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Review

Multifunctional carbon nanomaterial hybrids for magnetic manipulation and targeting

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ABSTRACT

Nanosized materials and multifunctional nanoscale platforms have attracted in the last years considerable interest in a variety of different fields including biomedicine. Carbon nanotubes and graphene are some of the most widely used carbon nanomaterials (CNMs) due to their unique morphology and structure and their characteristic physicochemical properties. Their high surface area allows efficient drug loading and bioconjugation and makes them the ideal platforms for decoration with magnetic nanoparticles (MNPs). In the biomedical area, MNPs are of particular importance due to their broad range of potential applications in drug delivery, non-invasive tumor imaging and early detection based on their optical and magnetic properties. The remarkable characteristics of CNMs and MNPs can be combined leading to CNM/MNP hybrids which offer numerous promising, desirable and strikingly advantageous properties for improved performance in comparison to the use of either material alone. In this minireview, we attempt to comprehensively report the most recent advances made with CNMs conjugated to different types of MNPs for magnetic targeting, magnetic manipulation, capture and separation of cells towards development of magnetic carbon-based devices.

1. Introduction

Carbon nanomaterials (CNMs) have shown great potential in biomedical applications, mainly due to their unique chemical and physical properties [1–5]. Carbon nanotubes (CNTs) and graphene are two of the most widely used CNMs due to their physical and chemical stability as well as their high surface area-to-weight ratio. In the field of nanomedicine, they are used as platforms for the immobilization of nanoparticles (NPs) [6,7] and as versatile carriers for a variety of bioactive molecules [8–10]. CNMs are also endowed with characteristic optical properties, such as fluorescence and Raman scattering, making them useful for sensing applications and a variety of imaging modalities such as magnetic resonance, near-infrared fluorescence, photoacoustic tomography, photothermal and Raman imaging [4,5,11–13].

Magnetic nanoparticles with appropriate physicochemically tailored surface properties, colloidal stability and biological behavior have been used in drug delivery, hyperthermia, magnetic resonance imaging (MRI), biosensing, biochemical separations and bioanalysis [14–17]. The combination of CNMs and different types of MNPs has recently attracted interest in biomedical applications [18–21]. In particular, CNM/MNP hybrids exhibit advantageous and often synergistic properties arising from their combination and molecular interactions [22,23]. For instance, in sensing applications, the association of NPs with graphene renders greater catalytic and conducting properties, enhancing their sensitivity and selectivity in comparison to graphene- or NP-based sensors alone [24]. Endowing CNMs with magnetic properties thanks to the association with MNPs is opening many opportunities for future biomedical applications.

In this minireview, we describe the association of CNMs, mainly CNTs and graphene, and MNPs for various biological applications. Specifically, we will focus on CNM/NP hybrids for magnetic targeting in multifunctional drug delivery and imaging, for biosensing, for magnetic molecular extraction, magnetic manipulation, capture and release of cells. We will also discuss the ability of CNT/NP hybrid for magnetic manipulation and fabrication of biomedical devices.

2. Magnetic targeting

The combination of CNMs and NPs has led to the generation of novel systems that are finding a wide range of applications in

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biomedicine due to their versatile magnetic properties. Advanced multifunctional magnetic CNM-based vectors bearing fluorescent moieties [*e.g.* fluorescein isothiocyanate (FITC)], proteins (*e.g.* transferrin), targeting ligands [*e.g.* folic acid (FA)] or therapeutic drugs [*e.g.* doxorubicin (DOX)] have been used not only in targeted therapies, but also in imaging and theranostics. In the context of therapy, CNM/MNP hybrids have shown great promise as drug carriers and have been exploited for targeting cancer cells.

The superparamagnetic graphene oxide (GO)-Fe_3O_4 NP hybrid loading DOX for controlled targeted drug delivery was first reported in 2009 [25]. This hybrid, with or without DOX, aggregated under acidic conditions, and was then reversibly redispersed under basic conditions. More interestingly, after aggregating at low pH, the GO/Fe_3O_4 hybrid can be dragged under the application of an external magnetic field. Thus, the transfer efficiency of drug vectors could be greatly improved by magnetic field guidance. This also indicated that at acidic pH, some functional groups on the GO, such as carboxylic acid groups, even after loading with a large amount of Fe_3O_4 NPs and DOX were still free for efficient formation of hydrogen bonding, making this hybrid a promising pH–triggered targeted carrier. Due to its pH–triggered magnetically controlled capabilities, this hybrid was functionalized with different biomolecules or drugs such as folic acid [26,27] and 5-fluorouracil (5-FU) [28], for specific multi-targeting or multi-drug loading and delivery. Indeed, it is known that the loading and release of DOX depends on the hydrogen bonding interaction with multifunctionalized GO [26]. At acidic conditions, protonation of amine groups on DOX can break the hydrogen bonding between DOX and GO, leading to a quick release of the drug. Hence, the multifunctionalized GO was able to first transport the drugs to the targeted tumor cells by the force of an external magnetic field localized at the site of the tumor, and then the drug-loaded carriers were taken up by the tumor cells.

