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Metal nanoparticles for miRNA detection

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ABSTRACT: Biosensing can be used for analysis, diagnosis and determination of biological target structures. But the improvement of sensitivity and sensing threshold is an important problem to overcome. It is possible to solve this problem with metal nanoparticles, in some linear response range while decreasing the threshold value. The synthesis of nanostructured materials, especially metallic nanoparticles, has accrued utmost interest over the past decade owing to their unique properties that make them applicable in different fields of science and technology. The article is divided into subsections on sensors based on nanoparticles made from Au, Cu and other metals for miRNA detection.

KEYWORDS: miRNA; biosensor; metal nanoparticles; detection.

1. INTRODUCTION

The 1993 discovery of microRNAs (miRNAs) has not been considered as a markedly event until it was revealed that they control as much as 30% of human genes, being deregulated in many diseases [1]. Since then, scientific progress in designing noteworthy platforms for microRNAs detection is in the focus of this rapidly growing research field. miRNAs belong to a class of small, non-coding endogenous RNAs that contain roughly 18–25 nucleotides [2-3]. miRNAs are considered as a class of potential biomarkers for diagnosis, prognosis, and therapeutic monitoring of various cancers. Because of their sequence homology, short chains, and low abundance, the accurate quantification of miRNAs remains challenging [4]. Up until now, different metal nanoparticles have been used in the field of electrochemical sensing for the ultrasensitive detection of chemical and biochemical species [5-12]. Further, optical sensors and electrochemical methods have been exploited for the detection of heavy metal ions in water and other environments [13-19]. In this line, the sensitivity was reported to be improved by the use of nanomaterials, in part because of a high degree of modification, bulky surface, high refractive index and more reactivity of nanoparticles [20-21]. The use of AuNPs in medicine, nanobiotechnology and diagnostic agents and theragnostic has paved the way for the development of highly sensitive nanosystems (NSs) used for the simultaneous detection and therapy of diseases, in large part because of having distinctive optical properties and diverse surface chemistry characterizations [22]. As we know, MoS2 is a graphene-like layered nanomaterial, which is considered as promising sensing platform for chemical/biological molecules detection combined with fluorescence, electrochemistry, surface-enhanced Raman spectroscopy (SERS) and field-effect transistor (FET) techniques. MoS_2 has an interesting indirect-to-direct bandgap transition with the thickness of MoS2 from bulk to single-layer, making it as a potential nanomaterial for constructing electrochemical sensors. It had been proved that MoS_2 nanosheet was a promising supporting material to decorate noble metal nanoparticles (such as Au, Ag, Pt and Pd nanoparticles), graphene and other organic compounds, which could greatly enlarge its electrochemical application due to the synergistic effect [23].

2. RESULTS

2.1. Metal Nanoparticles as Sensing Materials

Chand et al. designed a microfluidic stage incorporated with electrochemical sensing for miRNA based analytic diagnosis of pTb. The integration and electro-polymerization of MoS_2-$CuFe_2O_4$ nanocomposites onto the working electrode provided signal enhancement. The microfluidic stage can accomplish one-step detection of four pTb specific miRNA [24]. The immobilization of ferrocene thiol and molecular probes is more effective due to the high surface area of MoS_2 nanosheets. A novel electrochemical sensing method for miRNA

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analysis is proposed by Miao et al. Highly sensitive detection of miRNA is achieved by utilizing electrochemical techniques in tracing metallic nanoparticles and T7 exo-assisted amplification. The novelty of the study is the method that integrates the advantages of the copper nanoparticles templated by double-stranded DNA (dsDNA) and enzyme-assisted amplification. The results show that the method can successfully determine the differences between target miRNA and mismatched miRNAs [25]. High stability of the dsDNA allows high stability and reproducibility for the sensor. Another study is conducted by Xue et al. which developed a dual-mode electrochemical sensor that uses efficient electrocatalysts. The study uses catalysts such as CuCo−CeO_2 NSs in order to obtain high sensitivity detection of miRNA. The co-doping of Cu and Co into the CeO_2 lattice structure provides abundant oxygen vacancies. Efficient electrocatalytic activity levels were achieved in CuCo−CeO_2 NSs compared to pure or single-doped CeO_2 [26]. The use of CuCo−CeO_2 NSs as bifunctional electrocatalysts exhibits a lower detection limit and wider linear range than regular sensing methods and provides an easy way for monitoring other biomolecules, such as metal ions, proteins, miRNAs and small molecules at trace amounts. An Event-Condition-Action (ECA)-based detection method for miRNA is reported by Castañeda et al. They eliminated aggregation, which is an important problem in ECA, by adding ssDNA shell to the NP, which is later removed partially in order to create catalytic sites on the NP surface [27]. This method is simple to implement, robust and applicable to any biosensing method that uses enzymes as DNA-cleaver.

