Analytical Methods

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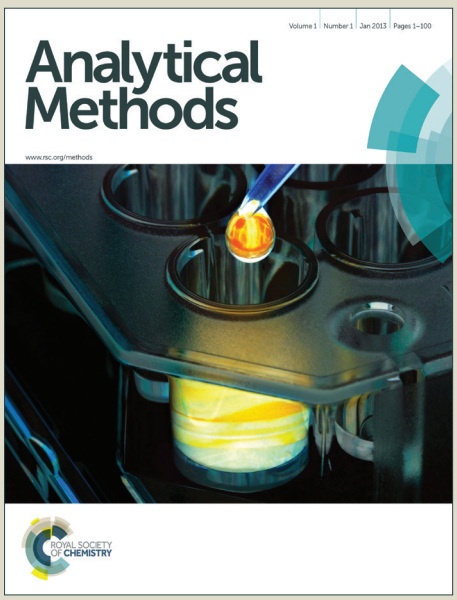

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Electrochemical Detection of DNA by Using "Pd/GO Label Copper Stain" for Signal Amplification

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Abstract:

To overcome the problem of non-specific silver precipitate occurred in the traditional silver staining, this work presents a new strategy of signal amplification by labeling the biological molecule with Pd/GO nanoparticles (NPs), which further act as catalysts to reduce copper ions to metallic copper to enhance the signal (denoted as "Pd/GO label copper stain" later). Based on this strategy, the electrochemical detection of a single-base mutation associated with the breast cancer gene TOX3 is specially studied by employing differential pulse voltammetry (DPV). The analytical performance of this system shows that after 15 min of copper staining there is a linear relationship between the peak current resulting from the oxidative dissolution of copper deposit and the logarithm of target DNA concentration in the range of 10 μM to 1 pM. The limit of detection can reach 1 pM, which benefits from the high catalytic activity of Pd/GO NPs along with low background level of "Pd/GO label copper stain". Therefore, this process can be expected to be a good alternative to the silver staining used in nanomaterial-based signal amplification strategies in future.

Keywords: signal amplification, copper staining, Pd/GO nanoparticle, label, electrochemical detection, breast cancer gene

1. Introduction:

In the past decades, nanomaterial-based signal amplification strategies have played an important role in the construction of an ultrasensitive DNA sensor.[1] Among them, gold label/silver staining amplification technique (denoted as gold label silver stain later) has attracted considerable attention since it was first presented by Holgate et al. in 1983.[2] This method is based on the idea that a DNA hybridization event can be marked by attaching gold nanoparticles (NPs), which further act as catalysts to reduce silver ions to metallic silver to enhance the signal. This signal was then detected by scanometric array,[3] conductivity measurements,[4] dissolution of silver deposit and their electrochemical detection by stripping voltammetry[5], or microgravimetric quartz crystal microbalance measurements.[6] However, despite being a versatile technique, the silver staining always has some inherent limitations, such as limited reproducibility and low signal-to-noise ratio, resulting from the non-specific precipitate of silver.[7] During silver staining, the reducing agent that triggers silver deposition is difficult to control, and nonspecific silver deposition on the substrate cannot be avoided. To alleviate this problem, one of the solutions is to replace the silver enhancer solution every 2 or 3 min to avoid the formation of silver particulates in solution during the experiment.[3] Therefore, in order to overcome the above limitations, it is of interest to construct the similar amplification strategy as "gold label silver stain" with more stability.

As an important industrial process used to deposit a coating of copper on a substrate, the electroless copper plating, which is also an auto-catalytic reaction similar to the procedure of "gold label silver stain" introduced above (Unlike electroplating, "the electroless plating" is known as chemical or auto-catalytic plating, involving the deposition of metals from solutions onto surfaces without applying an external electric voltage. This method is based on the chemical reduction of metal ions in the solution to metallic atoms on the surface through a reducing agent in the solution), has been widely used for the fabrication of printed circuit boards and other electronic devices over 40 years.[8] In this

