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Carbon Nanotubes-based Drug Delivery to Cancer and Brain*

Qing GUO (郭 晴), Xian-tao SHEN (沈先涛), Yuan-yuan LI (李媛媛), Shun-qing XU (徐顺清)#
Key Laboratory of Environment and Health (HUST), Ministry of Education & Ministry of Environmental Protection, and State Key Laboratory of Environmental Health, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China

Summary: Current treatments for cancer and the central nervous system diseases are limited, partly due to the difficulties posed by the insolubility, poor distribution of drugs among cells and lack of selectivity of drugs, the inability of drugs to cross cellular barriers and blood brain barrier (BBB). Carbon nanotubes (CNTs) possess many distinct properties including good electronic properties, remarkably penetrating capability on the cell membrane, high drug-loading and pH-dependent therapeutic unloading capacities, thermal properties, large surface area and easy modification with molecules, which render them as a suitable candidate to deliver drugs to cancer and brain. CNTs as a drug delivery could achieve a high efficacy, enhance specificity and diminish side effects. Whereas CNTs have been primarily employed in cancer treatment, a few studies have focused on the treatment and diagnosis of the central nervous system diseases using CNTs. Here, we review the current progress of *in vitro* and *in vivo* researches of CNTs-based drug delivery to cancer involving CNTs-based tumor-targeted drug delivery systems (DDS), photodynamic therapy (PDT) and photothermal therapy (PTT). Meanwhile, we also review the current progress of *in vitro* and *in vivo* researches of CNTs-based drug delivery to brain.
Key words: carbon nanotubes; blood brain barrier; drug delivery; cancer; brain

Nanomedicine, which plays a vital role in the diagnosis, treatment, monitoring and control of biological systems in the area of nanotechnology, has been referred by the National Institutes of Health[1]. Among the nanomedicine, the nanosized delivery vehicles have the ability to deliver drugs to a specific cell type or tissue[1, 2]. In addition, these delivery vehicles may also improve the pharmacological activity of drugs by precisely targeting and controlling the release of the drugs, as well as prolonging their short half-lives in the blood[3, 4]. Drug delivery systems (DDS) have gained tremendous attention ever since emerging in the early 1970s[5]. DDS are usually designed not only to surmount the defect of conventional drugs such as poor solubility and biodistribution, inability to cross blood-brain barrier (BBB) or cellular barriers and lack of selectivity, but also to diminish the inherent toxicity of drugs to normal cells or tissue[6, 7]. In comparison with the currently available delivery systems encompassing gold nanoparticles, dendrimers, polymer nanoparticles, ceramic nanoparticles and liposomes, carbon nanotubes (CNTs) have recently been concerned and demonstrated to possess immense potentials, particularly in the realm of drug carriers, therapeutic agents and diagnostic tools[8].

Qing GUO, E-mail: 295100071@qq.com
#Corresponding author, E-mail: xust@hust.edu.cn
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1 CNTs

Since emerging in 1991, CNTs have attracted increasing attention for their versatile applications[9]. Based on layers of CNTs, CNTs are generally divided into two categories: single-walled carbon nanotubes (SWCNTs), which consist of single layer of cylinder graphene; multi-walled carbon nanotubes (MWCNTs), which contain multiple layers of graphene sheets[10]. In fact, CNTs possess many distinct properties which render them as a suitable candidate for drug delivery carriers. Firstly, the cylindrical shape of CNTs shows great advantage in transmembrane penetration, which facilitates intracellular CNTs also to penetrate the BBB effectively[11]. Secondly, CNTs can serve as an electrical conductor and have the excellent photo-thermal feature[12, 13] with additional abilities to absorb optical intensity[13] and photoluminesce[14], in addition, to generate strong Raman signals[15]. These advantages provide the CNTs with capacity to apply in photothermal therapy (PTT) or photoacoustic therapy against cancer cells[12]. Thirdly, due to their large aspect ratio, CNTs have extremely high drug loading efficiency[16]. Besides, the ultrahigh surface area ratio of CNTs facilitates their chemical functionalization with different moieties[17]. Functionalization of CNTs with different agents shows high potency of specific cells or tissues targeting, imaging and therapy. For example, oxidized SWCNTs complexes wrapped with DSPE-PEG-NH2 to prolong blood circulation half-life, carry target tumors agent transferrin and antitumor agent meth-

otrexate[18]. This SWCNTs complex achieves a high antitumor efficacy.

