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Novel Drug Nanocarriers for Cancer Therapy: Carbon Nanotubes

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Abstract

Prevalent cancer therapies generally fail due to the improvement of the multidrug resistance, resulting in poor patient prognosis and high morbidity. Nano-sized drug delivery systems provide opportunities to deliver and target the anti-cancer molecules selectively to cancer cells. Among the various nano-sized drug carriers, carbon nanotubes (CNTs) have captivated the significant interest due to their versatile functionalization chemistry, unique physical characteristics, high specific surface area, biological compatibility and capability to pass the biological membranes of the cells. These characteristics offer an opportunity for the treatment of various types of cancer. In this review, the current state of the art applications of CNTs in cancer therapy as a novel drug delivery system will be evaluated. The main types and the structures of CNTs and also, functionalization strategies and cellular uptake mechanisms will be summarized in a general perspective. The potential clinical utilization of CNTs in cancer treatment will be discussed at a level of scientific research platform.

Key words: Carbon Nanotubes, Functionalization, Targeted Delivery, Cancer, Drug Delivery

Introduction

Characterized by the uncontrolled proliferation of cancerous cells as a result of various mutations, cancer is the second leading cause of mortality in the world after cardiovascular disorders. Current therapeutic strategies in cancer treatment are traditionally categorized into two classes: targeted drug delivery approaches and conventional therapies. Radiotherapy, surgery and chemotherapy are the major conventional treatments which are segmented as burning the diseased cells out, removing the cancer cells and poisoning the cancer cells, respectively. However, all these therapies severely damage healthy cells as well, whilst they simultaneously present serious toxic side effects due to the unspecific bio-distribution of the anticancer agents. Of course, it is needless to note that all these negative effects, reduce substantially the quality of life of patients [1-3].

Drug-targeting nano-based carriers offer a promising approach in cancer treatment to better the efficacy of treatment, improve the delivery of active agents, reduce the side effects, and overcome the resistance of anticancer drugs [4-6]. Hence, a wide variety of nano-sized drug carriers, spanning from polymer- and lipid-based nano-sized particles, dendrimers, vesicular systems, to carbon nanotubes (CNTs) and quantum dots, are increasingly investigated in terms of their potential in cancer treatment [3,7]. Of them, CNTs are more actively employed for cancer diagnosis (due to their excellent thermal, mechanical, and optical properties) and for the treatment of cancer (due to their inherent hydrophobic nature and unique sp2 carbon structure) [8]. Major superiorities of CNTs over the other nano-sized particles are bio-compatibility, greater stability, ease of size alteration, non-immunogenity and high drug loading capability [9]. CNTs were firstly described by Sumio Iijima in 1991 as molecular-scale tubes of graphitic carbon with hundreds to thousands of nanometers long, and 1-30 nanometers in diameter [10, 11]. Figure 1 represented the schematic illustration of the CNTs.

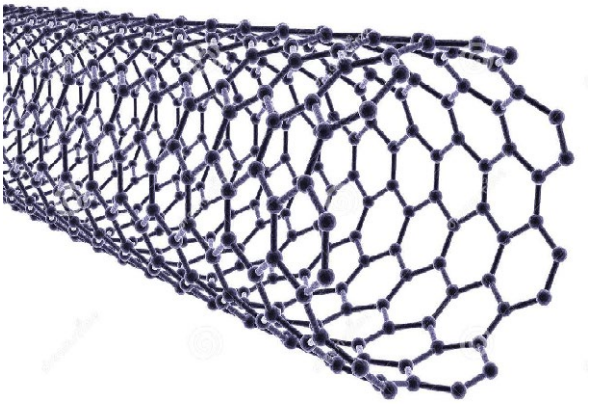

Figure 1. Schematic illustration of CNTs structure [3].

Structures of Carbon Nanotubes

CNTs are promising quasi one-dimensional nanomaterials with hollow graphitic cylindrical tubular structure consisting of hexagonal arrangement with sp2 hybridized carbon atoms [12]. CNTs are basically categorized according to their structures;

- Single wall carbon nanotubes (SWCNTs)
- Double wall or multi wall carbon nanotubes (MWCNTs)

SWCNTs consist of a single graphite sheet seamlessly wrapped into a cylindrical tube with a diameter of approximately 1-10 nm, whereas MWCNTs is comprised of an array of nanotubes which are concentrically nested like rings of a tree trunk with diameters ranging from 5 to 30 nm. The lengths of CNTs depend on the production technology preferred. One-dimensional structure and high specific surface area of the CNTs render them ideal candidates for cancer treatment [13, 14].

To become less toxic, highly dispersible, and more biocompatible, CNTs are functionalized. Both of the outer and inner surfaces of CNTs could be modified and thus used for the further conjugations with specific ligands, as well as the active compounds to maintain active targeting to the cancer cells. The inner empty cavity of CNTs mostly used for the incorporation of a variety of active molecules with high drug loading [9]. Main categories of functionalization technologies of CNTs are represented in Figure 2.

