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Application of Carbon Nanotubes in Breast Cancer Therapy

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Key words
carbon nanotubes, breast cancer cell line

received 17.12.2018
accepted 28.05.2019
published online 28.06.2019

Bibliography
Drug Res 2025; 75: 89–93
DOI 10.1055/a-0945-1469
ISSN 2194-9379

Georg Thieme Verlag KG, Oswald-Hesse-Straße 50,
70469 Stuttgart, Germany

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ABSTRACT

Conjugated single-walled carbon nanotubes (SWNT) have been shown to be promising in cancer-targeted accumulation and is biocompatible, easily excreted, and possesses little toxicity. The present study aims at reviewing the recent advancements in carbon nanotubes especially SWNT for improving the treatment of breast cancer. Nanotube drug delivery system is a potential high efficacy therapy with minimum side effects for future tumor therapy with low doses of drug.

Introduction

Cancer remain one of the greatest challenges faced across the world today. Deaths due to cancer accounted for approximately 8.2 million in 2012, and breast cancer leading to 521 000 deaths of all. According to American Cancer Society, the numbers of diagnosed and death by invasive breast cancers in 2014 was estimated to be respectively 232 670 and 40 000 [1].

Breast tumor remains the most common women malignant tumor throughout the world, and also a major cancer death cause [2]. According to American Cancer Society, it is the second main cause of cancer-related death in The United State of America. The basic hallmark of breast tumor is the progression and metastasis to several organs including liver, lung, bone and/or brain, which leads to a multiple organ dysfunction, thereby increasing the incidence of death in patients with breast cancer [3, 4]. Metastasis occur when cancer cells leaves the primary cancer site and travels to another organ through the blood vessels or lymphatic system [5, 6].

Nanomaterials possessing opto-thermal principles of transduction have been shown promising for cancer therapy. Nanotubes (NTs) are suitable in this regards, such that, they possess a high photothermal cell destruction and optical absorbance efficiencies [7, 8]. The quantity of light energy used is fairly small as compared to other procedures, since the optical absorbance of NTs is high in the 700–1 100 nm near-infrared (NIR) range. This has been used lately to design several kinds of optical actuators and sensors based on the photo-mechanical actuation of carbon nanotubes (CNTs) [9–11]. CNT [12] are regarded as a flawless materials for various uses [13], this ranges from field emission display [14] to ultrastrong fibers [15]. Lately, CNT have received great attention in the field of molecular biology [16], where appropriately functionalized CNT can serve as vaccine and drug delivery systems (DDS) [17] or protein transporters [18]. Due to the extensive π-π stacking reaction between associated ligand and CNTs side walls, conjugation of ligand and functionalization is possible [19, 20], multi-component targeting using photothermal cell destruction might lead to the improvement of microsurgery, cancer therapies, and cell repair [21].

The present study aims at reviewing the recent advances of carbon nanotubes especially Single-walled carbon nanotube (SWNT) for improving targeted breast cancer therapy.

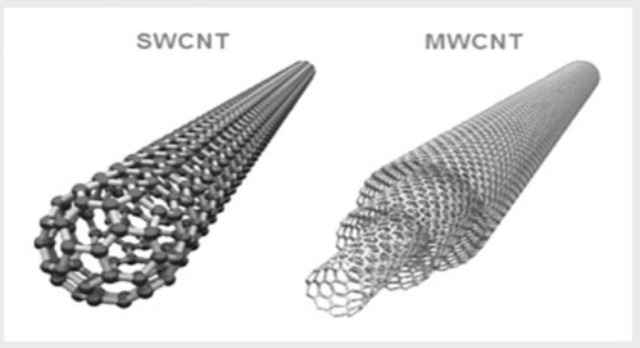
Carbon Nanotubes

CNTs are cylindrical carbons made of benzene rings, they finds applications in biology as protein and DNA detecting sensors, protein or vaccine carrier and diagnostic tool for several kinds of serum samples for proteins discrimination [22]. These structure can also be produced from graphite sheets where carbon atoms are located in the apexes of a hexagonal net. They are chemically stable, possess high thermal and electrical conductance, mechanical

