Biomaterials 133 (2017) 37–48

Contents lists available at ScienceDirect

Biomaterials

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

Cell-borne 2D nanomaterials for efficient cancer targeting and photothermal therapy

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ARTICLE INFO

Article history:
Received 27 January 2017
Received in revised form
7 April 2017
Accepted 10 April 2017

Keywords:
2D nanomaterials
Bi_2Se_3 nanosheets
Near-infrared
Drug delivery
Photothermal therapy

ABSTRACT

Two of the challenges for clinical implementation of nano-therapeutic strategies are optimization of tumor targeting and clearance of the nanoagents *in vivo*. Herein, a cell-mediated therapy by transporting 2D Bi_2Se_3 nanosheets within macrophage vehicles is described. The Bi_2Se_3 nanosheets with excellent near-infrared photothermal performance exhibit high macrophage uptake and negligible cytotoxicity thus facilitating the fabrication of Bi_2Se_3-laden-macrophages. Compared with bare Bi_2Se_3, the Bi_2Se_3-laden-macrophages after intravenous injection show prolonged blood circulation and can overcome the hypoxia-associated drug delivery barrier to target the tumor efficiently and dramatically enhance the efficiency of photothermal cancer therapy. The Bi_2Se_3-laden-macrophages possess good biocompatibility as demonstrated by the biochemical and histological analyses and furthermore, most of the materials are excreted from the body within 25 days. Our findings reveal a desirable system for highly efficient near-infrared photothermal cancer therapy.

1. Introduction

Since cancer poses one of the most serious threats to human health, new and more effective therapeutic strategies are demanded and novel nanotechnologies offer the unprecedented opportunity to promote precision treatment of cancer while mitigating undesirable side effects [1–3]. Among the various nano-therapeutic modalities, nanomaterials-mediated photothermal therapy (PTT) which enables localized conversion of tissue-transparent near-infrared (NIR) light into heat to ablate cancer cells has drawn considerable attention [4,5]. Compared to conventional cancer treatment approaches, PTT is minimally invasive, rapid, and easily combined with other therapeutic approaches [6–8]. As a new class of nanomaterials, two-dimensional (2D) nanomaterials are promising PTT agents on account of their intriguing physical and chemical properties [9]. Many types of 2D nanomaterials such as graphene, reduced graphene oxide (rGO), MoS_2, $MoSe_2$, Bi_2Se_3, and black phosphorus (BP) have recently been explored for *in vitro* and *in vivo* PTT of cancer [10–27]. In comparison with other types of PTT agents, 2D nanomaterials generally have large NIR extinction coefficients with little scattering and excellent photothermal stability without undergoing shape transformation upon irradiation with a high-power NIR laser [28]. Moreover, the large surface area of 2D nanomaterials offers plenty of space to engineer a variety of multifunctional nanocomposites suitable for drug delivery and cancer theranostic applications [29–33].

Nanomaterials-mediated cancer therapy generally involves delivery of nanoparticles to the tumor and subsequent light irradiation to produce a high local temperature. It is critical to distribute the nanoparticles evenly at an effective concentration throughout the tumor because nanoparticles cannot functionalize as designed if they do not accumulate at the diseased tissues at a sufficiently high concentration [34–36]. As a common strategy in tumor targeting, the size and surface properties of the nanomaterials are modulated so that they can be passively delivered into tumors by the enhanced permeability and retention (EPR) effect [37,38]. The

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http://dx.doi.org/10.1016/j.biomaterials.2017.04.012
0142-9612/

biodistribution is governed by several mechanisms including nonspecific binding to proteins in blood, removal by phagocytes, and limitation of the EPR effect which relies on the size, shape, coating, and surface charge of nanomaterials [39]. In this respect, development of new 2D PTT agents is highly desirable in order to improve the tumor-targeting efficiency in cancer therapy.

Since common drugs or nanomaterials delivered in human body often fail to reach many areas, the cell mediated strategy is attractive in therapeutic applications as the nearly impermeable biological barriers can be effectively circumvented [40,41]. Tumor-tropic cells including macrophages [42,43], neural stem cells [44], human CIK cells [45], human induced pluripotent stem cells [46], and mesenchymal stem cells [47] have been proposed as delivery vehicles to transport nanoparticles to tumor tissues. Among them, macrophages with innate phagocytotic capability are attractive as they are circulating cells in human body which can be readily gained [48,49]. It has been reported that macrophages can endocytose Au nanoshells, recognize the cytokines secreted by tumor cells, and migrate to tumor spheroids to produce photothermal effects [50,51]. Recently, our group has produced laden macrophages with gold nanorods and intratumoral injection improves the intratumoral distribution of the nanorods consequently enhancing the photothermal therapeutic efficacy [52]. Nevertheless, in spite of recent advances, there have been few reports on the use of 2D nanomaterial laden macrophages in tumor targeting.