In the case of CNTs, the functionalization of iron-decorated multi-walled CNTs (MWCNTs) with a targeting moiety (FA) and drugs (such as DOX) has also been reported [29,30]. For instance, FA/FITC/MWCNT-Fe has been used to deliver DOX in human cervical cancer HeLa cells [29]. Thanks to the adsorption of iron NPs on both the inner and outer surface of the MWCNTs, the nanocarriers were guided to the location of cancer cells by applying an external magnetic field. Then, the conjugates were specifically targeted to FA receptors that were overexpressed on cancer cells.

In addition to CNTs and GO, multifunctional carbon nanohorns (CNHs) have also been combined with MNPs. By using an external magnetic field, the targeted vectorization of CNHs loaded with

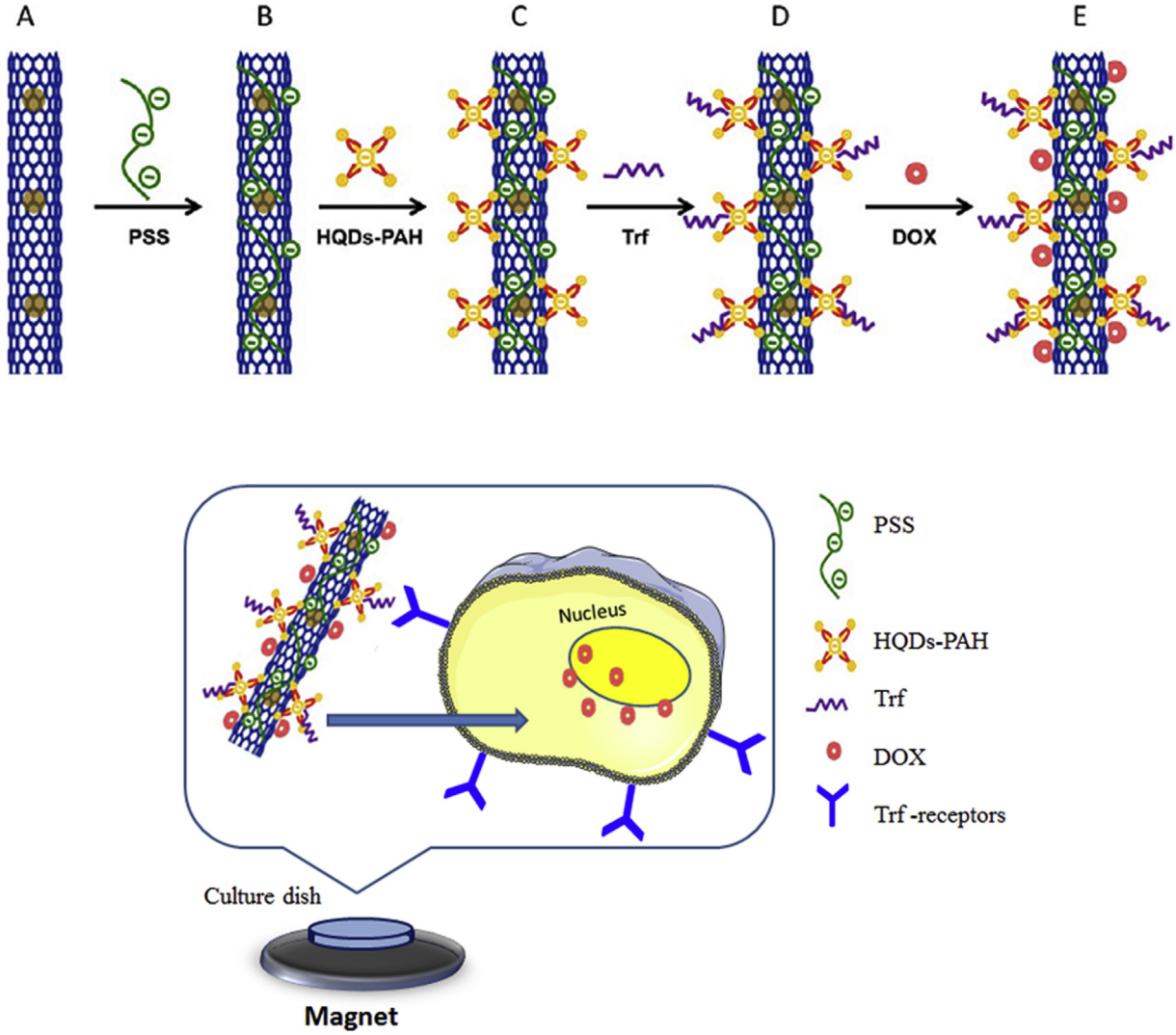

Fig. 1. Top: Preparation of water-dispersible DOX-Fe_3O_4@CNT-HQD-Trf conjugates. (A) Fe_3O_4@CNT; (B) PSS-coated Fe_3O_4@CNT; (C) Fe_3O_4@CNT-HQD; (D) Fe_3O_4@CNT-HQD-Trf; (E) DOX-Fe_3O_4@CNT-HQD-Trf. Adapted from Ref. [33]. Bottom: Schematic representation of *in vitro* (DOX) delivery and release using Fe_3O_4@CNT-HQD-Trf hybrids in the presence of a magnetic field. PSS: poly(sodium 4-styrenesulfonate); HQD-PAH: SiO_2-coated quantum dots-poly(allylamine); Trf: transferrin.