Applications of Graphene in Biosensors for Cancer Detection

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Biosensors are a very promising tool for the possibility of sensitive, specific, and non-invasive diagnosis for early detection of cancer. Effective, accurate methods of cancer detection and clinical diagnosis are urgently needed. Biosensors are devices that are designed to detect a specific biological analyte by essentially converting a biological entity (i.e., protein, DNA, RNA) into an electrical signal that can be detected and analyzed. The ultimate goal of biosensors is to detect signals specific to each disease and cancer, and recently nanoparticles have been widely used in the design of biosensors. Graphene and its derivatives are nanoparticles with unique properties and have many applications in nanobiosensors.

graphene cancer biomarkers nanobiosensor biosensing method diagnostic applications

1. Introduction

Biosensor technology is a growing field to satisfy the need for sensitive and rapid detection problems [1]. In addition to the use of commercial SPR-based biosensors using the Kerchman plasma excitation scheme [2], in recent years, the use of optical, electrochemical, piezoelectric, and other types of biosensors has shown successful results in low concentrations of biomarkers for the detection of cancers including breast cancer, lung cancer, and prostate cancer [3]. In fact, with the proliferation of biosensors capable of detecting cancer early, a major revolution has taken place in the field of cancer diagnosis [4]. Biosensors are a set of components that record a physical, chemical, or biological change and convert it into a measurable marking [5]. The main parts of biosensors include the bioreceptor, transducer, and read-out system [6]. The bioreceptor reacts with the target substance and is usually composed of an antibody, aptamer, cell, or enzyme. Another essential part is the transducer, which must convert the biological signal into a measurable signal. The transducer can be electrochemical, optical, or mechanical [7]. Finally, the read-out system displays the final response and reads the measured signal [6][7]. Electrochemical biosensors provide high sensitivity and selectivity for vital biomarkers that are responsible for vital molecular events in tumor formation and progression [8]. In fact, in addition to differentiating tumor cells from normal cells, these sensors lead to the targeted diagnosis of localized tumor cells and circulating tumor cells. Electrochemical sensors are suitable tools for cell counting, cell classification, and the detection of tumor cells. In the diagnosis of tumor cells, electrochemical biosensors achieve not only high sensitivity (limit of detection of 10 tumor cells in a 250 µL sample) and high specificity but also diagnose duplicate antigens at the tumor cell surface and successfully prevent false-positive results [9].

In electrochemical biosensors, a redox reaction takes place between the bioreceptor and the target molecule [10]. The reaction in the electrochemical transducer requires a reference, counter, and working electrode, the working electrode acts as a transducer [11], and tumor antigens are used as biomarkers for cancer diagnosis in biosensors [12]. The ultimate goal of biosensors is to detect signals specific to each disease and cancer, and recently nanoparticles have been widely used in the design of biosensors. These nanoparticles can react with the analyte in the sample and increase the detection range [13][14]. Nanostructured materials as guiding elements in biosensors that increase the stability of bioreceptor loading at the electrode surface by providing a more electroactive surface using functional groups. There are various purposes for using nanoparticles to make nanobiosensors, including increasing the surface to stabilize biomaterials and thus increasing sensitivity, catalyzing the process, large dynamic range, the possibility of reacting at low potentials, and helping the quick transfer of electrons from the active center of the electrode surface reaction in the electrochemical nanobiosensors [15]. Nanoparticles can be easily fabricated using chemical methods and react with the analyte in the sample, and their inherent properties, such as optical or magnetic properties, can be used [16][17]. Graphene and its derivatives are nanoparticles with unique properties and have many applications in nanobiosensors [18]. Graphene is a two-dimensional (2D) sheet of carbon atoms in a hexagonal (honeycomb) configuration that is an allotrope of carbon [19][20]. Graphene sheets are formed by placing carbon atoms side by side, and in a graphene sheet, each carbon atom is bonded to three other carbon atoms [21]. These three bonds are on the same sheet, and the angles between them are equal to 120°. The length of the C-C bond in graphene is about 0.142 nm [22]. The inherent strength of graphene layers results from these bonds, known as covalent bonds [23]. While the carbon bonds are sp^2 hybridized, and the σ C-C bond is the strongest bond in materials, the pi (π) bond is responsible for the electron conduction of graphene [24]. With these unique structural properties, graphene has been shown to have special properties and has attracted much interest in scientific research [25]. Graphene transfers heat better than any alternative material and is an excellent electrical conductor with unique optical properties. The derivatives of graphene such as Graphene Oxide (GO), Reduced Graphene Oxide (RGO), and Graphene Quantum Dots (GQDs) have entered the field of graphene research and nanobiosensors because of their unique properties [25]. GO is a derivative of graphene that is obtained by graphite using oxidizing materials [26]. GO is one typical 2D structured and oxygenated planer molecular material. RGO is a reduced form of GO that contains a π-conjugated system. The only major difference between GO and RGO is the number of oxygen atoms present and their conductivity [27]. RGO has low electrical conductivity due to the disruption of the main structure of graphene, but it has a high ability to be functionalized with a variety of chemical and biological molecules. GQDs consist of one or a few layers of graphite and are smaller than 100 nm [28].

