



Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: [www.elsevier.com/locate/ybbrc](http://www.elsevier.com/locate/ybbrc)

## Graphene-based materials: The missing piece in nanomedicine?

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### ARTICLE INFO

#### Article history:

Received 26 August 2018

Accepted 6 September 2018

Available online xxx

#### Keywords:

Graphene

Nanomedicine

Toxicity

Reactive oxygen and nitrogen species

Cancer diagnosis and treatment

Wound healing

### ABSTRACT

Nanomedicine utilizes biocompatible nanomaterials for therapeutic as well as imaging purposes for the treatment of various diseases including cancer, neurological disorders and wound infections. Graphene and its modified nanostructures have attracted much attention in recent years in nanomedicine owing to their scalable and cost effective preparation and physicochemical features (high specific surface area, ease in conjugation to peptides/antibodies/proteins and biocompatibility). However, the limited fabrication, functionalization, and *in vivo* functionalities available in literature indicate inconsistencies regarding the factors affecting *in vivo* metabolisms, biodistribution as well as toxicity patterns of graphene. It appears that redox signaling pathways, and their proper use to target specific diseases and to improve biocompatibility and interplay between size and optical properties are key determinants to investigate the metabolic fate of such materials. This featured letter provides key insights into the significance and multifunctional roles of redox regulated species in graphene-based materials which can be used to closely mimic therapeutic functions, navigating new paths to nanomedicine and synthetic biology. Furthermore, this letter focuses on the missing functionalities and challenges in using graphene-based materials as both nano-carriers and nano-drugs in various biomedical sectors which might be favorable for multiple payloads and drug targeting in upcoming years.

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### 1. Introduction

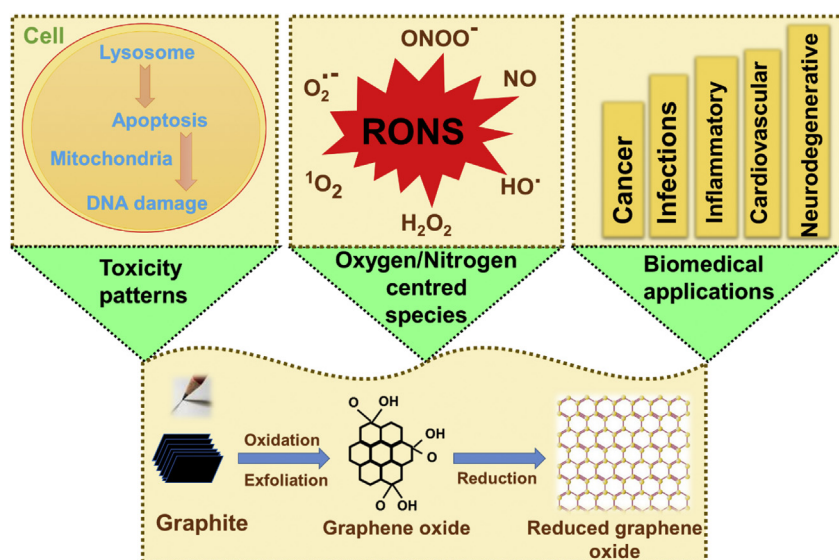
The use of graphene is becoming well established in the fields of photonics and electronics, but it is only now, with the technologies maturing, that it is branching out into new areas such as nanomedicine and synthetic biology, and it promises to revolutionize clinical settings across the board in areas including but not limited to drug delivery systems for theranostics, high throughput biosensors and bioassay, smart scaffolds for tissue regeneration, and ultra-high sensitive biomarkers [1–3]. Graphene is known as a relatively inexpensive archetypal monolayer framework of carbon species, amongst carbon nanotubes and fullerenes and many others [4]. The unique and tunable features of graphene-based materials (including pristine graphene, graphene oxide, reduced graphene oxide, graphene quantum dots (GQDs), graphene nanoribbons, graphene nanoplatelets, three dimensional graphene foam and many others) promise many new approaches in medical interventions, where its high surface area, exceptional electronic features and high mechanical strength could be a boon for drug delivery techniques [5] (See Fig. 1). Their lateral dimensions and

thickness can be tuned between nano-to milli-meters and mono-to few-layers, respectively; additionally, their two-dimensional nature can be modified to zero, one, and three-dimensional assemblies [6–8]. Graphene-based materials are perhaps the first systems to take advantage of such a tunability approach among other nanomaterials, improving the accumulation of drug vehicles and contrast agents at specific target sites in different diseases [9]. Graphite is a layered structure; each layer packed in a hexagonal lattice, while graphene is one atomic thin layer of graphite which is formed of  $sp^2$  hybridised carbon atoms composed in a hexagonal/honeycomb lattice [10,11]. In other words, graphite is composed of many layers of graphene [12]. It is well known that single layer graphene has not been achieved *via* exfoliation of graphite, which is another drawback in commercial applications of graphene [13–15]. As theoretically graphene has superficial electrical and mechanical properties which has not been obtained experimentally due to insufficient oxidation and/or inadequate reaction conditions that may importantly build-up for the isolation of single layer graphene and in turn achieve exceptional characteristics of graphene intercalated compounds.

