Short Communication

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Mof@Mos$_2$-Based Electrochemical Biosensor for Ca125 Detection

Chang Hu[1,2], Chong Chen[1,3], Jiawei Zhang[1], Yongchang Bai[1], Shuang Li[1], Weifeng Li[1,2]* and Dong Ming[1]

[1]*Academy of Medical Engineering and Translational Medicine, Tianjin University, China*

[2]*Tianjin International Engineering Institute, Tianjin University, China*

[3]*Department of Clinical Laboratory, Tianjin Medical University Cancer Institute and Hospital, China*

Corresponding author: Weifeng L, Academy of Medical Engineering and Translational Medicine, Tianjin University, Tianjin, 300072, China

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ABSTRACT

Metal organic framework (MOF) have exhibited great attention in the field of electrochemistry due to their excellent surface area and amplification effect towards electrical signal. In this work, molybdenum disulfide (MoS_2) was synthesized on MOF substrate to provide a sensitive platform for electrochemical detection. Screen printed electrodes were used for the point of care testing of carbohydrate antigen 125 (CA125) with the modification of MOF@MoS_2 and sensitive CA125 antibody. Differential pulse voltammetry (DPV) results showed that our sensing system exhibited excellent linear response towards the detection of CA125 from 10 pg/mL to 10 µg/mL.

Keywords: MOF: Metal organic framework (MOF); Molybdenum disulfide (MoS_2); Carbohydrate antigen 125 (CA125); Differential pulse voltammetry (DPV) carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP) and prostate specific antigen (PSA)

Abbreviations: OC: Ovarian cancer; WHO: World Health Organization; ELISA: Enzyme-Linked Immunosorbent Assay; MOF: Metal organic frameworks; PSA: Prostate Specific Antigen standard; AFP: Alpha Fetoprotein; CV: Cyclic Voltammetry; LSV: Linear Cyclic Voltammetry; DPV: Differential Voltammetry

Introduction

Ovarian cancer (OC) is known to be one of the most fatal gynecological malignancies [1-3]. According to World Health Organization (WHO), more than 200000 women suffer from ovarian cancer every year and 150000 women die of ovarian cancer worldwide [4]. Carbohydrate antigen 125 125 (CA125) is the most commonly used molecular marker in the clinical diagnosis of ovarian cancer, which is often called the "gold standard" tumor marker [5]. CA125 is a mucoid like glycoprotein with more than 200 kDa [6]. CA125 was expressed in more than 90% of patients with advanced epithelial OC and more than 50% of patients with early OC [7]. Therefore, rapid detection of CA125 in human serum is of great significance for ovarian cancer screening. In recent years, many different sensing technologies, such as enzyme-linked immunosorbent assay (ELISA) [8-11] immunoradiometric assay [12,13], have been used to detect different target molecules. But these methods need a lot of analysis time, high cost, professional operation, large and complex equipment. These make these methods have some limitations. Electrochemical technology is considered to be a promising technology because of its high sensitivity, great selectivity, simple usage method, and fast response time [14-18]. Metal organic frameworks (MOF) are crystalline materials with periodic network structure formed by self-assembly of organic ligands with metal ions or metal clusters [19]. The unique properties of MOFs (controllable pore structure, large surface area and good adsorption performance) [20-22] make MOFs to be an ideal sensor material for electrochemical applications. In this study, we designed a new electrochemical immunosensor based on MOF@MoS_2 modified screen printed electrode for CA125 detection.

Experimental Section

Reagents and Materials

All reagents and chemicals were of analytical grade. MOF was obtained from XFNANO, China. Sodium Molybdat Dihydrat (Na2MoO4·2H_2O) was obtained from PhytoTech. thiourea (CH_4N_2S) was obtained from KMS. Sodium tetrachloroaurate ($NaAuCl_4·2H_2O$), sodium citrate ($C_6H_5Na_3O_7·2H_2O$) was obtained from Alfa Aesar. potassium ferricyanide($K_3Fe(CN)_6$), potassium hexacyanoferrate(II) ($K_4Fe(CN)_6·3H_2O$), potassium chloride (KCl) were obtained from Chinese medicine reagent. CA125 antibody, CA125 standard products, bovine albumin (BSA) solution, prostate specific antigen (PSA) standard products, alpha fetoprotein (AFP) standard products, carcinoembryonic antigen (CEA) standard products were obtained from Standard information network. The coating of screen-printed electrode (SPE) whose working electrode and counter electrode are carbon, reference electrode is Ag/AgCl. All electrochemical measurements including cyclic voltammetry (CV), Linear cyclic voltammetry (LSV), differential voltammetry (DPV) was performed by CHI660E electrochemical workstation (Shanghai CH Instruments Co, China).

