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ORIGINAL PAPER

Carbon nanotubes/$(pLys/dsDNA)_n$ layer-by-layer multilayer films for electrochemical studies of DNA damage

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Abstract Carboxylic group-functionalized carbon nanotubes (c-CNT) were modified on the surface of carbon paste electrode to obtain a conducting precursor film. Positively charged poly-L-lysine (pLys) and negatively charged double-stranded DNA (dsDNA) were alternately adsorbed on the c-CNT-modified electrode, forming $(pLys/dsDNA)_n$ layer-by-layer (LBL) films. Cyclic voltammetry and electrochemical impedance spectroscopy of the electroactive probe $[Fe(CN)_6]^{3-/4-}$ could give the valuable dynamic information of multilayer films growth. The oxidative DNA damage induced by cadmium ion (Cd^{2+}) in the LBL multilayer films was studied by differential pulse voltammetry (DPV) with methylene violet (MV) as the intercalation redox probe. The electrochemical signals of MV on the multilayer films were effectively amplified via LBL technology. The specific intercalation of MV into dsDNA base pairs and the amplified electrochemical response of MV, combined with the unique feature of loading reversibility of MV in the DNA layer-by-layer films, made the difference in DPV response between the intact, and damaged dsDNA films become pronounced. This biosensor exhibited that the $(pLys/dsDNA)_n$ films could be utilized for investigations of DNA damage.

Keywords Layer-by-layer · DNA damage · Poly-L-lysine · Cadmium

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Introduction

In recent years, electrochemical techniques arouse increasing interests in detecting DNA damage because of their simplicity, fast response, high sensitivity, and low cost [1–6]. To detect DNA damage by electrochemistry, the natural DNA is usually immobilized on the surface of electrode modified with various chemicals or materials, forming DNA films. Several immobilization approaches have been developed, including adsorption [7], casting [8], covalently attachment [9], and LBL assembly [10, 11]. Compared with other film-forming methods, the LBL assembly demonstrates obvious advantages, such as the precise control of film thickness at molecular or nanometer level, the controllable layer sequence and composition according to a predesigned architecture, and the simplicity in film assembly. Rusling et al. constructed films of $[Ru(bpy)_2(PVP)_{10}Cl]Cl$ {PVP = poly(4-vinyl-pyridine)} and dsDNA by LBL alternate electrostatic assembly [10]. The redox polymer $[Ru(bpy)_2(PVP)_{10}Cl]Cl$ as an inner layer in films was used to catalyze the electrooxidation of guanine bases of dsDNA in the outer layers. This film architecture provided a reagentless sensor for toxicity screening of new chemicals based on detection of DNA damage. Later on, films containing $[Os(bpy)_2(PVP)_{10}Cl]^+$ and $[Ru(bpy)_2(PVP)_{10}Cl]^+$ metallopolymers were assembled layer-by-layer on pyrolytic graphite electrodes to obtain sensors for selective detection of oxidized DNA [11].

Recently, poly-L-lysine has been used for the modification of the electrode and applied for electrochemical determination, owing to its versatility and easiness of the preparation [12–14]. Furthermore, the amino groups of pLys can form an electrostatic affinity with the phosphate skeleton of DNA molecule to immobilize DNA [15, 16]. Jiang et al. established an electrochemical biosensor based

on pLys/c-CNT films for the detection of the transgenic gene fragment in the genetically modified plants by electrochemical impedance spectroscopy. The pLys/c-CNT films modified electrode exhibited very good conductivity. DNA probes were easily immobilized on the pLys films via electrostatic adsorption. This DNA electrochemical biosensor showed simplicity, good stability, fine selectivity, and high sensitivity [17].

One of the most important strategies of electrochemical methods for detecting DNA lesion is based on the redox signal of electroactive probes that have specific interactions with DNA [18–22]. Methylene violet (MV) features a planar phenazine ring (Fig. 1), which is expected to facilitate intercalation of MV into the relatively nonpolar interior DNA helix. Xie et al. used MV as the indicator for the sensitive detection of the hybridization of DNA [23].

Herein, LBL films of negatively charged natural DNA and positively charged pLys were assembled on carboxylic group-functionalized carbon nanotubes (c-CNT) modified electrode surface. The assemblies were characterized using cyclic voltammetry (CV) and electrochemical impedance spectroscopy (EIS) in ferricyanide/ferrocyanide solution. MV was loaded on the multilayer films as an electroactive probe to detect the damage of DNA. The CVs of MV on the electrode surface showed that the signal of MV was amplified owing to the DNA LBL assembly. $CdCl_2$ was chosen as the model agent for natural DNA damage. Differential pulse voltammetric (DPV) measurements of the loaded MV were used to detect DNA lesion in $CdCl_2$ solution. Compared with the intact DNA films, the Cd-damaged DNA films showed an obvious decrease of DPV peak currents of the loaded MV.

