with simple pH control, obtaining the recyclability of sensing platform. The electrochemical signal generated by the oxidation of o-phenylenediaminein the presence of H_2O_2 is amplified simultaneously by FcNS and HRPNS concatamers. This method presents great potential for promoting the development of breast cancer early diagnosis.

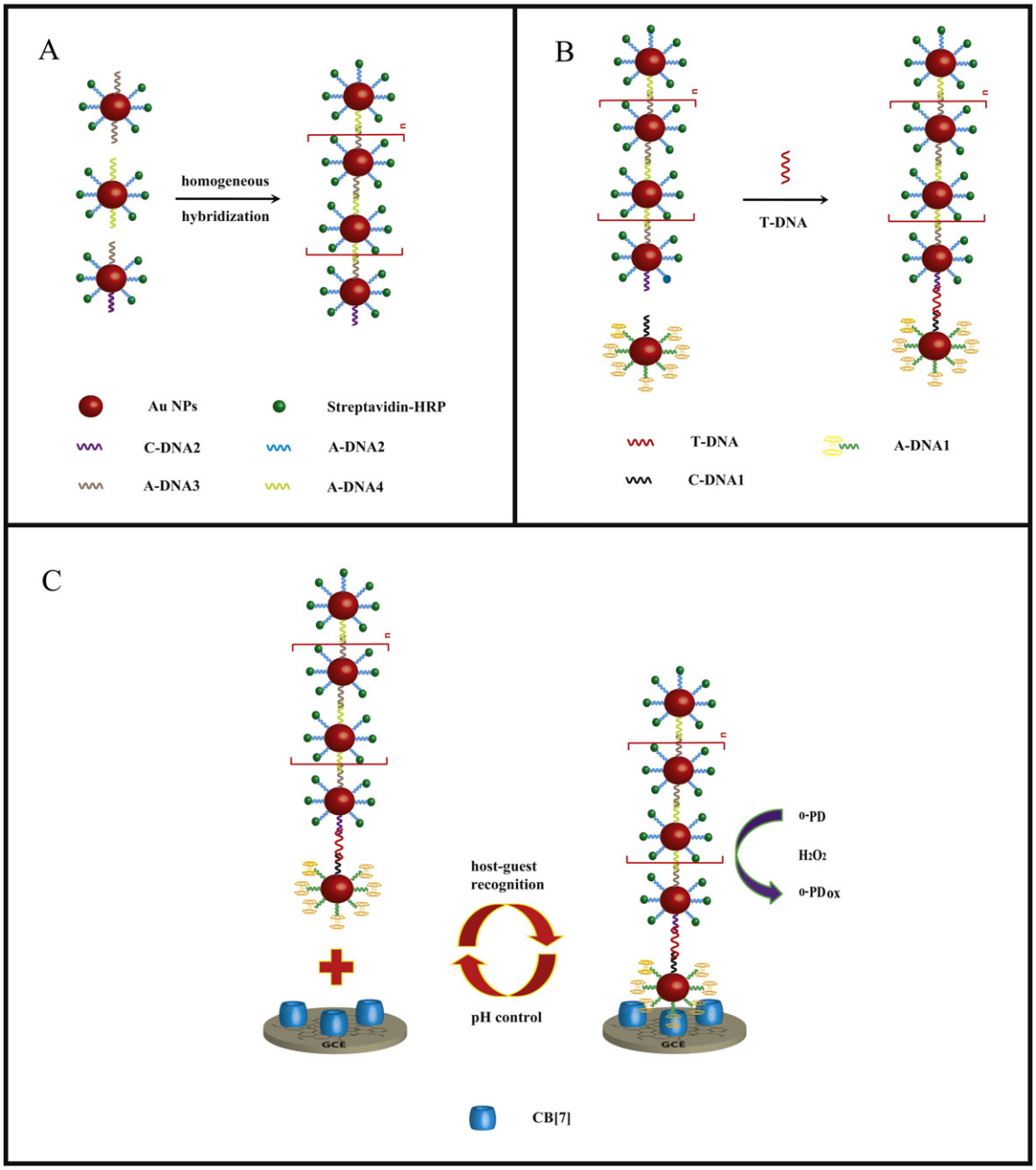
2. Experimental

2.1. Materials

$K_3Fe(CN)_6$, $K_4Fe(CN)_6$, KCl, Na_2HPO_4, NaH_2PO_4, HCl, NaOH, hydrogen peroxide, trisodiumcitrate (Sinopharm, Shanghai, China); $HAuCl_4$, o-phenylenediamine (Sigma-Aldrich, USA); Graphene oxide (JCNANO, Nanjing, China); Cucurbit [7]uril (Aisiweida, Taiyuan, China); Streptavidin-HRP (1 mg·ml^{-1}, Beyotime, China); DNA sequences (Sangon, Shanghai, China). All reagents were of analytical reagent grade and all the solutions were prepared with ultrapure water.

