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RESEARCH ARTICLE

CARBON NANOTUBES: A NOVEL APPROACH FOR CANCER DIAGNOSIS & THERAPY

Dr. Asha M. L., *Dr. LaboniGhorai, Dr. Mahesh Kumar H. M., Dr.BasettyNeelakantamRajarathnam, Dr. Lekshmy J. and Dr. SrilakshmiJasti

Department of Oral Medicine & Radiology, Dr.Syamala Reddy Dental College, Hospital & Research Centre, #111/1, SGR College Main Road, Munnekolala, Marathahalli (Post), Bangalore- 560037

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ABSTRACT

Head-and-Neck cancer is the sixth most common cancer worldwide, accounting for 5−6% of all cancer cases. Surgical resection and/or radiotherapy have long been regarded as the standard treatment, while chemotherapy can be added as an adjunct. However, conventional chemotherapy has certain drawbac7ks like non-specific distribution, short circulation time and tumour resistance. Recently, targeted therapeutics with nanoparticles have emerged as promising alternatives to overcome these drawbacks of conventional approaches and among the diverse classes of nanomaterials, Carbon Nanotubes (CNTs), due to their unique physicochemical properties, have become a popular tool in cancer diagnosis and therapy. CNTs are tubular materials with nanometer-sized diameters and axial symmetry, with the unique properties such as ease of cellular uptake, high drug loading and thermal ablation which render them useful for cancer therapy. The important biomedical applications of CNTs include their contribution in the field of drug delivery, thermal therapy, photodynamic therapy, gene delivery, biological detection and imaging. More recently, they have also been used as vehicles for antigen delivery, a novel immunization strategy against infectious diseases and cancer. These multifunctional and multiplex nanoparticles are now being actively investigated and are on the horizon as the next generation of nanoparticles, facilitating personalized and tailored cancer treatment. However, concerns over certain issues such as biocompatibility and toxicity have been raised and warrant extensive research in this field.

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INTRODUCTION

Cancer is one of the leading causes of death worldwide. According to the World Cancer Report 2012 issued by the World Health Organization, there were an estimated 14.1 million new cases of cancer worldwide in 2012 and 8.2 million deaths from the disease (Boyle and Levin, 2012). Early radical resection of the tumour is the most desirable treatment but only a few cases are diagnosed at an early stage. However, for most patients local invasion and distant metastasis are present at the time of diagnosis. For those un-operable patients and those who received palliative operation, chemotherapy and radiotherapy are the mainstay. Since chemotherapeutic drugs affect all rapidly dividing cells, including the healthy cells, they can cause several undesirable effects in the patient's body. Therefore, the challenge is to develop new methods for early detection of cancer and targeted delivery of drugs to the cancerous cells only. Recently, targeted therapeutics with nanoparticles have gained prominence in the biomedical field (Fukumori and Ichikawa, 2006; Vasir and Labhasetwar, 2007; Faraji and Wipf, 2009) and among these diverse classes of nanomaterials, Carbon Nanotubes (CNTs) have attracted particular attention due to their unique physicochemical properties. Since past 18 years, different carbon nanotube preparations have been reported to be used in drug delivery, cellular therapy and more recently in molecular imaging and as sensors for cancer biomarker detection in serum (Chen *et al*., 2008; Heister *et al*., 2009; Bhirde *et al*., 2009).

**Corresponding author: Dr. LaboniGhorai*
Department of Oral Medicine & Radiology, Dr.Syamala Reddy Dental college, Hospital & Research Centre, #111/1, SGR College Main Road, Munnekolala, Marathahalli (Post), Bangalore- 560037

CARBON NANOTUBES: STRUCTURE & PROPERTIES

Carbon nanotubes, first discovered by Iijima in 1991 can be imagined as the cylindrical roll-up of one or more graphene sheets containing only sp2 hybridized carbon atoms in a honeycomb arrangement (Tasis *et al.,* 2006). Both ends of the tubes are capped by a hemispherical arrangement of carbon networks called fullerenes, formed by warping of the graphene sheet. Structurally, CNTs are of two types: single-walled

(SWNTs), which consist of one layer of cylinder graphene and multi-walled (MWNTs), which contain several concentric graphene sheets. The length of the nanotubes ranges from several hundred nanometers to several millimetres but their diameters depend on their class, diameter of MWNT being greater than that of SWNT. CNTs possess remarkable properties such as high aspect-ratio, ultra-light weight, tremendous strength, high thermal conductivity and significant electronic properties ranging from metallic to semiconducting. However, in the field of cancer diagnostic and therapeutic, three main attributes of CNTs have been exploited:

