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Biomedical applications of the graphene-based materials

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ABSTRACT

Graphene, a rapidly rising star, has gained extensive research interests lately due to its excellent properties—such as the exceptional optical, electrical, thermal and mechanical features—which are superior to other materials, so it is called "two-dimensional magical materials". This article presents diverse types and various properties of graphene-based materials, and the current methods for the surface modifications of the graphene-based materials are briefly described. In addition, the *in vivo* and *in vitro* cytotoxicity of graphene-based materials are comprehensively discussed. What's more, a summary of its biomedical applications such as drug/gene delivery, photothermal therapy, photodynamic therapy and multimodality therapy is also offered. Finally, an outlook of the graphene-based materials and the challenges in this field are briefly discussed.

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1. Introduction

During the 21st century, the malignant tumor, a disease that could badly threaten people's health, became the first murderer in the world. With the development of technology, various tumor treatments were emerging such as operative treatment, chemotherapy, tumor radiotherapy and so on. Among these methods, chemotherapy was the primary approach. As for chemotherapy, appropriate chemical drugs and drug delivery systems (DDSs) were needed to cure the tumor with little side effects. However, most chemical anticancer drugs are hydrophobic and their bioavailabilities are poor. There were several impediments for their use in cancer therapy such as poor water-solubility, side effects and low specificity and finally leading to a low therapeutic effect [1]. So the development of new and effective DDSs with the ability to improve the therapeutic profile and efficacy of therapeutic agents was one of the key issues faced by modern medicine. Advances in nano-science and nanotechnology, enabling the synthesis of new nano-materials, have led to the development of a number of

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new DDSs [2]. Today, an increasing number of people devoted themselves to the study of graphene-based materials. The discovery of graphene has been accompanied by an increasing research attention to explore this new material for drug delivery applications. Graphene, a single layer of *sp*^{2}-hybridized carbon atoms arranged in a honeycomb two-dimensional (2-D) crystal lattice, has evoked enormous interests throughout the scientific community since its first appearance in 2004 [3], and the graphene "gold rush" had begun since then. Due to its unique structure and geometry, graphene possesses remarkable physical–chemical properties, including a high fracture strength, excellent electrical and thermal conductivity, fast mobility of charge carriers, large specific surface area and biocompatibility [4]. These properties enabled graphene to be considered as an ideal material for a broad range of applications, ranging from cancer therapy [5–8], medical imaging [9,10], tissue engineering [11–17], biosensing [18–20], DNA/RNA extraction [21] to bacterial inhibition [22–24], antiviral materials [25,26] and so on. In the area of nano-medicine, graphene-based materials have emerged as new biomaterials that provided exciting opportunities for the development of biomedical applications, including a new generation of nano-carriers for drug delivery and this could conquer some of the disadvantages of chemotherapy [27].

Today numerous literatures focused on graphene-based materials were emerging since 2004. Based on the previous studies about graphene, we had known that graphene, the thinnest known material, is a sheet of two-dimensional single layer sp^2 hybridized carbon atoms possessing exceptional mechanical [28], electrical [29], optical [30] and thermal properties [31]. The moment we discovered graphene, studies on it had increased exponentially. Thousands and thousands of papers were appearing about the graphene-based materials. So there was an urgent need to make reviews for people to form a clear and systemic knowledge of graphene and gave researchers a direction to pay attention to. In this review, not only the different types of graphene-based materials, their properties and modification strategies but also their *in vivo* and *in vitro* toxicity are discussed. What's more, various applications of graphene-based materials are offered such as drug/gene delivery, photodynamic therapy (PDT), photothermal therapy (PTT), multimodality therapy and theranostics. Finally, recent developments and the prospective outlooks for future trends in this field are also reviewed. From this review, we can have a better understanding of graphene-based materials.

