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Influence of carbon nanotubes and graphene nanosheets on photothermal effect of hydroxyapatite

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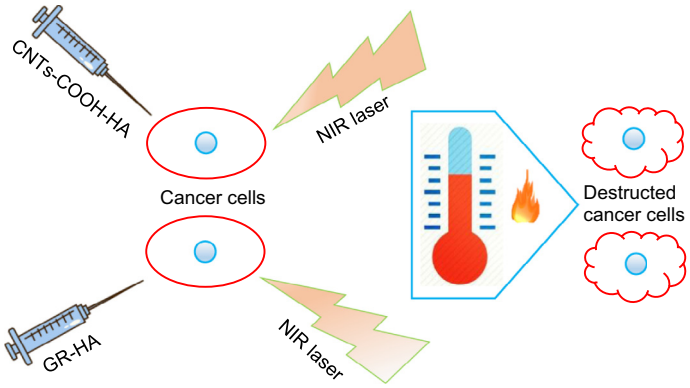
GRAPHICAL ABSTRACT



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ABSTRACT

Herein we present a successful strategy for enhancement of photothermal efficiency of hydroxyapatite (HAP) by its conjugation with carbon nanotubes (CNTs) and graphene nanosheets (GR). Owing to excellent biocompatibility with human body and its non-toxicity, implementation of HAP based nanomaterials in photothermal therapy (PTT) provides non-replaceable benefits over PTE agents. Therefore, in this report, it has been experimentally exploited that the photothermal effect (PTE) of HAP has significantly improved by its assembly with CNTs and GR. It is found that the type of carbon nanomaterial used to conjugate with HAP has influence on its PTE in such a way that the photothermal efficiency of GR-HAP was higher than CNTs-COOH-HAP under exposure to 980 nm near-infrared (NIR) laser. The temperature attained by aqueous dispersions of both CNTs-COOH-HAP and GR-HAP after illuminating to NIR radiations for 7 min was found to be above 50 °C, which is beyond the temperature tolerance of cancer cells. So that the rise in temperature shown by both CNTs-COOH-HAP and GR-HAP is enough to induce the death of tumoral or cancerous cells. Overall, this approach in modality of HAP with CNTs and GR provide a great potential for development of future nontoxic PTE agents.

1. Introduction

The employment of near-infrared (NIR) radiations in photothermal therapy (PTT) to treat cancer is current high pitched interest aside from its classical applications such as telecommunication and sensing ablation [1,2]. The reason is that NIR region (700–

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1100 nm) is ideal clinical phototherapeutic window for PTT as attenuation of NIR radiations by skin, blood and tissues is low and it allow for the treatment of deep-seated tumors [3–5]. The application of PTT in the treatment of tumors has been identified as a minimally invasive alternative to conventional hyperthermia treatment owing to its remote controllability, low systemic toxicity, and minor side effects [6,7]. The conventional hyperthermia treatment, currently in use induce the generation of reactive oxygen species. This oxidative stress gradually leads to destruction of plasma membranes, proteins, and nucleic acid [8–10]. For direct cell necrosis in conventional hyperthermia treatment, long-term exposures (>60 min) to temperatures is required [10,11]. On the other hand, temperature above 48 °C instantaneously cause irreversible protein coagulation and DNA damage that lead to death of cells even for a short time exposure (4–6 min) [10]. Under these circumstance, PTT is a suitable method to destroy tumor tissues as it possess supercritical benefits such as spatiotemporal controllability, minimal invasiveness, and independence of tumor type [12]. While, the implementation of PTT relies on the development of suitable photothermal coupling agents. Among the rest of PTT agents, typical sp^2 carbon nanomaterials, such as carbon nanotubes (CNTs), graphene (GR) and fullerene, have been intensely investigated for PTT applications owing to their exceptional structural and functional properties [10,13]. On a per-mass basis, both CNTs and GR possess a larger extinction coefficient of NIR light absorption than gold nanomaterials, and consequently leads to higher photothermal conversion efficiency [14,15].

Meanwhile, one-dimensional (1-D) CNTs possess strong absorption in NIR region between 700 and 1100 nm, which is particularly attractive as the living tissues do not strongly absorb in this region and tissue penetration is optimal during hyperthermia treatment, CNTs a promising agents of PTT [3,14–16]. It is revealed that execution of CNTs is a superlative platform for NIR triggered destruction of cancer cells through photothermal ablation [17–20]. In addition, selective destruction of cancerous cells is possible through proper functionalization of CNTs without healthy cells [21,22]. In particular, after functionalization, CNTs may easily come across the membrane into the cell via endocytosis and diffusion [23,24] CNTs can serve as carriers that deliver drug molecules for chemical therapy to the targeted cells. The large surface area of CNTs, together with their hollow structure, enables them to be loaded with a large quantity of drug molecules [25,26]. The attachment of drug molecules to CNTs can also effectively prolong the circulation time of drug molecules in blood and thus enhances cellular uptake of the drug by cancer cells [25,27]. Moreover, owing to characteristic of Raman scattering, CNTs can be used as tracer to monitor the distribution of drug molecules in human body as well [28,29]. Apparently, CNTs can take a multiple role in malignant tumor therapy, for instance, drug carrier, light-inducing heat treating agent, and drug molecule tracer. Additional critical aspect for the selective CNTs mediated thermal ablation of cells is the physiological stability of the linkage between the targeting moieties and the CNTs.

