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Biosensors based on graphene oxide and its biomedical application☆

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ABSTRACT

Graphene oxide (GO) is one of the most attributed materials for opening new possibilities in the development of next generation biosensors. Due to the coexistence of hydrophobic domain from pristine graphite structure and hydrophilic oxygen containing functional groups, GO exhibits good water dispersibility, biocompatibility, and high affinity for specific biomolecules as well as properties of graphene itself partly depending on preparation methods. These properties of GO provided a lot of opportunities for the development of novel biological sensing platforms, including biosensors based on fluorescence resonance energy transfer (FRET), laser desorption/ionization mass spectrometry (LDI-MS), surface-enhanced Raman spectroscopy (SERS), and electrochemical detection. In this review, we classify GO-based biological sensors developed so far by their signal generation strategy and provide the comprehensive overview of them. In addition, we offer insights into how the GO attributed in each sensor system and how they improved the sensing performance.

Contents

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1. Introduction

1.1. Brief introduction on graphene oxide (GO)

In 2004, Andre Geim and Konstantin Novoselov reported a methodology for isolation of graphene and were awarded the Nobel Prize in Physics in 2010 for "ground breaking experiments regarding the two dimensional material graphene" [1]. Since its isolation, this two-dimensional (2D) carbon sheet has drawn immense attention and researches revealed its high planar surface area calculated as 2630 $m^2\ g^{-1}$, superior mechanical strength with a Young's modulus of 1100 GPa, remarkable thermal/electrical conductivity, and optical property [2,3]. Owing to these exceptional properties, graphene and its derivatives have been actively employed in a lot of applications such as transparent electrode, energy storage, cell scaffold, biosensor, drug delivery system, and catalysis to date [3–6].

Graphene oxide (GO), generally obtained by oxidation of graphite in a mixture of strong acid and oxidizing agent, is a water-dispersible graphene derivative (Fig. 1a) [7–10]. The oxidation process results in partial breaking of the sp2 hybridized structure of graphite and increasing the distance between carbon layers [11,12]. The precise structure of graphite oxide is still under debate to date, but it is certain that GO possesses both hydrophobic part from pristine graphite structure and hydrophilic part with oxygen containing functional groups such as hydroxyl, epoxy, carbonyl, and carboxyl groups on the basal plane and at the edge, generated by oxidation process (Fig. 1b,c) [13,14]. In terms of its fabrication, GO is commonly produced by using the Brodie, Staudenmaier, and Hummers methods or these methods with minor modifications [8]. The partial breaking of the conjugated structure localizes pi-electrons, resulting in the decrease of the overall electrical conductivity. However, the remaining sp2 domains with added hydrophilic groups during oxidation process make GO exhibit unique properties, such as affinity for aromatic rings and fluorescence-quenching capability, while maintaining high dispersibility in aqueous solvents. The hydrophilic nature of GO generated from the oxygen containing functional groups gives good water dispersibility and biocompatibility, which are highly important features in bio-applications. These properties of GO have provided a lot of opportunities for the development of novel biological sensing systems [11,12,15–18].

GO can sometimes serve as a sensing element itself due to its own properties such as Raman signal or fluorescence observed in some specially prepared GO. Frequently, GO can be employed as a precursor of reduced graphene oxide (rGO) possessing chemical structures closer to pristine graphene or graphene nanocomposites [3,18,19]. The rGO can be prepared starting from GO by the treatment of various reducing agents, such as hydrazine monohydrate, sodium borohydride, and hydroquinone [20–22], which eliminate most of the oxygen containing functional groups of GO and partially restore the electrical conductivity of GO. For example, reduction process can lower the sheet resistance up to 14 kΩ/sq, which is about 2-order higher than that of pristine graphene, whereas as-synthesized GO exhibits a sheet resistance of about 10^{12} Ω/sq or higher [23]. In addition to rGO, graphene nanocomposites produced by the combination of rGO with other functional nanomaterials exhibited significant enhancement in the original properties of graphene or synergistic addition of new function to the properties of graphene [3,17,18,24–26]. In this review, we focus on the bioanalytical applications of GO and its derivatives and discuss the significance, shortcoming, and future perspectives of the GO-based bioanalytical systems.

1.2. General strategies for GO-based biosensors

We first offer brief overview on the role of the GO adapted in each sensor system and how it improved the sensing performance. Basically, properties of GO have been utilized in many different types of biosensors, which can be representatively classified into biosensors based on (1) fluorescence resonance energy transfer, (2) laser desorption/ionization mass spectrometry (LDI-MS), (3) surface-enhanced Raman spectroscopy (SERS), and (4) electrochemistry (Fig. 2, Table 1). First of all, the excellent efficiency of energy/charge transfer from dye to GO enabled the development of a lot of FRET-based biosensors. Common strategy in these applications relies on the high energy/electron transfer capability and the amphiphilicity of GO [12,27,28]. These properties make GO capable of (1) strong binding with biomolecules through pi-pi stacking and/or hydrogen bonding interactions and (2) the fluorescence quenching of nearby fluorescent dye by the process of energy transfer from the excited state of the dye to GO [29–34]. Particularly, preferential binding of single stranded nucleic acid (NA) on GO

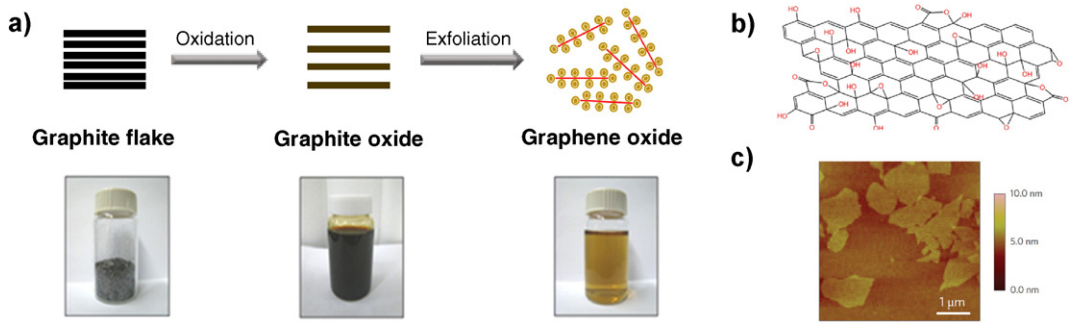

Fig. 1. (a) Chemical route to the synthesis of aqueous graphene dispersions. (b) The expected chemical structure of a single sheet of GO. (c) AFM image of the GO on a silicon substrate showing an average thickness of around 1 nm. Adapted and reproduced with permission from (c) Gao et al. [14], Copyright 2009, Nature Publishing Group.