Sequences information:

Capture DNA1 (C-DNA1): 5′-SH-$(CH_2)_6$-TAT GAA GCT GTA TGG-3′



Scheme 1. Schematic illustration of recyclable electrochemical sensing platform for BRCA DNA detection.

Capture DNA2 (C-DNA2): 5′-TTT CAG CAA CAG GGA-$(CH_2)_6$-SH-3′
Auxiliary DNA1 (A-DNA1): 5′-SH-$(CH_2)_6$- GCC ATT GGG TCT TGC-Fc-3′
Auxiliary DNA2 (A-DNA2): 5′-SH-$(CH_2)_6$- GCC ATT GGG TCT TGC-biotin-3′
Auxiliary DNA3 (A-DNA3): 5′-SH-$(CH_2)_6$- CGC TGA TCG ACA TTC-3′
Auxiliary DNA4 (A-DNA4): 5′-SH-$(CH_2)_6$- GAA TGT CGA TCA GCG-3′
Target BRCA DNA (T-DNA): 5′-TCC CTG TTG CTG AAA CCA TAC AGC TTC ATA-3′
One-base mismatched DNA: 5′-TCC CTG TTG CTG A***C***A CCA TAC AGC TTC ATA-3′
Three-base mismatched DNA: 5′-TCC CTG ***A***TG CTG A***C***A CCA TAC AG***G*** TTC ATA-3′
Non-complementary DNA: 5′-GAA TCA CCT AGT CGC TTG CCT GAT CCA CTC-3′
Fc-DNA1:5′-TTT CAG CAA CAG GGA GCC ATT GGG TCT TGC-Fc-3′
Fc-DNA2: 5′-SH-$(CH_2)_6$-TAT GAA GCT GTA TGG-3′

2.2. Apparatus

All electrochemical experiments were performed using a CHI 660C electrochemical analyzer with three-electrode configuration (Chenhua, Shanghai, China). A glassy carbon electrode (GCE) modified with CB [7] and graphene oxide (GO), an Ag/AgCl electrode with saturated KCl solution and a platinum wire served as working electrode, reference electrode and counter electrode, respectively. The average sizes of nanoparticles were characterized by scanning electron microscope (S-4800, Hitachi, Tokyo, Japan). The pH values of 0.1 M PBS were measured by a PHS-3C pH meter (Leici Instrumental Corporation, Shanghai, China). The ultrapure water was obtained from a Millipore Milli-Q system (BIORISE, Shanghai, China).

2.3. Preparation of FcNS and HRPNS

Au nanoparticles with 10–15 nm in diameter were prepared according to the literature [30]. Then, 5 μl of 0.1 mM A-DNA1 and 5 μl of 0.1 mM C-DNA1 were combined with 10 μl of Au nanoparticles for 16 h to form FcNS. The preparation of HRPNS was realized by incubating 10 μl of Au nanoparticles with 5 μl of 0.1 mM A-DNA2, and the following reaction with 5 μl of 1 mg/ml streptavidin-HRP for 3 h.

