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Developing the next generation of graphene-based platforms for cancer therapeutics: The potential role of reactive oxygen species

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ABSTRACT

Graphene has a promising future in applications such as disease diagnosis, cancer therapy, drug/gene delivery, bio-imaging and antibacterial approaches owing to graphene's unique physical, chemical and mechanical properties alongside minimal toxicity to normal cells, and photo-stability. However, these unique features and bioavailability of graphene are fraught with uncertainties and concerns for environmental and occupational exposure. Changes in the physicochemical properties of graphene affect biological responses including reactive oxygen species (ROS) production. Lower production of ROS by currently available theranostic agents, e.g. magnetic nanoparticles, carbon nanotubes, gold nanostructures or polymeric nanoparticles, restricts their clinical application in cancer therapy. Oxidative stress induced by graphene accumulated in living organs is due to acellular factors which may affect physiological interactions between graphene and target tissues and cells. Acellular factors include particle size, shape, surface charge, surface containing functional groups, and light activation. Cellular responses such as mitochondrial respiration, graphene-cell interactions and pH of the medium are also determinants of ROS production. The mechanisms of ROS production by graphene and the role of ROS for cancer treatment, are poorly understood. The aim of this review is to set the theoretical basis for further research in developing graphene-based theranostic platforms.

1. Introduction

Cancer is one of the leading causes of morbidity and mortality worldwide, with more than 14 million new cases and 8.8 million deaths in 2012 [1]. Globally, cancer accounts for nearly one of every six deaths. Cancer elicits a significant economic cost. The total annual economic cost of cancer in 2010 was estimated at approximately US$ 1.16 trillion [2]. Conventional therapeutic options including chemotherapy and radiation therapy are most commonly used in the treatment of cancer. However, these modalities yield low success rates and have profound adverse side effects on patients' physical and mental health [3]. Therefore less invasive, and more effectively targeted, treatments need to be developed for palliative care and improvement of quality of life. Novel regimes for simultaneous diagnosis and therapy, known as theranostics, have changed the cancer treatment algorithm by the combination of bio-imaging with site-specific and site-selective targeting of tumors, without damaging normal cells [4]. A schematic representation of the components of a typical theranostic platform is given in Fig. 1.

The two key components of this theranostic platform are: first, targeted diagnostic imaging modalities and, secondly, targeted delivery of therapies such as photodynamic therapy (PDT). An excellent review of targeted diagnostic imaging has recently been contributed by Cope et al. (2016) [5]. PDT has evolved into a practical, effective and systematic theranostic option comprising of the multiple-exposure, guided, non-invasive, treatment of tumors in combination with real-time detection and tracking of malignant tissue by fluorescence imaging. The basis of PDT is that light is utilized to activate a non-toxic photosensitizer, leading to the generation and localization of highly toxic reactive oxygen species (ROS) at the targeted site of cancerous tissue. PDT offers several advantages over traditional treatment options, typically including low toxicity of the photosensitizer in the absence of light interaction/irradiation, better efficacy, low side effects, selective and specific accumulation, and deep penetration of photosensitizer into the tumors [6]. Nevertheless, the mechanism of the selective and specific killing of tumor cells by ROS remains unclear. A better

Abbreviations: PDT, photodynamic therapy; ROS, reactive oxygen species; GO, graphene oxide; HIF-1α, hypoxia-inducible factor-1 alpha; NF-κB-NF kappa B, nuclear factor kappa-light-chain-enhancer of activated B cells; PTEN, phosphatase and tensin homolog deleted on chromosome 10; AP-1, activator protein-1; Hh, hedgehog; STAT3, signal transducer and activator of transcription 3; Rb, retinoblastoma; Nrf2, nuclear factor erythroid-derived 2-like 2; Sp1, specificity protein 1; PPa, Pyropheophorbide-a; mAb, monoclonal antibody