- Being small in size, they can pass through the leaky vasculature within the tumour or can transport DNA
- High surface area to volume ratio provides a good platform for their ability to efficiently transport different chemicals
- Their ability to contain chemicals

Although in recent years, a variety of different nanocarriers have been evaluated, carbon nanotubes have potential advantages over the others. The advantages include:

- Ability to carry a high cargo loading, intrinsic stability and structural flexibility, which will lead to increased circulation time, resulting in better bioavailability of the drug molecules carried
- Ability to enter the mammalian cells
- Requirement of lesser quantity of the drug for the desired effect
- No requirement of solvent for drug delivery, thereby preventing undesired health effects from the solvent
- No risk of the protective nanocarrier degrading
- A range of drugs can be attached for therapeutic and diagnostic purposes [10]

CARBON NANOTUBES: APPLICATIONS

Due to their amazing properties, CNTs have diverse applications in the field of cancer diagnosis and therapy. The important applications include:

1.Applications in Cancer Diagnosis

a) Molecular Imaging with SWCNTs
b) Cancer biomarker detection

2.Applications in Cancer Therapy

a) Drug Delivery
b) Lymphatic targeted Chemotherapy
c) Thermal Therapy
d) Photodynamic Therapy
e) Gene Therapy

Applications in Cancer Diagnosis

a) Molecular Imaging with SWCNTs

Since radical resection of the tumour at its early stage is the treatment of choice, early screening and detection are of immense importance. Most cancers are asymptomatic during their early stage. Since, the conventional clinical cancer imaging techniques, such as film radiography, computed tomography, magnetic resonance imaging and diagnostic ultrasonography require a macroscopic anatomic change for information to be recorded by an image receptor, they can easily avoid being detected by these imaging techniques. On the other hand, radionuclide imaging such as Positron emission tomography, though identify early-stage alterations in molecular biology, is not specific for malignant diseases but for increased metabolism (Levy, 2007; Papathanassiou *et al*., 2009; Delbeke *et al*., 2009). Hence, it is imperative to develop new aids for early cancer diagnosis. Hong *et al*. first viewed molecular imaging with single-walled carbon nanotubes. CNT can act as a contrast medium in different imaging modalities such as Magnetic resonance, Near-Infrared Fluorescence, Raman spectroscopy, Photoacoustic tomography and Radionuclide-based imaging, where Gadolinium functionalised Ultra-short SWCNT (Gadonanotube) improved resolution, sensitivity and tissue penetration as compared to the traditional contrast agents (Hong *et al*., 2009).

b) Cancer biomarker detection

Cancer cells often overexpress characteristic protein biomarker, which provide an opportunity for early diagnosis of the disease. CNT exhibiting unique electronic, mechanical and thermal properties, has been proposed as a promising tool for detecting the expression of indicative biological molecules at early stage of cancer with high sensitivity, selectivity, rapidity and low detection limit. Xin Yu *et al*. in 2006 reported a combination of electrochemical immunosensors using SWCNT forest platform with multi-label secondary antibody-nanotube biconjugates for highly sensitive detection of a cancer biomarker in serum and tissue lysates. Although further research is required in this field, it is believed that CNTs-based detecting measurement may serve as an alternative method for cancer biomarkers diagnosis in clinical analysis in the future (Yu *et al*., 2006).

Applications in Cancer Therapy

a) Drug Delivery by CNTs

Chemotherapy is generally used alongside surgery and/or radiotherapy in advanced cancer cases. The most common chemotherapeutic agents used are platinum-based drugs (cisplatin or carboplatin) and combinations with taxanes (e.g., docetaxel) or 5-fluorouracil. Clinical studies revealed that approximately 30% of patients with advanced Head and Neck Squamous Cell Carcinoma (HNSCC) responded to a single agent, such as cisplatin or 5-FU, but no improvement in overall survival was observed (Pinto and Jacobs, 1991). A combination of chemotherapeutic agents did improve the drug response but had no effect on overall survival (Jacobs *et al*., 1992). The conventional delivery methods of chemotherapeutic agents have several limitations:

- Firstly, some drugs have poor solubility and low bioavailability and contain toxic solvents in their formulation.

- Secondly, they have a short circulation time because of their physiological instability, degradation, and clearance.
- Thirdly, the nonspecific distribution of the drugs limits the concentration achieved in the tumour, and causes harmful side-effects because of their unwanted accumulation in healthy tissues (Pinto and Jacobs, 1991)

Therefore, advanced drug delivery systems (DDS), based on nanotechnology and a tumour-targeted strategy, hold considerable potential to enhance chemotherapeutic efficacy. Researchers have found that functionalized CNTs with the help of specific peptides or ligands on their surface recognize cancer-specific receptors on the cell surface, can carry therapeutic drugs more safely and effectively into the cells that are previously unreachable, which makes them ideal candidates for drug delivery (Chen *et al*., 2008).