procedure, Pd NPs pre-adsorbed in the substrate are always used as the catalyst to initiate the electroless copper deposition reaction. So it can be envisaged that this reaction can also be used to replace silver staining to enhance the signal as long as it encompasses high sensitivity and high selectivity while maintaining the high stability. However, although Pd NP as the label has already received attentions in DNA detection,[9] it still remains a great challenge to achieve highly active Pd NPs. As we know, Pd NPs are usually synthesized in the presence of capping agents (such as 11-mercaptoundecanoic acid) to protect them from aggregation.[9b] As for catalytic application, such capping agents at the surface of Pd NPs would act as poisons to partly or fully dampen the catalytically active sites. Recently, graphene oxide (GO) has been extensively used as a suitable matrix for the synthesis of various metal NPs because of its high surface area, distinguished electrical, and chemical performances.[10] In order to improve the catalytic activity of Pd NPs, the clean and well-dispersed Pd/GO nanocomposites (Pd/GO NPs) were used to label DNA instead.

Meanwhile, electrical detection of DNA using nanoparticle labels in combination with metal enhancement represents an interesting alternative to fluorescence readout schemes.[11] This electrical method is also hampered by unspecific metal deposition, resulting in a lower sensitivity of the assay. Based on the above consideration, herein, we present the electrochemical DNA sensing by using the strategy of "Pd/GO label copper stain" for signal amplification. As a target model, the detection of a single-base mutation associated with the breast cancer gene TOX3 is selected. The medical reports have indicated that the mutations in TOX3 would dramatically increase the risk of breast cancer.[12] The basic principle involved in the proposed method is schematically displayed in Fig. 1A. it can be found that the electrochemical DNA detection assay based on "Pd/GO label copper stain" mainly consists of four steps: (a) immobilization of single-stranded (ss) probe DNA (DNA_{probe}) on the p-aminobenzoic acid (ABA)-modified GCE, which was assembled via carbon-nitrogen linkage formed by cyclic voltammetry (CV); (b) hybridization

with target ss DNA, and then labeled by an ss DNA_{label}-functionalized Pd/GO NPs through a sandwiched hybridization; (c) catalytic precipitation of copper onto Pd/GO label in the copper enhancer solution; and (d) electrochemical differential pulse voltammetry (DPV) detection of the amount of copper atoms deposited around Pd/GO NPs.

2. Experimental Section

2.1 Materials

N-hydroxysuccinimide (NHS), 2-(N-mrpholino) ethanesulfonic acid (MES), 1-ethyl-3- (3-dimethylaminopropyl) carbodimide hydrochloride (EDC), p-aminobenzoic acid (ABA), silver enhancer solution A, and silver enhancer solution B were purchased from Sigma-Aldrich. Trisodium citrate ($Na_3C_6H_5O_7$), sodium chloride (NaCl), NaOH, $CuSO_4 \cdot 5H_2O$, and $KNaC_4H_4O_6 \cdot 4H_2O$, were obtained from Shanghai Chemical Reagent Corporation. All chemicals were used as received. Oligonucleotides were purchased from Shanghai Sangon Biotechnology Company. Milli-Q water (18.2 $M\Omega.cm^{-1}$) was used in all experiments.

2.1 Preparation of ss DNA_{label}-modified Pd/GO NPs

Pd/GO NPs were firstly prepared according to the literature.[10a] With the help of the sonication, 1 mg of Pd/GO NPs was then dispersed in 1 mL of 0.1 M MES buffer (pH 6). To the above mixture, the EDC solution (10 mg/mL) and Sulfo-NHS solution (10 mg/mL) were added, separately. The activation reaction lasted for 30 min. After that, the activated Pd/GO NPs were collected by centrifugation at 10000 rpm for 4 min under 4 ℃, and redispersed in 1 mL of icy PBS buffer (pH 7.4). Next, 30 μL of 100 μM ss DNA_{label} (5'-AGGACCTCTTATTTTTTT-3'-NH_2) was added into the above solution, and the reaction was kept for 24 h under 4 ℃. After the reaction, the unreacted DNA has been separated from the mixture by the ultracentrifugation and washed with PBS buffer for 3 times.