strength and surface area [23]. CNTs are completely insoluble in all solvents, which gives them toxicity and health-related concerns. Nevertheless, introduction of chemical modification to CNTs improves their solubility, and interaction with active molecules including proteins, peptides, nucleic acids, proteins, and other therapeutic agents [24]. Anticancer drugs (methotrexate) or antifungal agents (amphotericin B) have covalently been attached to CNTs with a fluorescent agent (FITC). Drugs attached to CNTs have been shown efficient internalized into the cells in comparison with drugs without CNTs [25, 26]. The multiple CNTs surface modification or tips of CNTs permits them to carry several molecules, and thus providing a fundamental merit for cancer therapy. CNTs come in two principal forms; these are the SWCNT and Multi-walled carbon nanotube (MWNTs) (▶ **Fig. 1**). Targeted drug delivery using CNTs have shown improvements by integrating molecules specific of the biological receptors with these nanotubes [27]. In a study, glycol-MWCNT were designed where glucosamine was covalently attached to the carbon nanotube. These tubes exhibited sugar-like interaction with breast cancer cells, hence assisting the biological molecules into the cells [28].

Single-walled carbon nanotube

SWCNT is a newer type of nanomaterial possessing unique mechanical, electrical, structural, and optical features which are promising for several biomedical applications, including biosensors [29], drug delivery transporters [30] and novel biomaterials [31]. In the quest of achieving a specific tumor cells targeting for photothermal ablation, SWNTs was attached to folate for targeting the receptors of folate in folate positive tumor cells [32, 33] or noncovalently conjugated (through adsorption) or indirectly through streptavidin-biotin conjugation [34] to antibodies targeting a specific receptors on the tumor cells. The direct covalent conjugation for specific cancer by targeting antibodies of SWNTs has also been studied [35], nevertheless, the application of such antibody-SWNT conjugates for specific photothermal ablation of tumor cells with NIR light has not been reported. Studies have also revealed that CNTs can enhance the pharmacokinetic properties of drugs like Docetaxel, which are insoluble and have low tissue permeability [36]. Needle-like structure of carbon nanotube ease internalization of the biomolecules into the target cells. CNTs have been reported effective for the administration of several antitumor drugs like topoisomerase I inhibitors, platinum and anti-microtubule drugs, genes, siRNA, immunogenic compounds and aptamers for anticancer treatments [37].



▶ **Fig. 1** Single-walled carbon nanotube (SWCNT) and multiwalled carbon nanotube (MWCNT). Source: [50] [rerif].

Multi-walled carbon nanotube

A MWNTs encompass an exclusive nanomaterial type that is remarkably durable and electrically conductive owing to the high aspect ratio and chemistry of the particles [38, 39]. MWNTs are comparatively long, with a cylindrical shaped-nanoparticles whose honeycomb structure produces high surface area relative to their volume, and high porosity. The size of these pores ranges from 4 and 30 nm in diameter [40]. The particles are flexible and durable [41], comparable to the extracellular matrix (ECM). Because of the importance of cells' physical microenvironment, the ability of MWNT to mimic the normal ECM might be able to modify tumor cell behavior in a way that is hypothetically clinically applicable.

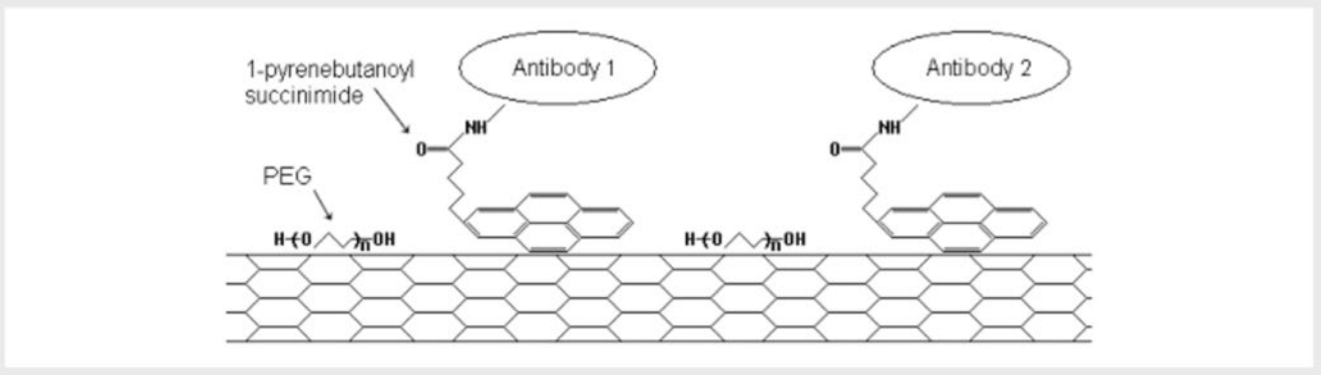
Characteristics of Carbon Nanotubes as a Drug Delivery System

