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Nanotechnology in cancer: A clinical review

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ABSTRACT

Emergence of modern nanotechnology has plethora of ideas in store for the mankind. It has led to the creativity without constraints for the scientific community Nanotechnology is uniquely promising as an early detection tool for several reasons. To successfully detect cancer at its earliest stages, scientists must be able to detect molecular changes even when they occur only in a small percentage of cells. This means the necessary tools must be extremely sensitive. The potential for nanostructures to enter and analyze single cells suggests they could meet this need. Current cancer therapy primarily involves surgery, radiation therapy, and chemotherapy. These methods of treatment are usually painful and kill normal cells in addition to producing adverse side effects. Carbon NanoTubes as drug delivery vehicles have shown potential in targeting specific cancer cells with a dosage lower than conventional drugs used, that is just as effective in killing the cells, however does not harm healthy cells and significantly reduces side effects Another method to detect cancer by nanotechnology in clinical research is using Nanoshells. A Nanoshell is a type of spherical nanoparticle consisting of a dielectric core which is covered by a thin metallic shell. Nanoparticle-base therapeutics have been successfully delivered into tumors by exploiting the enhanced permeability and retention effect, a property that permits nanoscale structures to be taken up passively into tumors with out the assistance of antibodies.

Key words: Nanotechnology, Cancer, drug delivery.

INTRODUCTION

What is nanotechnology? What is a nanometer?

Nanotechnology is the creation of useful materials, devices, and systems used to manipulate matter at an incredibly small scale -- between 1 and 100 nanometers. A nanometer is one billionth of a meter - 1/80,000 the width of a human hair, or about ten times the diameter of a hydrogen atom. Nanotechnology also is progressing rapidly with regard to in vivo imaging and therapeutics. This progress very likely will have important implications for management of the cancer patient in the near future. Recent improvements in engineering at the nanoscale level have lead to the development of a variety of new, novel nanoscale devices (quantum dots, nanoshells, gold nanoparticles, carbon nanotubes), which are currently under investigation.

Why Nanotechnology in Cancer?

Because of their small size, nanoscale devices can readily interact with biomolecules on both the surface of cells and inside of cells. By gaining access to so many areas of the body, they have the potential to detect disease and deliver treatment. It offers many new ideas for cancer treatment. The emerging roles of these new platforms for cancer imaging and therapeutics are the focus of this review. Two modalities have been used to target nanoparticles to tumor sites, active and passive targeting. **Active targeting** involves linking ligands to nanoparticles that are tumor specific. **Passive targeting** of nanoparticles takes advantage of size of nanoparticles and unique feature of tumor vasculature. In cancer therapy, targeting and localized delivery are the key challenges. However, because many anticancer drugs are designed to simply kill cancer cells, often in a semi-specific fashion, the distribution of anticancer drugs in healthy organs or tissues is especially undesirable due to the potential for severe side effects. Consequently, systemic application of these drugs often causes severe side effects in other tissues which greatly limit the maximal allowable dose of the drug. In addition, rapid elimination and widespread distribution into non-targeted organs and tissues requires the administration of a drug in large quantities, which is often not economical and sometimes complicated due to non-specific toxicity. This vicious cycle of large doses and the concurrent toxicity is a major limitation of current cancer therapy. In many instances, it has been observed that the patient succumbs to the ill effects of the drug toxicity far earlier than the tumor burden.

Nanomedical approaches to drug delivery center on developing nanoscale particles or molecules to improve the bioavailability of a drug. The two Nanomedical devices that can be used to detect and kill cancer cells are:

1. Carbon nanotubes
2. Nanoshells

Carbon Nanotubes (CNTs)

They have unique chemical, size, optical, electrical and structural properties that make them attractive as drug delivery and biosensing platforms for the treatment of various diseases. Due to their nanoscale dimensions, electron transport in carbon nanotubes will take place through quantum effects and will only propagate along the axis of the tube. These electrical and structural properties best serve CNTs as far as biosensing is concerned because current changes in the CNTs can signify specific biological entities they are designed to detect. The fact that CNTs are small (nm scale) allows them to deliver smaller doses of drugs to specific disease cells in the body thus reducing side effects and harm to healthy cells unlike conventional drugs. CNTs have been observed to have enhanced solubility when functionalized with lipids which would make their movement through the human body easier and would also reduce the risk of blockage of vital body organ pathways. CNTs have been shown to exhibit strong optical absorbance in certain spectral windows such as NIR (near-infrared) light and when functionalized with tumor cell specific binding entities have allowed the selective destruction of disease (e.g. cancer) cells with NIR in drug delivery applications. The CNTs are of two types: **SWCNT** and **MWCNT**. Further SWCNT are made of two types: with end caps and without end caps. Drug encapsulation has been shown to enhance water solubility, better bioavailability, and reduced toxicity. The basic point to use drug delivery is based upon three facts: a) efficient encapsulation of the drugs, b) successful delivery of said drugs to the targeted region of the body, and c) successful release of that drug there.