2.2 Fabrication of the sensing electrode and sandwiched hybridization

To fabricate the sensing electrode, the attachment of ss DNA_{probe}

(NH_2-5'-TTTTTTGTACCATACTGA-3') to ABA-modified GC electrode's surface (electrode diameter: 3 mm) was conducted according to the reported method.[13] The target DNA was then detected by the sandwiched hybridization as the following procedure: the sensing electrode GCE-ABA/DNA_{probe} was firstly immersed in ss DNA_{target}-containing reaction buffer (0.5×TBE) at 37 °C for 0.5 h, by which DNA_{target} hybridized GCE-ABA/DNA_{probe} (GCE-ABA/DNA_{probe}/DNA_{target}) was obtained. After careful rinsing with the washing buffer, the prepared electrode was then immersed in 100 μL of ss DNA_{label}-modified Pd/GO NPs solution at 37 °C for 0.5 h, yielding the Pd/GO-DNA_{label} hybridized GCE-ABA/DNA_{probe}/DNA_{target}. Finally, the resulting electrode was rinsed with the washing buffer and dried under a stream of nitrogen. It should be pointed out that for the complementary sequence of ss DNA_{target} (12 bases) both of the melting temperatures (Tm) are about 36.5 ^{o}C.

Table 1 The sequence of ssDNA_{target}

ssDNA_{target}	**Sequence (5′→3′)**
Complementary	ATAAGAGGTCCTCTTTAAGACATGACAATTTCAGTATGGTAC
One-base mismatch	ATAAGAGGTCCTCTTTAAGACATGACAATTTCAGT**T**TGGTAC
Two-base mismatch	ATAAGAGGTCCTCTTTAAGACATGACAATTTCAGT**TA**GGTAC
Three-base mismatch	ATAAGAGGTCCTCTTTAAGACATGACAATTTCAG**ATA**GGTAC

2.3 Signal amplification through the electroless deposition of copper (Copper staining)

For the copper enhancement, the electrode obtained above was further immersed in the optimized copper enhancer solution for 15 min at room temperature. After that, the resulting electrode was rinsed with water to remove any residual copper enhancer solution. Prior to use, the fresh copper enhancer solution was prepared by mixing 1 mL of solution A and 12 μL of solution B, simultaneously (Solution A was prepared by dissolving 0.0875 g of $CuSO_4 \cdot 5H_2O$, 0.1693 g of $KNaC_4H_4O_6 \cdot 4H_2O$, and 0.4 g of NaOH in 10 mL of water (pH 13.5). Solution B is formaldehyde solution (37 wt. % in H_2O)).

2.4 Electrochemical characterization

Electrochemical measurements were carried out in a standard three-electrode cell

with an Autolab electrochemical workstation. A platinum wire and Hg/Hg_2Cl_2 (SCE) were used as the counter electrode and reference electrode, respectively. DPV measurement were carried out in a PBS (pH7.4) containing137 mM NaCl, 2.7 mM KCl, 10 mM Na_2HPO_4, and 2 mM KH_2PO_4 by using NOVA software, and the potential range was -0.8 V-0.8 V.

2.5 Characterization

The morphology and size of the samples were analyzed by TEM JEOL-3010. Before the characterization, the sample for TEM was prepared by placing a drop of the colloidal dispersion of Pd/GO NPs onto a carbon-coated copper grid followed by naturally evaporating the solvent. UV-vis absorbance spectrum of ss DNA_{label}-Pd/GO aqueous solution was recorded on a Shimadzu spectrophotometer between 200 and 650 nm wavelength. The sample was measured in a 1-cm quartz cuvette using the corresponding pure solvent as a reference.

3. Results and Discussion

In the experiment, Pd/GO NPs were prepared by the redox reaction between $PdCl_4^{2-}$ and GO according to the literature.[10a] From Fig. 1B, the well-dispersed Pd NPs with the average size of about 2.1 nm can be seen on the surface of GO (see Supplementary Fig. S1). Their surfaces were then covalently modified with ss DNA_{label} using EDC coupling chemistry. From the UV-vis spectroscopy of resulting ss DNA_{label} modified Pd/GO NPs (see Supplementary Fig. S2), the typical absorption signal (at 260 nm) from DNA is observed compared with that of pure Pd/GO NPs, demonstrating that ss DNA_{label} was successfully linked to the surface of Pd/GO NPs.[14] Additionally, it is noteworthy that for the commercial electroless copper plating solutions NaH_2PO_2 is generally used as a reducing agent,[15] in which small of phosphorus could also be co-deposited in the deposit to form Cu-P alloy. This will affect the subsequent oxidative dissolution of copper during the DPV measurements. Thus, in the case of our copper enhancer solution, formaldehyde was preferred as the reducing agent over NaH_2PO_2, and its components have been optimized again with

the aim to accelerate the rate of copper deposition under the catalysis of Pd/GO NPs (see Supplementary Fig. S3).