2.4. Fabrication of the sensing platform

The bare GCE was firstly cleaned by ultrasonication in ethanol and ultrapure water for 5 min respectively, and then carefully polished to a mirror-like surface on a chamois leather with 0.05 μm and 0.3 μm alumina slurry, followed by the washing with ultrapure water. After that, 5 μl of homogeneous GO-CB [7] suspension (2:1 m/m) with ultrasonic mixing was dropped on the pretreated GCE and dried at the room temperature to form an uniform film through physical absorption, obtaining GO-CB [7]-modified electrode (which can be denoted as GCB [7]) [31]. Meanwhile, 5 μl of 0.1 mM A-DNA4, 5 μl of 0.1 mM A-DNA3 and the mixture of 5 μl of 0.1 mM C-DNA2 and 5 μl of 0.1 mM A-DNA3 were combined with HRPNS for 16 h, respectively, to form A-DNA4/HRPNS, A-DNA3/HRPNS and C-DNA2/A-DNA3/HRPNS, and then, these three nanospheres were hybridized for the synthesis of HRPNS concatamers. Subsequently, T-DNA at different concentrations was incubated with FcNS and HRPNS concatamers for 3 h, forming the complex of FcNS/T-DNA/HRPNS concatamers, which was captured by dropping 5 μl of the complex solution on GCB [7]. 5 h later, the unbounded complex were washed with ultrapure water, and dried at room temperature.

2.5. Electrochemical detection and recycle of the sensing platform

The responses of differential pulse voltammetry (DPV) were recorded in 0.1 M PBS containing 50 mM o-phenylenediamine and 50 mM H2O2 at room temperature in a range of −0.8 to −0.3 V. In order to regenerate GCB [7], the complex-modified electrode was immersed into 0.1 M PBS (pH = 12) for 3 h, followed by the washing with ultrapure water and the drying at room temperature.

2.6. Preparation of serum samples

Human serum samples were obtained from Shanghai Electric Power Hospital and centrifuged before stored in the refrigerator at −20 °C. The supernatant was diluted to 2% with 0.1 M PBS and mixed with T-DNA solution, obtaining 1×10^{-9} M, 5×10^{-9} M and 1×10^{-8} M spiked samples, respectively.

3. Results and discussion

3.1. Characterization of sensing platform

The electrochemical impedance spectroscopy (EIS) measurements were employed to monitor the impedance changes of different modified electrodes [32–36]. The electrochemical interface can be represented with the equivalent circuit shown in the inset of Fig. 1A, which consists of four elements: the ohmic resistance of the solution (R_s), the charge-transfer resistance (R_{ct}) representing the electron transfer difficulty of redox probe – $[Fe(CN)_6]^{3-/4-}$ between the solution and the electrode, the Warburg impedance (Z_w) resulting from the diffusion of ions from the bulk solution to the electrode interface and the

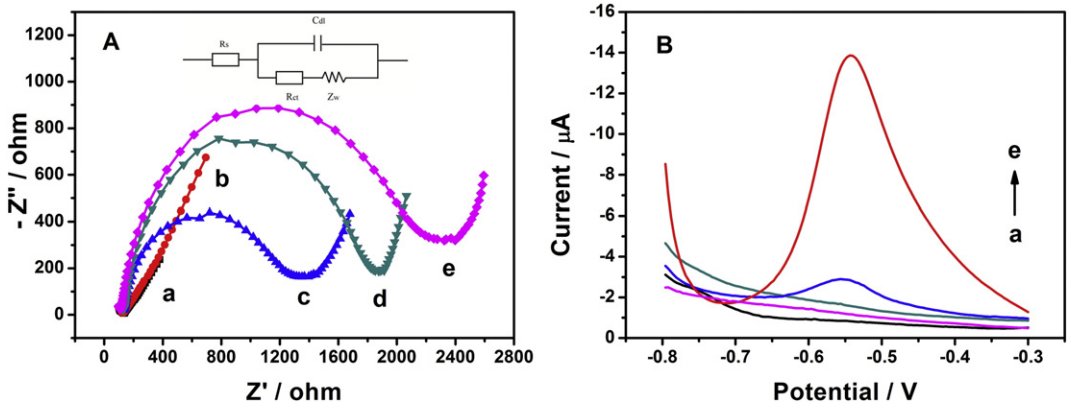


Fig. 1. (A) EIS of different modified electrodes in 0.1 M KCl containing 10 mM $Fe(CN)_6^{3-/4-}$: (a) bare GCE, (b) GCB [7], (c) GCB [7]/FcNS, (d) GCB [7]/FcNS/T-DNA/HRPNS and (e) GCB [7]/FcNS/T-DNA/HRPNS concatamers. (B) DPV curves obtained from different modified electrodes: (a) GCE, (b) GCB [7], (c)GCB [7]/FcNS, (d) GCB [7]/FcNS/HRPNS concatamers and (e) GCB [7]/FcNS/T-DNA/HRPNS concatamers.

