NIR initiated and pH sensitive single-wall carbon nanotubes for doxorubicin intracellular delivery

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Introduction Doxorubicin (DOX) is widely used in cancer therapy as a chemotherapy. However, DOX is toxicity to healthy cells as same as cancerous cells. To address these concerns, stimuli responsive material has gained its popularity. By responding to tumor chemical-physical environment, the stimuli responsive materials are able to deliver drug to cancerous cells and cause minimum damage to healthy cells. pH sensitive materials are frequently applied in cancer treatment for the fact of low pH in solid tumor. Carbon nanotubes (CNTs) have been used in many areas. CNTs can be covalently or non-covalently bonded with biomolecules. One of the most interesting part of CNTs is that they can absorb near-infrared radiation (NIR) and produce heat that can kill cancer cells. Another benefit using NIR at 808 nm is that NIR can penetrate skin and tissue with the minimum damage. In this work, we
first synthesized NIR and pH sensitive PEG-DOX-SWNTs for DOX delivery. The non-covalent attachment is accomplished by pi-pi stacking interactions, hydrophobic interactions between DOX and SWNTs. Then we tested prodrug release quickly from SWNTs upon NIR treatment and examined the drug release profiles in different pH environments. Multimodal nonlinear optical imaging microscopy (NLOM) was employed to acquire coherent anti-Stokes Raman (CARS) and two-photon excited fluorescence (TPEF) images of live MCF-7 cells to investigate intracellular delivery.

Materials and Methods

Synthesis of PEG-hydrazide: The typical synthesis of PEG-hydrazine was as follows: 600 mg of methoxy PEG (5k) succinimidyl carboxymethyl ester and 160 mg of hydrazine were dissolved in 10 ml phosphate buffer solution (PBS) (pH = 7.4) and stirred for 24 hours. The product was then dialyzed against distilled water for 2 days to remove the excess hydrazine molecules. Synthesis of PEG-hydrazone-DOX: The synthesis of PEG-hydrazone-DOX was performed according to
the reported method with modification.21,22 Briefly, 500 mg of PEG-hydrazine and 50 mg of DOX were dissolved in 10 ml of anhydrous DMSO and stirred for 3 days in darkness at room temperature. The product was then purified by precipitation using a large excess of diethyl ether twice.

Results

The successful pH sensitive poly(ethylene glycol)-doxorubicin (PEG-DOX) on single-wall carbon nanotubes (denoted PEG-DOX-SWNT) was determined by NMR, TEM and FTIR results (Figure 1). Using multimodal nonlinear optical imaging microscopy, we found that low power (1 mW cm^-2) near-infrared radiation can initiate drug burst release from the carbon nanotubes in seconds (Figure 2). The in vitro release of DOX from the PEG-DOX-SWNT showed quick release upon changes of pH values and NIR treating time (Figure 3A). The cytotoxicity of the PEG-DOX-SWNT was also evaluated (Figure 3B). This dual-sensitive delivery system based on SWNTs provides a facile approach to promote drug release and kill cancer cells.
Discussion and Conclusion

The possible mechanism of NIR sensitive release is as follows. SWNTs are a promising material in the application of photothermal therapy and lots of studies have been conducted. For example, Dai et al. have utilized SWNTs to kill cancer cells through the application of the NIR absorbance of CNTs (1). In the current research, after NIR irradiation, the heat transferred by CNTs from the absorbed laser energy could weaken the interaction between DOX and CNTs and render a greater amount of drug released from the PEG-DOX-SWNTs.
Figure 1. NMR and TEM showed the chemical and physical structures of PEG–DOX@SWNTs.

Figure 2. NLOM images of live MCF-7 incubated with SWNTs and PEG–DOX@SWNTs in pH 6.0 and 7.4 for 1 hour (a–d) and 24... the two-photon excited fluorescence (TPEF) of DOX. The green... shows CARS images for MCF-7 cell structures.

Figure 3. (A) The cumulative drug release from NIR–pH dual sensitive nanoparticles upon NIR irradiation and pH change, and after NIR irradiation the amount of DOX released at pH 7.4 and 5.

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References