Article

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Ultrasensitive Photoelectrochemical Biosensor Based on DNA Tetrahedron as Nanocarrier for Efficient Immobilization of CdTe QDs-Methylene Blue as Signal Probe with Near-Zero Background Noise

Mengjie Li, Chuan Xiong, Yingning Zheng, Wenbin Liang, Ruo Yuan*, Yaqin Chai*

Key Laboratory of Luminescent and Real-Time Analytical Chemistry (Southwest University), Ministry of Education, College of Chemistry and Chemical Engineering, Southwest University, Chongqing 400715, PR China.

* Corresponding author. Tel.: +86-23-68252277; Fax: +86-23-68253172.

E-mail address: yuanruo@swu.edu.cn (R.Yuan), yqchai@swu.edu.cn (Y. Q. Chai)

Abstract

Usually, photoelectrochemical (PEC) assays were devoted to the direct modification of photoactive materials on sensing interface, thereby producing high initial signal and unneglected background noise, which could further result in low sensitivity and restricted detection limit during the detection of targets. In this work, a PEC biosensor with near-zero background noise was established for ultrasensitive microRNA-141 (miRNA-141) detection based on DNA tetrahedron (TET) as nanocarrier for efficient immobilization of CdTe quantum dots (QDs)-Methylene Blue (MB) (TET-QDs-MB complex) as signal probe. Firstly, CdTe QDs as PEC signal indicator was bound to the TET through DNA hybridizations. Then, massive MB as PEC signal enhancer was attached to DNA duplex of the TET immobilized with CdTe QDs *via* intercalation. Thereafter, the as-prepared TET-QDs-MB complex was considered as an efficient PEC signal probe owing to its excellent photovoltaic properties, thereby avoiding direct modification of photoactive materials on sensing interface and producing a near-zero background noise to improve the sensitivity of this PEC biosensor. Besides, the detection sensitivity could be further improved with the help of the duplex specific nuclease (DSN) enzyme-assisted target cycling amplification strategy. The proposed PEC biosensor performs a wide linear range from 50 aM to 50 pM with a low detection limit of 17 aM for miRNA-141, paving a new and promising horizon for highly accurate and ultrasensitive monitoring of multifarious analytes such as proteins, DNAs and miRNAs in bioanalysis and disease diagnosis.

Keywords: Photoelectrochemical biosensor; DNA tetrahedron; CdTe quantum dots; Methylene blue

Introduction

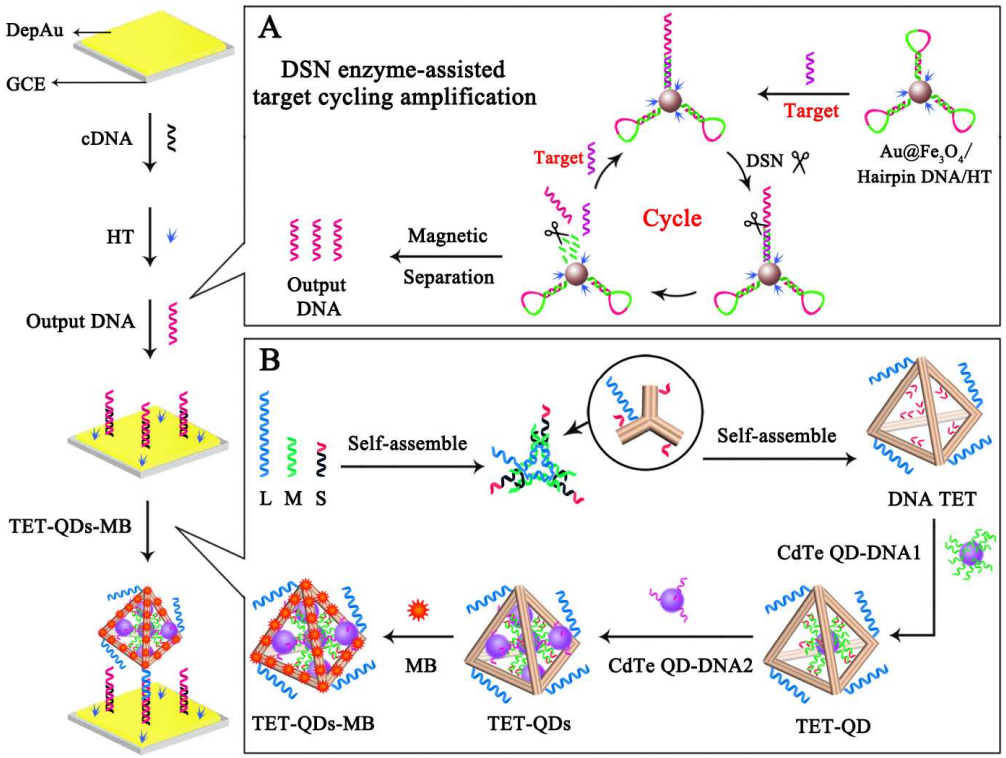
Photoelectrochemical (PEC) assay, as a newly burgeoning yet extremely promising analysis technique, has received considerable attention because of its inherent merits of simple instrumentation, low background signal, ultra-high sensitivity and excellent stability.[1-3] Traditional PEC assays were generally devoted to the direct modification of photoactive materials on sensing interface, and thus obtaining remarkable initial PEC signals.[4-6] With the addition of target, the signal enhancer or signal quencher could be introduced, resulting PEC signal differences, which could be employed to quantify the target.[7] Zhang's group developed a signal-off PEC aptasensor based on direct drop-coating BiOI-graphene nanocomposite on sensing interface.[8] Wei and co-workers reported a signal-off PEC cytosensing of RAW264.7 cells that selected TiO_2 nanoneedles@MoO_3 array as the photoactive material to directly modify electrode.[9] Great improvements to the photocurrent intensity have been obtained based on the conventional immobilization strategy of photoactive material. However, some inevitable limitations still existed such as high initial signal and unneglected background noise, which could further result in low sensitivity and restricted detection limit during the determination of targets. It is expected to develop an ultrasensitive PEC strategy with near-zero background noise based on a simple and highly efficient loading method to immobilize numerous photoactive material, which is urgently required in bioanalysis,

