REVIEW ARTICLE

Cancer nanotechnology

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Cancer nanotechnology is the latest trend in cancer therapy. It helps the pharmacist to formulate the product with maximum therapeutic value and minimum or negligible range side effects. Cancer is the disease in which the abnormal cells are quite similar to the normal cell with just minute functional or genetic change. Thus, it is very hard to target the abnormal cells by the conventional method of the drug delivery system. Nanotechnology is probably the only method that can be used for site-specific action without causing the side effects by killing the normal cells. This review article describes the possible way to exploit the nanotechnology to targeted drug therapy in cancer. The various methods used are: systemic delivery systems, passive targeting, active targeting, intracellular delivery, subcellular localization, and nanoparticle drugs. Different cancer detection techniques like carbon nanotubes, nanorods, and biosensors are also available. This review article gives an idea about the possible potential of nanotechnology in drug delivery, drug targeting, and the diagnosis of cancer.

Key words: *Cancer, delivery, nanotechnology*

INTRODUCTION

Nanotechnology is the creation of useful materials, devices, and synthesis used to manipulate matter at an incredibly small scale between 1 and 100 nm.[1,2] Although "nanotechnology" has been an academic and media buzzword for several years, the federal government and private investors are now backing a host of initiatives with huge sums. Nanotechnology is the science and technology of precisely manipulating the structure of matter at the molecular level.

Most current anticancer agents do not greatly differentiate between cancerous and normal cells, leading to systemic toxicity and adverse effects. This greatly limits the maximum allowable dose of the drug. In addition, rapid elimination and widespread distribution into targeted organs and tissues requires the administration of a drug in large quantities, which is not economical and often results in undesirable toxicity. Several programs have supported research on novel nanodevices capable of detecting cancer at its premalignant stage, locating cancerous tissue within the body, delivering antineoplastic drugs to the cancer cells, and determining whether these cells are being killed by the drugs. Nanocrystals and other nanoparticles have been receiving a lot of attention recently and their utilization in cancer therapeutics is becoming a growing industry. The recent Food and Drug Administration (FDA) approval of Abraxane (ABI-007), an albumin–taxol nanoparticle for the treatment of breast cancer, has opened the doors for the development of other nanoscale drug delivery devices with the aim of landing more of a drug onto the target tissue and less onto healthy tissues.[3] Here, we discuss the mechanism of nanoparticle drug delivery through passive and active pathways and the properties and biological utility of self-assembled nanoparticles in cancer therapeutics and promising directions for cancer research.

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Physiologic and biologic characteristics of nanoparticles

In chemotherapy, pharmacologically active cancer drugs reach the tumor tissue with poor specificity and dose-limiting toxicity. Conventional drug delivery methods include oral and IV routes. There are several disadvantages to these methods, e.g. oral administration of tablets or capsules could result in disorderly pharmacokinetics due to the exposure of these agents to the metabolic pathways of the body.[4] This can result in larger than necessary doses being administered, which can further cause increased toxicity.[5] The traditional IV routes are often even more problematic. The specificity of some conventional IV drugs is low, resulting in harmful effects to healthy tissues. Nanoparticle drug delivery, using biodegradable

polymers, provides a more efficient, less harmful solution to overcome some of these problems. It was in 1975 that Ringdorf proposed a polymer–drug conjugate model that could enhance the delivery of an anticancer model.[6,7] He proposed that the pharmacologic properties of a polymer–drug conjugate model could be manipulated by changing the physical and the chemical properties of the polymer. For example, an insoluble drug can be made water-soluble by introducing solubilizing moieties into the polymer, thereby improving its bioavailability and biodegradability. The delivery of the drug to the target tissue can be achieved primarily in two ways: passive and active.

NANOTECHNOLOGY IN CANCER THERAPY

Systemic delivery systems

Passive targeting

For systemic therapy, passive and active targeting strategies are utilized. Passive targeting relies on the properties of the delivery system and the disease pathology in order to preferentially accumulate the drug at the site of interest and avoid nonspecific distribution. Maeda and colleagues[8,9] first described the enhanced permeability and retention (EPR) effect in murine solid tumor models and this phenomenon has been confirmed. When polymer–drug conjugates are administered, 10- to 100-fold higher concentrations can be achieved in the tumors due to EPR compared with the administration of free drug.[10,11] Other approaches for passive targeting involve the use of a specific stimuli-sensitive delivery system that can release the encapsulated payload only when such stimuli are present.[12-14] The physically encapsulated DNA in polyethylene glycol (PEG)-modified gelatin nanoparticles was found to be more effective *in vitro* and *in vivo* in transfection of reporter plasmid DNA expressing green fluorescent protein and β-galactosidase.[15-19]