Signal amplification is another improvement that can be obtained by using metal nanoparticles. Zhang et al. developed a label-free electrochemical biosensor that shows high sensitivity for miRNA detection. The study is based on the RCA-mediated synthesis of PdNPs. The results are owed to two different mechanisms, which are the specific target recognition by generating several G-rich ssDNAs and the formation of PdNPs on the G-rich ssDNAs that amplifies signal [28]. MoS_2/Ti_3C_2 nanohybrids have been prepared by Liu et al. and applied in the detection of miRNA by the comprehensive utilization of Ti_3C_2 frames [29]. Both DPV signal and the peak current is increased due to the support nanohybrids and the swelling induced Au–S bond breakage after adding miRNA-182. Different kinds of miRNA sensing is not achieved by this method. Another facile and enzyme-free method is developed by Tian et al. that involves SDR signal-amplification strategy. The detection of miRNA-21 is obtained by combination of SDR signal with NCS/Mo_2C NS on electrode substrates. The amount of triggered signal molecules increased and improved electrochemical redox efficiency by bringing the Fc close to the electrode surface [30]. This method increases analytical performance specially for breast cancer-related miRNA-21 detection level and provides reliable reproducibility. Liu et al. reported an electrochemical biosensor that employs Fe_3O_4/CeO_2@Au MNPs as nanocatalyst and CHA for signal application. Cerium oxide (CeO_2) nanoparticles and Au nanoparticles improved the catalytic performance of the Fe_3O_4/CeO_2 @Au MNPs and prevented the agglomeration of Fe_3O_4 nanoparticles. In order to overcome some disadvantages of protein enzymes, the enzyme-free DNA circuits was introduced into miRNA-21 detection [31]. This method allows further signal response enhancing, which in turn allows wide linear range detection and low detection limit.

An immobilization-free electrochemical impedance biosensor that uses magnetic beads for miR-21 detection is developed by Zhang et al. The developed biosensor has no requirement for specific recognition sequence, which allows the detection of other miRNAs. This can be accomplished by designing the suitable capture probe for the target miRNAs [32]. The detection by magnetic beads improves the sensitivity and selectivity greatly. Azzouzi et al. reported the development and evaluation of an impedimetric biosensor which allows the detection of miRNA-21. The biosensor is based on a neutravidin modified transducer surface and an integrated dual functional probe. The use of neutravidin improved both overall sensor performance and sensitivity [33]. There are also various device configurations that show promise for detection of biological structures. Chen et al. fabricated a sensitive electrochemical biosensor in order to detect miRNA-21 by using a different configuration. The novelty of the study is between the target miRNA and the biotinylated miRNA. Assembling the hybrid thiolated complementary RNA on WSe_2 nanosheets creates a biosensor that shows good performance. One of the aspects is the large specific surface area of WSe_2 which can load more AuNPs. The hybrid configuration also increases the specificity and sensitivity of the sensor. The detection signal and detection limit are further improved by Hydrogen peroxide + Hydroquinone system [34]. Another dual-mode detection strategy based on AuNPs@MoS_2 nanocomposite is developed by Su et al. which uses AuNPs@MoS_2 nanocomposites not only as an electrode modifier, but also as a nanoprobe in order to amplify the detection limit [23]. DPV and EIS measurements shows two different electrochemical indicators that are used to monitor the detection performance of MoS_2-based biosensor.