These delivery systems generally consist of three parts:

- Functionalization of CNTs
- Anti-cancer drug loading
- Drug Targeting

Functionalization of CNTs

Functionalization is a process of attachment of appropriate molecules to the carbon nanotube surface to evade the host defences and to make them more biocompatible and less toxic. CNT tips have a higher affinity for binding functional groups than the side walls (Prato *et al*., 2008). Functionalization can be done non-covalently or covalently. Non-covalent functionalization involves VanderWaal interactions, π-π interactions and hydrophobic interactions of biocompatible groups with the surface of CNT. This method preserves the aromatic structure and electronic characteristics of CNTs but the bonding being weak it is not suitable for targeted drug delivery application. Covalent functionalization involves oxidation of CNTs with strong acid which attaches COOH group to the side wall of CNTs rendering them water soluble and biocompatible. Biocompatibility may be enhanced by further coating with Poly Ethylene Glycol (PEG), which is a hydrophilic substance. Thus this method is suitable for use as Drug Delivery System (Liu *et al*., 2007).

Anti-cancer Drug Loading

The location of the drug to be delivered by the CNT can be internal or external. Internalisation relies on Vander Waals force for insertion into the CNT and is the best method for the drugs that are sensitive to external environment and easily broken.

In this process, CNT caps are first opened by electric current or with acid. The most common mechanism for filling CNTs is by capillarity. Drugs can attach to the CNT via the functional group either by covalent bonding where a linker with which both the drug and CNT react to form covalent bond is used or by non-covalent bonding which involves physical conjugation of the anticancer drug to CNT via hydrophobic interaction, π-π stacking or electrostatic adsorption. Then, the CNTs are washed with a solution which is less soluble for the impregnating fluid and can dissolve only the deposits left outside CNT. Finally, CNTs are capped by passing a current which fuses the ends closed (Kushwaha *et al*., 2013).

Drug Targeting

Accumulation at a targeted location is important in Drug Delivery System. Targeted nanoscale drug delivery are of two types: Passive targeting and Active targeting.

In passive targeting, PEGylated conjugates are delivered to the tumour tissue in increased amount due to EPR effect. Due to angiogenesis, the new blood vessels that are formed are leaky promoting increased permeability of nanoparticles. Poor lymphatic drainage in tumour also causes retention of nanoparticles. This combined effect is called EPR or Enhanced Permeability and Retention.

Active targeting uses antibody or ligand targeted binding as a means of selective delivery to cancer cell or tumour (Kushwaha *et al*., 2013).

After targeted delivery, anticancer drug will be released in cancer cell by different techniques:

- Extracellular tumour tissue and intracellular lysosomes and endosomes are acidic and may help in release of anticancer drug at low pH
- Heat in acidic environment may help in release of drug
- Cleavage of disulphide bond by thiol reducing enzyme may help in release of drug (Samori *et al*., 2010; Kam *et al*., 2005)

b) CNTs in lymphatic targeting

Lymphatic metastasis is common in cancers and often contribute to tumour recurrence, even after extended lymph node dissection. CNTs can be used to effectively block the metastasis of cancers through the lymphatic system. A lymphatic targeted drug delivery system has been developed using magnetic multi-walled carbon nanotubes (mMWCNTs), which successfully delivered anticancer drug to lymph nodes with high efficiency under the guidance of a magnetic field (Yang *et al*., 2008; Yang *et al*., 2009). In another approach, Poly Acrylic Acid-grafted multi-walled carbon nanotubes have been tried, which were seen only in the local lymphatic nodes sparing the major organs, after 3 hours of subcutaneous injection, suggesting that they may have the potential to be used as a vital staining dye and simplify lymph node identification during surgery even when they are very small (Li *et al*., 2010; Pramanik *et al*., 2009). Thus, without the help of such a nanostructure, anticancer drugs cannot preferentially distribute in the lymphatic system.

c) Thermal therapy applications

There has been much interest into the use of CNTs in conjunction with radiofrequency and laser therapy in cancer treatment. Thermal Ablation above 55˚C has shown coagulative necrosis and protein denaturation of the malignant cells and also the permeability of the tumour vasculature is

increased due to the local rise in temperature. The transmission of laser beams could be divided into two different types: short laser nanosecond exposure and long laser exposure. Nanosecond exposure is usually used for the ablation of metastatic or individual tumour cells. Although temperatures using this method can reach a maximum of 300°C, its nanosecond exposure ensures minimal damage to surrounding tissues. The second method requires a few minutes of laser exposure and is generally used for ablation of primary cancer cells that are relatively large in size. The latter usually disables cell function by thermal protein denaturation and, unlike short laser exposure, may affect healthy cells as well as cancer cells. The temperature range for this type of laser is typically 45°C–65°C. Also, laser being a single point source of thermal energy, results in uneven tumour heating, or production of tumour seeding along the needle track that can result in tumour recurrence.