disease diagnosis, environment tests.

Recently, DNA nanostructures as promising candidates in nanotechnology have aroused tremendous concern because of their excellent programming properties, remarkable controllability and high precision, which has been extensively applied in the field of bioanalysis.[10-13] Among diverse nanostructures, DNA tetrahedron (TET) is a particularly outstanding nanoarchitecture. The merits of easy preparation, structural stability, mechanical rigidity and high loading capacity make DNA TET a significant engineering paradigm for immobilizing numerous biomolecules.[10, 14-18] For instance, Armitage's group reported a compact 3-dimensional DNA TET embedded with massive dye arrays for fluorescence detection.[19] Medintz and co-workers developed a novel quantum dot (QD) attached tetrahedral DNA cage formed by swallowing QD into DNA TET.[20] Inspired by these, we here attempted to employ DNA TET as the nanocarrier to immobilize the photoactive material CdTe quantum dots (QDs) and its signal enhancer methylene blue (MB) for forming the TET-QDs-MB complex as signal probe. In consequence, we have found the TET-QDs-MB complex possessed excellent photovoltaic properties and could be used as an efficient PEC signal probe, avoiding direct modification of photoactive materials on sensing interface and producing a near-zero background noise to improve sensitivity. Thereby, high sensitive detection of specific targets could be expected based on the high loading capacity of DNA TET and efficient signal indicator-enhancer system (CdTe QDs-MB).

Herein, DNA TET as nanocarrier for efficient immobilization of CdTe QDs-MB

(TET-QDs-MB complex) was proposed for construction of a PEC biosensor with near-zero background noise to fulfil the ultrasensitive determination with microRNA-141 (miRNA-141) as a target model (Scheme 1). The TET-QDs-MB complex was successfully prepared by using CdTe QDs as PEC signal indicator, MB as signal enhancer and DNA TET as the effective nanocarrier, which was employed as an efficient PEC signal probe. This strategy could avoid the direct immobilization method of photoactive material, leading to a near-zero background noise. Besides, the duplex specific nuclease (DSN) enzyme-assisted target cycling amplification strategy was employed, which would convert small amounts of target miRNA-141 into massive output DNA. These output DNA could hybridize with cDNA on the modified electrode surface, and then captured the TET-QDs-MB complex through DNA hybridizations, producing a desirable photocurrent signal for miRNA-141 quantitative detection. The proposed PEC biosensor avoids the direct modification of photoactive materials on sensing interface and features with near-zero background noise for ultrasensitive estimation of miRNA-141. Importantly, with the high sensitivity and accuracy, the developed PEC biosensor holds great potential for further bioanalysis and disease diagnosis.