Ma et al. have developed a sensitive and selective miRNA detection platform that utilizes functionalized multienzyme magnetic microcarrier assisted isothermal strand-displacement polymerase reaction. The dual amplication of the assay allows the sensor to lower the detection limit (9 fM).

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This approach enables efficient, isothermal detection of miRNAs [35]. The sensitive, low-cost and convenient miRNA diagnosis sensor is a potential candidate for point-of-care testing in hospitals. Another label-free and enzyme-free ratiometric homogenous electrochemical biosensing platform is developed by Gai et al. that detects miRNA-21 via redox recycling and target-triggered Ru(III) release. The high accuracy and sensitivity is owed to the IRu(III)/IFe(III) value variation [36]. This approach combines the advantages of homogenous electrochemistry and ratiometric detection modes. The combination of the mentioned modes further lowers the detection limit (33 aM).

Islam et al. developed a sensitive electrochemical method for the detection of small miRNAs by multiple electrocatalytic signal amplification. Target miRNAs were separated magnetically and adsorbed on Au-NP Fe_2O_3NC nanocomposites that show high electrocatalytic activity. The electrocatalytic cycle that occurs between miRNA-107 that is adsorbed onto the gold nanoparticle-containing composite and $Fe(CN)_6$ system significantly enhances the signal [37].The results have potential applications on screening other cancer biomarkers including miRNAs. In situ growth of 3D GFs on gold substrate is studied by Kong et al. This approach takes advantage of large surface area of the substrate and strong binding properties of the 3D GFs. The detection of nucleic acid (miR-155) and protein (Lyz) can be carried out with high efficiency and excellent performance. The employment of MNPs both simplify the experimental operations and facilitate a signal-on response mechanism. The study expects that specially aptasensors to be established for the analysis of wide-range target molecules owing to its different recognition elements, such as DNA/RNA hybridization and specific recognition of aptamers [38]. Another study that focuses on the advantage of Fe3O4 NPs as an excellent nanomaterial is utilized byYuan et al. in a dual signal amplification sensor that uses simultaneous detection of miRNAs. The superiority of the target-triggered HCR method is used in the design of the sensor, which renders the limits of the practical application in clinic diagnosis of cancers obsolete such as high costs and complex procedures. Simultaneous detection of different types of miRNAs' can also be realized with this sensor model by corresponding oligonucleotide sequences or using distinguishable electrical signal molecules [39].

As a study that focuses on the properties of magnetic nanoparticles, their paramagnetism, biocompatibility and easy surface modification methods; a sensor that can be utilized in detection of miRNA in cell lysates is produced and shows promise for clinic diagnosis of cancers by detection of various miRNA biomarkers. An efficient metal mimic enzyme of Pt/Sn-In_2O_3 is studied by Zhang et al. which possesses high oxygen reduction catalytic properties. High sensitivity and inherent selectivity are owed to the catalytic capability of Pt/Sn-In_2O_3 NPs and hairpin capture probe. The interaction between Pt and Sn both increases the catalytic activity and stability. The precision, reproducibility and stability are also feasible for real sample detection [40]. Zhu et al. fabricated a label-free detection of miR-21 as a simple and efficient electrochemical platform that is based on a MoS_2-Thi-AuNPs nanocomposite. In this sensor, Thi was used both as a reducer for the reduction of $HAuCl_4$ and an indicator for electrochemical signal. The group also demonstrated the distinguishing ability of the mentioned sensor by determining target miRNA-21 from mismatched miRNA [41]. The MoS_2-based biosensor shows potential application in cancer-related biomolecules analysis, while it does not require labeling and relatively short detection time. Another novel electrochemical nanobiosensor that utilizes gold nanorods (GNR) is reported by Azimzadeh et al. miRNA detection in early stages of the breast cancer. The sensor is based on a graphene oxide/GNR modified glassy carbon electrode that uses Oracet Blue as a label which allows the direct detection of the miR-155 without sample extraction or amplification. The combination of graphene oxide/GNR and Oracet Blue is the main reason of the high sensitivity and selectivity. Along with these properties, the long storage ability also allows the sensor for medical applications. With a simple modification of the capture probe, it is also possible to use the sensor for the detection of virtually any miRNA sequence [42]. This approach allows the sensor to be used in the clinical applications and as early detection in the breast cancer patients. Although the biosensors have been around more than six decades [43], the method of using metal nanoparticles in biosensors is relatively new. In this chapter, it has been shown that the functionalization with metal nanoparticles allows the interaction with different biological materials, changes the threshold value and linear response gap and has effect on device structure that makes different application methods possible.

