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$Ni(OH)_2$/NGQDs-based electrochemiluminescence immunosensor for prostate specific antigen detection by coupling resonance energy transfer with Fe_3O_4@MnO_2 composites

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ABSTRACT

An efficient quenching electrochemiluminescence (ECL) immunosensor based on ECL resonance energy transfer (ECL-RET) was studied for sensitive analysis of prostate specific antigen (PSA). In this protocol, nitrogen-doped graphene quantum dots (NGQDs) which could produce excellent ECL emission, were loaded onto $Ni(OH)_2$ with the three-dimensional (3D) hierarchical and stacked lamellar structure. Taking advantages of high conductivity and large specific surface area of $Ni(OH)_2$, the better electrochemical and ECL behavior of $Ni(OH)_2$/NGQDs were presented. As another part of immunosensor, the Fe_3O_4@MnO_2 composites with wider ultraviolet absorption range were successfully assembled. The absorption spectra of Fe_3O_4@MnO_2 precisely overlapped with the ECL spectra of NGQDs, leading to the significant decrement of ECL signal. Herein, the sandwich-type immunosensor was developed based on the quenching mechanism between NGQDs (ECL donor) and Fe_3O_4@MnO_2 (ECL acceptor). The system was optimized to realize reliable determination of PSA concentration within the linear range of 10^{-5}–10 ng/mL and a detection limit of 5 fg/mL (S/N = 3). Eminently, the developed method was successfully applied in real serum samples with good recoveries in a range from 94.0% to 102%, indicating the good accuracy of the proposed method for PSA detection.

1. Introduction

Recently, electrochemiluminescence resonance energy transfer (ECL-RET) which often occurs with overlapped emission/absorption spectra of donor/acceptor pair has attracted widespread research interest (Dong et al., 2016; Feng et al., 2016). Benefited from its remarkable advantages, including no background from unselective photo-excitation, the nonuse of additional light source as well as cheap instrument, ECL-RET has been intensively investigated for analysis of biomarkers (Ma et al., 2016), heavy metal ions (Lei et al., 2015b), DNA (Wu et al., 2014b; Zhou et al., 2012). Through ECL-RET, ECL emission of luminophor could be enhanced (Hong et al., 2016) or quenched by energy acceptor (Wu et al., 2012). The target analyte could be quantitatively detected according to the variation of ECL signals. In order to achieve a lower detection limit and higher sensitivity, more attention was focused on the ECL quenching principles.

There have been reports that the target analyte, as energy acceptor, can directly restrain the ECL emission of luminescent species based on ECL-RET from the excited luminophor to the target analyte, thus being detected quantitatively (Liu et al., 2007). Previous studies have demonstrated that ECL-RET between CdSe/ZnS quantum dots (QDs) and cyanine dye (Cy5) molecules was indeed efficient for the detection of Cy5 (Li et al., 2011). However, it was somewhat demanding for the appropriate selection of energy donor/acceptor pairs based on the ECL-RET between the luminophor and target analytes. Therefore, another method that was based on ECL-RET from the excited species to other quencher (rather than analytes) received significant attention, which further broadened the field of detection species. Chen groups have described a ECL-RET system for the sensitive detection of target DNA that adopted graphene oxide (GO) Au/RuSi@$Ru(bpy)_3^{2+}$/chitosan (CS) composites and Au@Ag_2S nanoparticles (NPs) as the ECL donor and acceptor, respectively (Wu et al., 2014a). This model can also be used to detect other proteins or other biological molecules. Here, we explored a new suitable donor/acceptor pair to develop a novel ECL-RET immunosensor for prostate specific antigen (PSA) determination.

Recently, graphene quantum dots (GQDs) have sparked attention in the field of ECL due to its low cytotoxicity and excellent biocompatibility (Dong et al., 2015; Yang et al., 2017). However, pure GQDs have lower quantum yields (Yuan et al., 2016). According to the reports, the intrinsic properties of GQDs could be well tuned via heteroatom