Active targeting

Active targeting to the disease site relies on addition to PEG modification of nanocarriers to enhance circulation time and achieve passive targeting coupling of a specific ligand on the surface that will be recognized by the cells present at the disease site.[20,21] When the surface of the nanocarriers is modified with folic acid, they can be targeted to the tumor cells that overexpress folate receptors. Recently, Farokhzad *et al*.[22] have elegantly described the use of aptamers, nucleic acid constructs that specifically recognize prostate membrane antigen on prostate cancer cells. The aptamer technology provides an additional strategy for active targeting to tumor cells in the body using a monoclonal antibody, 2C5, which specifically recognizes antinuclear histones. Scientists have developed various strategies for active targeted delivery of drugs to the tumor mass using liposomes and micellar delivery systems.[23,24] Other groups have used transferrin, an iron-binding protein,[25] for surface modification of nanocarriers for delivery to tumors.[26] [Figure 1].

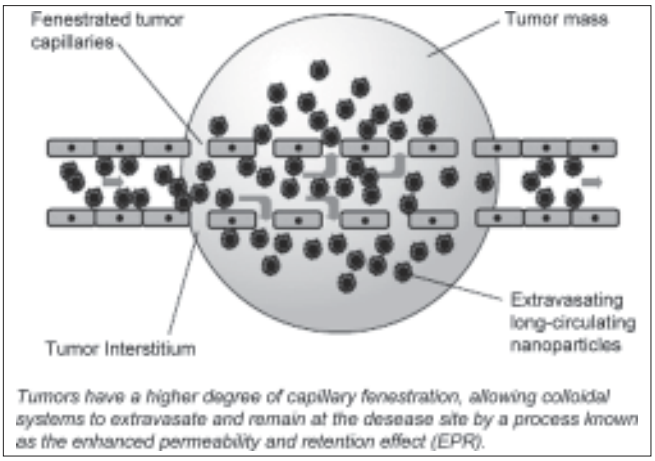

Figure 1: Passive tumor-targeting ptencio flong circulation (e.g. poly(ethylene glycol)-modified nanoparticles to solid tumor upon systemic administration by exploiting the difference in the vasculature

Cancer statistics

Cancer type	Estimated new cases	Estimated deaths
Bladder	67,160	13,750
Breast (female - male)	178,480 - 2,030	40,460 - 450
Colon and rectal (combined)	153,760	52,180
Endometrial	39,080	7,400
Kidney (renal cell) cancer	43,512	10,957
Leukemia (all)	44,240	21,790
Lung (including bronchus)	213,380	160,390
Melanoma	59,940	8,110
Non-Hodgkin lymphoma	63,190	18,660
Pancreatic	37,170	33,370
Prostate	218,890	27,050
Skin (nonmelanoma)	>1,000,000	<2,000
Thyroid	33,550	1,530

Intracellular delivery and subcellular localization

Once the nanocarriers are delivered to the specific diseased organ or tissue, they may need to enter the cells of interest and ferry the payload to subcellular organelles. In this case, nonspecific or specific cell penetrating strategies need to be adopted.[27] Recently, in order to enhance cellular uptake, a surge of research effort has been directed toward development of argenine-rich cell-penetrating peptides.[28]

Nanoparticle drugs

Nanotechnology is beginning to change the scale and methods of drug delivery. Therapeutic and diagnostic agents can be encapsulated, covalently attached, or adsorbed onto nanoparticles. These approaches can easily overcome drug solubility issues, which has significant implications because more than 40% of the active substances being identified through combinatorial screening programs are poorly soluble in water.[29] Conventional and most current formulations of such drugs are frequently plagued with problems such as poor and inconsistent bioavailability. The widely used attempt at

