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Role of Nanotechnology in Cancer Therapy.

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ABSTRACT

Oral cancer is a deadly and disfiguring disease that could greatly benefit from new diagnostic approaches enabling early detection. Nanoparticulate technology is of particular use in developing a new generation of more effective cancer therapies capable of overcoming the many biological, biophysical, and biomedical barriers that the body stages against a standard intervention. Nanoparticles show much promise in cancer therapy by selectively gaining access to tumor due to their small size and modifiability. In cancer treatment and detection nanoparticles serve many targeted functions in chemotherapy, radiotherapy, immunotherapy, photodynamic therapy, imaging and Nanoparticulate Targeting. This article is an overview of advances and prospects in the applications of nanocarrier technology in cancer therapy.

Keywords: Nanotechnology, Chemotherapy, Imaging, cancer.

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INTRODUCTION

Oral squamous cell carcinoma is the sixth most common cancer for both sexes worldwide with a five years survival rate of about 5%. This high mortality rate in cancer is attributed to the difficulties in detecting cancer at an early treatable stage. Detecting oral cancer at it is earliest is thus vital for improving the survival rate of this disease and imaging plays a critical role in overall cancer management: in diagnostics, staging, radiation planning, and evaluation of treatment efficiency. With the advent of nanotechnology, which is an interdisciplinary research field involving chemistry, engineering, biology, and medicine, a great potential for early detection, accurate diagnosis, and personalized treatment of cancer is being suggested [1].

What are Nanoparticles?

The prefix of nanotechnology derives from 'nanos' the Greek word for dwarf. A nanometer is a billionth of a meter, or to put it comparatively, about 1/80,000 of the diameter of a human hair. Nanoparticles are typically smaller than several hundred nanometers in size, comparable to large biological molecules such as enzymes, receptors and antibodies. With the size of about one hundred to ten thousand times smaller than human cells, these nanoparticles can offer unprecedented interactions with biomolecules both on the surface of and inside the cells which may revolutionize cancer diagnosis and treatment. Nanoparticulate delivery systems in cancer therapies provide better penetration of therapeutic and diagnostic substances within the body at a reduced risk in comparison to conventional cancer therapies [2]. Nanoparticle distribution within the body is based on various parameters such as their relatively small size resulting in longer circulation times and their ability to take advantage of tumor characteristics. For example, nanoparticles less than 20 nm in size are able to pass through blood vessel walls and such small particle size allows for intravenous injection as well as intramuscular and subcutaneous applications [3].

Nanoparticles may also be composed of or transport a variety of substances such as silica, gold or other heavy metals, medicaments, quantum dots, nanocrystals, quantum rods, and various contrast agents. Surface properties' modifications allow for greater and more accurate tumor as well as conferring advantageous properties to the particle, such as increased solubility and biocompatibility useful in the crossing of biophysical barriers like the bloodbrain barrier. Nanoparticulate surface modifications include coating/linking with folate, antibodies, adjuvants, ligands, antigens, proteins, enzymes, pH sensitive agents, and a plethora of other substances. In transportation, nanoparticles are prepared to prevent degradation of the carried load and protect transported substances from contact with healthy tissues thereby reducing peripheral effects and increasing the relative amount of the load reaching the diseased tissue [4].

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TARGETED FUNCTIONS OF NANOPARTICLES IN CANCER THERAPY

CHEMOTHERAPY

Chemotherapeutic agents are cytotoxic drugs used to treat cancer that function by targeting fast growing cells and by blocking some critical element of the cell division process impairing mitosis as well as promoting apoptosis. Four major chemotherapeutic agents utilized are plant alkaloids, antimetabolites, antitumor antibiotics and, the most commonly utilized type, alkylating agents. Oncologists administering conventional chemotherapy must balance drug dosage with the severity of side effects [5]. Successful chemotherapy of cancer depends on the delivery of sufficient concentrations of an effective drug to tumor cells without causing intolerable toxicity to the patient. Nanoparticles and their use in drug delivery is a far more effective antitumor method than conventional chemotherapy, which is typically limited by the toxicity of drugs to normal tissues, short circulation half-life in plasma, limited aqueous solubility, and non-selectivity restricting therapeutic efficacy [6]. Nanoparticulate drug delivery systems are being developed to deliver smaller doses of chemotherapeutic agents in an effective form and control drug distribution within the body. Nanoparticles useful in transportation of anticancer drugs may consist of polymeric matrixes or of a reservoir system in which an oily or aqueous core is surrounded by a thin polymeric wall. Other reservoir systems can also be formed from natural macromolecules, non polar lipids, and inorganic materials such as silica. Transported chemotherapeutic agents that are lipophilic in nature may have some solubility either in the polymeric matrix or in the oily core of a reservoir system while hydrophilic agents may be adsorbed onto the particle surface [7].