Mechanism

Boron Neutron Capture Therapy is used in the treatment of cancer using substituted Carborane-Appended Water-Soluble single-wall carbon nanotubes. In this therapy, Substituted carborane cages were successfully attached to the side walls of single wall carbon nanotubes (SWCNT) via nitrene cycloaddition. During base reflux, 3-membered ring of nitrene and SWCNT was opened to give water soluble SWCNT. Boron atoms were found to be more concentrated in tumor cells than in normal body cells, blood. Thus, making it an attractive nanovehicle for delivery of Boron to tumor cells for effective therapy.

Selective Cancer cell destruction

Carbon nanotubes can be used as multifunctional biological transporters and near-infrared agents for selective cancer cell destruction. The strong optical absorbance of single-walled carbon nanotubes (SWCNT) in these special spectra can be used for optical stimulation of nanotubes inside living cells to afford multifunctional nanotube biological transporters. They used oligonucleotides transported by nanotubes. The oligonucleotides translocated into the cell nucleus upon endosomal rupture triggered by NIR laser pulses. Continuous NIR radiation caused cell death because of excessive local heating of SWCNT in vitro.
Selective cancer cell destruction was achieved by functionalization of SWCNT with a folate moiety. A folic acid molecule (Vit.) is placed internally in SWCNT. A cancer cell has more vitamin receptors than normal cells so the SWCNT laden with vitamin will be absorbed by cancer cells. After which continuous NIR radiation causes excessive local heating and thus the destruction of the tumor cell. CNTs as drug delivery vehicles have shown potential in targeting specific cancer cells with a dosage lower than conventional drugs used that is just as effective in killing the cells, however does not harm healthy cells and significantly reduce side effects. CNTs have an effective structure that has high drug loading capacity and good cell penetration quality.

Advantages

- Nanovectors for drug delivery
- They are less harmful as nanovehicles for drugs
- The cell uptake of these structures is quite efficient

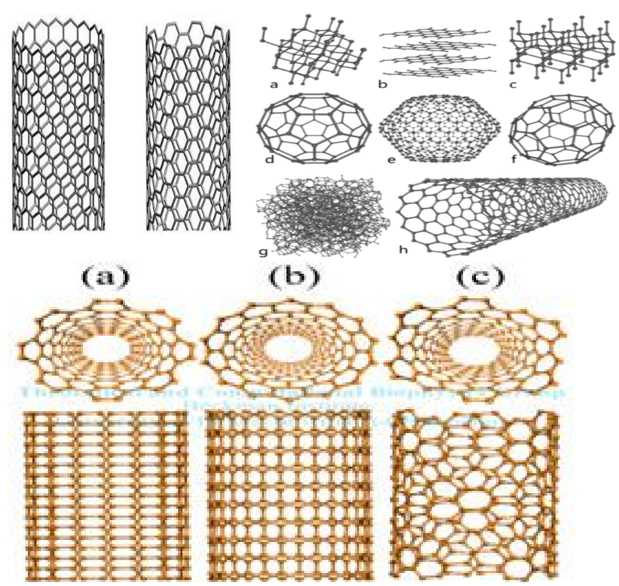

Fig.1: Carbon nanotubes

Nanoshells

A Nanoshell is a type of spherical nanoparticle consisting of a dielectric core which is covered by a thin metallic shell (approximately 10–300 nm in dimension).

Nanoshells are composed of a dielectric core, usually silica, surrounded by a thin metal shell, typically gold. Nanoshells rely on the conversion of electrical energy into light. Nanoshells have the ability to be tunable optically and have absorption properties that range from the UV to the infrared. Nanoshells are attractive because they offer imaging and potential therapeutic properties without the potential for heavy metal toxicity. Because of their size, nanoshells will preferentially concentrate in cancer lesion sites. This physical selectivity occurs through a phenomenon called enhanced permeation retention (EPR). The specific properties associated with nanoshells allow for the absorption of this directed energy, creating an intense heat that selectively kills the tumor cells. The external energy can be mechanical, radio frequency, optical - the therapeutic action is the same. The result is greater efficacy of the therapeutic treatment and a significantly reduced set of side effects.

Cancer treatment

The Gold Nanoshell is shuttled into tumors by the use of phagocytosis where phagocytes engulf the nanoshells through the cell membrane to form an internal phagosome, or macrophage. After this it is shuttled into a cell and enzymes are usually used to metabolize it and shuttle it back out of the cell. These nanoshells are not metabolized so for them to be effective they just need to be within the tumor cells and photo induced cell death is used to terminate the tumor cells. The nanoshells have been successfully delivered into tumors by exploiting the enhanced permeability and retention effect, a property that permits nanoscale structures to be taken up passively into tumors without the assistance of antibodies. Delivery of nanoshells into the important regions of tumors can be very difficult. Once the nanoshells are at the necrotic center, near-infrared illumination is used to destroy the tumor associated macrophages.

Since nanoshells are easily optically tuned so that they absorb light in near infrared region, where there is a minimal optical absorption in tissue and penetration by the radiation is optimal for deep tissue treatments. Also prior to any illumination the nanoshell will be inert within the cell. This nanoshell-based photo thermal ablation therapy shows success in mice with tumor remission with rates over 90%.