2. Graphene-Based Materials and Their Properties

The physical properties of carbon materials are related to their hybridization stats (sp, sp^2, sp^3) [29][30][31][32]. Graphene with sp^2 hybridization is a fine and zero bandgap semiconductor, but the sp^3 hybridization diamond is a hard insulator. Graphene is highly thermally conductive, chemically stable, and flexible [33]. One of the superior properties of graphene is that its charge carriers treat as massless particles, and they can move with little scattering in an ambient condition [34]. The charge transport of graphene and its electronic properties are due to its great electronic band structure [35]. Especially among all nanomaterials, graphene has a wide surface area (2630

m^2g^{-1}) [24][25] and is available for direct interaction with many biomolecules [36]. It can be wielded with structural defects using low-cost fabrication methods by chemical modification [37]. The sensitivity of the electrical resistance of graphene to the adsorption makes it highly useful for highly sensitive sensing applications [33].

Other unique properties of graphene, including its optical, magnetic, and high elasticity, make it a suitable monolayer structure for preparing several graphene-based nanocomposites. Graphene has one of the highest tensile strengths of all materials and a high Young's modulus, which is the relation between stress and strain, that gives graphene its great mechanical properties [38][39]. Using graphene in several sensing applications based on an electrochemical read-out has been offered in various chemical and biological sensors [40]. Graphene derivatives, such as GO and RGO, have been consumed for the fabrication of a diverse range of graphene-based nanocomposites in biosensors by a mixture of metal and biomolecules with enhanced sensitivity [33][41]. Because of the great surface-to-volume ratio and functional chemical groups, GO has broad capacities for the adsorption of biomolecules [42]. GO is composed of graphene layers with active oxygen-containing functional groups on its surface, such as hydroxyl, epoxy, and carboxyl. GO has unique physicochemical properties such as its small size between 20 nm–100 nm, conductivity, and optical and electronic properties [43][44]. Furthermore, GO is hydrophilic and water soluble, whereas graphene is hydrophobic and does not dissolve easily in water [25]. GO has a significantly disrupted sp^2 carbon network and shows many defects, and functional groups make its insulators [24]. GO is not conductive and has reduced mechanical properties compared to graphene. Accordingly, to improve the conductivity of GO, it is necessary to convert GO into RGO. Graphene nanomaterials can be successfully functionalized through non-covalent or covalent interactions. Typical covalent reactions include oxidation, reduction, radicals, and nucleophilic/electrophilic additives [45].

3. Graphene-Based Biosensors

3.1. Graphene-Based FET Biosensors

Over the last few decades, attempts have been made to utilize semiconductor field-effect transistors (FETs) in biological and chemical sensors due to their well-characterized behavior and ease of use of portable devices. In addition, the electrical measurement of bimolecular interactions is particularly desirable due to its adequacy for low-cost mobile sensors that could be used in the area by non-technical individuals [46]. FET-based biosensors are excellent candidates for several label-free transducers. They have gained much more attention in recent years for their considerable advantages, such as high scalability, ultra-sensitivity, rapid real-time analysis, inherent amplification, reduced power needs, direct electrical read-out, and low-cost bulk development, as opposed to surface plasmon resonance, microcantilever sensors, fluorescence instruments, and other approaches [4][47].