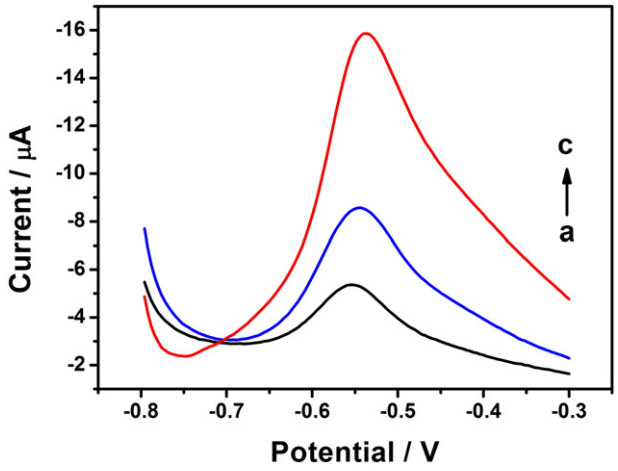


Fig. 2. DPV responses with the amplification by HRPNS concatamers and FcNS: (a)GCB [7]/Fc-DNA1/T-DNA/Fc-DNA2/HRPNS, (b) GCB [7]/FcNS/T-DNA/HRPNS and (c) GCB [7]/FcNS/T-DNA/HRPNS concatamers.

interfacial double layer capacitance (C_{dl}) between the electrode and the solution characterizing the surface condition of the electrode.

Compared with bare GCE (Fig. 1A, curve a), GCB [7] has the enhanced R_{ct}, indicating the successful chemisorption of GO-CB [7] on the electrode (Fig. 1A, curve b). The capture of FcNS (Fig. 1A, curve c), FcNS/T-DNA/HRPNS (Fig. 1A, curve d) and FcNS/T-DNA/HRPNS concatamers (Fig. 1A, curve e) by GCB [7] result in a successive increase in R_{ct} value, demonstrating the feasibility of immobilizing the complexes via host-guest interaction between Fc and CB [7] and thus the successful development of the sensing platform.

The electrochemical performance of this sensing platform was demonstrated with the technique of differential pulse voltammetry (DPV) in Fig. 1B. Clearly, GCE (curve a) and GCB [7] (curve b) have no obvious electrochemical signals. With the capture of the homogeneous hybridization complex formed by HRPNS concatamers, T-DNA and FcNS, the oxidation of o-PO catalyzed by HRP generates a significantly improved DPV signal in the presence of H_2O_2 at GCB [7]/FcNS/T-DNA/HRPNS concatamers (curve e). While, GCB [7]/FcNS/HRPNS concatamers without T-DNA just displays a signal in much low intensity (curve d), which was caused by the physical absorption of HRP. In addition, considering the electrochemical activity of Fc, the DPV response at GCB [7]/FcNS (curve c) was also recorded and no signal was presented, which shows that Fc doesn't influence the electrochemical determination. Thus, this fabricated electrochemical sensing platform can be employed for the detection of sequence-specific DNA.

3.2. Electrochemical signal amplified by HRPNS concatamers and FcNS

The effects of HRPNS concatamers and FcNS on electrochemical signal amplification were investigated and shown in Fig. 2. In comparison with GCB [7]/Fc-DNA1/T-DNA/Fc-DNA2/HRPNS (curve a), GCB [7]/FcNS/T-DNA/HRPNS (curve b) displays twice the peak current, because FcNS gathers abundant Fc-DNA through Au—S bonds, which greatly improves the capture ratio of the hybridization complex on the electrode through the host-guest interaction between CB [7] and Fc [37,38]. With the self-assembly of A-DNA3/HRPNS and A-DNA4/HRPNS, HRPNS concatamers was formed, which was confirmed by SEM (Fig. S1). The DPV signal is further amplified with the capture of FcNS/T-DNA/HRPNS concatamers (curve c) by GCB [7], due to a large amount of HRP linked to the concatamers. Therefore, the dual amplification of electrochemical signal by HRPNS concatamers and FcNS endows the high sensitivity to the DNA sensing platform.