Scheme 1. Schematic diagrams of this proposed PEC biosensor for miRNA-141 determination. (A) DSN enzyme-assisted target cycling amplification strategy; (B) Preparation of the DNA TET-CdTe QDs-MB complex.

Experimental Section

Synthesis of Au@Fe_3O_4, CdTe QDs-DNA1 Complex and CdTe QDs-DNA2 Complex

Au@Fe_3O_4 was synthesized based on our previous report.[21] The CdTe QDs were synthesized in accordance with the established protocol.[22] N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride/N-hydroxy succinimide (EDC/NHS) was employed as coupling reagent to link CdTe QDs and amino modified DNAs (DNA1 and DNA2) *via* a classic acylation reaction. Briefly, the CdTe QDs (1 mL, 10 μM) was mixed with 2 mL coupling reagent containing NHS (20 mM) and EDC (10 mM) at room temperature to activate -COOH groups of CdTe

QDs. After 1 h, the mixture was washed by centrifugation, redispersed in phosphate buffered solution (PBS, 1 mL, 0.1 M), and then divided into two parts equally. These two parts of CdTe QDs were mixed with 500 μL 8 μM DNA1 and 500 μL 2 μM DNA2, respectively. After reaction in darkness for 2 h, the unreacted DNA was removed by centrifugation. Finally, the obtained CdTe QDs-DNA1 complex and CdTe QDs-DNA2 complex were stored at 4 ℃ before use.

Signal Amplification for miRNA-141 Detection

As shown in Scheme 1A, the DSN enzyme-assisted target cycling amplification procedure was implemented according to the literature[23] with some modifications. Briefly, 100 μL 5 mg/mL Au@Fe_3O_4 was diluted with PBS (900 μL, 0.1 M). Then, 20 μL 100 μM Hairpin DNA was added to the mixture for 16 h under stirring, followed by magnetic separation and dispersion in PBS (1 mL, 0.1 M). After blocking with hexanethiol (HT, 10 μL, 1 mM), the mixed solution containing target, 1 × DSN master buffer and 1 U DSN enzyme was dropped and incubated for 40 min at 65 °C. DSN enzyme exhibits strong preference for selectively cleaving DNA in DNA-RNA duplex (⩾15 bp) and double-stranded DNA (⩾10 bp), while possesses minor activity towards double-stranded RNA, single-stranded RNA, single-stranded DNA.[24, 25] Here, the target miRNA-141 could open the Hairpin DNA to form DNA-RNA duplex. With the help of DSN enzyme, DNA in DNA-RNA duplex would be cleaved into pieces and the target miRNA-141 would be released to open another Hairpin DNA. As a result, the exposed single-stranded DNA (output DNA) would be released in solution for further separation. Afterward, 5 μL 2 × DSN stop solution was injected into the

above mixture for denaturation of DSN enzyme. Finally, the solution containing numerous output DNA was collected by magnetic separation for further modification of PEC biosensor.

Preparation of the DNA TET-CdTe QDs-MB Complex

The DNA TET-CdTe QDs-MB complex was prepared according to the previous report[26] with minor modification, which was shown in scheme 1B. Firstly, DNA strands (L:M:S = 1:3:3) were mixed in Tris-Acetic-EDTA-Mg^{2+} (TAE-Mg^{2+}) buffer, followed by heating up to 95 °C for 2 min and cooling to 25 °C in 48 h. The as-prepared DNA TET was ready for further modifications of CdTe QDs and MB. Next, 500 μL the as-prepared DNA TET was mixed with 500 μL CdTe QDs-DNA1 complex, and then the mixture was incubated at 25 °C for 12 h. Afterward, 500 μL CdTe QDs-DNA2 complex was dropped and then incubated for another 12 h at 25 °C. Finally, 500 μL 1 mM MB was added to the above mixture and stored for 4 h. The obtained DNA TET-CdTe QDs-MB complex was collected by centrifugation and stored at 4 °C before use.