The hollow tube structure of CNTs is also a key advantage when CNTs are used as drug delivery carriers. The drugs can be encapsulated in their inner hollow core, while other molecules can be attached to the external surfaces to render them to be dispersible and biocompatible for targeting purposes[19]. Currently, various therapeutic agents, such as anticancer drugs[20], central nervous system disorders therapy drugs[21], anti-inflammatory[22] and anti-microbials drugs[23], have been successfully delivered with CNTs utilizing versatile strategies, demonstrating superior efficiency and minimized toxicity to cells or tissues.

Although CNTs have been widely used for drug delivery, concerns about potential toxicity of CNTs via its biomedical applications have been raised[24, 25]. The pristine CNTs with poor aqueous dispersibility and high aggregation tendency tend to be more cytotoxic[26, 27]. Surface functionalization has been an appropriate way to reduce the cytotoxicity of the CNTs. Among the agents used for functionalization of CNTs, polyethylene glycol (PEG) is the most common material because the PEG-coated CNTs can increase the circulation time and thus prolong the concentration gradient of CNTs[28]. Up to date, PEG has been the gold standard for stealth polymers in the emerging field of polymer-based drug delivery and it has been approved by the Food and Drug Administration for many applications[29]. Some other methods can be also used to decrease the cytotoxicity of the CNTs. For example, the purity of the CNTs affects their cytotoxicity. The non-purified SWCNTs tend to inflict greater cytotoxicity[30], which can be resolved by purification[31]. Moreover, the length also has some bearings on the toxicity of CNTs. The long fiber CNTs are shown to be more toxic to cells or tissue[17]. Thus, researches in order to further optimize their length for drug delivery are in demand. Last but not the least, the toxicity of CNTs exhibits a concentration-dependent manner[32], in that, researches concerning the safe dose of CNTs are still to be conducted. Therefore, the toxicity of CNTs is relevant to the physicochemical property of CNTs, such as, surface modification, metal impurities, size and concentration of CNTs.

2 CNTs-based Drug Delivery System: Cancer Therapy

Current novel anti-cancer therapy drugs are limited, partly due to the difficulties posed by their insolubility, poor distribution among cells, lack of selectivity, the inability of drugs to cross cellular barriers[29] and inefficiency in overcoming multi-drug resistant (MDR) cancer[30]. Recently, these issues are subjected to holding intense interest. Therefore, various kinds of DDS, such as graphene oxide, magnetic chitosan nanoparticles, silica-based nanoparticles, selenium nanoparticles and dendrimers, have been reviewed[31–35]. Compared with these nanoparticles, CNTs have raised considerable attention as an emerging and promising nanostructured material for biomedical applications due to their remarkable physicochemical properties as mentioned above. In the review, a wide range of different types of anti-cancer DDS are examined.

2.1 CNTs-based Tumor-targeted DDS

2.1.1 CNTs-based Tumor-targeted DDS *In Vitro*

Many beneficial anti-cancer drugs can be integrated to the walls and tips of CNTs, whilst others can be functionalized on their external walls[19]. Previous studies have reported that part of functionalized CNTs can traverse cell membranes by energy independent pathways, while others are dependent on energy, such as endocytosis or phagocytosis[33, 34]. With specific ligands on their surface to recognize cancer-specific receptors on the cell surface, CNTs can deliver therapeutic drugs selectively and effectively into the tumor cells[35] (fig. 1).