Preparation of CuBTC@MoS_2

The synthesized MOF (40 mg), $Na_2MoO_4·2H_2O$ (80 mg) and thiourea (160 mg) were completely dispersed in 40 mL of deionized water by shaking and stirring, and then the mixture was transferred to a 40 mL teflon lined autoclave and heated at 200 °C for 12 h. Then, the mixture naturally cooled to room temperature, centrifuged at 10 rpm for 10 min and dried at 80 °C for 60min. Lastly, obtained 23 mg of polymer, dissolved them in 2.3 mL of ultrapure water, made a 10 mg/mL solution, and put it on the bottle for later use.

Fabrication of immunosensor

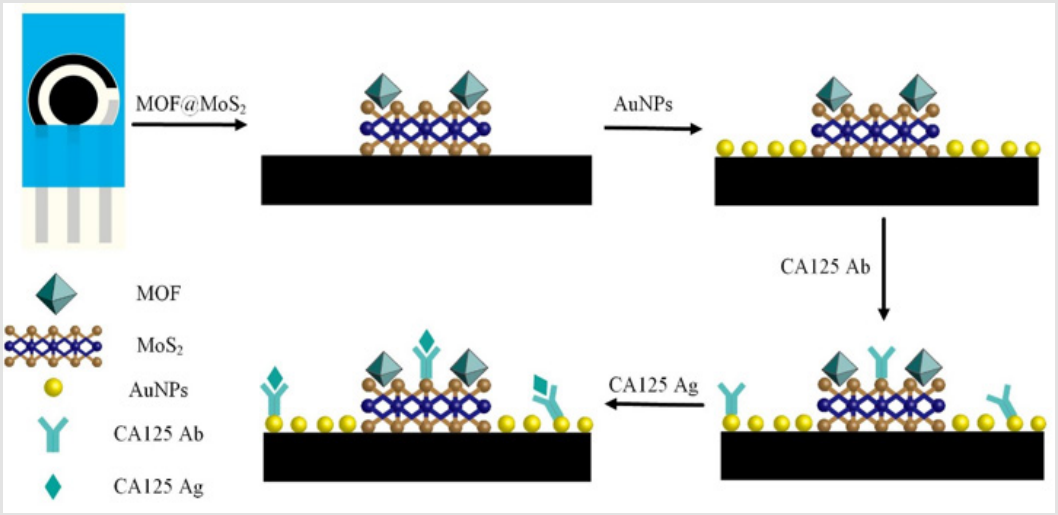

Figure 1: Fabrication scheme of MOF@MoS_2 biosensor electrochemical immunosensor for CA125 detection.

In the first step, the sensitive layer was modified as followed: 4 μL CuBTC@MOF was dropped on the center of the SPE a 2 mm×2 mm area (Figure 1). Put the electrode in the oven at 80 °C for 10 min. The next step is electrodeposition of AuNPs. Mix 1% NaAuCl4 solution and 0.5 M NaSO4 solution in equal volume. LSV scans from -0.2 V to -1.0 V, scan rate 0.1 V/s, current level 10-4 A. Finally, the modified SPE was incubated at 30°C for 30 minutes before washing with water, which could remove the unbound 4 μL 0.1 mg/mL CA125 antibodies. Different concentrations of CA125 Ag (10 pg/mL, 10^2 pg/mL, 10^3 pg/mL, 10^4 pg/mL, 10^5 pg/mL, 10^6 pg/mL and 10^7 pg/mL) were detected using a three-electrode electrochemical system. All measurements were repeated three times.