Fabrication of the PEC Biosensor

The cleaned glassy carbon electrode (GCE) was pretreated before modification according to the previous report.[27] Subsequently, it was immersed in 1% gold chloride tetrahydrate ($HAuCl_4$) solution for electrochemical deposition to gain gold nanoparticles (Au NPs) layer (DepAu) modified electrode (deposition time, 30 s; constant potential, -0.2 V). Next, 20 μL 2 μM cDNA was dropped onto the DepAu/GCE surface for incubating 16 h at 4 °C, which was followed by blocking

with 15 μL 1 mM HT. Then, 20 μL the preceding output DNA was attached on the obtained electrode for 2 h at 37 ℃ to hybridize with cDNA. Ultimately, 20 μL the DNA TET-CdTe QDs-MB complex was dropped onto the modified electrode and incubated at 37 ℃ for 2 h, aiming to complete the hybridization between DNA TET-CdTe QDs-MB complex and cDNA. The fabrication of PEC biosensor was exhibited in Scheme 1.

PEC Measurement

PEC measurement was implemented in PBS (5 mL, 0.1 M) containing 0.09 M ascorbic acid (AA), which was employed as electron donor. The LED lamp was served as the excitation light source (λ = 590 nm) and switched off-on-off for 10 s - 20 s - 10 s under 0.0 V potential.

Results and Discussion

Characterizations of CdTe QDs and DNA TET

As shown in Figure 1A, the high-resolution transmission electron microscopy (HRTEM) was utilized for characterizing the as-synthesized CdTe QDs. The well dispersion and lattice fringes of CdTe QDs could be evidently observed, and their average sizes were about 4 nm. The result confirmed the successful preparation of CdTe QDs. Besides, the polyacrylamide gel electrophoresis (PAGE) was executed to characterize the self-assembled DNA TET, which was exhibited in Figure 1B. The emission bands of lane 1, 2 and 3 demonstrated the distinct single strand DNA of L, M and S, respectively, because different molecular weight could lead to different migration. After the single strand DNA of L, M and S self-assembled into the DNA

TET, a bright emission band could be clearly observed (lane 4). Compared with L, M and S, the DNA TET with the highest molecular weight revealed much slower migration. The PAGE results demonstrated the successful formation of the DNA TET.

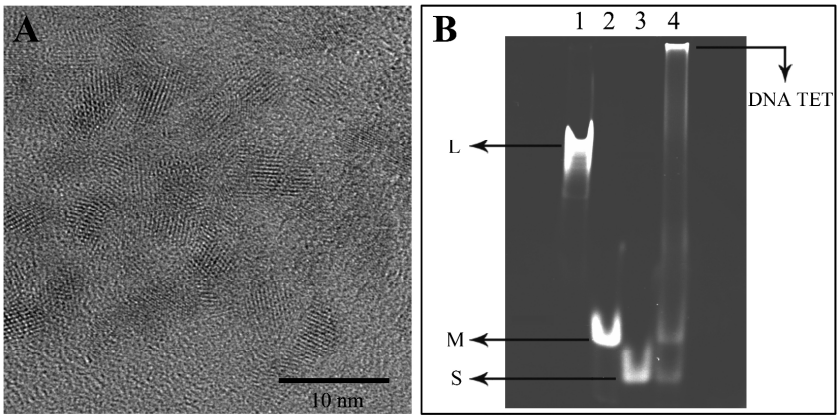


Figure 1. (A) HRTEM image of CdTe QDs and (B) PAGE characterization of the self-assembled DNA TET: lane 1, L; lane 2, M; lane 3, S; lane 4, DNA TET.

PEC Characterization of the Biosensor

As displayed in Figure 2, the photocurrent characterization of the step-by-step construction for the developed PEC biosensor was performed. Comparing with the photocurrent response of bare GCE (curve a), an extremely weak photocurrent was observed for the DepAu modified electrode due to the conductivity of Au NPs (curve b). The photocurrent responses closing to zero were consecutively obtained with the successive modification of cDNA (curve c), HT (curve d) and output DNA (curve e), which could be ascribed to the poor charge transmission of DNA skeletons and organic small molecules. However, the photocurrent response increased dramatically after the above electrode modified with the DNA TET-CdTe QDs-MB complex (curve f), due to the prominent photoelectric activity of CdTe QDs and MB. The PEC characterization reveals the successful construction of the biosensor. Moreover, the

related electrochemical characterizations of this biosensor were presented in Figure S1, Supporting Information.