Large surface area and thermal and electrical stability of carbon nanotubes allow the attachment of various biological molecules to its surface, making them suitable candidate to form drug delivery system. For example, Cationic fullerenes have tendency to bind to anionic tumor cells hence providing affinity for targeted delivery of the drugs [23] The conjugation scheme of antibodies (Ab) is shown in ▶ **Fig. 2**. This strategy works fine for the attachment of specific and non-specific Abs on the surface of the NT. TEM of the Ab conjugated SWCNT shows a direct confirmation that the Ab were functionalized on the SWCNT on several sites, as depicted in ▶ **Fig. 3**. This has been confirmed in previous research using atomic force microscopy (AFM) and confocal microscopy [42]. Since the NTs conjugated with Abs were washed three times prior to imaging, it is predictable that all the Abs aggregates are covalently LINKED to the CNTs. This depicted a greater number of Abs molecules in a specific site, capable of attachment to SWCNT without any activity loss for drug delivery.

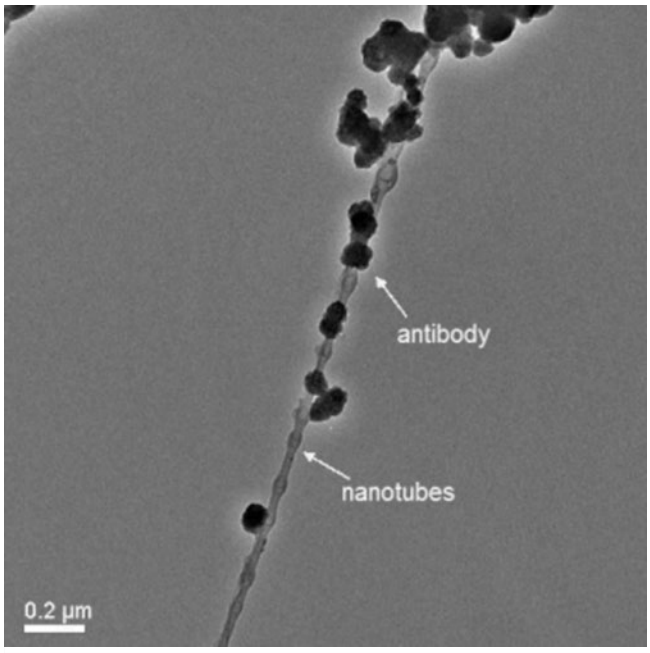
Carbon Nanotubes Improves Breast Cancer Therapy

The improvement of efficient and novel DDS is critical for developing the pharmacological profiles of several therapeutic molecules classes. Several DDS are presently in use. Amongst nanomaterials, CNT have materialized as an effective tool and new substitute for translocating and conveying therapeutic molecules. They can act as a surface modifier using proteins, bioactive peptides, drugs and nucleic acids for carrying the drugs they contain into the target organs and cells. Since surface modified CNT are not immunogenic, and possesses a lower toxicity, such a design is of a great potential in nanomedicine and bionanotechnology [43].

Singh et al. [44] synthesized and studied paclitaxel loaded thiamine and riboflavin conjugated multi walled CNT (PTX-Tm-MWCNTs and PTX-Rf-MWCNTs) for targeted delivery to MCF-7 breast cancer cell lines. They found that PTX-Tm-MWCNTs and PTX-Rf-



▶ **Fig. 2** Conjugation schematic of SWNTs with mAbs. 1-pyrenebutanoyl succinimide was adsorbed on the NT via π–π stacking. The succinimidyl ester can react with lysine side chain amines available on Abs to form amide bonds. PEG serves the purpose of insulator to hinder possible bio-fouling. Source: [32] [rerif].



