Advanced Drug Delivery Reviews 105 (2016) 228–241

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Stimuli responsive drug delivery systems based on nano-graphene for cancer therapy☆

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ARTICLE INFO

Article history:
Received 19 January 2016
Received in revised form 13 April 2016
Accepted 18 May 2016
Available online 24 May 2016

Keywords:
Nano-graphene
Drug delivery
Stimuli-responsive
Cancer therapy

ABSTRACT

Nano-graphene as a class of two-dimensional sp^2 carbon nanomaterial has attracted tremendous attentions in various fields in the past decade. Utilizing its unique physical and chemical properties, nano-graphene has also shown great promises in the area of biomedicine, for application in biosensing, imaging and therapy. In particular, with all atoms exposed on its surface, nano-graphene exhibits ultra-high surface area available for efficient binding/loading of various biomolecules of interests, and has been widely used as multifunctional nano-carriers for drug and gene delivery. In this review article, we will summarize the recent advances in the development of nano-graphene as stimuli-responsive nano-carriers for drug delivery, as well as the applications of these smart systems for cancer therapy.

Contents

1. Introduction

While cancer has become the major global healthcare problem in this century [1], cancer chemotherapy currently used in the clinic on one side has severe side effects, and on the other side shows limited and individually varied therapeutic responses [2,3]. With the hope to overcome those existing problems (at least some of them) in current cancer therapy strategies, various drug delivery systems (DDSs) have been explored in the past few decades, aiming at cancer-targeted delivery and controlled release of therapeutic agents inside the lesion [4–7]. In particular, in order to further improve therapeutic specificity, different types of stimulus-responsive DDSs have been successfully designed with the help of nanotechnology, and demonstrated to be effective by

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Graphene-based materials in nanomedicine".

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http://dx.doi.org/10.1016/j.addr.2016.05.015
0169-409X/

pre-clinic animal experiments in recent years [8–14]. An excellent stimuli-responsive drug delivery carrier for cancer therapy should be featured with not only excellent in vivo pharmacokinetic profiles and tumor homing ability, but also enhanced cell uptake and/or controlled release of drugs selectively in the diseased region (e.g. cancer) under stimulations, so as to achieve cancer-specific treatment with high efficacy and reduced side effects [15–17].

Graphene, as a class of two-dimensional (2D) nanomaterials, has attracted extensive attention in various different fields including nano-electronic devices, transparent conductors, energy and catalysis [18–23]. Owing to their intrinsic physical and chemical properties, graphene, graphene derivatives and various graphene-based nanocomposites have also been widely explored in the area of biomedicine, for application in bio-sensing, bio-imaging, drug/gene delivery, different types of cancer therapies, as well as tissue engineering [24–34](Fig. 1). As far as cancer theranostic applications are concerned, nano-graphene and its derivatives with high near-infrared (NIR) absorbance could act as photothermal agents for efficient photothermal therapy (PTT) of cancer [35–38]. With an extremely high specific surface area, graphene can be loaded with various types of biomolecules with high efficiencies for applications in drug delivery and gene transfection [25,39–48]. Moreover, various inorganic nanoparticles could be anchored onto the surface of nano-graphene to offer additional optical and magnetic properties which could be useful to provide contrast for in vivo tumor multimodal imaging [36,49–52]. In addition, functionalized nano-graphene labeled with radionuclides such as ^{64}Cu, ^{66}Ga, ^{125}I and ^{131}I could find interesting applications in nuclear imaging and radiotherapy of cancer [53–58]. Beyond graphene oxide, other graphene related nanomaterials including graphene nanoribbons and graphene quantum dots have also been used as nano-carriers for drug delivery in recent years [59–63]. Meanwhile, many research groups including ours have investigated the in vivo behaviors and toxicology of functionalized nano-graphene via different administration strategies [57,64–69], and uncovered that the toxicity of nano-graphene could be closely related to its surface chemistry and sizes. Nano-graphene with well-engineered surface coating and small sizes exhibited no obvious toxic effect to treated mice in a reasonable dose range and could be gradually excreted from the body via urine and feces [55,56,58,64,70–74].