3.3. Optimization of experimental variables

In order to further improve the detection sensitivity, the experimental variables, including the ratio between A-DNA3 and A-DNA4, pH value, the capture time between CB [7] and Fc, and the concentrations of o-PD and H2O2, have been optimized. As shown in Fig. S2A, A-DNA3 and A-DNA4 were hybridized with the ratio ranging from 3:1 to 1:3. When the ratio reaches 1:1, the signal amplification effect is optimal. Fig. S2B exhibits the effect of pH value on DPV signals. Obviously, the optimal response is obtained at pH 7.0. The time of host-guest capture between CB [7] and Fc was investigated from 1 h to 10 h. From Fig. S2C, it could be observed that the DPV signal is enhanced with increased capture time until 5 h, and then experiences a little decline. Thus, 5 h was chosen as the optimal capture time. The concentrations of o-PD and H2O2 were another key factors to affect the sensitivity of the sensing platform, which were examined from 10 mM to 100 mM ($c_{o\text{-}PD} = c_{H_2O_2}$, Fig. S2D). When the concentration of o-PD and H2O2 increases from 10 mM to 50 mM, the peak current enhances rapidly. However, when the concentration continuously increases to 100 mM, the peak current gradually trends to maintain constant. Therefore, 50 mM was selected in the experiment as the optimum concentrations of o-PD and H2O2.

3.4. Quantitative analysis of BRCA DNA

The specificity of fabricated sensing platform was investigated by capturing the complexes – FcNS/T-DNA/HRPNS concatamers containing different T-DNA sequences, including complementary DNA, one-base mismatched DNA, three-base mismatched DNA and non-

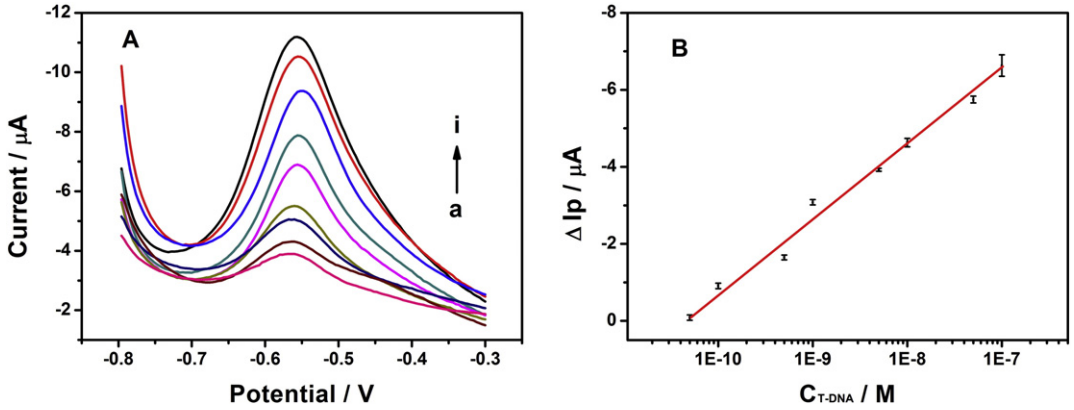


Fig. 3. (A) DPV responses at the sensing platform of GCB [7]/FcNS/T-DNA/HRPNS concatamers with T-DNA at different concentrations: (a) 0 M, (b) 5×10^{-11} M, (c) 1×10^{-10} M, (d) 5×10^{-10} M, (e) 1×10^{-9} M, (f) 5×10^{-9} M, (g) 1×10^{-8} M, (h) 5×10^{-8} M and (i) 1×10^{-7} M. (B) Calibration curve of peak currents towards different concentrations of T-DNA.

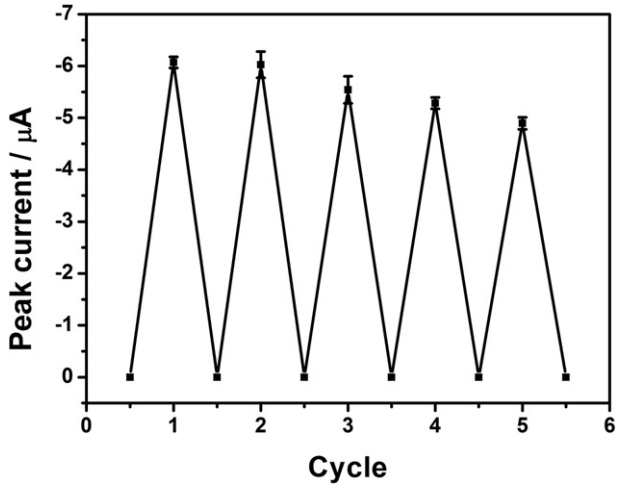


Fig. 4. Recyclability of the electrochemical sensing platform for 1×10^{-8} M T-DNA detection.

