Nanotechnology in cancer treatment
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ABSTRACT
The purpose of this paper is to analyze the current evolutions on nanotechnology and its applications on cancer theragnostics. Rapid advances and emerging technologies in nanotechnology are having a profound impact on cancer treatment. Applications of nanotechnology, which include liposomes, nanoparticles, polymeric micelles, dendrimers, nanocantilever, carbon nanotubes and quantum dots have significantly revolutionized cancer theragnostics. From a pharmaceutical viewpoint, it is critical that the biodistribution of active agents has to be controlled as much as possible. This aspect is vital in order to assure the proper efficiency and safety of the anticancer agents. These biocompatible nanocomposites provide specific biochemical interactions with receptors expressed on the surface of cancer cells. With passive or active targeting strategies, an increased intracellular concentration of drugs can be achieved in cancer cells, while normal cells are being protected from the drug simultaneously. Thus, nanotechnology restricts the extent of the adverse effects of the anticancer therapy. Treatment for metastatic breast cancer, sarcoma in AIDS patients, ovarian and lung cancer is already on market or under final phases of many clinical trials, showing remarkable results. As nanotechnology is perfected, side effects due to normal cell damage will decrease, leading to better results and lengthening patient’s survival.

Keywords: nanotechnology, cancer, treatment, nanosystems, anticancer agents.

1. INTRODUCTION
Cancer has one of the highest mortality rates, including all ages. The average age of diagnosis for cancer of all sites is about 66 years of age. 1% were diagnosed under age 20; 2.5% between 20 and 34; 6% between 35 and 44; 14% between 45 and 54; 22% between 55 and 64; 25% between 65 and 74; 28% between 75 and 84; and about 8% 85+ years of age. In the United States there are approximately 11 million men and women alive who had a history of a type of cancer of all sites, with 5.5 million men and 6.5 women[1]. It was estimated that a total of 1,529,560 new cancer cases and 569,490 deaths from cancer occurred in 2010 in the United States only[2]. Worldwide more than 10 million people are diagnosed annually with cancer. The great reduction in death rates from heart diseases and infectious diseases over the past years was not followed by the reduction of the cancer’s death rate.

The pathogenesis of the disease is a combination of genetic and environmental factors leading to carcinogenesis, Metabolic paths which regulate apoptosis, proliferation of cells and other signaling pathways, are considered to be involved in the path to carcinogenesis, although it is not yet fully understandable which are the exact dysfunctions in the paths to certain cancer types. To date, treatment of cancer is based on pathologic staging and the type of the malignancy. Chemotherapy and radiotherapy, with or without surgical removal of the tumor, are the most potent types of treatment, although there are many challenges yet to be faced. These methods lack the ability to diagnose and cure cancer at early stages and produce a number of considerable problems, including insufficient amount of drug reaching the tumor’s site and cytotoxicity.

2. NANOTECHNOLOGY AND BENEFITS
Nanotechnology has shown remarkable advance, especially leading us to the last decade. As a combination of engineering, medicine and biology, nanomedicine is emerging rapidly leading us to new therapeutic and diagnostic possibilities.
Thus many researchers turned their attention to new methods occurring effective drug delivery. Nanocomposites offer a list of advantages considering drug delivery, contrary to other administration methods[3,11]. Nanosystems are easily administrated, and can reach non accessible areas through intravenous (iv), intramuscular (im) or administration per os. Regarding this, many nanocomposites through the blood stream are capable of breaching the blood-brain barrier, enter the central neural system and release the therapeutic agent directly to the target. Nanocarriers can be made to carry more than one drug molecule, enabling simultaneous action of multiple anticancer agents[4,11].

