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Interactions of graphene with mammalian cells: Molecular mechanisms and biomedical insights☆

Bo Zhang [a,1], Peng Wei [a,b,1], Zhixiang Zhou [c,1], Taotao Wei [a,*]

[a] National Laboratory of Biomacromolecules, Institute of Biophysics, Chinese Academy of Sciences, Beijing 100101, China
[b] University of Chinese Academy of Sciences, Beijing 100049, China
[c] College of Life Science and Bioengineering, Beijing University of Technology, Beijing 100124, China

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ABSTRACT

Carbon-based functional nanomaterials have attracted immense scientific interest from many disciplines and, due to their extraordinary properties, have offered tremendous potential in a diverse range of applications. Among the different carbon nanomaterials, graphene is one of the newest and is considered the most important. Graphene, a monolayer material composed of sp^2-hybridized carbon atoms hexagonally arranged in a two-dimensional structure, can be easily functionalized by chemical modification. Functionalized graphene and its derivatives have been used in diverse nano-biotechnological applications, such as in environmental engineering, biomedicine, and biotechnology. However, the prospective use of graphene-related materials in a biological context requires a detailed comprehension of these materials, which is essential for expanding their biomedical applications in the future. In recent years, the number of biological studies involving graphene-related nanomaterials has rapidly increased. These studies have documented the effects of the biological interactions between graphene-related materials and different organizational levels of living systems, ranging from biomolecules to animals. In the present review, we will summarize the recent progress in understanding mainly the interactions between graphene and cells. The impact of graphene on intracellular components, and especially the uptake and transport of graphene by cells, will be discussed in detail.

Contents

Abbreviations: ATP, adenosine triphosphate; CDDP, *cis*-diamminedichloroplatinum; DOX, doxorubicin; ETC, electron transfer chain; EGFR, epidermal growth factor receptors; ESR, electron spin resonance; EA, electron affinity; ECM, cell-extracellular matrix; FLG, few layer graphene; FADH, flavin adenine dinucleotide; FBS, fetal bovine serum; GM-CSF, granulocyte macrophage colony-stimulating factor; GO, graphene oxide; GNR, graphene nanoribbon; GONR, graphene-oxide nanoribbon; GONP, graphene-oxide nanoplatelet; GQD, graphene quantum dot; GO-NH_2, aminated GO; GO-PAM, poly(acrylamide)-functionalized GO; GO-PAA, poly(acrylic acid)-functionalized GO; GO-PEG, poly(ethylene glycol)-functionalized GO; GTPase, guanosine triphosphate hydrolase; HPV, human papillomavirus; HPS, human plasma serum; IFN, interferon; IgG, immunoglobulin G; IL, interleukin; LDH, lactate dehydrogenase; MCP, monocyte chemotactic protein; MIP, macrophage inflammatory protein; MMP, mitochondrial membrane potential; MD, molecular dynamics; NGO, nanographene; NADH, nicotinamide adenine dinucleotide; OXPHOS, oxidative phosphorylation; PEG, polyethylene glycol; Path-Net analyses, pathway analysis using network information algorithm; PCGO, protein-coated GO nanosheet; RANTES, regulated on activation, normal T cell expressed and secreted; ROS, reactive oxygen species; rGO, reduced graphene oxide; SILAC, Stable isotope labeling by amino acids in cell culture; TCA, tricarboxylic acid cycle; TEM, transmission electron microscopy; TGF, transforming growth factor; TLR, toll-like receptor; TNF, tumor necrosis factor.

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* Corresponding author.
E-mail address: weitt@moon.ibp.ac.cn (T. Wei).

[1] BZ, PW, and ZZ contributed equally to this work.

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1. Introduction

Graphene is a single layer of carbon packed in a hexagonal (honeycomb) lattice with carbon–carbon distances of 0.142 nm. It was first isolated by Andre Geim and Konstantin Novoselov, the 2010 laureates of the Nobel Prize in Physics, from its three-dimensional parent material, graphite [1]. Since then, this research area has exploded, producing a rapidly growing number of papers concerning graphene and graphene-related materials (Fig. 1) [2], including few layer graphene (FLGS), ultrathin graphite, graphene oxide (GO), reduced graphene oxide (rGO), and graphene nanosheets.