In order to straightforwardly compare the performance of "Pd/GO label copper stain" with that of "gold label silver stain", we firstly examined the color change of enhancer solution with the progress of reaction with (or without) the addition of the same amount (2 mM, 10 μL) of catalyst Au NPs (for silver deposition) or Pd/GO NPs (for copper deposition), respectively. As shown in Fig. 1C, for "Pd/GO label copper stain", it can be found that after 5 min the color of enhancer solution has changed from blue to brownish black due to the deposit of copper, indicating that Pd/GO NPs possess high catalytic activity for copper deposition reaction. As the reaction proceeded, the color of enhancer solution had gradually become characteristic copper red. After 30 min of reaction, even some bubbles adsorbed on the wall were found due to the production of H_2. Meanwhile, in the control group, no obvious color change was observed, demonstrating that the copper enhancer solution has the high stability and the deposition reaction only occurs in the presence of catalyst Pd NPs. For "gold label silver stain", however, although the silver deposition reaction performed high sensitivity to Au NPs and the color of silver enhancer solution had already changed from colorless into black in 5 min, the silver enhancer solution was not stable. In the corresponding control group without the presence of Au NPs, it can be observed that the color of silver enhancer solution also turned into brown, which is attributed to the occurrence of non-specific silver precipitate. The electroanalytical performance of copper deposition under the catalysis of Pd/GO NPs was also investigated by DPV measurements in advance. As illustrated in Fig. 2A, for the electrode precoated with Pd/GO NPs (1.5 μg/mL, 5 μL), there is a strong anodic current peak resulting from the oxidative dissolution of copper at around -0.11 V after copper staining for 15 min. At the same staining time, no obvious anodic current peak was observed for bare electrode in the control group, which further illustrates the high stability of the copper enhancer solution, well consistent with the results obtained in above colorimetric reaction. As a control, under the similar condition, the anodic current peak resulting from the oxidative dissolution of silver was observed for the bare electrode after being

immersed in silver enhancer solution for 5 min (see Supplementary Fig. S4). The above results clearly demonstrate the shortcoming of traditional silver enhancement and further verify the advantage of proposed "Pd/GO label copper stain" as signal amplification.

To further optimize the experimental condition, the influence of copper staining time on the signal amplification was studied. As shown in Fig. 2B, it can be found that with the increase of the staining time the peak currents dramatically increased in 5 min and then tended to be steady after 15 min deposition reaction, which is thus chosen for the optimized deposition time in following experiment. As we know, the peak current is generally proportional to the rate of the oxidative dissolution of copper, which mainly depends on the surface area of deposited copper layer on the electrode. Meanwhile, the excessive deposits of copper just lead to the increase in the thickness of the deposited copper layer and have little effect on the surface area of copper. Therefore, that is why the peak current tends to be steady after 15 min of deposition reaction. In addition, the effect of different amount of Pd/GO NPs on the peak currents was examined. As shown in Fig. 2C, at the same deposition time, with the increase in the amount of Pd/GO NPs coated on the electrode the peak current increases. Moreover, from the inset in Fig. 2C, we can see that the increase of the peak current is nearly linear in the range of 0.01 to 8 μg/mL. This lays a good foundation for the future quantitative analysis.

Before assessing the performance of "Pd/GO label copper stain" in electrochemical detection of DNA, we have characterized the GCEs modified with ss DNA_{probe} step by step using CV and electrochemical impedance spectroscopy (EIS). The corresponding results were given in Fig. S5, Fig. S6, and Fig. S7 respectively, clearly demonstrating that the ss DNA_{probe} has been successfully attached to the surface of GCE (See them in the Supplement). To further evaluate the single-base-pair discriminating capability of both the as-designed DNA biosensor and Pd/GO label, four target probes with different DNA sequence were characterized with a sandwiched hybridization according to the procedure described in the Experimental Section. DPV responses were obtained after successive hybridization with ss DNA_{label}-Pd/GO labels

followed by copper staining. In the procedure, the concentration of the above sequences was kept constant at 10 μM in each experiment. Fig. 2D respectively shows the peak currents of the above-mentioned four target DNA sequences and blank solution. The complementary sequence exhibited the highest peak current (2.13 μA) among the one-base mismatch target (0.618 μA), two-base mismatch target (0.510 μA), and three-base mismatch target (0.215 μA). The blank solution without target DNA also exhibited a peak current attributed to non-specific absorption (0.047 μA). The relative ratio of complementary: one-base mismatch: two-base mismatch: three-base mismatch is described as 10: 2.8: 2.4: 1, which means that the resulting ss DNA_{label}-Pd/GO conjugates have the high single base pair mismatch-discrimination capability and the subsequent staining procedure doesn't affect the result of hybridization behavior of oligonucleotides.