enhancing solubility is to generate a salt. For nonionizable compounds, micronization, soft-gel technology, cosolvents, surfactants, or complexing agents have been used.[30] For decades, researchers have been developing new anticancer agents and new formulations for delivering chemotherapy drugs.[31] Paclitaxel (TaxolTM) is one of the most widely used anticancer drugs in the clinic. It is a microtubule-stabilizing agent that promotes tubulin polymerization, disrupting cell division and leading to cell death.[32] Because it is poorly soluble in aqueous solution, the formulation available currently is Chremophor EL[33] (polyethoxylated castor oil) and ethanol.[34] In a new formulation approach used in AbraxaneTM,[35] recently approved by the FDA to treat metastatic breast cancer, paclitaxel was conjugated to albumin nanoparticles.[36] The formulation is very effective in circumventing side effects of the highly toxic Chremophor EL, which include hypersensitivity reactions, nephrotoxicity, and neurotoxicity.[33] Although the secreted protein, acidic, cysteine-rich, also called osteonectin, protein is believed to improve albumin drug uptake,[36] this nanoparticulate drug still exhibits significant side effects. Carrier design and targeting strategies may vary according to the type, developmental stage, and location of the cancer.[37]

EARLY CANCER DETECTION

Bioconjugated particles and devices are also under development for early cancer detection in body fluids such as blood and serum. These nanoscale devices operate on the principles of selectively capturing cancer cells or target proteins. The sensors are often coated with a cancer-specific antibody or other biorecognition ligands so that the capture of a cancer cell or target protein yields an electrical, mechanical, or optical signal for detection. Another promising area of research is the use of nanoparticles for detection and analysis of circulating tumor cells and biomarkers in blood/serum samples.[34] Vessella *et al*.[35] have demonstrated the ability to enrich for circulating cancer cells from both bone marrow aspirates and peripheral blood samples. Through the combinatorial use of magnetic nanoparticles and semiconductor quantum dots (QDs), it is possible to increase the ability to capture and evaluate these rare circulating cancer cells.

Nanobarcodes

Mirkin *et al*.[36] reported an innovative approach for both protein and nucleic acid detection based on biobarcode amplification. This approach uses both colloidal gold nanoparticles and magnetic microbeads, gold nanoparticles modified with both target capture strands and bar code strands that are subsequently hybridized to bar code DNA, and magnetic microparticles modified with target capture strands. In the presence of target DNA,[37] the gold nanoparticles and the magnetic microbeads form sandwich structures that are magnetically separated from the solution and are further washed to remove the unhybridized barcode DNA. The barcodes (hundreds to thousands per target) are detected by using a colorimetric method.

Nanowires

Nanowires are available in metallic, semiconductor, magnetic, oxide, and polymer compositions and are promising as ultrasmall chemical and biological sensors.[38,39] Functionalized nanowires are coated with capture ligands such as antibodies or oligonucleotides. In the presence of target molecules, the specific binding between target molecule and capture molecule generates an immediate conductivity change within the nanowire that can be measured. Hahm *et al*.[40] measured the achieved detection limit to be on the order of 10 femtomolar (10×10^{-15} M). They have also developed nanowire arrays for multiplexed cancer biomarker detection,[41] which consist of many individual nanowires, each coated with a distinct surface receptor.

Carbon nanotubes

Another type of nanodevice for biomarker detection is the carbon nanotubes (CNTs).[42] Use of single-walled CNTs as high-resolution atomic force microscopy tips showed that specific sequences of kilo base size DNA can be selectively detected from single-base mismatch sequences.[43] This technique enabled the simple and direct detection of specific haplotypes that code for genetic disorders such as cancer. CNT-modified electrodes can amplify the electrochemical signal of guanine bases, which has been used by Wang *et al*.[44] for label-free electrochemical detection of DNA at nanomolar concentrations. More recent work has utilized CNTs coated with alkaline phosphatase as labels for amplified DNA and protein detection.[45]

Tumor-targeted specific ligands on long-circulating nanocarriers

To achieve better selective targeting by PEG-coated liposomes or other particulates, targeting ligands were attached to nanocarriers via the PEG spacer arm such that the ligand was extended outside of the dense PEG brush, excluding steric hindrances for its binding to the target receptors.[46,47]

Nanobiosensors and cancer

With the progress of biosensor technology, the range of applications expands. Numerous biosensor applications for cancer diagnostics are described. Nanobiosensor plays a very important role in cancer care. Bioconjugated particles[48] and devices are also under progress for early cancer detection in body fluids such as blood and serum. These nanoscale devices operate on the principles of selectively capturing cancer cells or target proteins. The sensors are often coated with a cancer-specific antibody or other biorecognition ligands so that the capture of a cancer cell or target protein yields an electrical, mechanical, or optical signal for detection.

CONCLUSION

Nanotechnology, although in its nascent stage, has a great potential to cure the cancer, with least side effects. It is the technology that will grow in years to come and, probably, the human race will have a 100% cure to cancer.

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