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Review

What are the reasons for low use of graphene quantum dots in immunosensing of cancer biomarkers?

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ABSTRACT

Graphene quantum dots-based immunosensors have recently gained importance for detecting antigens and biomarkers responsible for cancer diagnosis. This paper reports a literature survey of the applications of graphene quantum dots for sensing cancer biomarkers. The survey sought to explore three questions: (1) Do graphene quantum dots improve immunosensing technology? (2) If so, can graphene quantum dots have a critical, positive impact on construction of immuno-devices? And (3) What is the reason for some troubles in the application of this technology? The number of published papers in the field seems positively answer the first two questions. However additional efforts must be made to move from the bench to the real diagnosis. Some approaches to improve the analytical performance of graphene quantum dots-based immunosensors through their figures of merit have been also discussed.

Contents

1. Introduction

Research on graphene quantum dots (GQDs) has grown exponentially in recent years, Graphene quantum dots (GQDs), are graphene fragments small enough to cause exciton confinement in 3–20 nm particles and quantum-size effect. Although graphene is a zero band gap nanomaterial and hence non-luminescent it has an infinite excitation Bohr radius and affords quantum confinement in finite sized specimens [1]. The band gap in GQDs is non-zero and can be tuned by altering the size and the surface chemistry of the dots [2].

The preparation methods of GQDs can be classified into two categories: top–down and bottom–up methods. The strategy of top-down methods is to cut down large graphene sheets, carbon nanotubes, carbon fibers or graphite into small pieces of graphene sheet, while in the bottom–up methods, small molecules are used as starting materials to build the GQDs. Until now, for top-down approaches, nanolithography technique, acidic oxidation, hydrothermal or solvothermal microwave assisted, sonication-assisted, electrochemical, photo-Fenton reaction, selective plasma oxidation and chemical exfoliation methods have been used to synthesize GQDs; while for the bottom–up techniques, using benzene derivatives as starting materials through stepwise solution chemistry methods, carbonization as starting materials through microwave-assisted hydrothermal method, fullerenes as

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starting materials through ruthenium-catalyzed cage-opening and unsubstituted hexaperihexabenzocoronene as starting materials through the process of carbonization, oxidization, surface functionalization, and reduction successively have been utilized to prepare GQDs successfully [3]. GQDs provide an effective alternative to colloidal inorganic semi-conductive quantum dots (QDs), which have attracted much attention in the past two decades due to their electronic and optical properties [4]. However, QDs are highly toxic due to the release of heavy metals, such as cadmium, selenium, tellurium and zinc, from their core and their coating. In the early research on GQDs, tremendous effort was devoted to developing methods for the preparation of GQDs and exploring their properties [5–10]. Their application in the analytical field has not been explored until very recently. Sensors based on GQDs can achieve a high level of performance due to their novel properties.

In the recent years, graphene quantum dots (GQDs) has become an emerging class of the nano-carbon family, due to their low toxicity, easy preparation, high chemical stability, environmental friendliness, their luminescence and ability to transfer photoinduced electron [11, 12]. It has shown great promise applications in the fields of bioimaging [13,14], photo-luminescence [15], catalysts [16], and fluorescent sensor [17]. In addition, GQDs have been recognized as both, excellent electron donors and acceptor, making them interesting candidates for producing electrode materials [18,19]. GQDs can be functionalized [20] especially with oxygen containing groups such as hydroxyl, carboxyl and epoxy groups which can greatly enhance their hydrophilia and biocompatibility. Therefore, GQDs have significant potential for bio- and immunosensing applications.

On the other hand, there is a continuous demand for fast and simple analytical methods for the determination of many clinical, biochemical and environmental analytes useful as markers of illness or contamination. In this respect, immunosensors that rely on antibody-antigen (Ab-Ag) interactions provide a promising means of diagnostics due to their specificity and sensitivity. Immunological sensors are based on recognition of the coupling of an Ag with an Ab to form a complex. Immobilization of one of the aforementioned elements onto a sensing surface will cause a signal change upon formation of a complex with the corresponding Ab or Ag. Highly-sensitive immunosensors can thus be constructed using enzymatic reactions involving fixed enzyme-labeled Ag. Immunosensors can be competitive or non-competitive, homogeneous or heterogeneous. Non-competitive immunoassays are usually more sensitive and more specific than competitive ones. Immunosensors can be classified as electrochemical, optical, piezoelectric, thermometric or magnetic, according to the type of transduction [21].