The sensitivity of this signal amplification strategy was investigated by detecting the complementary target DNA with various concentrations. The different current value obtained in the DPV response after hybridization of probe with target was recorded with three repetitive measurements. As illustrated in Fig. 3A, the amount of target DNA bound to the GCE/ABA-DNA_{probe} surface was reflected by the magnitude of the anodic peak current. This result was expected, as an increasing concentration of target DNA translates into an increasing amount of captured Pd/GO NPs by the formation of sandwich-layered structure. From Fig. 3B, we can also find that the peak current of the sensor is linearly increased with the logarithm of the target DNA concentration in the range of 10 μM to 1 pM (the linear relationship can be described as $I=0.9259 + 0.2612\times\log c$ with the correlation coefficient of $R=0.998$, where I is the peak current and log c is the logarithm of the target DNA concentration). The detection limit (LOD) of target DNA reaches 1 pM considering the result that its current (0.149 μA) is three times higher than that of the background (S/N=3). When compared to others systems that employed gold NPs for DNA labeling and further used silver staining to enhance the electrochemical signal (As shown in Table 1, for most of methods, the detection limit is more than 10 pM),[5a,11] the proposed strategy of signal amplification herein has the lower detection limit due to the high catalytic

activity of Pd/GO NPs along with low background level of "Pd/GO label copper stain".

4. Conclusions

In summary, as the new strategy of signal amplification, the copper staining with high stability was presented instead of the traditional silver staining. The electrochemical detection of a single-base mutation associated with the breast cancer gene TOX3 is specially studied by employing this strategy. The analytical performance of this system shows that after 15 min of copper staining there is a linear relationship between the anodic peak current and the logarithm of target DNA concentration in the range of 10 μM to 1 pM and LOD can reach 1 pM, which benefits from the high catalytic activity of Pd/GO NPs along with low background level of "Pd/GO label copper stain". As the strategy of signal amplification, this procedure can be expected to be suitable for other analysis techniques, such as scanometric DNA array, and quartz crystal microbalance.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online.

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Figure Caption

Fig. 1 (A) Schematic illustration for the electrochemical detection of DNA by using "Pd/GO label copper stain"; (B) TEM and HRTEM images of the as-prepared Pd/GO nanocomposites; (C) Photographic images that show the time-dependent color changes of copper enhancer solution without (a) or with (b) the addition of Pd/GO NPs (10 μL, 2 mM). As a control, the corresponding color changes of silver enhancer solution without (c) or with (d) the addition of Au NPs (10 μL, 2 mM) were also given.

Fig. 2 (A) DPV response curves of both bare GCE and the GCE with its surface precoated with Pd/GO NPs after being immersed in copper enhancer solution for 15 min. (B) Effects of copper staining time on the peak current. (C) Effect of the concentration of Pd/GO NPs on the DPV response of deposited copper with the staining time of 15 min. (D) DPV response curves of the electrochemical DNA sensor after the sandwiched hybridization with various target ss DNA.

Fig. 3 (A) DPV response curves of the electrochemical DNA sensor at various complementary target DNA concentrations; (B) Linear relationship between the peak current and logarithm of target DNA concentration. The error bars represent one standard deviation from the average.