An FET-based biosensor includes three electrodes—the source, the drain, and the gate—such that the section between the drain and the source functions as a biological detection component that interacts with the target analyte/biomolecules and senses their presence, concentration, and electrical activity. The biosensor then converts the biological information directly into a detectable signal [48]. Subsequently, based on the implementation, the signal acquired can be illustrated, amplified, stored, and analyzed or sent to the data center for additional

processes [49]. The function of the FET-based biosensor can be encapsulated as: (1) an alteration in the concentration of the sample solution leads to a difference in the charge close to the interface of the sensor; (2) this shift of charge causes a decrease in the effective gate voltage; (3) this variation in the effective gate voltage contributes to a change in the current flow of the drain [50].

Due to the linear dispersion relation of the charge carriers in graphene, they have a very small effective mass and excellent carrier mobilities [51]. Furthermore, graphene-based nanomaterials have high thermal conductivity, as well as availability and low cost. The charge transfer nature of graphene enables a special channel material that replaces silicon and other common semiconductors. In comparison to other semiconductors, graphene does not require impurity doping to conduct electricity. It demonstrates self-doping phenomena that cause the carrier type and concentration to be regulated with the aid of an external electrical field. The alternating ability between GFET's n- and p-channel varies from other FET technologies [52][53][54].

As a conductive channel substrate, many findings have been obtained through research on the contact resistance between graphene and metal to enhance the efficiency of the field-effect transistor. In addition, the need for high carrier mobility and luxurious functional groups has prompted a great deal of effort, such as the heating-assisted spray system for manufacturing mass production of RGO sheets and the interlayered quantum dots for elevating carrier mobility. Biocompatibility, ease of functionalization, and biocatalysis in the oxygen reduction reaction (ORR) are other outstanding features of graphene-based nanomaterials that are useful in the fabrication of GFETs for ultrasensitive and low-noise cancer detection [54][55][56].

It is important to maintain the stability of the antibody-modified surface during FET measurements. However, unlike other measurement methods, FET measurements use an electrical application on the gate area that can damage the surface. Electrical application may repel antibodies that are immobilized on the surface. Thus, preserving antibody-modified FET properties during measurements improves the reliability of FET antigen detection. Hidshima et al. evaluated three types of FET-modified antibodies to measure stability. The change in FET properties was determined three times in a row by calculating the change in the amount of threshold voltage change (C_V). Modified C_V FET with electrically activated antibodies showed good stability [57].

3.2. Graphene-Based Surface Plasmon Resonance (SPR) Biosensors

SPR-based technologies have proven to be one of the most effective tools for real-time tracking of molecular dynamics, alongside quantitative measurement of numerous biomarkers such as proteins, DNA, entire cells, etc. [58][59][60]. One of the most critical aspects of the SPR biosensors is the surface of the sensor, as it plays a crucial role in the overall efficiency of the sensor. Many experiments have also concentrated on the use of smart sensing layers for more adjustable implementations [61][62][63]. SPR sensing is a powerful, label-free method for investigating noncovalent molecular interactions as a non-invasive method, and in the last two decades, SPR has been widely used in the study of noncovalent protein–DNA, protein–cell, DNA–RNA, DNA–DNA, protein–protein, etc., interaction experiments [64].

SPR biosensors have the potential for extensive implementation in biomarker diagnostics due to the very high surface plasmons' sensitivity to the alternation in the reflective index (RI) of the dielectric medium. Interaction between the immobilized receptors on the metal surface and the analyte molecules causes a variation in the sensed medium's refractive index (dielectric), which leads to an alteration in the propagation constant of the surface plasmons. This phenomenon affects the resonance condition of surface plasmons with specific surface plasmon waves (SPW) that have interactions with the incident p-polarized light of the same propagation constant. The energy of light photon transfers to the surface plasmons at the resonance angle, and the reflectance of the light significantly decreasing, results in forming a sharp dip in the SPR curve (reflectance with respect to the incident angle) [65][66]. The measured interacting optical wave can be used to fabricate various types of SPR biosensors with angular, intensity, phase, or wavelength modulation [67].