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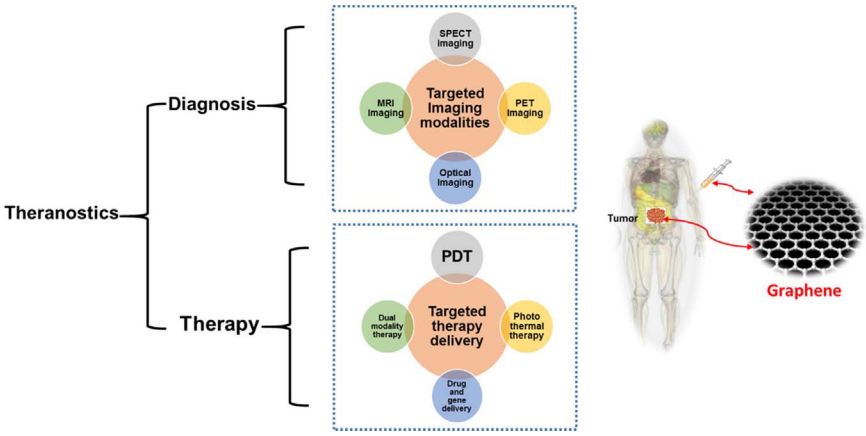

Fig. 1. Schematic representation of a typical theranostic platform for the combined use of a range of imaging and therapeutic approaches. Imaging modalities include: ultrasonography, positron electron tomography, fluorescence imaging, magnetic resonance imaging and single-photon emission computed tomography. Therapeutic approaches include: drug delivery, photothermal therapy, photodynamic therapy, or a combination of two therapies. Based on its unique properties, graphene can be employed as a theranostic agent that combines the capabilities of diverse imaging and therapeutic modalities to target tumors.