Experimental

Apparatus and reagents

A CHI 660C electrochemical analyzer (Shanghai CH Instrument Company, China), which was in connection with a working electrode (carbon paste electrode (CPE)), an Ag/AgCl reference electrode and a platinum wire auxiliary electrode, was used for the electrochemical measurements. The pH values of all solutions were measured by a model pHS-25 digital acidimeter (Shanghai Leici Factory, China).

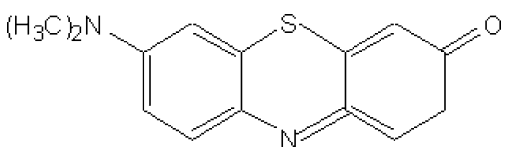

Fig. 1 The molecular structure of methylene violet

The following reagents were all used as received: Carbon powder and paraffin were purchased from Shanghai Colloid Laboratory and Shanghai Hua Ling Healing Appliance Factory, respectively. Single-walled carbon nanotubes were purchased from Shenzhen Nanotech Port Company (Shenzhen, China); poly(L-lysine) hydrobromide (pLys, MW66,700 g/mol) from Sigma (St. Louis, MO, USA); and herring sperm dsDNA from Sigma. Sodium dodecylsulfate (SDS) and MV ($C_{14}H_{12}ON_2S$) were both purchased from Shanghai Reagent Company; 18.2 MΩ cm aquapro ultrapure water (Ever Young Enterprises Development. Co., Ltd., Chongqing, China) was used to prepare all aqueous solutions and for rinsing. Before use, all of the glassware were cleaned with freshly prepared aqua regia (HNO_3/HCl) 1:3, *v*/*v*, rinsed abundantly with ultrapure water, and dried.

Preparation and modification of the working electrode

Single-walled carbon nanotubes were suspended in a 3:1 concentrated HCl (12 mol/L)/HNO_3 (16 mol/L) mixture and sonicated in a water bath for 5 h, then filtered and washed with ultrapure water until the filtrate became neutral, and finally dried under vacuum. The obtained carboxylic group-functionalized carbon nanotubes were denoted as c-CNT; 1 mg c-CNT was added into 1 mL *N*, *N*-dimethylformamide (DMF) to prevent from rapid coagulating and keep well dispersed.

The mixture of 3 g graphite powder and 1 g solid paraffin was heated at 70°C for 2 h and mixed by hand to obtain homogenous carbon paste, which was then tightly packed into a glass tube from one end, and a copper wire was introduced into the other end for electrical contact. A fresh electrode surface was generated rapidly by extruding a small plug of the paste with a stainless steel rod and smoothing the resulting surface on a white paper; 5 μL of 1 mg/mL c-CNT solution (1 mg c-CNT in 1 mL DMF) was dripped onto the fresh surface of the CPE and naturally dried in the air to form CPE/c-CNT. The electrode was placed in the pLys of pH8.0 PBS solution for 30 min to obtain pLys adsorptive layer on the surface. The positively charged pLys layer was the anchor for the electrostatic deposition of dsDNA (1.0 g/L in 5.0 mmol/L Tris buffers (pH7.0) containing 0.05 mol/L NaCl) for 500 s at 0.5 V. The optimal potential and time for the electrodeposition of dsDNA were tested by a comparative study with different potentials (0.3, 0.4, 0.5, 0.6, 0.7, and 0.8 V) and different times (100, 200, 300, 400, 500, and 600 s); 0.5 V and 500 s were appropriate, because the multilayer film obtained under these conditions was mechanically robust and stable during all of the measurements. The above manipulations were repeated when $(pLys/dsDNA)_n$ LBL films for $n > 1$ were prepared.

MV-loaded $(pLys/dsDNA)_n$ film, which was designated as $(pLys/dsDNA)_n$-MV, was constructed by immersing $(pLys/dsDNA)_n$ film electrode in 2.0×10^{-5} mol/L MV of pH7.0 Britton–Robinson (B-R) buffer solution containing 0.02 mol/L NaCl with stirring for at least 2 h until the loading equilibrium or the steady state was reached. The $(pLys/dsDNA)_n$-MV film was rinsed with B-R buffer, dried with nitrogen stream, and placed in B-R buffer of pH7.0 for DPV scans. The state of $(pLys/dsDNA)_n$-MV at this stage was defined as state I. The $(pLys/dsDNA)_n$-MV film was then kept in B-R buffer overnight, making most of the loaded MV diffuse off the films, and DPV was subsequently performed in B-R buffer. The state of $(pLys/dsDNA)_n$-MV at this stage was defined as state II.