complementary DNA. The highest peak current is observed by hybridizing with complementary DNA (column a) in Fig. S3. While, the signal intensities obtained from one-base mismatched DNA (column b) and three-base mismatched DNA (column c) are only 39.90% and 23.54% of that from complementary DNA (column a), respectively, and the hybridization with the non-complementary DNA (column d) results in a negligible response, generated by the physical adsorption of HRP. The reason is that the hybridization efficiency decreased along with the increasing of mismatched base number. The significant current distinction reveals that this sensing platform has excellent specificity for BRCA DNA against base mismatched sequences, due to the intrinsic recognition ability of DNA.

The DPV responses at the fabricated sensing platform were exhibited with T-DNA at various concentrations under the optimal experimental conditions. As indicated in Fig. 3A, the signal intensity increases with the increasing of T-DNA concentration ranging from 5×10^{-11} M to 1×10^{-7} M. From the calibration curve for the quantitative detection of T-DNA in Fig. 3B, the regression equation is obtained as ΔIp (μA) $= -1.922 \lg c_{T\text{-}DNA}$ (M) - 19.96 with a correlation coefficient of 0.993. The detection limit is as low as 25 pM (S/N = 3). Compared with other strategies for BRCA DNA detection (Table S1) [39–42], this fabricated sensing platform has a wider linear range and a higher sensitivity.

3.5. Recyclability of sensing platform

Due to the host-guest interaction and dissociation by pH change between CB [7] and Fc, the sensing platform is endowed the property of recyclability for the detection of BRCA DNA. As shown in Fig. 4, the peak current is 6.07 μA with capturing FcNS/T-DNA/HRPNS concatamers in the first cycle, and it is down to almost zero after washing with alkaline solution [29], demonstrating that Fc is out of the CB [7] cavities, and the dissociation is complete. After five cycles, the peak current remains 80.66% of the initial value, demonstrating that the recyclability of sensing platform for quantitative analysis of BRCA DNA could be achieved with simple pH control.

Table 1
BRCA DNA detection in human serum samples using the sensing platform.

Samples	Spiked DNA concentration (nM)	Measured DNA concentration (nM)	Recovery (%)
1	1	1.03 ± 0.03	103.4
2	5	5.31 ± 0.16	106.3
3	10	9.86 ± 0.13	98.6

In addition, the reproducibility of the sensing platform was estimated by five different electrodes and the relative standard deviation (RSD) is 3.43%, indicating the good reproducibility. Meanwhile, DPV responses of the sensing platform have no obvious changes after storage at 4 °C for one month, showing the satisfactory stability.

3.6. Real sample measurements

In order to investigate the practical application of the fabricated sensing platform in the clinical analysis, the DPV determination of human serum samples was performed under the optimized conditions, as shown in Table 1. With the standard addition method, the recoveries of BRCA DNA in the real samples are obtained in the range of 98.6%–106.3% ($n = 3$), demonstrating the reliability and applicability of this sensing platform in real human serum sample analysis.

4. Conclusions

In conclusion, a sensitive and recyclable sensing platform for the electrochemical detection of BRCA DNA was fabricated based on host-guest recognition and homogeneous DNA hybridization. With BRCA DNA as target sequence introduced into the solution, FcNS was hybridized homogeneously with HRPNS concatamers, forming a hybridization complex, which was immobilized on the electrode by the host-guest interaction between CB [7] and Fc. Under the optimized conditions, the significantly amplified oxidative current of o-PD by FcNS and HRPNS concatamers in the presence of H_2O_2 increased logarithmically in the DNA concentration range of 1×10^{-7} M–5×10^{-11} M with the detection limit as low as 25 pM (S/N = 3). This sensing platform exhibited also impressive specificity towards BRCA DNA, compared with the sequences containing base mutation. Following the DPV detection, the captured complex was dissociated from the electrode surface with pH control, achieving the recyclable property of the sensing platform. Moreover, this platform was exploited to detect BRCA DNA in real human serum samples, providing a reliable and facile approach for the early diagnosis of breast cancer.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jelechem.2016.11.027.

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