Another carbon nanomaterial which has equal prominence like CNTs is graphene (GR) and recently it attracted tremendous attention owing to its two-dimensional (2D) structure, high surface area, easy surface functionality [30], biocompatibility [31–33], high thermal stability, and enhanced NIR absorption capability in the first and second biological window (650–950 nm and 1000–1350 nm) made it as an ideal theranostic platform for future nanomedicine [14,15,34]. Due to its excellent photon-thermal transfer efficiency under NIR irradiation, GR has been used for PTT in vitro [14,15,35] and in vivo [36] for combined PTT and chemotherapy or photodynamic therapy (PDT) [37]. This type of strategy is advantageous by minimizing therapy time and avoiding the utilization of multiple laser systems.

Therefore, the execution of CNTs and GR could help in development of innovative multimodal therapies that combine PTT and PDT. The PDT is a noninvasive phototherapy, which is currently using in clinical practice [38–40], so that combination of PTT with PDT is highly feasible great clinical. However, the poor dispersibility of CNTs and GR in water has restricted their application in PTT. To overcome this problem, functionalization of CNTs and GR with hydrophilic materials is needed. Among a series of hydrophilic conjugatives used in functionalization of CNTs and GR, hydroxyapatite (HAP) is frontline one as it possess excellent biocompatibility and bioactivity with human tissues owing to its identical chemical composition and crystal structure to mineral component present in human hard tissue such as bone and tooth [39–41]. Due to its high binding activity to DNA and proteins, HAP-based biomaterials are currently used in bone and tooth repair [42,43]. In addition, since more than a decade, HAP has been used as a drug carrier [44,45]. The HAP can safely deliver the drug by protecting gene, drug and protein present in cells because of its good adsorption capacity and increasing solubility in the lower pH or acidic environment of cells [46–48]. Since the 1990s, the inhibitory effect of HAP on the proliferation of cancer cells was investigated and reported [49,50]. It is revealed that HAP inhibit the proliferation of cancer cell and it demonstrated higher inhibitory effect on cancer cell than normal cells by preventing the synthesis of protein [51]. Therefore, execution of HAP in PTT is a smart movement to overcome from toxic effects caused over human tissue by use of non-biocompatible materials in the treatment.

In consideration of its importance and biocompatibility, herein we prepared the NIR active, HAP based nanocomposites comprised of CNTs and HAP (CNTs-COOH-HAP) and GR and HAP (GR-HAP). Both, CNTs-COOH-HAP and GR-HAP have exhibited excellent photothermal conversion ability under exposure to 808 and 980 nm NIR laser systems. While the biological systems are transparent to 700–1100 nm NIR radiations, the strong absorbance of CNTs-COOH-HAP and GR-HAP nanocomposites can be used for optical stimulated thermal generation inside body cells to afford various useful functions such as destruction of cancer cells. The CNTs-COOH-HAP and GR-HAP have demonstrated a significant photothermal conversion efficiency of 22.2% and 25.9%, respectively at 980 nm, and it is comparable with the efficiency of reported photothermal agents. The CNTs-COOH-HAP and GR-HAP hybrid assemblies rise in temperature above 50 °C 980 nm laser, which is beyond the temperature tolerance of cancer cells. Owing to its difficult in the accomplishment of perfectly homogeneous composition between CNTs and HAP, and GR and HAP by traditional mixing technology, herein we developed the facile *in-situ* method for uniform deposition of HAP over CNTs and GR nanosheets.

2. Experimental section

2.1. Materials

All the reagents were purchased from Aldrich and used without further purification unless otherwise noted. All the aqueous solutions were prepared with ultrapure water obtained from Milli-Q Plus system (Millipore).

2.2. Preparation of CNTs-COOH-HAP nanocomposite

Prior to grafting of HAP over CNTs, the CNTs were converted to CNTs-COOH to achieve an effective grafting of HAP over their surface. The carboxylation of CNTs was performed by refluxing the CNTs in a mixture of 1:3 (v/v) nitric acid and sulfuric acid under stirring at 70 °C for 24 h, followed by centrifugation, repeated washings with DI water and drying under vacuum [52,53]. Thus