For DNA damage experiments, the $(pLys/dsDNA)_n$-MV film at state II was incubated in 4.0×10^{-5} mol/L $CdCl_2$ solution with stirring for a certain time. After being rinsed with ultrapure water, the film was soaked in 2.0×10^{-5} mol/L MV solution again for 2 h to reload MV until the steady state was reached. The electrode was then placed in pH7.0 B-R buffer for DPV scans. The state of damaged $(pLys/dsDNA)_n$-MV film at this stage was defined as state III. Each measurement was repeated at least three times.

The DPVs were recorded in the pH7.0 B-R buffer with pulse amplitude 50 mV, pulse width 60 ms, and pulse period 0.2 s. The CVs were performed in 1.0 mmol/L $K_3Fe(CN)_6/K_4Fe(CN)_6$ (1:1) solution containing 0.1 mol/L KCl at a scan rate 50 mV/s. The EIS was also measured in 1.0 mmol/L $K_3Fe(CN)_6/K_4Fe(CN)_6$ (1:1) solution containing 0.1 mol/L KCl over the frequency range 10 kHz to 1.0 Hz, with a 5 mV a.c. voltage superimposed on a d.c. bias of 0.172 V, which corresponds to the formal potential of the redox couple.

Results and discussion

Electrochemical behavior of $(pLys/dsDNA)_n$ multilayers

Figure 2a showed the CVs of the electroactive probe $[Fe(CN)_6]^{3-/4-}$ at bare CPE (*a*), CPE/c-CNT/pLys (*b*), and $(pLys/dsDNA)_n$ membranes (*c*, *d*, and *e*). Curve *a* displayed a couple of ill-defined redox peaks in the potential range from +1.0 to −0.6 V, probably due to the poor electrical conductivity of the bare CPE. Curve *b* displayed a couple of well-defined redox peaks with much smaller peak-to-peak separation and much larger peak currents than those of curve *a*, which indicated that the electron-transfer rate at the CPE/c-CNT/pLys electrode was significantly speeded than at bare CPE. C-CNT modified on CPE could act as "conductive wire." The conductive wire established the electrical channel between the electrode and the ferricyanide solution to accelerate the electron transfer and decreased the surface resistance. Furthermore, the c-CNT surface had a great promotion on the formation of the positively charged pLys film. Because dsDNA is negatively charged, $(pLys/dsDNA)_n$ films will block the electron transfer of $[Fe(CN)_6]^{3-/4-}$, and the redox peak currents would decrease with the growth of the bilayer number (*n*) gradually, accompanied by the increase of the peak-to-peak separation. These trends could be seen from curves *c*, *d*, and *e*. Both the peak currents and peak-to-peak separation changed little when the bilayer number was larger than 3. The results of the electrochemical characterization for CVs using $[Fe(CN)_6]^{3-/4-}$ were coincided with the previous work [17].

Figure 2b showed the Nyquist diagrams at different modified electrodes in the presence of equimolar 1.0 mmol/L $[Fe(CN)_6]^{3-/4-}$ containing 0.1 mol/L KCl, which were measured at the formal potential of $[Fe(CN)_6]^{3-/4-}$. Following the theoretical shape, the impedance spectra all include a semicircle portion at higher frequencies, which corresponds to the electron-transfer limiting process, and a linear part characteristic of the lower frequencies to the diffusion-controlled process. From Fig. 2b, significant differences in the electrochemical impedance spectra were observed upon