Results and Discussion

Characterization of the Immunosensor Fabrication

50 mL of 5.0 mM $K_4Fe(CN)_6$ solution was prepared by $K_4Fe(CN)_6·3H_2O$ (0.1055975 g) and KCl (1.86375 g), and 50 mL of 5.0 mM $K_3Fe(CN)_6$ solution was prepared from $K_3Fe(CN)_6$ (0.08231 g) and KCl (1.86375 g). The Fe2+/Fe3+ solution was prepared by mixing K4Fe(CN)6 solution and K3Fe(CN)6 solution in volume ratio of 1:1. In the blank control experiment, scan the electrode on the electrochemical workstation, titrate 70μL of Fe^{2+}/Fe^{3+} redox solution on the electrode, find the peak range of cyclic voltammetry (CV), set the parameter -0.4 - 0.6V scan, scan with a speed of 50mV/s and a current level of 10^{-4}A. After modification of the MOF@MoS_2 complex in the working electrode, we add 70 μL redox pair to measure CV Curve. It is found that the electrochemical effect has been significantly enhanced which can be proved that MOF@MoS_2 have successfully synthesized. The curve of scanning deposition process of electrodeposited gold is shown in Figures 2A & 2B. Gold has been deposited in the first scan, and a peak of gold deposition appears at -0.70V, and gold is no longer deposited in the following continuous scans. After the gold is deposited, add 70μL of Fe^{2+}/Fe^{3+} redox to the solution to measure the CV curve.

After incubation with CA125 Ag on the electrode, we found that the current decreased due to the addition of macromolecules. Compare the step-by-step modification with the original curve, as shown in the Figure 2A .

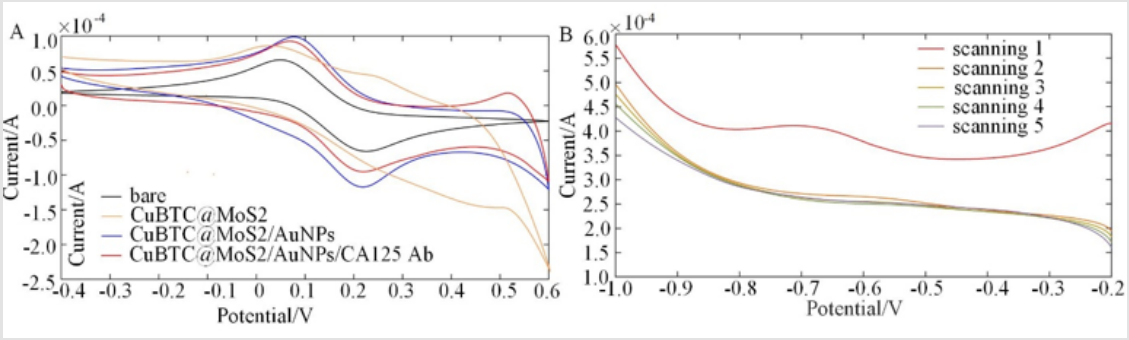

Figure 2: Characterization of electrode. (A) CV responses of SPE sensor at different steps of fabrication containing 5 mM $[Fe(CN)_6]^{3-/4-}$; (B) LSV curve of electrodeposited AuNPs.

CA125 detection

On the electrode of the modified antibody, it is planned to detect different concentrations from 10 pg/mL to 10 μg/mL of CA125 Ag by DPV scanning. Drop 100 μL of phosphate buffer saline (PBS) on the electrode and set the DPV parameters from -0.2 V to 0.4 V scans, the pulse amplitude is 50 mV, and the pulse period is 0.3 seconds. The control group did not add CA125 Ag, and the rest were added with seven different concentrations of CA125 Ag. The comparison curves are as follows Figure 3A. The calibration curve (Figure 3B) displays a great linear relationship between current slope and ln (C_{CA125}). The variance of the calibration curve of the immunosensor is shown below:

$$Y = 0.006678X + 0.00110$$

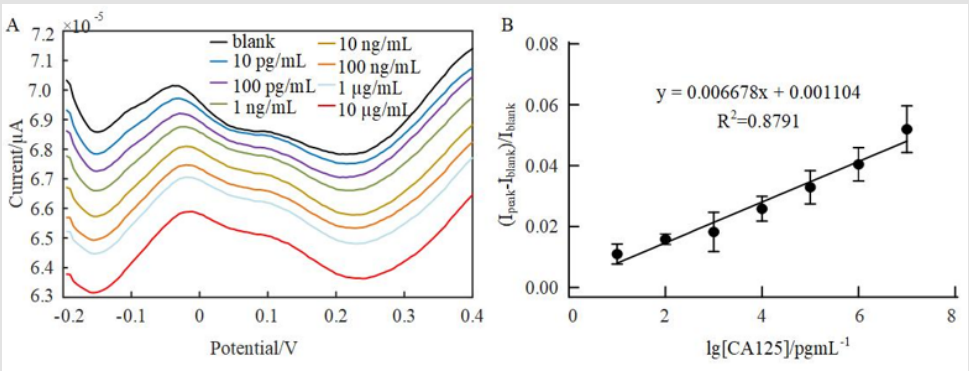

Figure 3: CA125 detection. (A) DPV responses toward different concentrations of CA125 (0.01, 0.1, 1, 10, 100, 1000, 10000 ng/mL). (B) Concentration linear fitting curve (n=3).

Selectivity of the immunosensor

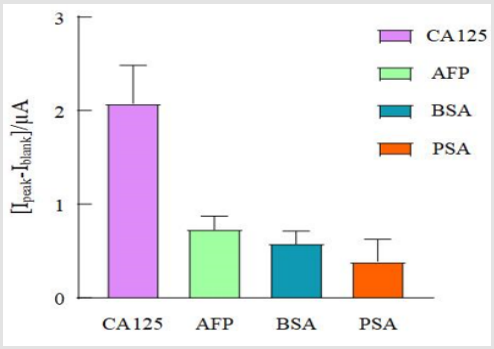

Figure 4: Specificity characterization of CA125 biosensor.

There are many interfering substances in human serum, so the selectivity of the sensor is particularly important. To evaluate the selectivity of immunosensors, some possible interfering species are common in human serum, including carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP) and prostate specific antigen (PSA). Drop various substances 10 ng/mL on the electrode of the control group, and the contrast diagram of the measured current changes is shown in Figure 4.

Conclusion

In the present work, a novel immunosensor for the detection of CA125 was engineered based on MOF@MoS_2. The MOF@MoS_2 could improve both the SPE conductivity and the surface area.

Our results show that the developed immunosensor has excellent sensitivity with a low LOD (10 pg/mL) and a wide range of CA125 concentration (to 10 μg/mL). The immunosensor shows great selectivity. Taken all, the designed immune sensor has excellent analytical performance in CA125 detection, so it can be considered as a method that can be further studied and applied in clinical practice in the future.