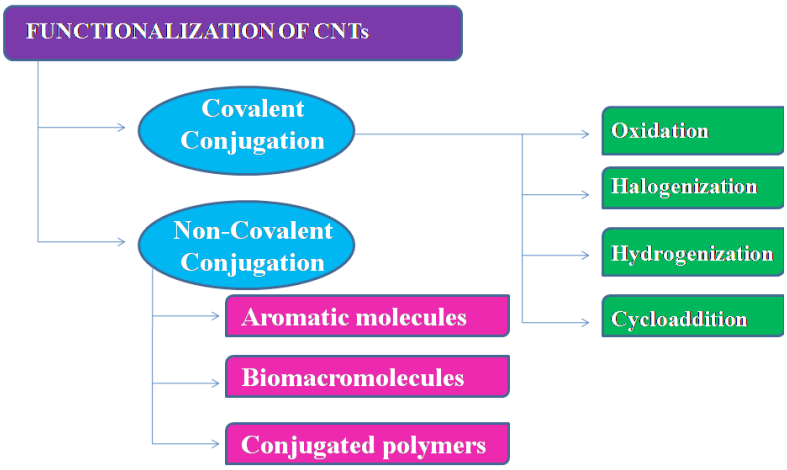

Figure 2. Functionalization categories of CNTs–based nanomaterials.

Numerous researchers reported the effectiveness of CNTs as drug delivery systems to target different kinds of cancer cells through conjugation or functionalization with various ligands on the surface and at the ends of the CNTs [9]. Schematic presentation of the targeting moieties of CNTs are given in Figure 3 [3].

Figure 3. Possible moieties for targeting strategies of CNTs [3].

Generally, covalent conjugation is more controllable, accurate and robust compared to non–covalent functionalization. Intrinsically, non–covalent–based conjugated structures have some limitations such as likely dissociation in biological media and potential hazardous effects arising from the exchange of the conjugated molecules with serum proteins, and the undesired detachment of targeting agents after application [16, 17]. However, non–covalent–based conjugation is more preferable as this functionalization preserve the optical, electrical and structural characteristics of the CNTs, while assuring the invariance of the specific properties of the targeted ligands. A well–acknowledged non–covalent functionalization of CNTs is the adsorption of aromatic molecules to the surface of the nanotube structure through $\pi-\pi$ interaction [19]. On the other hand, covalent–based conjugation causes some dramatic changes on the conjugated π–electron framework of CNTs by inducing rehybridization of the sp2 derivatized carbon atoms to sp3, leading to reduced intrinsic Raman scattering and NIR fluorescence [18].

Cellular Uptake Mechanism of CNTs by Cancer Cells

CNTs are primarily delivered into the cancer cells through receptor mediated endocytosis [9]. They attach to the surfaces of the biological membranes through electro–static effects or adsorption process, depending on the functional targeting group. Subsequently, this initial binding cause

a dramatic damage on the cancer cells through generation of reactive oxygen species, resulting in protein denaturation, lipid peroxidation, DNA damage, which result in the death of cancer cells [20]. The transport mechanism of CNTs into the cancer cell compartments are independent from the characteristics of nanotubes and the types of cancer cells. When CNTs are contacted with plasma membranes, they are transferred into the cytoplasma region of the cell without the apparent need of engulfment into a cellular compartment to facilitate intracellular transport [21, 22]. Dimensions of the CNTs are more effective than the surface chemistry on the uptake capacity of CNTs.

Raffa et al., indicated that short CNTs function as nano-needles and in this way more efficinetly penetrated into the cancer cell membrane than the longer ones which often aggregated [23]. Liu et al., developed a SWCNT-paclitaxel conjugate by functionalization paclitaxel to branched polyethylene glycol (PEG) on the surface of CNTs via a cleavable ester bond. The anticancer activity of the SWCNT-paclitaxel conjugate was evaluated on a murine 4T1 breast cancer cells and it was demonstrated that the tumor uptake of developed nanotubular system was 10-fold higher than that of the commercial product of paclitaxel-TAXOL, probably through enhanced permeation and retention (EPR) effect [24].

In another research, Vittoria et al., investigated the biocompatibility and toxicity profiles of the MWCNTs on cultured human neuroblastoma cells SH-SY5Y. After the incubation of these nanomaterials, the maximum cell death (92 %) was observed when covalent-based MWCNTs are functionalized with the technique of oxidation process, while the non-modified form of MWCNTs showed only at the level of 1 % of cell death [25]. In 2010, Coccini and co-workers investigated the cytotoxicity profile of non-covalent conjugation based MWCNTs with amine-, and carboxyl-functionalized on two lung cancer cell lines (human A549 pneumocytes and D384 astrocytoma cells). Their result indicated that amine-functionalization grants MWCNTs a more cytotoxic character than carboxyl-functionalization does [26].

Conclusion

The utilization of CNTs as nano-sized drug delivery vehicles may be a good approach in the treatment of various cancers. Targeted delivery of anti-cancer compounds via CNTs provides selectivity, enhanced drug efficacy, reduced undesired systemic side effects and thus, improved quality of patient life. CNTs have the potential to serve as optimal candidates for anti-cancer drug delivery vectors for the further clinical cancer treatment. Scientific cancer searches must progress to allow CNTs to be effective in the future.

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