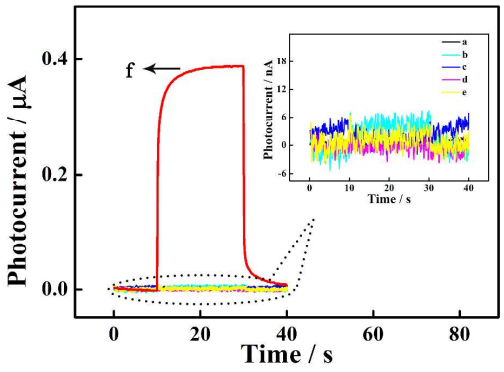


Figure 2. PEC responses of (a) bare GCE, (b) DepAu/GCE, (c) cDNA/DepAu/GCE, (d) HT/cDNA/DepAu/GCE, (e) output DNA/HT/cDNA/DepAu/GCE and (f) DNA TET-CdTe QDs-MB complex/output DNA/HT/cDNA/DepAu/GCE. 5 mL PBS containing 0.09 M AA was performed as detection buffer.

Comparison of PEC Responses

As presented in Figure 3A, the signal probe couldn't be immobilized on the sensor surface without addition of target miRNA-141, thereby producing a zero background noise. However, in the presence of 10 fM miRNA-141, two kinds of signal probes including DNA TET-CdTe QDs complex and DNA TET-CdTe QDs-MB complex could be captured on sensing interface, which were shown in Figure 3B and Figure 3C, respectively. The PEC response of biosensor with DNA TET-CdTe QDs complex as signal probe was 0.33 μA (Figure 3B). For the proposed PEC biosensor with DNA TET-CdTe QDs-MB complex as signal probe (Figure 3C), the received PEC response (0.82 μA) was about 2.5-fold higher compared with the PEC response based on DNA TET-CdTe QDs complex as signal probe, which was

ascribed to the significant signal enhancement effect of MB toward CdTe QDs. Therefore, the result demonstrated the DNA TET-CdTe QDs-MB complex could be used as an ideal PEC signal probe for fabrication of sensors.

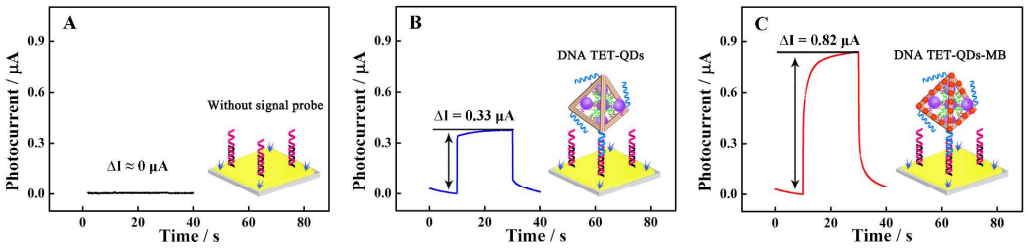


Figure 3. Photocurrent response of the biosensor without addition of miRNA-141 (A); photocurrent responses of this biosensor with signal probes of DNA TET-CdTe QDs complex (B), DNA TET-CdTe QDs-MB complex (C) in the presence of 10 fM miRNA-141.

PEC Analysis of this Proposed Biosensor for miRNA-141 Detection

The performance of this proposed PEC biosensor for determination of various concentrations of miRNA-141 was evaluated under optimal conditions (Figure S2, Supporting Information). According to Figure 4A, the PEC responses continuously increased with incremental miRNA-141 concentration from 50 aM to 50 pM. Also, a good linear relationship between the PEC responses and the logarithm of miRNA-141 concentrations could be observed from the calibration plot (Figure 4B). The linear equation for miRNA-141 expressed as $I = 0.239\lg c_{\text{miRNA-141}} + 1.25$ ($r = 0.994$), where I, c and r represented the PEC response, the miRNA-141 concentration and the correlation coefficient, respectively. And the detection limit was 17 aM, which was calculated according to the reference.[28] Furthermore, a comparison between the proposed PEC biosensor and the previously reported strategies was performed in Table 1. These results figured out this proposed PEC biosensor possessed superior

performances for miRNA detection with a wide linear range and low detection limit.