Graphene and graphene-related nanomaterials have attracted tremendous attention and research interest owing to their physical properties, such as their exceptionally large surface area, high electronic conductivity, good thermal stability, and excellent mechanical strength [2]. They have a wide range of potential applications in electronics and optoelectronics [3,4], energy conversion [5,6] and storage [7], catalysis [8,9], and environmental applications [10]. Recently, the biological applications of graphene and graphene-related nanomaterials have attracted attention in the scientific community based on their great potential for use in bio-imaging [11,12], cancer theragnosis [13–15], gene delivery [16], tissue engineering [17,18], biosensing [19], DNA sequencing [20], and drug delivery [21–23]. Several reviews have summarized the applications of graphene-related nanomaterials in biology and medicine [24–29].

Graphene-related nanomaterials have now been developed in many different forms in terms of their shapes, sizes, and surface modifications, which endow them with versatile physical, chemical, and biomedical characteristics. In vitro cytotoxicological investigations are required in order to develop graphene-related biomedical materials, and systematic evaluations of the biocompatibility of graphene-related materials are essential before their application in vivo. Since 2008, numerous studies have investigated the nanotoxicology and biocompatibility of graphene-related materials, and several reviews have been published [25,30,31]. However, how graphene-related materials perform these biomedical effects is still not clearly summarized; there is still a lack of a systematic review on the interaction between graphene and biological systems at the cellular level. In this paper, we aim to summarize the recent research advances in this field. We begin by reviewing three systems biology-based studies on the biological effects of graphene in different cell types. By assessing the omics data with Gene Ontology analyses, Path-Net analyses, and other bioinformatics approaches, we show that graphene and its derivatives impact the cell components, especially the plasma membrane and the membrane organelles, and interfere with the cellular metabolism. Next, we discuss how the structure and function of the plasma membrane, lysosomes, mitochondria, and other cellular components are affected by graphene. Considering the application potential of graphene as drug or gene carriers, we discuss in detail the interactions between graphene and certain types of cells, including hemocytes, blood vessel endothelial cells, macrophages, cancer cells, and stem cells.

2. Systems biology-based analyses of the biological effects of graphene

Systems biology approaches based on integrated omics and bioinformatics analyses have undergone rapidly and could be used as powerful tools to explore the interactions between nanomaterials and biosystems. Chatterjee and coworkers profiled the gene expression at the mRNA level in HepG2 hepatoma cells treated with graphene oxide (GO). The differential gene expression of a normalized microarray analysis revealed that 1224 genes were induced or repressed by more than 1.5-fold under GO treatment. The Gene Ontology analysis indicated that genes related to the regulation of cell growth and apoptosis, the

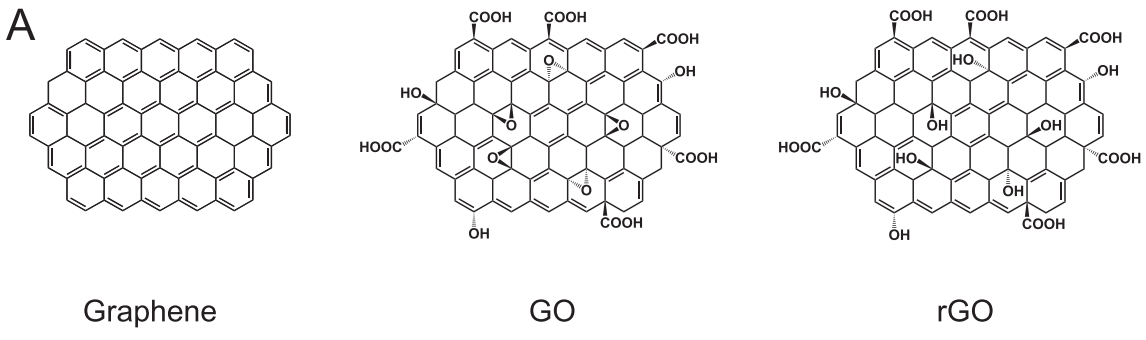

Fig. 1. Structure of graphene, graphene oxide (GO) and reduced graphene oxide (rGO) [2].