Achieving the proper concentration of the anticancer agent in tumor sites and causing simultaneously the less possible systemic toxicity is the key to a successful treatment. Nanotechnology offers a list of biocompatible composites, based on ligand targeting strategies. These particles show specific biochemical interaction with receptors and molecules expressed usually on the surface of the cancer cells[5]. Attachment to multivalent ligands increases rapidly the affinity of the procedure[6]. These unique abilities allow the agents to bind directly to cancerous tissues, avoiding normal cells with different surface molecule expression. New therapy perspectives have emerged through this ability, including photodynamic and hyperthermia therapies, which previously were prohibited, due to extended normal tissue damage[7]. Furthermore identification of normal-sized tumor to micrometastases, will be available through this special ligand targeting ability, providing the opportunity to diagnose the disease at the first stages, and leading to good prognosis and high patient’s expected survival [8].

3.PASSIVE AND ACTIVE TARGETING

Using passive or active targeting strategies, the nanocarrier with the drug shows high affiliation with the tumor’s cells instead of the healthy ones. The Enhanced Permeability and Retention (EPR) effect is the property by which certain sizes of molecules (liposomes or macromolecular drugs), are accumulating in tumor tissue more than in normal tissue, reaching high concentrations of the drug-carrier formation on the tumor site. The nano-sized macromolecular anticancer drugs, due to their size, escape the renal cleavage[9]. Therefore their concentration increases in the blood circulation and so to the tumor’s site, rendering them long plasma half-life. In order for tumor cells to grow quickly, they must stimulate the production of blood vessels through a list of factors implicated in the neoangiogenesis. The new vessels lack normal structure, showing great abnormality[10]. Those facts, including the ineffective lymphatic drainage of the cancerous tissue, lead to abnormal molecular and fluid transport dynamics, and high local concentrations of nano-sized anticancer drugs in tumor tissues. This phenomenon is joined with new ligand-targeted strategies. Specified ligands on the surface of the nano-carriers are recognized by receptors on the surface of cancerous cells, causing the release of the drug only inside the tumor’s tissue. Paclitaxel, doxorubicin, methotrexate, and docetaxel are already being used through such formations[11].
Figure 1. Active and passive targeting. ERP effect shown on particles with no ligands on their surface and active targeting with nanocarriers with cancer-specified ligands on their surface.

4. BIODISTRIBUTION

The success of the nanotherapy relies on many factors occurring the structure of the nanosystems. The biodistribution of these particles depend on the characteristics of blood capillaries in the organs as well as the administration site, the particle's size and the surface's properties. Particles bigger than the smallest blood capillaries, could possibly induce embolization throughout the body[12]. Thus it has to be smaller than a few micrometers in order to circulate through the capillary system. One more critical subject is their interaction with the reticuloendothelial system (RES) especially in spleen and liver. Association with RES leads to degradation and the decrease of their circulation time. For this reason, many techniques have been tried in order to restrict this interaction. The modification of liposomes surface with polyethilenglycol(PEG) led to a prolonged circulation time due to minimized interaction of the nanoparticle with immunoglobins and other opsonins which activate the RES[3,12]. Consequently their life duration and effectiveness depend on their molecular stability and the physical parameters on their surface. Furthermore, the materials used to create the nanocomposite should have the proper biochemical characteristics in order to release the drug once it reaches the tumor’s site, being in the right environmental conditions. Finally the pathophysiology of the patient should always be considered due to the changes that may occur, during the progression of the disease, which may interfere with the biodistribution of the nanosystem[4,11,13].

5. APPLICATIONS OF NANO-TECHNOLOGY

The rapid advance on the field of nanotechnology and especially nanomedicine offered a list of possible nanosystems for diagnostic and therapeutic purposes. Liposomes, dendrimers, micelles, nanoparticles, quantum dots, nanocantilevers are the basic applications used in nanomedicine and each of one is going to be separately analyzed.