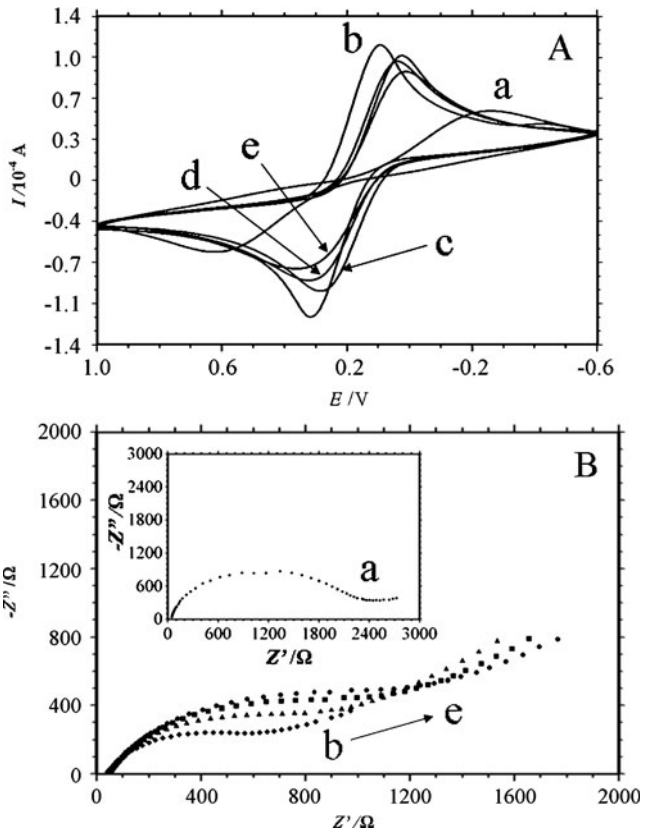

Fig. 2 Cyclic voltammograms (**a**) and Nyquist diagrams (**b**) of 1.0 mmol/L $[Fe(CN)_6]^{3-/4-}$ recorded at *a* bare CPE, *b* CPE/c-CNT/pLys, *c* CPE/c-CNT/(pLys/dsDNA), *d* CPE/c-CNT/$(pLys/dsDNA)_2$, and *e* CPE/c-CNT/$(pLys/dsDNA)_3$

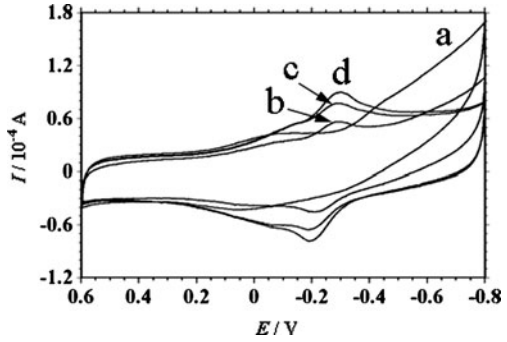

Fig. 3 Cyclic voltammograms of *a* CPE/c-CNT/pLys-MV, *b* CPE/c-CNT/(pLys/dsDNA)-MV, *c* CPE/c-CNT/(pLys/dsDNA)$_2$-MV, and *d* CPE/c-CNT/(pLys/dsDNA)$_3$-MV. Supporting electrolyte solution is pH7.0 B-R buffer solution. Scan rate, 100 mV/s

the stepwise formation of the multilayers. For the bare CPE, the impedance spectrum exhibited a visible semicircle. The semicircle diameter corresponds to the interfacial electron-transfer resistance R_{et}. Compared with curve *a*, the R_{et} value of curve *b* decreased obviously. This could be mainly attributed to the large surface area and the attractive electrical conductivity of c-CNT, and the positive charge of pLys also produced attraction to $[Fe(CN)_6]^{3-/4-}$. When the pLys/dsDNA bilayers were assembled, the semicircle portions became larger at the higher frequencies, which indicated that negatively charged DNA layer on the electrode surface was formed. The diameter of the semicircle part increased significantly with the growth of *n*. The increase of the R_{et} value showed the enhanced hindrance effect on the electron transfer of $[Fe(CN)_6]^{3-/4-}$.

Voltammetric studies on (pLys/dsDNA)$_n$-MV films

The redox response of MV was also used to monitor the assembly process of (pLys/dsDNA)$_n$ films on CPE/c-CNT electrode. Figure 3 showed the CVs at the CPE/c-CNT/pLys-MV (*a*) and CPE/c-CNT/(pLys/dsDNA)$_n$-MV (*b*, *c*, and *d* for *n* equaling to 1, 2, and 3, respectively) in pH7.0 B-R buffer solution. On curves *b*, *c*, and *d*, a pair of well-defined redox peaks was observed at about −0.25 V, owing to the electrochemical reaction of MV. Both reduction and oxidation peaks grew with the number of the pLys/dsDNA bilayer (Table 1). When *n* exceeded 3, there was little increase of the peak currents, indicating that a saturated adsorption of MV was essentially achieved when *n* was 3. The results also showed that an enhanced signal of MV on the DNA-modified electrode was obtained due to the LBL assembly of (pLys/dsDNA)$_n$ for $n < 4$. MV, a nontoxic water-soluble dye, with obvious electrochemical redox peaks, was expected to be an ideal substrate for DNA damage monitoring.