Recently, novel SWCNT-based tumor-targeted DDS consisting of functionalized SWCNTs, tumor-targeting ligands and anti-cancer drugs have already been developed by several investigators. For example, Kaur *et al* examined the *in vitro* delivery of 5-fluorouracil into MCF-7 human breast cancer cells using PEG-SWCNTs with the targeting ligand folic acid (FA)[36]. PEG conjugation not only achieved excellent water solubility and good biological compatibility of the DDS, but also extended the circulation period of the DDS in the blood. Meanwhile, FA improved the delivery efficiency. This drug delivery system increased loading efficiency as well as drug accumulation in the target tissue. Moreover, with the advantage of FA, the efficacy of antitumor activities to MCF-7 human breast cancer cells was elevated. Another investigation confirmed the preferential higher uptake of DOX onto PEG-MWCNTs with the targeting ligand estrone (ES) on the human breast MCF-7 cells than that on PEG-FA/MWCNTs[37]. Therefore, present outcomes from the *ex vivo* and *in viv*o studies asked investigators to further explore the safer and targeted drug delivery formulation.

These prior successes cases inspired investigators to explore other targeting ligands anchored CNTs for targeted cancer therapy applications. Recently, MWCNTs are not only covalently conjugated with hyaluronic acid for targeted delivery of DOX to cancer cells overexpressing CD44 receptors, but also with fluorescein isthiocyanate for imaging the distribution of MWCNTs[38]. In this study, DOX was encapsulated into the inner cavities of MWCNTs for targeted delivery. The new carrier system achieved a high DOX loading efficiency and controllable DOX releasing rate (fast DOX releasing under acidic environment and slowly releasing at a physiological pH condition). Importantly, the multifunctional hyaluronic acid-targeted MWCNT/DOX complexes can target delivery of DOX to HeLa cells overexpressing CD44 receptors, and diminish the growth of cancer cells. 1.25–10 mg/mL MWCNT/DOX complexes exhibited good biocompatibility to HeLa cells. Beside for ligands of cancer cell surface receptors anchored CNTs, antibodies are also conjugated to assist the targeted drug delivery formulation to the desired site of action. For example, chitosan antibodies-fluorescein was used as typical antibodies to functionalize. SWCNTs attached with SNX-2112 were coated[39]. SWCNTs-chitosan with high drug-loading capability, compared

with that of SWCNTs, caused higher cell apoptosis. Overall, these results clearly exhibit that CNTs have shown great potential applications in a dual-targeting drug delivery in the near future, which deserves extensive further research.

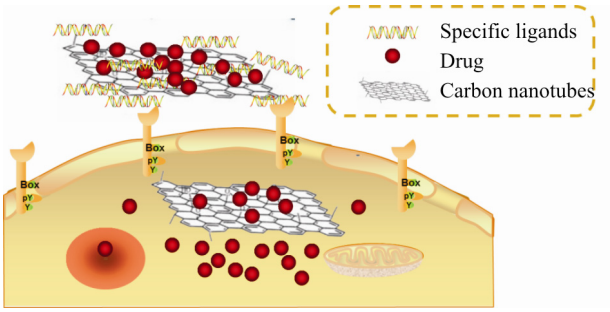

Fig. 1 Schematic diagram of CNTs-based tumor-targeted DDS

2.1.2 CNTs-based Tumor-targeted DDS *In Vivo* As mentioned above, surface functionalization of CNTs could not only achieve a good biological compatibility, but also facilitate versatile molecules loading onto the surface or within the interior core of CNTs. However, whether CNT adsorption influences the functions and structures of drug is not clear. Recently, Li *et al* investigated the effects of the CNT surface functionalization on the *in vivo* biodistribution of platinum-based DDS[40]. Mice were intravenously injected with $MWCNT_{OX}$ and $MWCNT_{TEG}$. Compared with pristine MWCNTs, an enhanced tissues uptake of platinum was observed in these DDS. Importantly, functionalized-CNTs did not affect the biodistribution of platinum-based molecules, but initiated the abnormal immune response or inflammation. In addition, PEG functionalized SWCNTs are also usually used to delivery molecules into cancer cells or tissues. DOX anchored onto PEG-functionalized SWCNTs by noncovalent π-π stacking was injected via the tail vein into mice and the *in vivo* pharmacokinetics, biodistribution and therapeutic efficacy were studied[41]. PEG prolonged blood circulation time of drug delivery and most nanotubes were excreted via the biliary system into the feces. The therapeutic efficacy of SWNT-DOX complex was hugely enhanced as compared with free DOX.