In Table 1, It is summarized some selected electrochemical biosensors for nanoparticles and other electrode modifications.

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Table 1. Summary of selected electrochemical biosensors for nanoparticles and other electrode modifications

miRNA	Nanoparticles and other electrode modifications	Electrochemical method	Linear range	Detection Limit	Ref.
miRNA-155	Gold nanowire+reduced graphene oxide	DPV	2 fM-8.0 pM	0.6 fM	[42]
miRNA-205 miRNA-92 miRNA-7857 miRNA-378	MoS_2 nanosheets decorated with copper ferrite nanoparticles	SWV	1 pM-1.5 nM	0.48 fM	[24]
miRNA-141	DNA-templated copper nanoparticles	CV-DPV	0.1-100 fM	0.045 fM	[25]
miRNA-141	CeO_2 nanospheres codoped with Cu and Co	DPV-CV-EIS	0.1 fM-10 nM	33 aM	[26]
miRNA-203	ssDNA decorated PtNP	ECA	0.10-10.0 nM	100 pM	[27]
miRNA-21	RCA-mediated palladium nanoparticles	CV	50 aM-100 fM	8.6 aM	[28]
miRNA-21	N-carboxymethyl chitosan/molybdenum carbide nanocomposite	DPV-IT	1.0 fM-1.0 nM	0.34 fM	[30]
miRNA-21	Au nanoparticle decorated Fe_3O_4/CeO_2	EIS-DPV	1 fM-1 nM	0.33 fM	[31]
miRNA-21	Streptavidin-modified magnetic beads	EIS	0.5-40 fM	60 aM	[32]
miRNA-21	Gold nanoparticles conjugated biotinylated DNA/LNA molecular beacon	EIS	1-1000 pM	0.3 pM	[33]
miRNA-182	MoS_2/Ti_3C_2 nanohybrids	DPV-CV-EIS	1 fM-0.1 nM	0.43 fM	[29]
miRNA-21	Thiolated RNA probe immobilized onto tungsten diselenide nanosheets	DPV-CV-EIS	0.0001-100 pM	0.06 fM	[34]
miRNA-21	Gold nanoparticle decorated MoS_2 nanosheet	DPV-EIS	10 fM-1 nM	0.78 fM	[23]
miRNA-21	Magnetic micro-carriers functionalized with molecular beacons	DPV-CV	10 fM-10nM	9 fM	[35]
miRNA-21	Positively charged mesoporous silica nanoparticle decorated with Ru(III) complex	DPV	0.1-1500 fM	33 aM	[36]
miRNA-107	Gold-loaded nanoporous ferric oxide nanocubes	CV	-	100 aM	[37]
miRNA-155	3D graphene films on gold substrates	SWV-CV-EIS	-	5.2 pM	[38]
miRNA-141 miRNA-21	DNA1/Fe_3O_4 NPs/Thi and DNA2/ Fe_3O_4 NPs/Fc	EIS-DPV	1 fM-1 nM	0.44 fM and 0.46 fM	[39]

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miRNA-21	Pt/Sn-In_2O_3 nanoflower	EIS-CV-LSV-DPV	5 pM-0.5 fM	1.92 fM	[40]
miRNA-21	Thionine and gold nanoparticles co-functionalized MoS_2 nanosheet	EIS- SWV	1 pM-10 nM	0.26 pM	[41]

3. CONCLUSION

Some works based on metal nanoparticles are of high quality and achieved successful applications. Achieving strong sensitivity, efficiency, selectivity and simplicity has been always the driving forces for the biosensor design for a long time. As I have outlined in this commentary, the metal nanomaterials has inspired the rapid development of electrochemical sensing approaches.

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