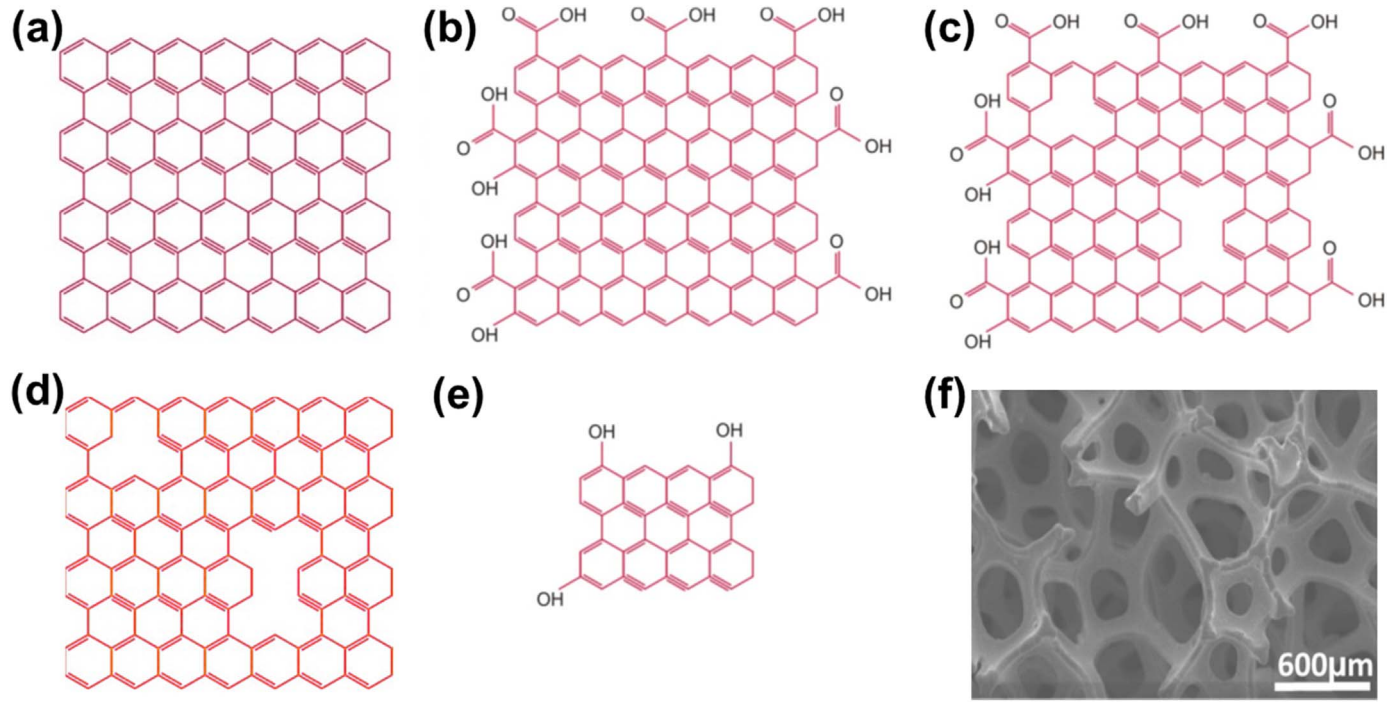

Fig. 2. Summary of structural models of various derivatives of graphene. (a) Graphene, (b) graphene oxide (GO), (c) reduced graphene oxide, (d) porous graphene, (e) graphene quantum dots and (f) three dimensional graphene foam. Graphene is a sp^2 hybridized model of carbon atoms in a repeated manner, forming a regular lattice structure (as shown in panel a), while GO and reduced GO have functional groups and defects in their basal planes (panels b and c). The physicochemical properties and structures of different graphene variants depend on the fabrication method and conditions. The presence of both defects and functional groups provides potential advantages for the efficient utilization of graphene variants in the production of ROS. The chemical exfoliation method is thought to be an efficient route for synthesizing graphene on a large scale and at low cost. Porous graphene is a graphene sheet that is missing carbon atoms from its plane. The various forms of porous graphene provide fascinating materials for biological applications owing to their high specific surface areas, hydrophobic nature and biocompatibility. Graphene nanopores usually have pore sizes of 1–30 nm. Pores and vacancies can clearly be seen in the porous graphene sheet, as represented in panel (d). Graphene quantum dots are luminescent nanocrystals having a size less than 50 nm. These have attractive properties and potential applications in cancer diagnosis and treatment. Water soluble graphene quantum dots, shown in panel (e), have functional groups (C–OH, C = O, C–O–C, C–H) on their surface. Three-dimensional graphene networks in the form of a foam, sponge or aerogel have recently been assembled from individual graphene sheets using chemical vapour deposition templated methods, which also preserve the unique properties of individual graphene sheets. [Panel (f) is adapted from [12], with permission of MDPI Publishing Group, Copyright 2015].

understanding of this phenomenon will empower patients and clinicians with a greater confidence in this treatment option.

A key feature of PDT is to exploit the light source for selective activation of the photosensitizer within the tumor cells. A light source of appropriate wavelength (visible or near-infrared) is used to activate a photosensitizer that generates and releases ROS, for the selective killing of tumors [7]. The photo-activation of the photosensitizer initially enables its excitation to a triplet state through a short-lived intermediate called the ‘singlet state’. The electron and energy transfer to the surrounding free oxygen produces ROS, including singlet oxygen, the superoxide anion radical, the hydroxyl radical, and hydrogen peroxide. Highly toxic ROS cause tumor cell death by oxidative stress.

Historically, the development of photosensitizers has resulted in three eminent generations of photosensitizer types. The first generation is porphyrins [8]. The clinical limitations of porphyrins are poor selectivity, poor photosensitivity, a low clearance rate, and a low light penetration within tumors. The second generation of photosensitizers - including chlorins, porphyrinoids and transition metal complexes - also has several problems such as: high hydrophobicity, poor tumor selectivity, complex surface chemistry, and aggregation in aqueous media. The third generation includes biomolecule conjugates and covalently attached peptides [8]. The selection of biomolecules is critical for their clinical efficacy because of the selective targeting capability, the structural and photochemical properties of these conjugates,