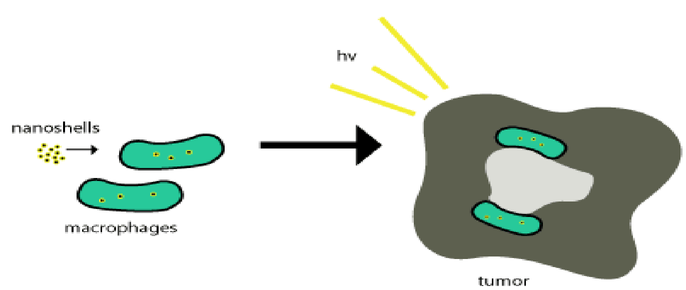

Fig.2: Nanoshells being taken in tumor cell

In core shell particles-based drug delivery systems either the drug can be encapsulated or absorbed onto the shell surface. When it comes in contact with the biological system, it directs the drug. In imaging applications, nanoshells can be tagged with specific antibodies for diseased tissues or tumors. When these nanoshells are inserted in the body, they get attached to diseased cells and can be imaged. Once the tumor has been located, it is irradiated with resonance wavelength of the nanoshells. This leads to localized heating of the tumor and it is destroyed. The power required for destroying diseased cells is almost half that required to kill healthy cells. The process of attacking the tumor, also leads to the loss of many healthy cells. Nanoshells offer an effective and relatively safer strategy to cure these ailments.

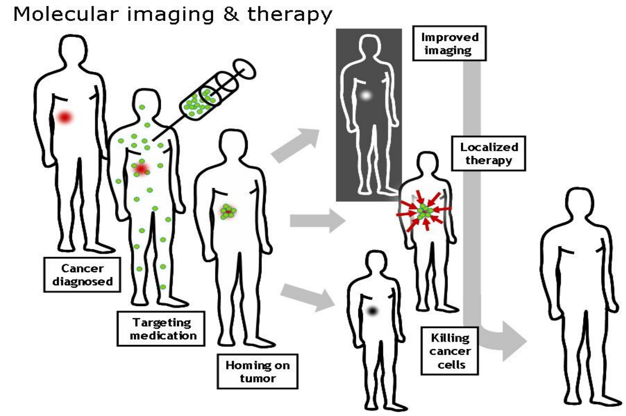

Fig.3: Nanoparticles used to treat cancer

Experimental Data

The field of nanotechnology has already yielded specific products and proofs of principle demonstrated to be of value in clinical applications:

- **Liposomes** are being used as drug delivery vehicles in several products. For example**, liposomal doxorubicin** is used to treat some forms of cancer.
- Another recent example is work done by researchers at Massachusetts General Hospital, led by Ralph Weissleder, M.D., Ph.D., which has shown that **nanoparticulate iron oxide particles can be used with magnetic resonance imaging (MRI) to accurately detect metastatic lesions in lymph nodes without surgery.**
- In May 2004, two companies (American Pharmaceutical Partners and American Bioscience) announced that the FDA accepted the filing of a New Drug Application (NDA) for **a nanoparticulate formulation of the anticancer compound taxol to treat advanced stage breast cancer.**

Examples of nanotechnology in cancer research today include the following:

- Nanoparticles can aid in imaging malignant lesions, so surgeons know where the cancer is, and how to remove it.
- Nanoshells can kill tumor cells selectively, so patients don't suffer terrible side effects from healthy cells being destroyed.

- Biosensors can monitor genetic changes and hyperplasia to prevent cancer progression.
- Carbon nanotubes are also used to detect and selectively kill only the tumor cells.

Future Scope

In the near future, nanoscale devices could offer the potential to detect cancer at its earliest stage and simultaneously deliver anticancer agents to the discovered tumor. Indeed, nanoscale devices could be the crucial enabling technology that will turn the promise of personalized cancer therapy -- where a patient receives a drug based on the exact genetic and molecular characteristics of his or her particular type of cancer -- into reality. Nanotechnology provides opportunities to prevent cancer progression. We need to understand the importance of nanotechnology in cancer therapy. Earlier there were several methods to treat cancer like chemotherapy, radiation therapy and surgery. But all these methods have several side-effects like:

- Hair loss
- Loss of appetite and nutritional problems
- Peripheral neuropathy
- Diarrhea
- Skin damage

Nanotechnology has proved to be very effective in treating cancer and is much safer than the usual chemotherapy.

There are several reasons that nanotechnology could help transform cancer research and clinical approaches to cancer care:

- Most biological processes, including those processes leading to cancer, occur at the nanoscale. For cancer researchers, the ability of nanoscale devices to easily access the interior of a living cell affords the opportunity for unprecedented gains on both clinical and basic research frontiers.
- The ability to simultaneously interact with proteins and nucleic acids at the molecular level will provide a better understanding of the complex regulatory patterns that govern the behavior of cells in their normal state as well as the transformation into malignant cells.
- Nanotechnology provides a platform for integrating research in proteomics -- the study of the structure and function of proteins, including the way they work and interact with each other inside cells -- with other scientific investigations into the molecular nature of cancer.

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