In this work, a cell-borne 2D nanomaterials drug delivery system is designed and produced by loading Bi_2Se_3 nanosheets into macrophages to improve the photothermal therapeutic efficacy. As a member of the 2D layered topological insulators, Bi_2Se_3 nanosheets [53,54] and other bismuth based composites such as MoS_2/Bi_2S_3 [55], MnSe@Bi_2Se_3 [56], and PEG-Bi_2Se_3@PFC@O_2 [57] have recently been demonstrated to be promising tumor imaging or therapy agents delivering high efficiency and multifunctionality. Furthermore, both Se and Bi have excellent biocompatibility and Bi_2Se_3 nanosheets are metabolizable thereby allowing natural clearance from the human body [58]. As shown in Fig. 1, the Bi_2Se_3-laden-macrophages can overcome the hypoxia-associated drug delivery barrier as a “Trojan Horse” delivery vector and infiltrate tumor tissues efficiently. When combined with NIR light irradiation, the strong NIR absorbance of Bi_2Se_3 nanosheets can be exploited to ablate tumor tissues and minimize recurrence.

2. Materials and methods

2.1. Materials

The Dulbecco's modified Eagle's medium and penicillin/streptomycin were obtained from Hyclone Company, South Logan, UT, USA, fetal bovine serum was obtained from Gibco (New York, USA), and near infrared fluorescent dye DIR (KGMP0026) was obtained from Keygen Biotech (China). The other reagents were obtained from Sigma-Aldrich and used without further purification unless mentioned otherwise. Ultrapure water with a resistivity value of about 18.25 MΩ cm^{-1} was obtained from a Milli-Q ion-exchange system (Millipore, USA).

2.2. Synthesis of Bi_2Se_3 nanosheets

The Bi_2Se_3 nanosheets were prepared according to the method described previously [59]. In brief, sodium selenite solution (0.242 g in 35 mL of ethylene glycol) and bismuth nitrate pentahydrate solution (0.452 g in 25 mL of ethylene glycol) were successively added into the poly (vinyl pyrrolidone) solution (PVP, 1.0 g in 40 mL of ethylene glycol) under magnetic stirring at room temperature, by using a 250 mL round-bottom flask as the container. After flask sealing and heating at 160 °C under nitrogen condition, the mixture changed from transparent to milky white and then yellow-white. A hydroxylamine solution (2.4 mL in 20 mL of ethylene glycol) was rapidly injected into the mixture to fabricate Bi_2Se_3 nanosheets. Subsequently, the resultant mixture was cooled down at room temperature, precipitated by centrifuging (12,000 rpm, 10 min), then rinsed three times with a mixture of acetone and D. I. water (300 mL: 60 mL). Finally, the Bi_2Se_3 nanosheets were resuspended in sterile phosphate buffer saline (PBS)

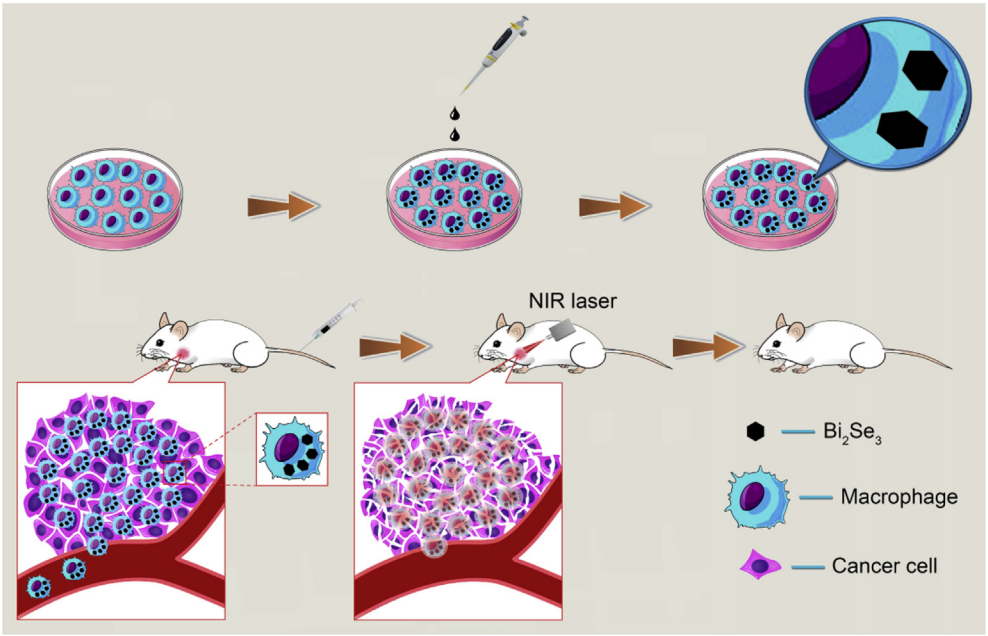

Fig. 1. Schematic illustration of the macrophages loaded Bi_2Se_3 nanosheets delivery system expected to overcome the hypoxia-associated drug delivery barrier to enhance tumor coverage and PTT efficiency.