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Review article

Graphene-based nanomaterials and their potentials in advanced drug delivery and cancer therapy

Jinzhao Liu[a], Jia Dong[a], Ting Zhang[b], Qiang Peng[a,*]

[a] State Key Laboratory of Oral Diseases, National Clinical Research Center for Oral Diseases, West China Hospital of Stomatology, Sichuan University, Chengdu 610041, China

[b] Department of Pharmacy, West China Hospital, Sichuan University, Chengdu 610041, China

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ABSTRACT

The continuing increase of cancer morbidity and death rate requires efficient therapeutic strategies. The traditional chemotherapy usually fails to treat cancer or prolong survival rate due to its toxicity to normal cells, side effects and lack of targeting capacity. In recent years, nanomaterials have shown great potentials to treat various cancers efficiently. Graphene-based nanomaterials, especially graphene oxide (GO) and reduced GO (rGO), have arisen as promising candidates for cancer therapy. Due to their unique physicochemical and optical properties including the extremely large surface area, modifiable active groups, great biocompatibility and strong photothermal effect, they can act either as tunable carriers or active agents for advanced chemotherapeutics delivery and cancer therapy. Therefore, combing the photothermal therapy, targeted drug delivery and chemotherapy would have great potentials for efficient cancer therapy. Herein, the comprehensive understandings of the physicochemical properties and various anti-cancer applications of GO and rGO as drug delivery systems or photothermal agents are described. Also, the concerns in using GO and rGO, such as the nano-protein interaction, and possible solutions are discussed.

1. Introduction

The continuing increase of cancer morbidity and death rate requires the highly efficient strategies for cancer therapy. The traditional chemotherapy usually fails to treat cancer or prolong survival rate due to its toxicity to normal cells, side effects and lack of targeting capacity. With the rapid development of the biomaterial industry and medical detecting devices, many novel anti-cancer strategies have been proposed, such as the carbon-, silica- or gold-based photothermal, photodynamic and tumor targeted therapy [1–4]. Among those, graphene-based nanomaterials and the related therapeutic approaches have shown great potentials in cancer therapy [5, 6].

Since the first time graphene was isolated from a bulk of graphite, many new methods to obtain graphene have been developed, including micromechanical exfoliation [7], exfoliation in solvent [8], epitaxial growth [9] and chemical vapor deposition [10]. Generally, graphene-based nanomaterials are classified into several types, such as graphene with varied layers, graphene oxide (GO) and reduced GO (rGO) [11]. Among these nanomaterials, GO and rGO are of greatest interests and potentials in biomedical fields due largely to their tunable physicochemical properties, high biocompatibility and easy availability [10, 11].The reports on the application of GO and rGO in drug delivery, cell targeting, biosensors and bioimaging have been well-documented [12–15]. Besides, the photothermal properties of GO and rGO confer them great potentials in targeted cancer therapy [16–18].

As mentioned above, GO and rGO, either as delivery vehicles or photothermal agents, have great potentials in cancer therapy (Fig. 1). The aim of this work is to provide comprehensive understandings of the physicochemical, photothermal and biological properties of GO and rGO, as well as why and how they can be used for cancer therapy. In addition, the current problems (like toxicity and protein corona formation) and possible solutions are discussed.

2. Physicochemical properties of GO and rGO

Although both GO and rGO belong to graphene family, they are significantly varied in physicochemical properties due to their differences in chemical structure. Generally, GO has a higher wettability than rGO due to the presence of much more oxygen-containing groups (Fig. 2) [19]. Accordingly, the water solubility of GO is also higher than that of rGO. It is reported that the solubility of GO in distilled water is 6.6 μg/ml and the water solubility of rGO is 4.74 μg/ml [20]. Due to

* Corresponding author.
E-mail address: qiangpengzz@scu.edu.cn (Q. Peng).

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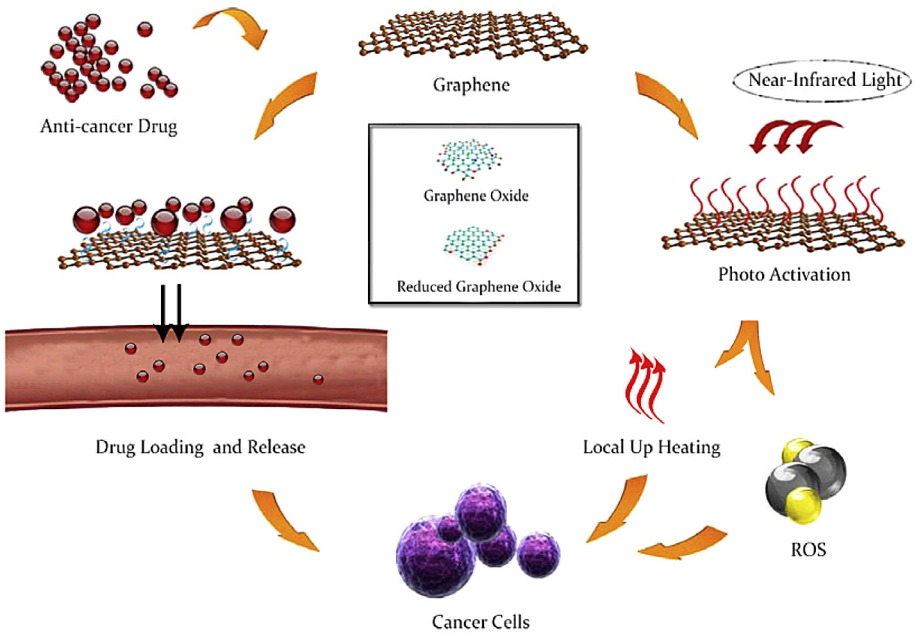