While the biomedical applications of graphene have been intensively reviewed in the past several years [26,28,64,75–81], a review article focusing on stimuli-responsive graphene-based nano-platforms for cancer therapy may still be needed in the community of nanomedicine. In this article, therefore, we would like to discuss the development of graphene-based stimulus-responsive DDSs for cancer therapy applications, a relatively focused direction with many latest interesting results promising to the area of nanomedicine. As summarized in Table 1, nano-

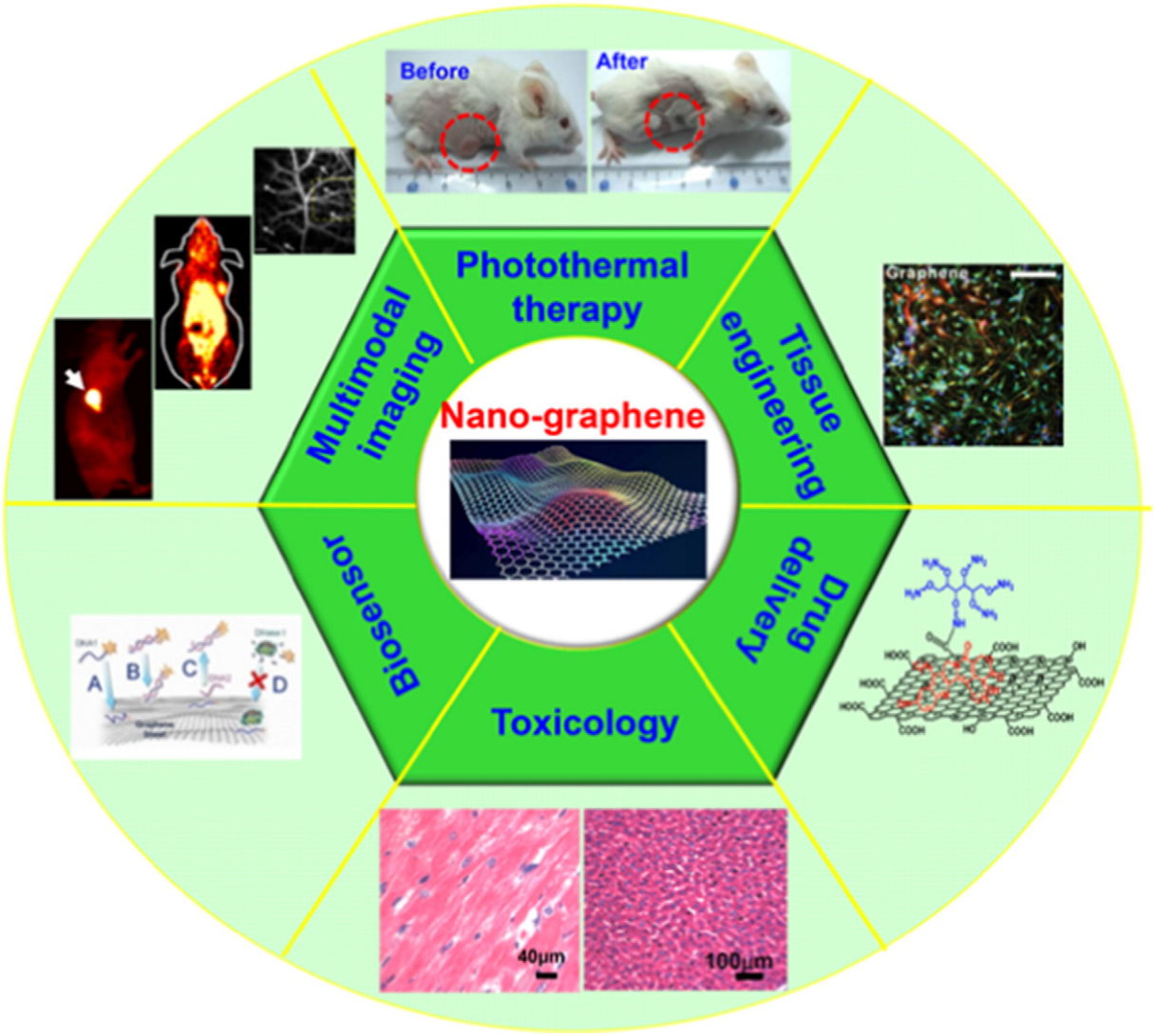

Fig. 1. A scheme showing the exploration of nano-graphene in different fields of biomedicine.