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Functionalized graphene nanocomposites for enhancing photothermal therapy in tumor treatment☆

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ABSTRACT

Graphene and its derivatives have unique physical and chemical properties that make them promising vehicles for photothermal therapy (PTT)-based cancer treatment. With intrinsic near-infrared (NIR) absorption properties, graphene-based nanomaterials can be used for PTT and other therapeutics, particularly in combination therapy, to provide successful thermal ablation of cancer cells. In the recent years, advances in graphene-based PTT have produced efficient and efficacious tumor inhibition *via* nanomaterial structural design and different functionalizations of graphene-derived nanocomposites. Graphene-based nanosystems exhibit multifunctional properties that are useful for PTT applications including enhancement of multimodalities, guided imaging, enhanced chemotherapy and low-power efficient PTT for optimum therapeutic efficiency. Therefore, in this review, we address critical issues and future aspects of PTT-based combination therapy.

Contents

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1. Introduction

Conventional strategies such as surgical resection, chemotherapy, and radiotherapy, alone and in combination, are still used for cancer treatment even though only limited therapeutic efficacy can be achieved. Recently, advances in nanoscience and nanotechnology have led to the development of a number of new antitumor therapy strategies including drug/gene delivery systems, photothermal therapy (PTT), photodynamic therapy (PDT), and immunotherapy because of their unique physicochemical properties [1–5]. In the past decade, PTT has received wide attention; it is minimally invasive and can produce effective thermal ablation of targeted cancer cells.

So far, several nanomaterials with strong NIR absorbance have been developed as photothermal agents for killing cancer cells, including gold-based structures, carbon-based materials (carbon nanotube and graphene), Pd sheets, CuS particles, and even organic particles [6–10]. More importantly, these light-absorbing nanoparticles can be actively delivered to the tumor site where hyperthermia therapy can be used to release therapeutic reagents and kill cancer cells at target sites. The thermal enhancement of therapeutic efficacy reduces side effects of therapeutic agents, in comparison to either systemic delivery or passive targeting at the tumor site [11,12].

Graphene-based materials (such as graphene oxide (GO), reduced graphene oxide (rGO) and GO-nanocomposites) have shown promise when applied to photothermal treatment of cancer because of NIR absorbance, large specific surface area and abundant functional groups, which are available for efficient biomolecular loading or bioconjugation [13–16]. Orecchioni et al. performed a comprehensive study on the latest progress of graphene to fight cancer and found that PTT is the second biggest portion for cancer therapy and has the possibility to become a promising method for cancer treatment in a minimally invasive manner [17]. Liu et al. was the first group to report the use of GO combined with PTT for successful suppression of the tumor *via* intravenous administration [13]. To further improve PTT efficacy, nano-sized rGO with noncovalent polyethylene glycol (PEG) was shown to exhibit a remarkable increase in high biocompatible and photothermal conversion [18]. However, it is not likely that PTT alone can be used to eradicate malignant cells because of the locally heterogeneous distribution of heat in the tumor [19]. Therefore, it would be optimal to integrate photothermal ablation therapy with other strategies or to modify the physiochemical properties of GO to enhance the therapeutic efficacy.

To date, there have been considerable efforts to explore graphene-based nanomaterials in the PTT, particularly in combination therapy for cancer treatment. Table 1 summarizes the recent studies and important results of graphene-based materials used in NIR photothermal destruction to enhance the efficacy of tumor therapy. There are several key considerations in the design of a graphene-based nanosystem with multifunctional PTT or combination therapy to achieve efficiently efficacious therapy for future clinic applications. For example, an ideal system would have a stimuli-responsive targeted drug-carrier that combines physical (photothermal) therapy with on-demand high concentration drug release over a large treatment area. Therefore, in this review, we report on the current progress in the therapeutic strategy of PTT-based combination therapy and further describe the recent studies to achieve efficiently efficacious PTT *via* nanomaterial structure design and different functionalization of graphene-derived composite. This review is divided into five parts: 1) PTT with combination treatments; 2) bio-functionalized PTT; 3) multimodalities-enhanced PTT; 4) low-power efficient PTT; and 5) nanocomposite structure-modified PTT (Fig. 1). It is believed that this review article could help researchers understand the whole picture of progress, recent advances and future prospects with graphene-based PTT for tumor treatment.