Optical immunosensors involve coupling immunoassay techniques with surface plasmon resonance (SPR) technology [22,23]. A change in refractive index of the medium upon interaction of Ag (tumor marker) with Ab immobilized on the sensor surface can be measured [24]. Alternatively, Ab could be immobilized on the surface of an optical fiber and change in refractive index, fluorescence or luminescence correlated with the amount of Ag interacting with the Ab. Piezoelectric immunosensors are generally based on evaluating the change in frequency of oscillation as result of change in mass on interaction of Ag with Ab immobilized on quartz crystal [25].

Electrochemical immunosensors allow quantitative estimation of tumor markers by detecting the change in potential (potentiometric) [26], current intensity (amperometric) [27] or capacitance (capacitive) [28] as a result of Ab-Ag interaction. Potentiometric immunosensors generally use techniques that are non-dependent on labels and can directly detect the change in potential due to Ab-Ag interaction at the surface of the detection device. The first potentiometric immunosensor for an ovarian cancer-related tumor marker was developed for hCG by Yamamoto and co-workers in 1978 [29] using a non-labeled antibody. Capacitive immunosensors detect alterations in capacitance following an immunoreaction (Ab-Ag interaction) on the application of a potential pulse. Suwansa-ard and co-workers in 2009, developed a capacitive immunosensor for a flow injection-based label-free detection of CA125 in human serum [30].

Amperometric immunosensors have been by far more extensively studied as compared to others. This could be attributed to their ease fabrication, miniaturization, robustness, and cost-effectiveness and detection sensitivity. On the other hand, piezoelectric immunosensors, provide low detection limits (~pico-molar or femtomolar concentrations), but have not replaced amperometric immunosensors because of their high cost, difficulty in mass production or miniaturization and problems with mechanical and electromagnetic interference. Hence, the next section will focus on the historical development of electrochemical immunosensors and more specifically amperometric immunosensors

Amperometric immunosensors are based on measurement of the current intensity from electrochemically active redox species produced during the reaction. In immunoreactions, analytes (Ag/Ab) do not act as redox partners themselves; hence an enzyme-labeled Ag or Ab may be used to provide electroactive species as reactants or products. The current generated gives an indirect measure of the analyte concentration. Enzymes such as horseradish peroxidase [31,32] and alkaline phosphatase [33] are most commonly used to catalyze such electrochemical reactions.

The determination of the levels of cancer biomarkers provides crucial information for the screening diagnostics of cancer, and the development of sensing devices or other analytical methodologies for their sensitive and reliable point-of-care measurement. It has been a significant challenge for the early cancer detection and treatment monitoring, since high sensitivity, accuracy, minimal technical expertise, rapid and easy system maintenance should be obtained [34]. In this review examples from the literature describing cancer biomarker immunosensors based on GQDs were collected. These systems use a biorecognition element according to the definition given above. GQDs-based immunosensors for detection of different biomarkers were selected from latest research articles from 2000 to July 2016to be included in this review. Type of modifiers for GQDs, injection and detection techniques, labels, target analytes and the corresponding sample matrix were discussed in detail, paying special attention to the sensitivity of assays. In the case of GQD-based immunosensors for detection of cancer biomarkers, in our knowledge, only six studies have been published til now. Therefore, this review would like to explore the reason and possible problems involved in this research area. In general, we summarize below examples of GQD applications in electrochemical immunosensing reported so far in the literature, and compared with the other prepared immunosensors based on nanomaterials. Finally, we stress their potential for future development in this research field.

1.1. Do graphene quantum dots improve immunosensing technology?

The present paper has the objective of reviewing the state of the art of recent GQDs based immunosensors employed in cancer biomarkers analysis covering the period of 2000-July 2016 for comparison of their analytical performance, and also considering their advantages and limitations according to the transduction principle. Some approaches are also reported in order to improve the analytical performance of these immunosensors. The study of the analytical performance of GQD-based immunosensors is reported in the following discussions through the estimation of associated analytical figures of merit and taking into account the configuration of the various GQD-based immunosensors applied to the detection of cancer biomarkers considered.

In the first report, a highly sensitive 3D origami device combined with electrochemiluminescence (ECL) immunosensor was introduced by Li and coworkers [35] for sensitive point-of-care testing of carcinoembryonic antigen (CEA). This immunodevice was developed based on nanoporous gold/chitosan modified paper working electrode (NGC-PWE) as sensor platform and green-luminescent graphene