IMMUNOTHERAPY

Immunotherapy is a form of treatment that stimulates the immune system, utilizing agents such as monoclonal antibodies, cytokines, or vaccines to attack tumor cells. Immunotherapeutic agents function in anticancer therapies by decreasing suppressor mechanisms, by stimulating the antitumor response due to increasing the number of effector cells, or by producing one or more soluble mediators. Immunotherapeutic agents may also function by altering tumor cells to increase their immunogenicity and by making them more susceptible to immunologic defenses or by increasing tolerance to cytotoxic drugs [8]. In immunotherapy, nanoparticle delivery systems utilize markers that are expressed only by cancer cells or over-expressed by cancer cells relative to normal cells to target tumor cells and stimulate immunological responses in immunotherapy.

RADIOTHERAPY

Radiotherapy is the use of ionizing radiation for the curative, palliative, and prophylactic treatment for almost every type of solid cancer. Normal healthy cells possess mechanisms for repairing DNA breakage, whereas rapidly reproducing cancer cells have a diminished capacity for repairing DNA breakage due to their undifferentiated and stem cell-like nature. Radiotherapy induced DNA damage is inherited through cell division thus accumulating damage

to the cancer cells that causes them to reproduce more slowly resulting in shrinkage or total destruction of the tumor. Additional radiotherapy antitumor capabilities result from the production of free radicals that damage the DNA of cells [9]. The major source of toxicity of ionizing X-rays is thought to originate from the secondary species such as Auger electrons and radicals generated in aqueous solutions. Auger electrons cause single- and double-strand breaks in DNA through direct interactions and they interact with water molecules to produce radicals that react to break the backbone of the DNA [10]. Nanoparticles serve as and transport various compositions in radiation therapy to increase the effectiveness of cancer treatment and imaging for example, radiopharmaceuticals, radiosensitizers, radioprotectors, radioimmunodection agents, and radio-immunotherapy agents. Radioprotectors serve to protect normal tissues from the damaging effects of radiation whereas radiosensitizers function to condition the tumor cells to be more easily damaged by making DNA more susceptible to radiation or extending the life of free radicals produced by the radiation [9, 10].

Nanoparticle radiosensitizers served as an important component in a novel X-ray therapy developed by Guo. The treatment, termed Nanoparticle Enhanced X-ray Therapy (NEXT), used targeted nano material radiosensitizers (NMRS) to enhance electromagnetic radiation absorption causing localized damage to DNA or other cellular structures for cancer therapy. The NMRS were comprised of spherical or near spherical pure gold nanoparticles ranging from 2 to 20 nanometers in diameters. The core was solid gold while the surface of the nanoparticles was covered with a mixture of alkanethiol and trimethylammonium thiol ligands. The alkanethiol functioned as a protective layer for the nanoparticles, and the trimethylammonium thiol ligands made the nanoparticles more soluble in water and targeted DNA through electrostatic interactions. In response to exposure from electromagnetic radiation, the NMRS emitted Auger electrons, generated radicals, and directly damaged DNA eventually leading to the death of the targeted cells [11].