Furthermore, the length and size of CNTs also play roles in application of drug delivery. Sui *et al* proved the MWCNTs with a diameter of 20–50 nm exhibited a great advantage for drug delivery[42]. Cisplatin-inner-cavity loaded PEG functionalized MWCNTs showed high loading efficiency. Moreover, MWCNTs with diameters of 11 nm and 18 nm were able to adhere to the urothelium of mouse bladders[43]. Therefore, besides the *in vivo* pharmacokinetics, biodistribution and therapeutic efficacy of CNTs-based tumor-targeted DDS, the length and size of CNTs are also needed to be considered.

2.2 CNTs-based Photodynamic Therapy (PDT) and Photothermal Therapy (PTT)

2.2.1 CNTs-based PDT and PTT *In Vitro* At the same time, due to their remarkable physicochemical properties as mentioned above, CNTs have drawn tremendous attention for PDT and PTT with a non-invasive, innocuous, and highly efficient technology (fig. 2). This strategy has opened another research area on CNTs as DDS. According to Yang *et al*[44], near-infrared (NIR) laser field would release heat significantly by functional SWCNTs with anti-cancer drug DOX, double-stranded DNA, PEG and a fluorescent dye. This would hybridize the double-stranded DNA and then release the aptamer sequence for recognizing specific cancer-cell targeting. 5 μg/mL DOX loaded 50 nmol/L SWCNT-PEG-Apt/DNAs showed the highest level of cellular binding/uptake contributing to the NIR-activated cancer-cell binding as well as the photothermally enhanced cellular uptake of the nanotubes. Although 50 nmol/L SWCNT-PEG-Apt/DNA could not inflict obvious cell death even after 10 min of laser irradiation at 0.5 W/cm^2, it was worth doubting the long toxicity to human leukemic lymphoblast cells and normal tissues *in vivo*. Among various anticancer drugs, cisplatin (CP) appears to be a promising drug entrapped in SWCNTs in the field of PDT and PTT. In this work, a new medical nanofluid was developed, which could be employed as a DDS consisting of oxidized SWCNTs (OX-SWCNTs) as a drug carrier and CP as an anticancer drug[45]. Even more importantly, an interesting report about the release of CP was indicative of a change in the thermal conductivity values. Thus, the thermal conductivity value plays an important role in heating mediators for cancer therapy (hyperthermia) and can be used as one of the important parameters for optimizing the drug release in the targeted tumors. But the feasibility, efficacy and safety of OX-SWCNTs-CP are highly desired. Compared to PDT or PTT alone, the combined phototherapy improves efficacy of CNT-based anticancer DDS without detectable toxicity[26]. In summary, CNTs as drug delivery for selective cancer cells are a promising strategy for cancer treatment under the control of physical stimuli. Yet, the toxicity of drug carrier under the control of physical stimuli is worth more studies. Currently, the knowledge of CNT-based PDT and PTT is limited and further research is demanded in this area.