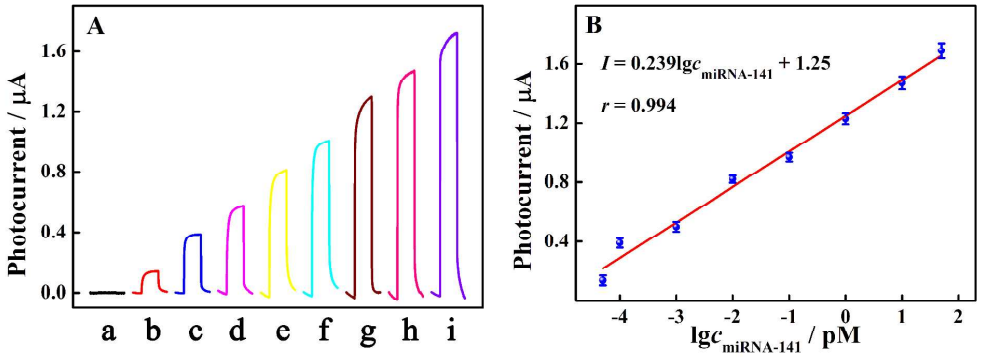


Figure 4. (A) PEC responses of this biosensor incubated with various miRNA-141 concentrations: 0 aM, 50 aM, 100 aM, 1 fM, 10 fM, 100 fM, 1 pM, 10 pM and 50 pM (from a to i). (B) The calibration curve for miRNA-141 detection.

Table 1. Comparison for this miRNA determination with other determination methodologies.

Analytical method	Detection background	Detection limit	Linear range	Ref.
fluorescence	1.00 a.u.	1.5 fM	1.5 fM-9 fM	29
electrochemistry	75 μA	10 fM	5 fM-5 pM	30
ECL	400 a.u.	0.16 fM	0.5 fM-50 pM	31
PEC	14.9 μA	0.2 fM	1 fM-100 pM	32
PEC	160 μA/cm^2	1.67 fM	5 fM-5pM	33
PEC	---	83.3 aM	0.25 fM-25 pM	23
PEC	Near Zero	17 aM	50 aM-50 pM	***Our work***

Abbreviations: electrochemiluminescence (ECL); photoelectrochemical (PEC).

Stability and Selectivity of this PEC Biosensor

To assess its stability, PEC responses of this biosensor towards 50 pM miRNA-141 were investigated under continuous "off-on-off" light for 8 cycles. As illustrated in Figure 5A, the proposed biosensor possessed an ascendant stability along with a satisfied relative standard deviation (RSD) of 0.9 %. Moreover, the selectivity

of this biosensor was also investigated by employing miRNA-21, miRNA-155 and thrombin as interferences. As shown in Figure 5B, no obvious PEC responses for miRNA-21 (100 pM), miRNA-155 (100 pM) and thrombin (100 pM) were observed in comparison with the PEC response for 1 pM miRNA-141. In addition, the PEC response of blank detection was similar to that of these interferences. These results suggested an excellent selectivity of this biosensor for miRNA-141 determination.

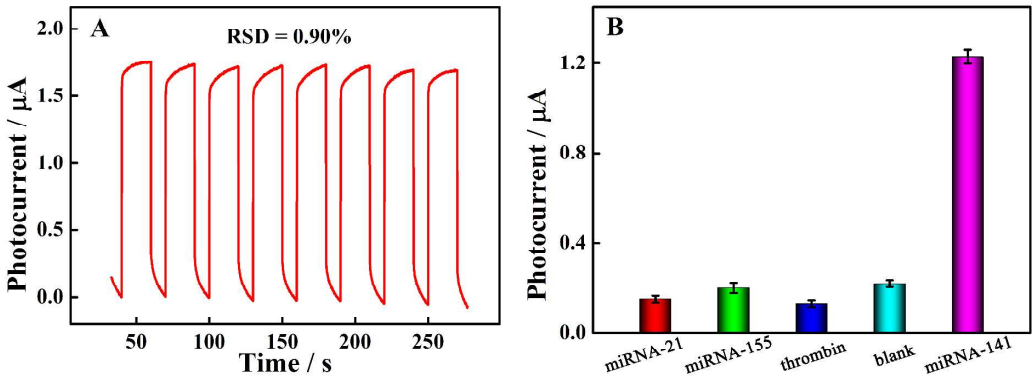


Figure 5. (A) Stability of this biosensor in the presence of 50 pM miRNA-141 with continuous off-on-off light for 8 cycles. (B) Selectivity of this biosensor with different targets: miRNA-21 (100 pM), miRNA-155 (100 pM), thrombin (100 pM) and miRNA-141 (1 pM).