CNT-mediated thermal ablation has potential advantages over the conventional ones. The advantages include:

- Targeting of malignant tumour site specifically and selectively ablating the tumour cells
- Prevention of uneven tumour heating
- Prevention of tumour seeding
- Production of temperature gradients that extend more deeply into the tissue
- Ability to carry magnetic nanoparticles which can be localized in deep tissue, fixed at a specific position by an external magnetic field and then alteration of the AC field can be used to change the temperature of the magnetic nanoparticles. Here, CNT acts as a shell, protecting the biological environment against oxidation and toxicity of the magnetic nanoparticles (Kam *et al*., 2005; O'Neal *et al*., 2004; Imamura *et al*., 2008; Burke *et al*., 2009; Liu *et al*., 2007; Klingeler *et al*., 2008)

d) CNTs-mediated photodynamic therapy

The use of CNTs as a new photosensitizer for photodynamic therapy (PDT) is another area of research currently under investigation. PDT is a confined therapy capable of efficiently destroying tumours while at the same time sensitizing the immune system to seek out and destroy metastases. Hence, it could be a better alternative for cancer therapy in comparison to the conventional treatments like surgery, radiation therapy and chemotherapy, which tend to be immunosuppressive (Robertson *et al*., 2009). Singlet oxygen generated during PDT, can react rapidly with cellular molecules and mediate cellular toxicity to cause cell damage, ultimately leading to cell death. However, the lifetime and diffusion distance of singlet oxygen are very limited. To overcome this drawback, CNTs-based photodynamic therapy with a novel molecular complex of a photosensitizer consisting of an ssDNAaptamer and single-walled carbon nanotubes has been developed by Zhu *et al*., which can control and regulate singlet oxygen generation (Robertson *et al*., 2009). However, presently the knowledge of CNTs-based photodynamic therapy is limited and further research is needed in this area.

e) Delivery of therapeutic gene by CNTs

Gene Therapy involving transport of the correct gene by viral or non-viral vectors to the affected area, is the most promising method in cancer treatment and is expected to be an alternative method to traditional chemotherapy. Although viral gene delivery achieves a high level of gene expression, the currently used viral vectors are immunogenic & have limited packaging capacity. These limitations have made non-viral vectors an attractive alternative to viral vectors. However, the non-viral vectors have lower efficiency of gene expression due to poor pharmacokinetic profile. CNTs seem to represent a very good non-viral vector for gene therapy because of low immunogenicity, good membrane penetration, higher level of gene expression compared to the naked DNA alone and ability to transfer DNA without degradation (Yang *et al*., 2007; Mintzer and Simanek, 2009; Gao and Huang, 2009; Seow and Wood, 2009; Ragusa *et al*., 2007; Klumpp *et al*., 2006). Thus, it is believed that carbon nanotube-based gene transfer vector systems will play a great role in the treatment of cancer in the future.

CARBON NANOTUBES: TOXICITY

Although there are exciting prospects for the application of CNTs in medicine, concerns over adverse and unanticipated effects on human health have also been raised.

- CNTs may exert dose-dependent cytotoxicity, a high dose of nanoparticles having major impact on toxicity (Lam *et al*., 2004).
- Toxicity may be relevant to the route of administration, the subcutaneous route of administration being the least toxic (Yang *et al*., 2009).
- CNTs seem to possess fibrous characteristics having high length to diameter (aspect) ratio resulting in low solubility (Berhanu *et al*., 2009; Wang *et al*., 2011).
- CNTs have been found to be associated with defective phagocytosis, leading to chronic inflammation (Brown *et al*., 2007).
- Low clearance rate of CNTs could lead to the formation of granulomas (Yang *et al*., 2007).

CONCLUSION

The introduction of nanotechnology in biological systems has led to the beginning of a new chapter in the field of research. The novel properties of Carbon Nanotubes allow them to be multifunctional therapeutic agents in cancer treatment. However, a detailed understanding of the pharmacological and toxicological properties of carbon nanotubes and a balanced evaluation of risk/benefit ratio are required before they can be implemented for routine clinical use.

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