▶ **Fig. 3** TEM of the functionalization of mAbs aggregates specific to IGF1 receptor in breast cancer cells. Each site comprising 10–25 Ab molecules. Source: [32] [rerif].

MWCNTs showed a great potential in breast cancer treatment, however, more thorough findings are required in future.

Al Faraj et al. [45] fabricated a new diagnostic and therapeutic method through doxorubicin-loaded SWCNTs, targeting treatment of metastatic regions, they followed preferential improved and homing therapeutic effects through noninvasive free-breathing bioluminescence imaging and magnetic resonance imaging (MRI). The noninvasive MRI combination to localize sensitively of cancer sites, through specific magnetic positioning that improves nanocarriers magnetic targeting permitted increasing efficacy of treatment.

Molecular targeting and photodynamic therapy is promising for selective treatment of tumor. Monoclonal antibodies that are specific to the HER2 and IGF1 cell surface antigens can bind to SWCNT for targeting SWCNT on breast cancer cells for specific near-infrared phototherapy. When this nanotube is conjugated with both the receptors, there is a selective attachment to the breast cancer cells as compared to those conjugated with non-specific antibodies.

Mashal et al. showed that SWCNTs is a probable dielectric contrast enhancer between normal and malignant breast tumor microwave detection and enhances selective malignant tissue heating for microwave hyperthermia treatment of breast cancer. This study was the first step in the direction of fabricating functionalized, cancer-targeting SWCNTs as theranostic (integrated therapeutic and diagnostic) agents for microwave breast tumor diagnosis and treatment. It was observed that in microwave heating studies, there was a significantly higher temperature increase in SWCNTs containing mixtures. This increase in temperature was linearly scaled with the efficient mixtures conductivity [46].

Metastasized cancerous cells lack contact inhibition where past studies have proposed that restoration of these contact inhibition may restore the normal cells properties. Dineshkumar et al. aimed at restoring the contact inhibition of cancer cells with multi-walled CNTs. They analyzed the adhesion, proliferation, western blots, autophagy assays, and immunochemical staining to evaluate E-cadherin expression and adhesion. Breast cancer cells seeded on a MWCNT-collagen coated surface showed an increased cell adhesion and decreased cell migration indicating an upregulation of E-cadherin. This study provided an alternative approach to cancer therapy [47].

Xiao et al., [48] investigated two unique optical characteristics of SWNTs - very strong NIR absorbance and a very strong Raman signals. HER2 IgY-SWNT complex was synthesized through covalently functionalizing SWNTs with anti-HER2 IgY antibody to produce SWNTs possessing high sensitivity and specificity for the IgY antibody. The complex formed was effectively applied in vitro for the selective destruction and detection of HER2-expressing breast cancer cells. Raman signal arising from tumor cells was identified at the unicellular level. The uniqueness of this dual-function agent lies in the fact that it needs no internalization by the tumor cells for achieving selective photothermal ablation, and therefore offering the merit of being easily extended to other tumor types. Conversely, more research is required for this investigation to be applied in the clinical trials. In a recent study, polyethylene glycol (for its physiochemical characteristics and biocompatibility) and estradiol-E2 (es-

tradiol receptors are over expressed in breast cancer cells) were used for CNT modification and lobaplatin (third generation, platinum anticancer drug) was loaded for the treatment of breast cancer. It was seen that incubating cells after 72 h at the dose of 200 µg/ml of PEG-E2-CNT-lobaplatin significantly inhibited the tumorigenic activity of the cells, without any toxic effects [49].

Conclusion

This review reveals the understanding of the relationship between cells and their microenvironment. It has been shown that CNTs specifically SWNTs, can imitate the natural ECM to facilitate the adhesion of cell and regulates the expression of gene. This area of research offers a novel method of diagnosing and treating breast cancer and should be considered for additional investigation to develop it towards clinical use.

Contributors' Statement

Dr. Mahdis Tajabadi: conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. Designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript. Coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.

Conflict of Interest

The authors deny any conflict of interest in any terms or by any means during the study. All the fees provided by research center fund and deployed accordingly.

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