Gold nanoparticles serving as radiosensitizers were designed and prepared by Hainfield et al. to enhance the dose and effectiveness of x-rays for promoting the shrinkage and/or elimination of target cancerous tissues without unacceptable damage to surrounding normal tissues or substantial toxicity. Gold nanoparticles 0.8-3 nm in diameter were coated with thioglucose molecules serving as an organic shell and attached to anti-epidermal growth factor receptor (aEGFr) antibody for specific targeting of cancerous tissue. The nanoparticles were injected intravenously into an animal model and were found to selectively accumulate in solid tumors and remain in high concentration in tumors for a significantly longer period than surrounding non-tumor tissue. Results showed that 86% of tumors were reduced in size and eventually disappeared when treated with the gold nanoparticles and radiation compared to 20% reduction in size of tumors receiving radiation alone. Further results indicated there was no acute toxicity at given doses [12].

PHOTODYNAMIC THERAPY

Photodynamic therapy (PDT) is a form of cancer treatment that utilizes a photosensitizing agent and a fixed frequency laser light. Photosensitizers are injected into the

blood stream and absorbed by cells throughout the body. The photosensitizing agent is absorbed by both healthy cells and cancer cells whereas the healthy cells are more efficient at eliminating the agent. After timing the treatment so that there will be a significant concentration of the photosensitizer in the target cancer cells, and not the healthy cells, the desired area is exposed to light having a wavelength or a waveband corresponding to a characteristic absorption wavelength of the photosensitive compound. The photosensitizer absorbs the light, consequently triggering the production of singlet oxygen and other highly reactive free radical species. This leads to a number of biological effects including damages to proteins, nucleic acids, lipids, and other cellular components, and often resulting in cell death and possible activation of the immune system to attack the tumor. PDT is mainly used to treat tumors on or just below the skin or on the lining of internal organs as the laser light currently in use cannot pass through more than approximately 3 centimeters of tissue and thus cannot treat tumors that have metastasized [13]. Nanoparticles are currently being utilized for targeted transportation of photosensitizers to increase the effectiveness of PDT against cancers.

NANOPARTICULATE TARGETING

Nanoparticles may be delivered to specific sites by size dependant passive targeting or by active targeting. Passive targeting is dependent on both tumor structure and the structure of surrounding inflamed tissues. Nano particulate delivery systems may exploit a characteristic of solid tumors such as the enhanced permeability and retention (EPR) effect in which tumor tissues display several distinctive characteristics such as hyper vasculature, defective vascular architecture and a deficient lymphatic drainage which leads macromolecules and particulates to be accumulated preferentially and to be retained for a longer time in tumors (Fig. **1**).

Active targeting has been performed to obtain a high degree of selectivity to specific tissues and to enhance the uptake of nanoparticles into target areas such as cancer cells and angiogenic microcapillaries growing around malignant cells (Fig. **2**). Nanoparticles are modified to target inherent characteristics of cancer cells such as rapid proliferation and particular antigen presentation [14]. Nanoparticulate delivery systems utilizing specific targeting agents for cancer cells minimize the uptake of the anticancer agent by normal cells and enhance the entry and retention of the agent in tumor cells. These delivery systems include the anticancer agent, a targeting moiety-penetration enhancer, and a carrier. The types of molecules which are capable of specifically recognizing and binding to other biomolecules are receptors, receptor ligands, enzymes, and antibodies. In all cancer therapies, targeting through surface modification provides numerous avenues for increasing treatment specificity and accuracy while reducing toxicity to healthy cells.

IMAGING USING GOLD NANOPARTICLES

These metallic gold nanoparticles exhibit a unique optical response to resonantly scatter light when excited at their surface plasmon resonance frequency. The epidermal growth factor receptor is a cell surface receptor biomarker that is overexpressed in epithelial cancer but not

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in normal cells. Briefly, the gold nanoparticles can be conjugated to antiepidermal growth factor receptor by incubating both together for about 10 minutes at room temperature as according to a modified procedure reported. The successful conjugation of antibodies on gold nanoparticles can be ascertained by addition of 10% common salt solution and observing any visible color change in the colloidal solution. The presence of salt cause unconjugated gold nanoparticles to aggregate and result in a visible color change from red to purple or gray. These will then bind to the epidermal growth factor receptor present over the cancer cells specifically and elicit an optical contrast to discriminate between cancerous and normal cells [15].

Fig 1: Pasive targeting, the EPR effect. Tumor tissues are known to have leaky vasculature and results in a passive accumulation of nanoparticles and this phenomenon is referred to as EPR.