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<https://doi.org/10.1016/j.bbrc.2018.09.029>

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**Fig. 1** A schematic illustration of the biological applications of graphene-based materials, the potential mechanism of toxicity and graphene-mediated reactive oxygen and nitrogen species (RONS) generation. The lower panel represents the synthesis and structural models of graphene oxide and reduced graphene oxide. Chemical preparation of graphene is generally carried out by oxidation and exfoliation of graphite flakes while reduced graphene oxide is prepared by reduction of graphene oxide using a variety of reducing agents such as hydrazine, sulfur, nitrogen etc, which helps eliminate the oxygen containing functional groups existing on the surface of graphene. The upper right panel refers to the biomedical application of graphene-based materials such as cancer, infectious, inflammatory, and cardiovascular and neurodegenerative diseases and the middle panel represents the oxygen and nitrogen centred species such as hydroxyl radical ( $\cdot\text{OH}$ ), hydrogen peroxide ( $\text{H}_2\text{O}_2$ ), superoxide ( $\text{O}_2^{\cdot-}$ ), singlet oxygen ( $^1\text{O}_2$ ),  $\text{ONOO}^-$  (peroxynitrite), nitric oxide (NO). The left panel shows the potential toxic pathways of graphene within a cell such as cell cycle arrest, apoptosis, damage to the cell membrane, mitochondrial and DNA damages.

## 2. Toxicity of graphene

Biomedical applications of graphene are currently in their infancy, and over the past decade, the use of graphene-based nanomaterials in cancer diagnosis and therapy along with their potential toxic effects have become increasingly important [16]. The continuous and widespread exposure of graphene-based materials raises urgent occupational, environmental and health concerns to living organisms. Although recent studies have demonstrated the *in vitro* and *in vivo* applicability of graphene in nanomedicine, there still exists a critical need to explore the potential health benefits and risks of three-dimensional graphene foam and graphene nanoribbons in living models [17]. We have recently undertaken the first pilot toxicology study on 3D graphene foam, and have demonstrated that graphene foam does not show any acute toxicity in common carps (a standard test-bed for toxicology); histological imaging revealed that graphene foam indeed remained within liver and kidney macrophages for 7 days without severe inflammation and damages to the tissues [8], providing evidence that these materials are both eco-friendly and highly biocompatible in a dose- and time-dependent manner. Nanostructured graphene can enter and be deposited at non-target cells intracellularly *via* their translocation across biological barriers. Consequently, graphene can induce off-target adverse effects. Recent *in vitro* and *in vivo* studies on the anticancer activities associated with toxicity of graphene nanostructures in mammalian and non-mammalian cells, and non-primate models have also demonstrated that graphene oxide, and reduced graphene oxide can provoke toxic effects [18]. Most importantly, surface functionalization of these materials may considerably help reduce their apparent toxic interactions with cellular and animal model's biochemistry. However, the dissemination of redox signaling (reactive oxygen and nitrogen species) is considered to be of critical importance in the expansion of such novel nanoformulations to improve the bioavailability and unattainable functionality [19,20]. Selection of precursors, residual solvents, and reaction conditions are critically important in

evaluating the potential toxic effects of graphene-based materials in disease diagnosis and treatment. PEGylation and other non-toxic and -biodegradable functionalization routes have recently been reported to reduce toxicities and side-effects in non-specific shielding of graphene, which have been widely explored in *in vitro* cell cultures [21,22]. Furthermore, tagging of such peptides and antibodies to the graphene nanostructures may affect the pharmacokinetics, targeting efficacy and safety of nanomedicines [23]. *In vivo* toxicity findings for long-term acute and chronic circulation, biodistribution, specific targeting within diseased cells and clearance of nanomedicines have not been fully understood.

## 3. Applications of graphene-based materials in nanomedicine

Graphene-based materials have extensively been exploited for standard treatment options including surgical resection alongside therapeutic strategies (such as chemotherapy, radiotherapy and photodynamic therapy). The first study on graphene in drug delivery was reported by the Hongjie Dai group in 2008 [24] demonstrating that doxorubicin, a widely used cancer drug can be loaded to nano-graphene oxide functionalized with antibody for selective targeting of tumors *in vitro*. Since then, many significant studies on graphene-based materials for biosensors, drug delivery systems and bio-imaging have further been reported [25,26]. The sustained release and capacity of graphene can potentially be triggered to granules/cell membrane interaction for improved release and delivery of therapeutic drugs to be expressed first at cell membrane and become subsequently internalized in a cell. Some evidences of such capacity for graphene oxide and GQDs have also been reported [27,28], but the mechanistic explanation of the generation of reactive oxygen and nitrogen species by graphene-based materials is still lacking in a way to empirically inform their multifunctional role in disease management. Another photomedicinal process of great importance is the significant influence of the stimulus of light on graphene nanostructures (such as GQDs), which directly effects the production of reactive oxygen species

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