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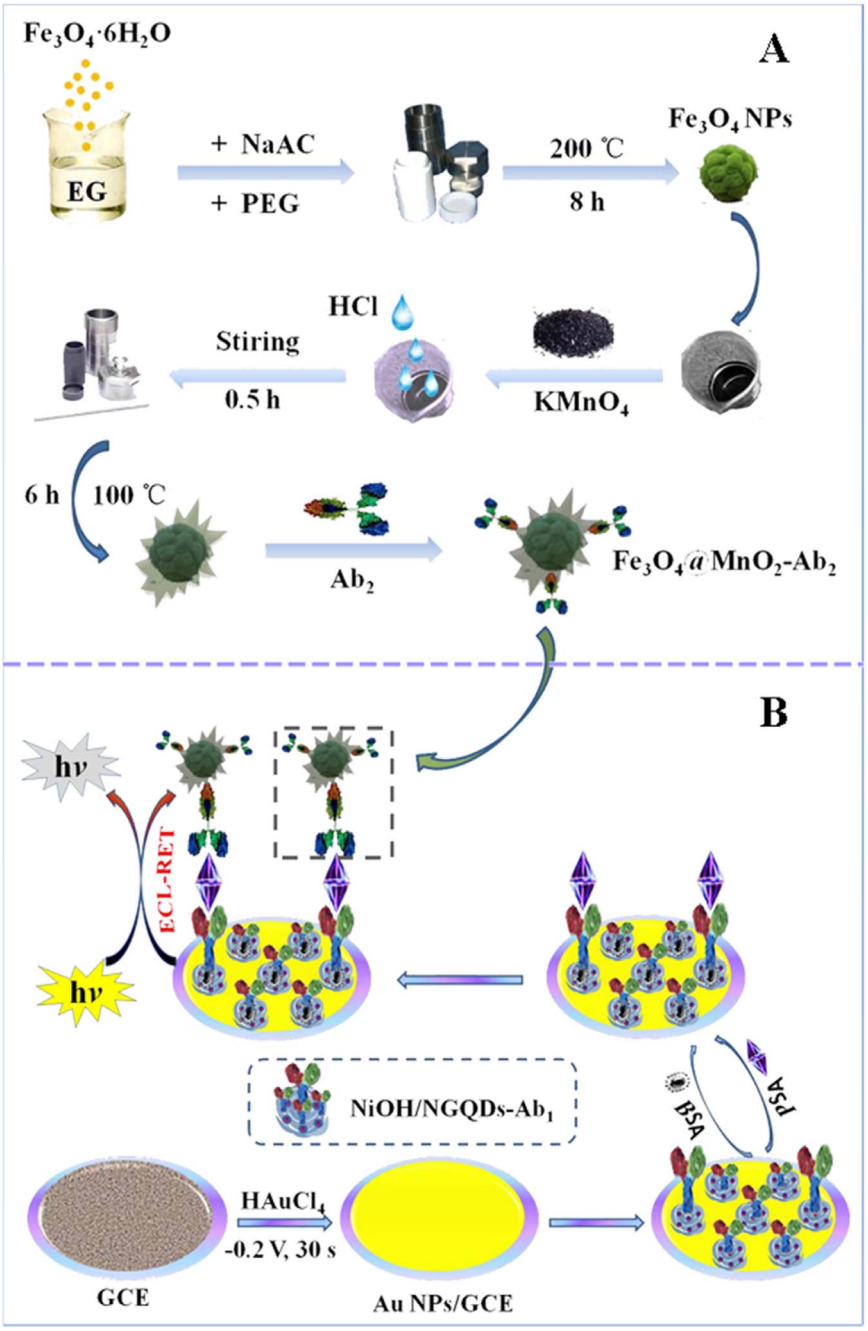

Fig. 1. (A) Preparation of $Fe_3O_4@MnO_2$-Ab_2 conjugates. (B) Illustration for the fabrication process of the immunosensor.

doping, such as electronic characteristics, surface and local chemical features (Chen et al., 2015; Li et al., 2012). Among the doped GQDs, nitrogen-doped GQDs (NGQDs) could provide more active sites and improve its quantum yields (Li et al., 2015b). It has been used to establish ECL sensors for detection of proteins (Zhou et al., 2015), small molecules (Wang et al., 2015), and so on (Du et al., 2015).

Ferroferric oxide (Fe_3O_4) nanomaterial has attracted much attention because of its advantages of superparamagnetic properties, chemical stability, low toxicity, ease of preparation and functionalization (Lin et al., 2007). It has been widely applied in the field of cell and protein separation (Chiu et al., 2015; Demeritte et al., 2015), drug delivery vehicle (Guo et al., 2009) and so on. Furthermore, core-shell semiconductor composites based on Fe_3O_4 were also studied due to their tunable absorption frequency and integration of chemical composition (Liu et al., 2012). Qiao et al. have synthesized the composite microspheres with Fe_3O_4 as cores and flake MnO_2 as shells, which presented three-dimensional (3D) hierarchical surface architecture (Qiao et al., 2016a). There has been reported that when MnO_2 was assembled on Fe_3O_4, a lager blue shift and wider ultraviolet absorption range were shown compared with pure Fe_3O_4 (Liu et al., 2017; Ma et al., 2016). Moreover, it was noteworthy that the absorption spectra of $Fe_3O_4@MnO_2$ precisely overlapped with the ECL spectra of NGQDs. Thus NGQDs and $Fe_3O_4@MnO_2$ were chosen as an ideal donor/acceptor pair and have a potential prospect in ECL-RET immunosensor.

Therefore, based on the ECL-RET between NGQDs (ECL donor) and $Fe_3O_4@MnO_2$ (ECL acceptor), a sandwich-type ECL immunosensor was developed for PSA determination. In this work, the hierarchical $Ni(OH)_2$ was used to load NGQDs by strong chemical interactions or van der Waals interactions between $Ni(OH)_2$ and NGQDs. $Ni(OH)_2$ with 3D nanostructure has been recognized as a promising electrode materials with high theoretical specific capacitance, excellent electronic