2. Structural features of graphene-based materials for PTT

PTT mainly uses an optical-absorbing agent with electromagnetic radiation (most often in infrared wavelengths) for the treatment of tumors and other diseases. When the PTT agents absorb light, the electrons transition from the ground state to the excited state, and then the energy relaxes through nonradiative decay, resulting in an increase in the kinetic energy to overheat the local environment around the light-absorbing species [20,21]. Recently, Melamed et al. tried to elucidate the fundamental mechanisms by which PTT triggers cell death. They found that PTT can be used to induce apoptosis rather than necrosis, thereby preventing an inflammatory response [22]. Pérez-Hernández et al. studied the components of the extrinsic and intrinsic apoptosis pathways activated by PTT and revealed that the intrinsic pathway is the major mediator of PTT-induced apoptosis under low-energy irradiation [23]. The evidence supporting this hypothesis for PTT-triggered apoptosis (shown in Fig. 2) includes (i) loss of Bid and increased production of tBid determined by Western blotting following PTT, (ii) loss of mitochondrial membrane potential assessed by flow cytometry following PTT, and (iii) activation of caspase-3 following PTT. These observations confirm that PTT can initiate apoptosis through the intrinsic pathway under appropriate therapeutic conditions.

Graphene consists of sp^2-hybridized honeycomb two-dimensional carbon lattice [41], which displays extraordinary properties because of its dimensionality and unique electronic band structure [24]. Graphene can behave as a semimetallic carbon material with linear dispersion [25] due to its Dirac fermions (zero effective mass) [26], which suppress carrier backscattering [27]. Therefore, some interesting physical properties such as high intrinsic carrier mobility [28], room-temperature ballistic transport on a submicrometer scale [29] with large mean free path [30], and enhanced Coulomb interaction [31] have been exhibited. In contrast to graphene, GO is covered by oxygen-containing functional groups such as hydroxyls and epoxies on the basal plane arising from various preparation processes. The non-uniform coverage of oxygen-containing functional groups on the graphene basal plane of ordered small (2–3 nm) sp^2 clusters isolated within the sp^3 C–O matrix can be detected by Raman spectroscopy [32,33], scanning tunneling microscopy [34,35] and high-resolution transmission electron microscopy [36,37]. The reduction of GO formed new sp^2 clusters after the removal of oxygen and provided percolation pathways between the 2–3-nm sp^2 domains. These sp^2 states can be viewed electronically as the creation of isolated molecular states that aided transport by hopping [38,39].

Owing to the unique structure and strong interactions between graphene and low-frequency photons at infrared and terahertz frequencies, graphene exhibits plasmonic effects under specific wavelengths like NIR that generates heat through plasmonic photothermal conversion. Once irradiated with NIR, graphene surface plasmons are excited and induced, followed by transmitting random dipoles and resonance, which are ultimately converted to thermal photon energy output, so graphene-based materials are considered excellent photothermal agents. Although graphene has emerged as a novel material in nanocarbon research, the photothermal conversion efficiency is obviously affected by physiochemical properties. As compared to GO, rGO, which is derived by chemical reduction to partially restore the aromatic character of the graphene sheets, can increase NIR absorbance to six times greater than that of GO because of the highly intact aromatic structure of graphene [18]. In addition, the laser-induced temperature displayed a non-linear variation depending on the nano-GO concentration. A critical value of 0.0005 mg/mL of nano-GO solution is needed to obtain a gain on energy transference from the particles to the solution through irradiation (980 nm; intensity of 1.0×10^5 Wm^{-2}) [40]. A giant infrared-absorption band in rGO with oxygen atoms aggregated at the edges of defects, arising from the coupling of electronic states to the asymmetric stretch mode, significantly enhanced the infrared absorption [41]. With cross-section and blackbody power irradiated