The loading/releasing behavior of MV on CPE/c-CNT/(pLys/dsDNA)$_3$-MV films was studied by DPV technology, which is more sensitive than CV technology. In Fig. 4a, after the fully loaded CPE/c-CNT/(pLys/dsDNA)$_3$-MV films (curve *a*) were immersed in pH7.0 B-R buffer, the DPV response declined with immersion time (data not shown), implying that parts of the loaded MV on the films would be gradually released off the films and into the B-R buffer. The MV reduction peak current became smaller and smaller with the increase of the immersion time and eventually reached a stable value after the time was 12 h, as shown in curve *b*. The plot of the logarithm of the reduction peak currents [ln (I_{pc}/μA)] against the releasing time (*t*) was a straight line (Fig. 4b), illustrating that the release of MV obeyed the first-order kinetics according to the following equation [24].

$$\mathrm{CPE/c\text{-}CNT/(pLys/dsDNA)_3 - MV} \xrightarrow[\text{Dissociation}]{k} \mathrm{CPE/c\text{-}CNT/(pLys/dsDNA)_3 + MV}$$

Thus, $\ln I_{pc} = -kt + \text{constant}$, where *k* is the release rate constant of MV. The linear regression equation was obtained as $\ln I_{pc} = -0.0024t + 4.13$. The *k* value was $2.4 \times 10^{-3}\,s^{-1}$ with the half-life period ($t_{1/2}$) of 289 s.

Curve *c*, which was the DPV curve of the MV-reloaded CPE/c-CNT/(pLys/dsDNA)$_3$ films, had nearly identical peak potential and equal peak current with those of curve *a*, respectively, implying that the loading/releasing of MV on CPE/c-CNT/(pLys/dsDNA)$_3$ films was quite reversible, and also, the CPE/c-CNT/(pLys/dsDNA)$_3$ films were stable.

Detection of DNA damage

Figure 4c showed the DPVs of CPE/c-CNT/(pLys/dsDNA)$_3$-MV films in the B-R buffer at state III. The reduction peak current decreased with the prolongation of the incubation time in $CdCl_2$ solution, indicating that Cd^{2+} could damage DNA, and the damaged DNA films could not reload MV to the same level as that of the intact DNA films. The DNA damage could be detected by DPV with this "loading/releasing/reloading" procedure for MV. In this experiment,

Table 1 Effects of the number of the pLys/dsDNA bilayer on the reduction and oxidation peak currents of MV

The number of the bilayer	Reduction peak current/10^{-5}A	Oxidation peak current/10^{-5}A
1	1.295	1.145
2	3.136	2.958
3	4.369	4.068