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References

1. Razmi N, M Hasanzadeh (2018) Current advancement on diagnosis of ovarian cancer using biosensing of CA 125 biomarker: Analytical approaches. Trac-Trends in Analytical Chemistry 108: 1-12.
2. Dochez V, Helene C, Edouard V, J Dimet, Norbert W, et al. (2019) Biomarkers and algorithms for diagnosis of ovarian cancer: CA125, HE4, RMI and ROMA, a review. Journal of Ovarian Research: 12.
3. Orr B, RP Edwards (2018) Diagnosis and Treatment of Ovarian Cancer. Hematology-Oncology Clinics of North America 32(6): 943-964.
4. Jemal A, Brey F, Melissa M, Elizabeth W, David F, et al. (2011) Global Cancer Statistics. Ca-a Cancer Journal for Clinicians 61(2): 69-90.
5. Matte I, Denis L, Claudine R, Alian P, Marianne B (2014) MUC16 mucin (CA125) attenuates TRAIL-induced apoptosis by decreasing TRAIL receptor R2 expression and increasing c-FLIP expression. Bmc Cancer: 14.
6. Ravalli A, G Pilon, M Ferrone, G Fagile, H Yamanaka, et al. (2013) New label free CA125 detection based on gold nanostructured screen-printed electrode. Sensors and Actuators B-Chemical 179: 194-200.
7. Pakchin PS, M Fathi, H Ghanbari, R saber, Y Omidi, et al. (2020) A novel electrochemical immunosensor for ultrasensitive detection of CA125 in ovarian cancer. Biosensors & Bioelectronics pp. 153.
8. Ambrosi A, F Airo, A Merkoci (2010) Enhanced Gold Nanoparticle Based ELISA for a Breast Cancer Biomarker. Analytical Chemistry 82(3): 1151-1156.
9. Wang SM, Ge L, Song X, Yu J, Ge S, et al. (2012) Paper-based chemiluminescence ELISA: Lab-on-paper based on chitosan modified paper device and wax-screen-printing. Biosensors & Bioelectronics 31(1): 212-218.
10. Alberti D, Mark Vant E, Rachele S, Maria Rosaria R, Marata T, et al. (2014) A Quantitative Relaxometric Version of the ELISA Test for the Measurement of Cell Surface Biomarkers. Angewandte Chemie-International Edition 53(13): 3488-3491.
11. Wang YG, Huan W, Wei C, Bin D, Qin W, et al. (2018) Sandwich-type electrochemical immunoassay based on Co3O4@MnO2-thionine and pseudo-ELISA method toward sensitive detection of alpha fetoprotein. Biosensors & Bioelectronics 106: 179-185.
12. Rundekar AN, PC Vrinda, N Sivaprasad (2011) Solid phase immunoradiometric assay for CA125 antigen levels in blood using monoclonal antibodies. Journal of Radioanalytical and Nuclear Chemistry 288(1): 31-36.
13. Sallam KM, ASA El Bayoumy, NL Mehany (2016) Development of solid phase immunoradiometric assay for determination of carcinoembryonic antigen as a tumor marker. Journal of Radioanalytical and Nuclear Chemistry 307(2): 1375-1383.
14. Bansod B, T Kumar, Ritula T, Sakshi R, Inderbir S, et al. (2017) A review on various electrochemical techniques for heavy metal ions detection with different sensing platforms. Biosensors & Bioelectronics, 2017. 94: 443-455.
15. Xie FY, Fengli Qu, Adullah MA, X Sun, S Cao (2018) Cobalt nitride nanowire array as an efficient electrochemical sensor for glucose and H2O2 detection. Sensors and Actuators B-Chemical 255: 1254-1261.
16. Meng W, Wen Y, dai L, He Z, Wang L (2018) A novel electrochemical sensor for glucose detection based on Ag@ZIF-67 nanocomposite. Sensors and Actuators B-Chemical 260: 852-860.
17. Huang RR, He L, Xia Y, Xu H, Liu C, et al. (2019) A Sensitive Aptasensor Based on a Hemin/G-Quadruplex-Assisted Signal Amplification Strategy for Electrochemical Detection of Gastric Cancer Exosomes. Small 15(19).
18. Khanmohammadi A, Ali A, Ensieh V, Ali Q, Mostafa G, et al. (2020) Electrochemical biosensors for the detection of lung cancer biomarkers: A review. Talanta pp. 206.
19. Cao Y, L Wang, Chao S, C Wang, X Hu, et al. (2019) An electrochemical sensor on the hierarchically porous Cu-BTC MOF platform for glyphosate determination. Sensors and Actuators B-Chemical 283: 487-494.
20. Chang JF, Xin W, Jiao W, Haiyin L, Feng Li (2019) Nucleic Acid-Functionalized Metal-Organic Framework-Based Homogeneous Electrochemical Biosensor for Simultaneous Detection of Multiple Tumor Biomarkers. Analytical Chemistry 91(5): 3604-3610.
21. Baghayeri M, Masoud G, Reza T, Maryam F, Fatemeh N, et al. (2020) Application of graphene/zinc-based metal-organic framework nanocomposite for electrochemical sensing of As(III) in water resources. Analytica Chimica Acta 1099: 60-67.
22. Zhou KF, D Shen, X Li, Y Chen, L Hou, et al. (2020) Molybdenum oxide-based metal-organic framework/polypyrrole nanocomposites for enhancing electrochemical detection of dopamine. Talanta pp. 209.

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Weifeng Li. Biomed J Sci & Tech Res