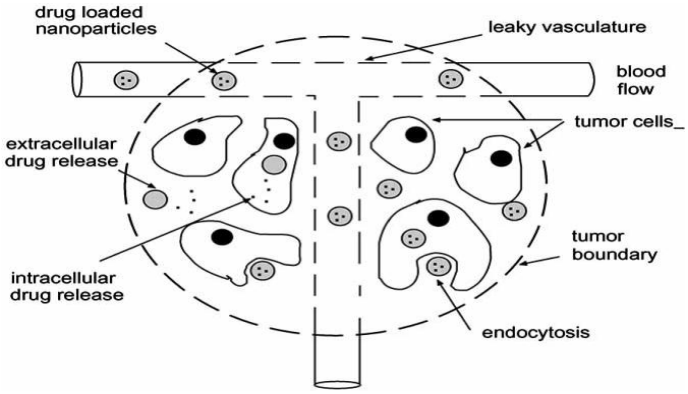
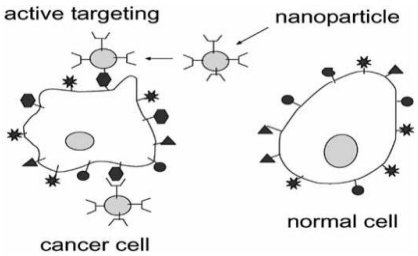


Fig 2: Active targeting. Nanoparticles with ligands or molecules attached to their surface can target tumor cells preferentially over healthy cells.



Raman spectroscopy is the most promising imaging technique for gold nanoparticles based contrast agents. Antibody conjugated gold nanorods were reported to give a Raman spectrum that is greatly enhanced, sharpened, and polarized. Molecules near the nanorods on the cancer cells are found to give a Raman spectrum that is greatly enhanced (due to the high surface plasmon field of the nanorod assembly in which their extended surface plasmon fields overlap), sharp (due to a homogeneous environment), and polarized (due to anisotropic alignments). These observed properties can be used as diagnostic signatures for cancer cells. Surface enhanced Raman scattering spectra of saliva from closely packed gold nanoparticles of normal cells and oral cancer cells were also differentiable. Thus, showed a promising result of using saliva as an assay for early diagnosis of oral cancer [16]

One of the promising nanoscale tools for cancer diagnosis is fluorescent nanoparticles, such as organic dye doped nanoparticles, quantum dots and upconversion nanoparticles that enable highly sensitive optical imaging of cancer at cellular and animal level. Furthermore, the emerging development of novel multifunctional nanoparticles, which can be conjugated with several functional molecules simultaneously including targeting moieties, therapeutic agents and imaging probes, provides new potentials for clinical therapies and diagnostics and undoubtedly will play a critical role in cancer therapy [17,18].

Advantages

Advantages of using gold nanoparticles for diagnosis is that it is simple, less invasive, provides increased contrast for diagnosis of oral cancer, is nontoxic to human beings, with no photobleaching or blinking which is inherent to many other fluorophores [19] Other advantage of multiphoton luminescence using gold nanoparticles is their important implications for use in stem cell proliferation experiments and *in vitro* experiments to monitor differentiation [20]

Disadvantages

Optical signal of gold nanoparticles may not be as strong as that of quantum dots, and other difficulties like biocompatibility, *in vivo* kinetics, tumor targeting efficacy, acute and chronic toxicity, and ability to escape the Reticuloendothelial system need further researches.3 Results of various studies suggest that physiochemical surface properties of nanomaterials change substantially after coming into contact with biological media. Such changes should be taken into consideration when examining the biological properties or environmental impact of nanoparticles [21].

CONCLUSION

Combining advances in biomedical optics and nanotechnology offers the opportunity to significantly impact future strategies towards the detection and cancer therapy. These multimodal nanoparticles have the potential to be used as diagnostic as well as therapeutic agents. Moreover, multifunctional nanoparticles perform many of these tasks simultaneously such as targeted delivery of a potent anticancer drug at the same time as an imaging material to visualize the effectiveness of the drug utilized for treatment follow-up.

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