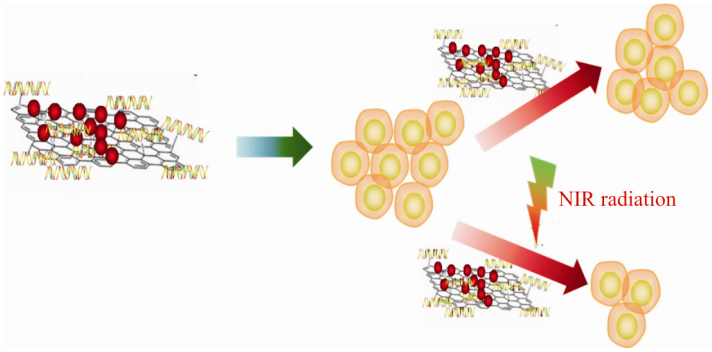

Fig. 2 Schematic diagram of CNTs-based tumor-targeted PDT and PTT *in vitro*

2.2.2 CNTs-based PDT and PTT *In Vivo* Based on the discussion above, PDT and PTT combinational therapy presents a promising therapeutic efficiency. Liang *et al* employed SWCNTs as a drug delivery to deliver cyanine 5.5 (Cy5.5) for PTT against breast tumors under the guidance of NIR imaging[46]. Cy5.5-conjugated SWCNTs treated mice exhibited higher tumors suppression rate without adverse effects. To improve the biocompatibility of SWCNTs, PEG conjugated short SWCNTs for cancer imaging and therapy[47]. The PEG functionalization and short length of SWCNTs tended to remain good biocompatibility and highly effective tumor elimination after more than 6 months post-treatment. Interestingly, another study utilized both SWCNT and poly(n-isopropyl acrylamide) as a thermo-sensitive drug delivery[48]. DOX conjugated thermo-sensitive hydrogel (SWCNT-GEL) with NIR radiation demonstrated higher tumor suppression rate *in vitro* and *in vivo*. 20 mg/mL SWCNT-GEL without NIR radiation could not induce discernible organ pathology reaction, while 0, 1, 2, 5 and 10 μg/mL SWCNT-GEL with NIR radiation inflicts a reduction in cell viability in a dose- and time-dependent manner. Therefore, more researches are needed to focus on the intensity and time of NIR radiation exposed DDS and the safety to cells or tissues with NIR radiation.

3 CNTs-based Drug Delivery to the Brain

The relative impermeability of the BBB results from tight junctions that are formed by endothelial cells of the brain capillaries, and results in the inability of some small and large therapeutic compounds to cross the BBB[49]. While intracranial drug delivery is a useful approach, it can lead to the risk of infection and edema[50]. For this reason, many nano-therapeutics have been widely studied and employed as a useful and prospective way to deliver drugs into the brain (fig. 3). Many studies have shown that CNTs could effectively penetrate the BBB[51, 52]. Herein, many researchers engineered a novel molecular complex of CNTs to deliver drugs to the brain with high therapeutic efficacy.