Fig. 1. Schematics of the anti-cancer function of graphene-based nanomaterials, either as drug carriers or photothermal agents.

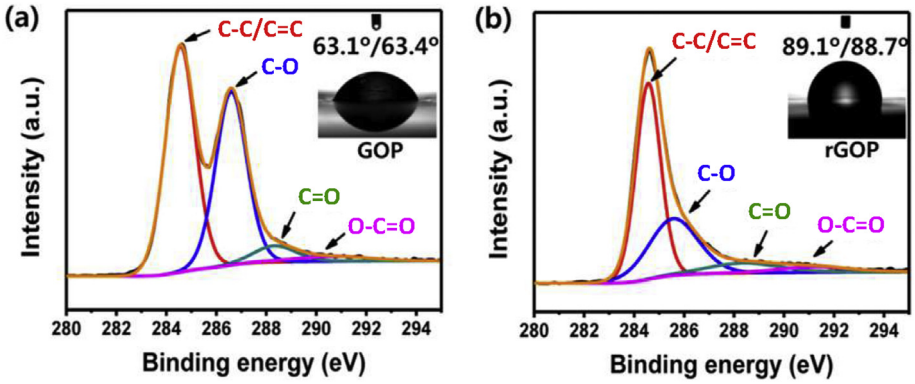

Fig. 2. X-ray photoelectron spectrum and contact angle data showing the C1s peaks and corresponding wettabilities of (a) graphene oxide paper (GOP) and (b) reduced graphene oxide paper (rGOP). Reprinted from Ref. [19].

those reactive groups, such as –OH and –COOH, GO can be easily modified and functionalized and thus has great potentials in advanced drug delivery [21–23]. In contrast, rGO maintains the sp2 bonding networks and thus has a significantly higher electric conductivity and photothermal effect [24, 25]. These physicochemical properties have substantial effects on their biomedical applications.

2.1. Graphene oxide (GO)

GO is synthesized mainly by three methods: the Brodie method [8], the Staudenmaier method [26] and the most commonly used Hummers method [27]. There are also some extensions and modifications of these methods [28, 29]. GO derived from different synthesis methods tends to have some differences in some aspects or properties, though they are basically coincident. The basic principle of all these methods is to use chemical reagents like potassium chlorate, nitric acid, sulfuric acid and potassium permanganate to oxidize graphite into different levels [30, 31]. Similar to graphite, the oxidized graphite also has layered structure and honeycomb lattice in each single layer. The difference is that graphite oxide also has many oxygen-containing groups in its structure, which endows graphite oxide the hydrophilicity and allows GO to be exfoliated from graphite oxide in water under sonication [25].

Mkhoyan et al. observed GO by means of composition sensitive annular dark field (ADF), atomic force microscopy (AFM) and electron energy loss spectroscopy (EELS) and measured its several parameters like roughness, O/C ratio, thickness of single sheet [32].The results show that the average sheet roughness, the single sheet thickness and the O/C ratio of GO is 0.6 nm, 1.6 nm and 1:5, respectively. The structure of GO is found to be mostly amorphous due to distortions from the high percentage of sp3 C—O bonds and randomly dispersed oxygen-containing functional groups [32]. Due to the disrupted sp2 bonding networks, GO is also reported to be an electrically insulating material.

The basic structure of GO is simply described as a graphene sheet modified with different kinds of functional groups, like carboxyl (−COOH), hydroxyl (−OH) and epoxy (—O—) (Fig. 3) [33]. That is these oxide groups that confer GO the hydrophilicity and the potential to improve the solubility of some water-insoluble drugs, and make GO more suitable for drug delivery than pristine graphene. Liu et al. reported that the solubility and the anti-cancer efficacy of a water insoluble drug SN38 was improved by loading onto the polyethylene glycol (PEG)-grafted GO [34]. Lei et al. also showed that the solubility of doxorubicin (DOX) increased after being loaded on GO functionalized by chitosan and sodium alginate [35]. In addition to hydrophilicity, those oxide functional groups also make GO able to attach covalently or non-covalently to other groups like small molecules and polymers, endowing GO with new and improved physicochemical,