2. Graphene family nanomaterials and their physicochemical properties

Graphene family nano-materials (GFNs) were classified based on either number of layers in the sheet or their oxygen content, or their chemical modification. Graphene, the parent of other graphite forms, had become one of the most interesting focuses of research in the last decade [32]. The single layer graphene possesses an extended honeycomb network — the basic building block of other important allotropes (Fig. 1). We can stack the graphene to form 3D graphite, roll it to form 1D carbon nanotubes (CNTs) and wrap it to form 0D fullerenes [33]. Graphene is the youngest member of carbon-based materials following behind CNTs and fullerene, so we can use the similar method applying to the CNTs to explore graphene. Since said to CNTs, here a comparison between graphene-based materials and CNTs is given. Compared to CNTs, graphene presents some advantageous features over CNTs. For example, its surface area is larger and can be easily modified by other molecules, which ensures a large number of different possible applications [34]; it also presents better dispersivity, which helps to reduce its cytotoxicity and improve its photothermal sensitivity [35] and so on; PEGylated nanographene is easily uptaken by cells and can be retained easily in tumors *via* enhanced permeability and retention (EPR) effect when compared with CNTs and graphene's production costs are inexpensive [34]. Based on the discussion, graphene-based materials can be the material of choice for biomedical use.

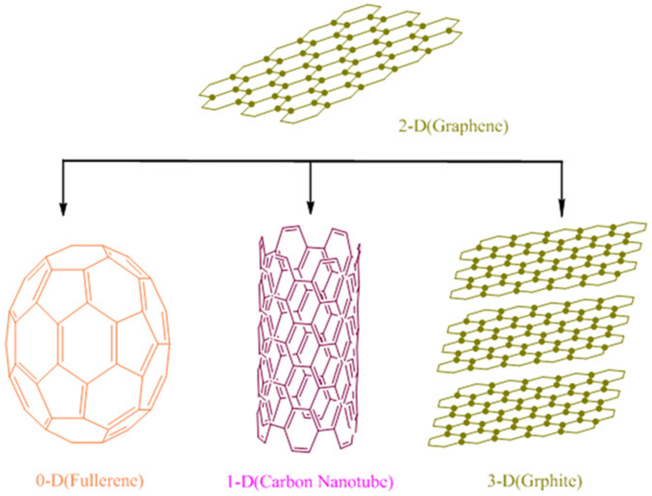

Fig. 1. The structure of graphene and its derivatives.

The single layer graphene, bi-layer graphene, multilayer graphene, graphene oxide (GO), reduced graphene oxide (rGO) and chemically modified graphene are widely used GFNs. Each member of GFNs differs from the other in terms of oxygen content, number of layers, surface chemistry, purity, lateral dimensions, defect density and composition. Due to its highly reactive surface, single layer defect-free graphene is arduous to synthesize and it is also difficult to suspend in solution. Hence, compared to the single layer graphene, GO or rGO is widely used in biomedical applications.

GO, consisting of a single atom thick layer of graphene sheets with carboxylic acid, epoxide and hydroxyl groups in the plane, is a highly oxidized form of chemically modified graphene. The structures and some properties of GO and graphite are shown in Fig. 2. The colloidal stability and pH-dependent negative surface charge of graphene-based materials are derived from its peripheral carboxylate group [36]. Epoxide (–O–) and hydroxyl (–OH) groups presented on the basal plane are uncharged but polar allowing for weak interactions, hydrogen bonding and other surface reactions [37]. There also exists free surface πelectrons from unmodified areas of graphene on the basal plane, which are hydrophobic and capable of π–π interactions for drug loading and non-covalent functionalization. Thus, GO is an amphiphilic sheet-like molecule, which can be used as surfactant to stabilize hydrophobic molecules in water solutions [38,39]. Additionally, because of the functional groups on it, GO possesses a high defect density so its mechanical, electrical and thermal properties are reduced when compared with graphene or rGO.

rGO can be derived from GO in a reducing environment such as hydrazine or other reducing agents [36]. There are many differences between GO and rGO, for example, structural differences. The degree of oxygen-containing functional groups is higher in GO but less in rGO. So the crystal texture of rGO is better than GO. Their structural differences give rise to their different physicochemical properties. For example, rGO possesses better optical absorbance, electrical conductivity than GO while its hydrophilicity and the surface charge are lower than GO [40]. The comparison among GO, rGO and graphene is offered here. Graphene has a defect-free plane and there almost exists no oxygen groups, so its electrical and optical conductivity is superb. While GO, with ample oxygen-containing groups on it, owns relatively poor electrical and optical conductivity. In order to boost its electrical conductivity of GO, we look for ways to reduce it. In a nutshell, the electrical conductivity of rGO is better than GO but less than graphene. As to water-solubility, rGO is better than graphene but less than GO due to the different degree of oxygen-containing groups, respectively. So GO is a hydrophilic material, while graphene, poorly dispersible in water,