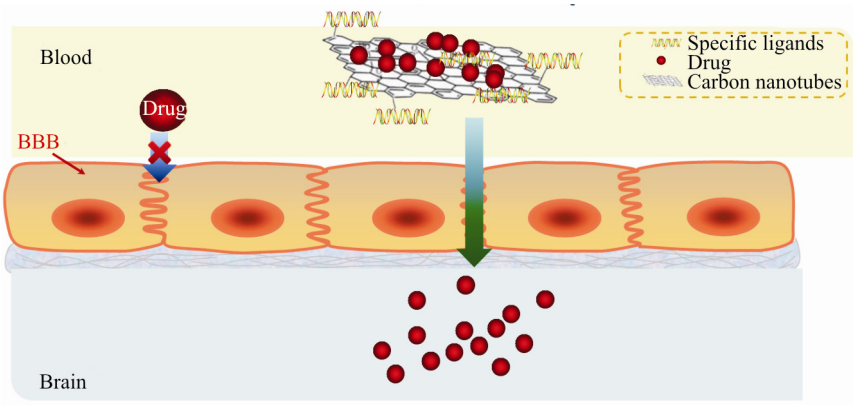

Fig. 3 Schematic diagram of CNTs-based drug delivery to the brain

3.1 CNTs-based Drug Delivery to the Brain *In Vitro*

In one study, functionalized PEG-CNTs attached with an immunoadjuvant CpG oligodeoxynucleotides (CpG) were fluorescently labeled with Cy5.5 and were intratumorally injected into an intracranial GL261 glioma for antiglioma effect[53]. CpG uptake by GL261 gliomas cells was augmented by PEG-CNTs. Subsequently proinflammatory cytokines were released and tumor growth was inhibited. However, it was uncertain whether there were unfavorable effects and inflammatory responses induced by intracranial injection itself and the efficiency was analogous to those observed by other injection. Another research was conducted by Tan *et al*[54]. Functionalized SWCNT-COOH could attach levodopa into PC12 cells to evaluate their possible effects in normal neuronal cells *in vitro*. The study suggested the release of levodopa (LD) was pH-dependent and SWCNT-COOH-LD could not compromise the cell viability of PC12 cells. These studies suggested that CNTs-based drug delivery was a promising DDS for the delivery of drugs to the nervous system.

3.2 CNTs-based Drug Delivery to the Brain *In Vivo*

Based on the reports about CNTs-based drug delivery to the brain *in vitro*, *in vivo* studies have been also widely welcomed. Khuloud *et al*[55] reported that the apoptosis was reduced after the endothelin-1-induced stroke rat model was cortically injected with functionalized CNT-siRNA and the cognitive ability of stroke rats was increased. However, the injection manner was still far from actual clinical settings. As noted above, it is necessary to further explore a systemic administration route to favor clinical translation of functionalized-CNTs. Acetylcholine (Ach) conjugated SWCNTs were developed to deliver Ach into the brain of mice with Alzheimer disease for relieving Alzheimer disease by gastrogavage[21]. Intriguingly, the target organelles were dependent on the doses of SWCNTs by gastrogavage. SWCNTs are targeted into lysosomes at doses of 5–300 mg/kg and Ach would be released with the environmental pH change. Importantly, 5 mg/kg Ach-loaded SWCNTs improved the learning and memory capability of Alzheimer disease mouse model and the safe dose of SWCNTs was 12 mg/kg. Furthermore, in order to accurately deliver the drug to the brain, a proper brain-targeting ligand is required. In this field, many ligands have been investigated, such as vascular endothelial growth factor[56], angiopep-2[57] and lactoferrin[58]. PEG-MWCNTs attached with angiopep-2 were success-

fully developed for treatment of brain glioma[49]. Because of the high affinity between angiopep-2 and LRP receptor, this drug delivery exhibited highly tumor suppression rate on the BCEC and C6 cells as well as glioma male Balb/c mice. In a word, CNTs are welcomed in the realm of drug delivery and gain tremendous attention in delivering drug into the brain. However, the distribution and insidious toxicity of CNTs in organelles, cells and tissues are necessary to be addressed and the safety and efficiency should be guaranteed.

4 Conclusion

As noted above, CNTs exhibit a great promise in the realm of drug delivery. In general, the surface functionalization, length, and size of CNTs play roles in their application of drug delivery. Based on previous reports, the appropriate length of SWCNTs used for targeted drug delivery was around 200 nm[59]. Furthermore, Hu *et al* suggested that the prepared NP and Lf-NP with a size below 150 nm were favorable for brain transport[60]. In addition, PEG functionalization was also applied to improve the feasibility and efficacy of CNTs-DA for treatment, which not only prolonged circulation time and increased the concentration gradient to the brain[28], but also was rapidly cleared from systemic blood circulation via the biliary and renal pathways[61].

However, CNTs-based DDS for diseases treatment is still in its infancy, which remains several challenges. The issues of toxicity of CNTs-based DDS still remain controversial and a hot topic to this date. The long-term toxicity studies on CNT carriers, appropriate targeting molecules to target pathology and ultrastructural pathological changes at the subcellular level are needed to be further explored, which could minimize the detrimental factors to normal tissue and surrounding environment. In addition, how is drug-coated CNT system distributed, circulated, delivered to specific cells or tissues and released *in vivo*? Does CNT adsorption influence the functions and structures of drug? These issues all are needed to further investigate. In the future, we wish to explore CNTs-based DDS with more effectiveness and safety.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

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