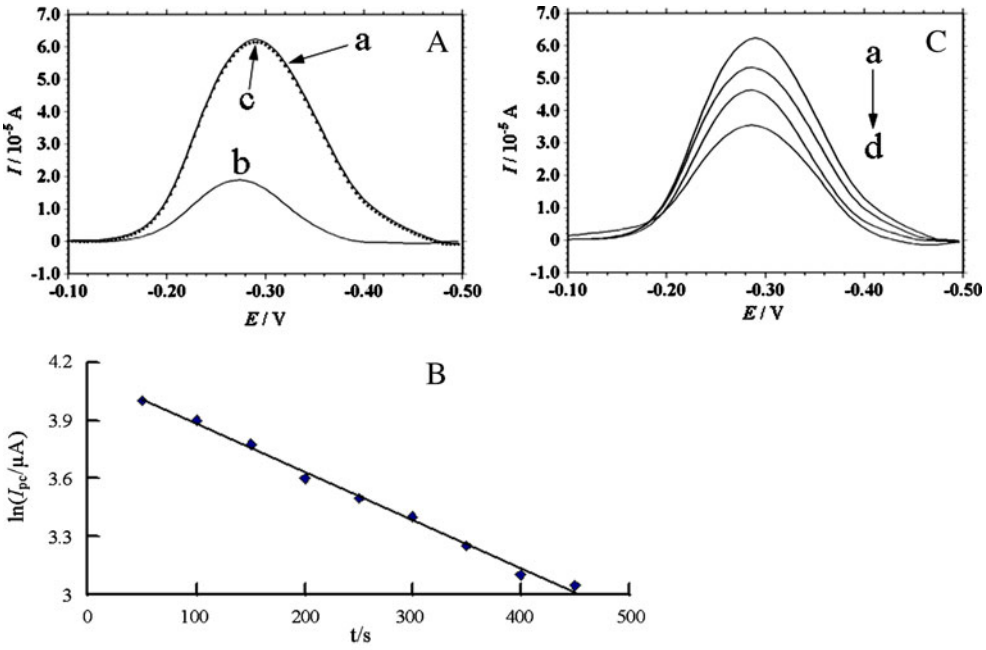

Fig. 4 Background-subtracted DPVs in pH7.0 B-R buffer at **a** CPE/c-CNT/(pLys/dsDNA)$_3$-MV films in pH7.0 B-R buffer at state I (*a*), at state II after 12 h immersion of the films at state I in B-R buffer (*b*), and at the MV-reloaded films of state II re-immersed in 2.0 × 10^{-5}mol/L MV solution for 2 h (*c*). **b** The plot of the logarithm of the reduction peak currents [ln(I_{pc}/μA)] versus the releasing time (*t*). **c** Background-subtracted DPVs in pH7.0 B-R buffer at CPE/c-CNT/(pLys/dsDNA)$_3$-MV films after incubation in 4.0 × 10^{-5}mol/L $CdCl_2$ solution for different times (min): (*a*) 0, (*b*) 10, (*c*) 20, and (*d*) 30

DPVs were preformed in the B-R buffer without MV for distinguishing the DPV responses between the diffused MV from its solution and the adsorbed MV on the films. In contrast, for control experiments under the same incubation conditions but without $CdCl_2$, essentially no decrease of DPV response for the films was observed.

The molecular structure of MV is similar to methylene blue (MB), which is known as the intercalated indicator for DNA electrochemical sensors. Hu et al. used MB as an electroactive probe to detect the DNA damage induced by styrene oxide based on dsDNA LBL films [25]. In comparison with MB, MV had one order of magnitude improvement in the electrochemical redox response for DNA in the CVs under the same scan rate in this work (this work, 10^{-5}A; Hu's work, 10^{-6}A). The greater electrochemical signal of MV could do a great favor for enhancing the sensitivity of the DNA sensors.

Various oxidants, particularly reactive oxygen species such as hydroxyl radicals (OH·), play an important role in DNA oxidative damage [26]. In addition to the destruction and release of the nucleobases, these free radicals also attack the deoxyribose moieties of DNA, which causes interruption of the phosphodiester bonds, resulting in double strand breaking [27]. A typical route for DNA lesions caused by many heavy metals is through metal catalyzed generation of reactive oxygen species such as hydroxyl free radical in the presence of H_2O_2, the so-called Fenton reaction, for example, Fe^{2+}/H_2O_2 reaction. Even if Cd is not a Fenton metal, it has been shown to induce the production of hydroxyl radicals. Chou et al. had investigated the effect of Cd^{2+} on the induction of oxidative DNA damage in human lymphoblastoid cells. Their results showed that Cd^{2+} at low concentrations of 5–50 μmol/L could induce the formation of 8-hydroxy-2′-deoxyguanosine (8-OHdG) and cause nuclear DNA strand breaks [28].

Conclusion

The assembly of pLys and dsDNA multilayer films by alternately electrostatic layer-by-layer adsorption was studied in this work. Cyclic voltammetry and electrochemical impedance spectroscopy were used to characterize the nature of these (pLys/dsDNA)$_3$ multilayers. The results showed that (pLys/dsDNA)$_3$ multilayer could be successfully fabricated on the c-CNT modified CPE surface. The adsorption amount of electroactive probe MV on the electrode increased with the growth of the pLys/dsDNA bilayer number (*n*) until n equals to 3. On this basis, the amplified signal of (pLys/dsDNA)$_3$-MV films was successfully applied to detect the oxidative damage of natural DNA utilizing DPV technique. The main interaction mode of MV with dsDNA was the intercalation of MV between base pairs of dsDNA. The "loading/release/reloading" mode was used to highlight the difference of loading capability between intact and damaged dsDNA in the films and minimize the influence of MV leaking from the films. For Cd-damaged dsDNA, while Cd induced the formation of 8-OHdG and caused nuclear DNA strand breaks, it would hinder or block the intercalation of MV into base pairs of dsDNA, thus resulting in less loading amount of MV in the films. This DNA damage sensor may provide a general approach to detect DNA lesion and promising applications in screening new chemicals in vitro for their potential genotoxicity.

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