Phase detection based on coherence is usually very sensitive to mechanical movements in optical components and ambient noise, which leads to phase measurement errors. The stability of the SPR biosensor in the time axis is also required to monitor the biological response over time.

3.3. Graphene-Based Fluorescent Biosensors

Biomolecular imaging and biomarker detection can be performed using fluorescent nanomaterials and labels, a highly sensitive and selective method with adequate spatiotemporal resolution and low cost for application [68]. Numerous fluorimetric diagnostic tests and fluorescent-based biosensors focused on biocatalyst behavior have been documented using organic dyes, inorganic semiconductor quantum dots (QDs), and carbon nanomaterials as fluorimetric indicators [69][70]. The operation of these biosensors is based on the fluorescence phenomenon that happens when a fluorophore or fluorescently labeled molecule absorbs the corresponding electromagnetic radiation. According to the signal generating technique in fluorescent biosensors, they are categorized into four types, including FRET (Förster Resonance Energy Transfer), FLIM (Fluorescence Lifetime Imaging), FCS (Fluorescence Correlation Spectroscopy), and FI (change in fluorescence intensity) [71]. The main advantages of fluorescence-based biosensors are extreme sensitivity, they are minimally invasive or non-invasive, they have the ability to utilize fluorescence intensity and fluorescence lifetime, and they provide the structure and microenvironment of molecules [72][73][74].

3.4. Graphene-Based Electrochemical Biosensors

Electrochemical sensing essentially needs a reference electrode, a counter (auxiliary electrode), and a working electrode, sometimes termed as the sensing or redox electrode. The reference electrode, usually produced from Ag/AgCl, is held at length from the reaction site to preserve a specified and consistent potential [75]. The working electrode acts as a transduction component in the biochemical reaction, while the counter electrode links the electrolytic solution so that the current can be delivered to the working electrode. These electrodes ought to be conductive and have chemical stability [76]. According to the Institute of Clinical and Laboratory Standards (CLSI; EP05-A3, EP24-A2, EP25-A), a change factor (CV) of less than 10% is required for reproducibility, accuracy, and stability. Therefore, further improvements in biosensors, especially in the case of electrodes and intermediates, are

two components that determine the reproducibility, accuracy, and stability of all electrochemical biosensors [77]. Platinum, gold, carbon (e.g., graphite), and silicone derivatives are thus widely utilized based on the analyte [76].

3.5. Graphene-Based Surface-Enhanced Raman Scattering (SERS) Biosensors

In Raman scattering, photons inelastically lose (Stokes) or gain (anti-Stokes) energy because of molecular vibrational events and represent information about the molecular structure enabling in situ and real-time detection [78]. Surface-enhanced Raman scattering (SERS) is a subset of Raman scattering, a widely used sensing technique in which when the molecules are adsorbed on corrugated metal surfaces such as silver or gold nanoparticles, inelastic light scattering by molecules is greatly improved [79][80]. By way of plasmonic nanostructures, it provides a million-fold improvement, making the efficiency of detection down to the level of single molecules. Two different pathways, namely electromagnetic enhancement and chemical enhancement, accomplish SERS enhancement [81].

3.6. Graphene-Based Electrochemiluminescent Biosensors

Electroluminescence or electrogenerated chemiluminescence (ECL) is the shared area of electrochemistry and chemiluminescence (CL). In this mechanism, by applying a potential on the electrode's surface, the electrochemical energy is being converted to radiative energy [82][83][84]. This phenomenon can happen by utilizing species that undergo electron transfer reaction to form an excited state and, after that, produce light when molecules return to the ground state [85][86]. Therefore, ECL does not need external light sources, so problems of light scattering inherent in photoluminescence (PL) can be avoided [84]. In the ECL method, the electrochemical reactions take place through the interplay of the luminophore and a co-reactant molecule by applying only one single potential step. Two approaches to the co-reactant ECL mechanism are available. The first one is the oxidative reaction, in which a potent reducing radical agent is produced by oxidation of the co-reactant in a homogeneous follow-up reaction. This radical can reduce the oxidized luminophore, so the luminophore becomes excited and emits light. The second one is reductive oxidation, in which the reduction takes place straightforwardly [87].

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