Table 1 Performance comparison of various electrochemical detection of DNA via "gold label silver stain" with that via "Pd/GO label copper stain"

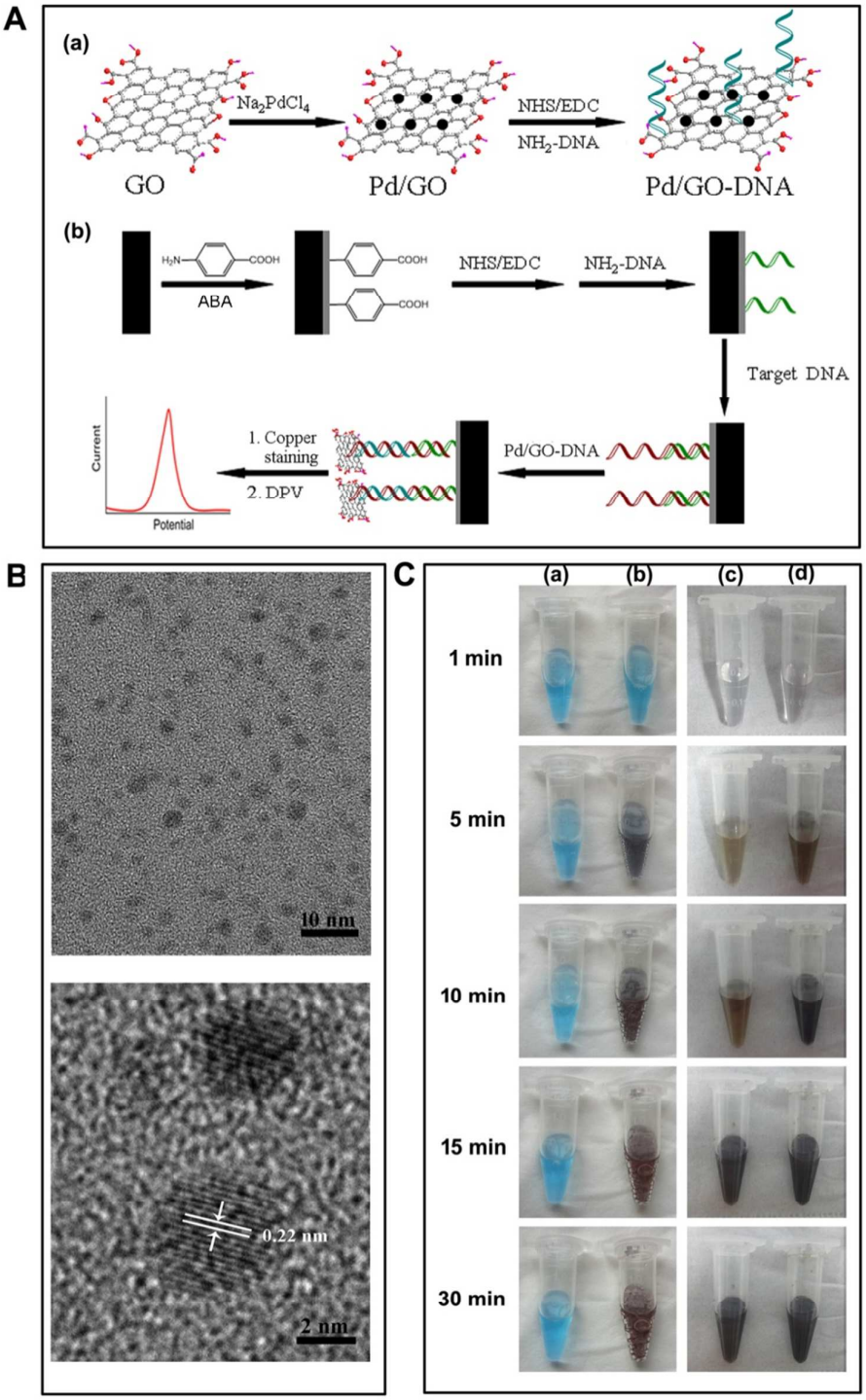

Fig. 1

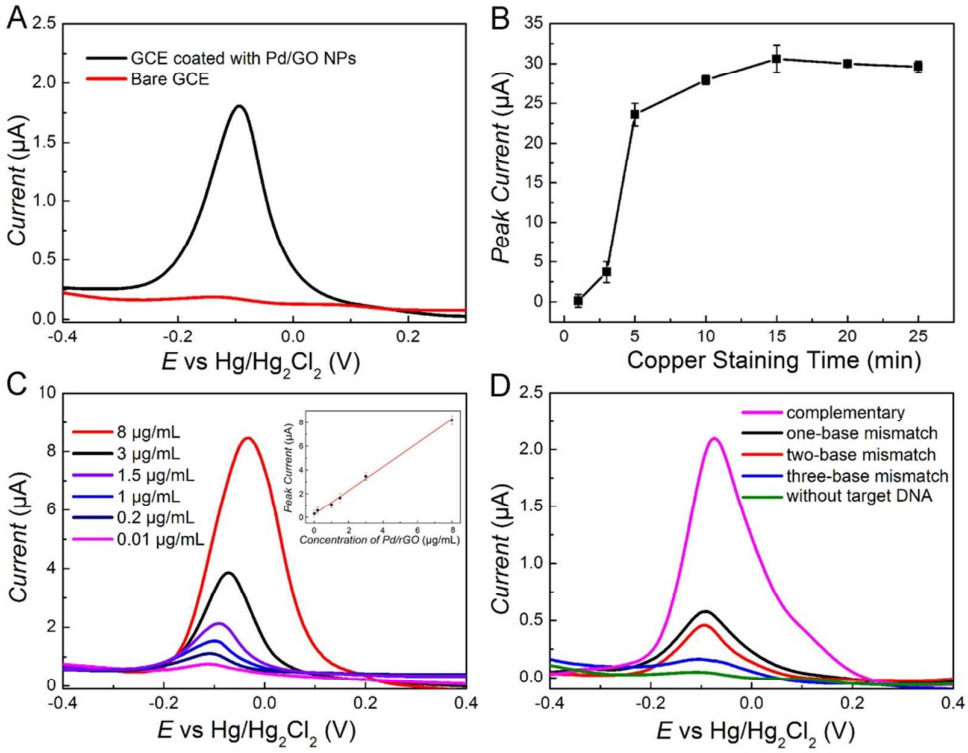

Fig. 2

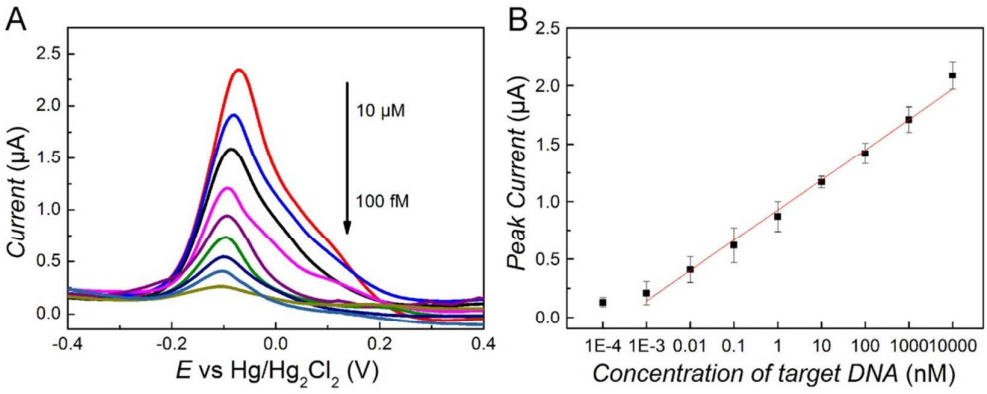

Fig. 3

Detection technique	Type of assay	Linearity range (M)	Detection limit (M)	References
DPV	direct	10^{-10}-10^{-8}	50 pM	11a
PSA	direct	10^{-11}-10^{-8}	~10 pM	11e
Conductivity*	direct	No Data	5 pM	11d
DPV	sandwich	2×10^{-10}-2×10^{-7}	70 pM	5a
DPV	sandwich	10^{-12}-10^{-5}	1 pM	This work

PSA: Potentiometric stripping analysis; DPV: differential pulse voltammetry; Conductivity*: Conductivity measurement.

Table 1

Table of contents entry

Electrochemical Detection of DNA by Using "Pd/GO Label Copper Stain" for Signal Amplification

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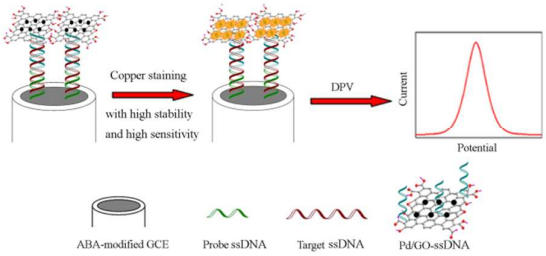

A new strategy of signal amplification by labeling DNA with Pd/GO nanoparticles, which further act as catalysts to reduce copper ions to metallic copper to enhance the signal, was presented.