Application in Cancer Cells of this PEC Biosensor for miRNA-141

To explore the feasibility of this PEC biosensor for the determination of miRNA-141 in practical samples, two kinds of cell lysate samples including human cervical cancer cell (HeLa) and human prostate cancer cell (22 Rv1) have been detected using this strategy. As seen from Figure 6, the PEC signal exhibited an obvious increase as the number of 22 Rv1 cells increased from 10 to 5000, while the relatively low PEC signal could be observed as the number of HeLa cells increased from 10 to 5000. These results suggested that miRNA-141 is high expressed in the 22

Rvl cell and low expressed in the HeLa cell, which fits well with previously reported articles.[34, 35] Thus, this PEC biosensor holds great potential for clinical applications in early diagnosis of cancers.

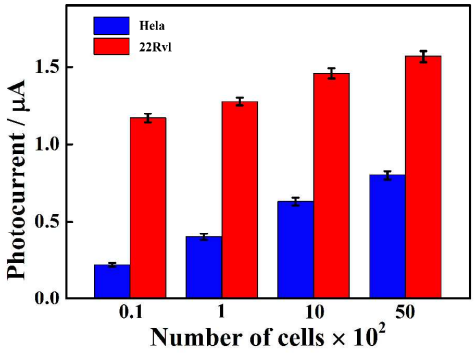


Figure 6. PEC responses of the developed biosensor from Hela and 22 Rvl cells with different cell numbers.

Conclusions

In summary, a PEC biosensor with near-zero background noise was proposed for ultrasensitive determination of miRNA-141 on the basis of DNA TET as nanocarrier for efficient immobilization of CdTe QDs-MB as signal probe. The synthesized TET-QDs-MB complex with excellent photovoltaic property showed nearly 2.5-fold higher PEC signal than that of TET-QDs complex owing to the signal enhancement effect of MB toward CdTe QDs. Moreover, the TET-QDs-MB complex was used as an efficient PEC signal probe, which could avoided direct modification of photoactive materials on sensing interface and produced a near-zero background noise to raise the sensitivity of this biosensor. With the aid of DSN enzyme-assisted target cycling amplification strategy, the detection sensitivity of this biosensor could be further improved. With the successful establishment of the PEC biosensor for ultrasensitive

miRNA-141 estimation, this strategy reveals a versatile tool for various targets analyses, which possesses great significance in bioanalysis and disease diagnosis.

AUTHOR INFORMATION

*Corresponding authors:

Tel.: +86-23-68252277; Fax: +86-23-68253172.

E-mail address: yuanruo@swu.edu.cn (R. Yuan), yqchai@swu.edu.cn (Y. Q. Chai)

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ASSOCIATED CONTENT

Supporting Information

Materials and reagents, apparatus, gel electrophoresis, cell culture and total RNA extraction, electrochemical characterization of the PEC biosensor (Figure S1), condition optimization (Figure S2) and photophysical characterizations of CdTe QDs (Figure S3) were supplied in Supporting Information.

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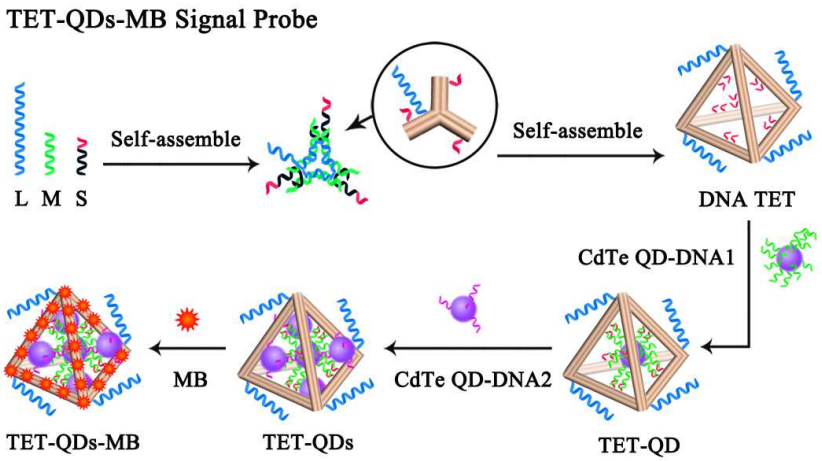
TET-QDs-MB Signal Probe
L M S
Self-assemble
Self-assemble
DNA TET
CdTe QD-DNA1
TET-QD
CdTe QD-DNA2
TET-QDs
MB
TET-QDs-MB