5.1. Liposomes

Liposomes have been thought to be a very promising drug delivery formation, thus they have been studied in many researches on cancer drug delivery in the last 25 year. Liposomes are artificially created vesicles made of lipid layers...
and by their type of layers and space structure they are categorized in 4 groups: 1. small unilamellar vesicles (SUV), 2. large unilamellar vesicles (LUV), 3. large multilamellar vesicles (MLV), 4. large multivesicular vesicles (MVV). SUVs show a diameter of 20 to approximately 100 nm but LUVs, MLVs, and MVVs range from over 100 nm to several microns. The thickness of the phospholipid bilayer reaches 5 nm. In the center of the liposome, the hydrophilic environment offers safe conditions for drugs which do not have the ability on their own to reach the final target through the circulation (possible degradation on the way) [11, 12, 15].

Doxorubicin is one of the most common anticancer agents based in liposome-mediated drug delivery. Polyethylene glycol (PEG)ylated liposomal doxorubicin had shown interesting pharmacokinetic characteristics, with half-life reaching 55 hours in humans. Furthermore its chemical structure prevents it from interaction with plasma proteins or the reticuloendothelial system, increasing its circulation time. ERP effect combined with special ligand, the agent is targeted directly to cancerous tissue [16, 17].

Figure 2. Structure of small unilamellar vesicles (SUV), large unilamellar vesicles (LUV), large multilamellar vesicles (MLV), large multivesicular vesicles (MVV)

5.2. Dendrimers

The word dendrimer comes from the greek word dendron which means tree, due to its tree-shaped structure. Many branches are held symmetrically on a central core. Two methods are followed for the synthesis of the dendrimers, both of them including polymerization reactions. Layers of monomeric particles are added one after the other. The divergent method indicates that the synthesis begins from the core and synthetic or physical substrates are added after. On the contrary using the convergent method, synthesis begins from the surface and proceeds to the core. A variety of biocompatible materials can be used, including polyamidoamin and polyethylene oxide [18, 19].

5.3. Quantum Dots

Quantum dots are semiconductor nanocrystals ranging 2-10 nm in size (clusters of 100-100.000 atoms) with the property of omitting fluorescence from visible to infrared wavelengths upon excitation with a light source. They possess unique (optical) properties making them ideal for medical imaging. Current imaging techniques due to insufficient sensitivity can detect neither small numbers of metastatic malignant cells nor specific cancer cell-surface markers. Highly sensitive and biospecific Quantum Dot based imaging probes are very promising and provide the potential to address these issues [20].

Quantum dots having broad absorption and narrow emission characteristics make it feasible to perform multicolor imaging using a single excitation source. High fluorescence quantum yield allowing high brightness upon excitation and resistance to photobleaching, both being crucial for long-term real time image tracking, make them excellent...
candidates for fluorescent tagging for in vivo molecular and cellular imaging. The composition of their surface properties allow for tunable emission spectra and wavelength while their intense fluorescent signals and multiplexing capabilities enable remarkable selectivity and sensitivity. The most encountered quantum dots used in biomedical applications are Cadmium Selenide (CdSe), Cadmium telluride (CdTe), indium phosphide (InP) and indium arsenide (InAs).

Applications in cancer treatment among others include sentinel lymph node mapping and detection of primary tumor and regional or distant metastases. Sentinel lymph nodes are the first nodes to receive malignant metastasizing cancer cells from primary tumors. Quantum dots have been used in sentinel lymph node mapping in mice and pigs. The future goal is cancer detection that involve visceral organs that have highly complex lymphatic-draining systems. When a cell becomes cancerous certain proteins called “cancer cell-specific antigens” appear on its surface. Primary tumor and regional or distant metastases can be detected by Quantum Dots conjugated with the specific antibodies for these antigens.

Challenges involved in Quantum dots usage in biomedical applications include the high potential toxicity as quantum Dots are made of heavy metals and their tendency to accumulate in the reticuloendothelial system which not only prevents tumor targeting but also further contributes to toxicity. However there have been several reports of biocompatible surface coatings such as PEG-silica that are well tolerated in vitro. Reticuloendothelial system accumulation is being addressed by surface modifications that render Quantum dots long-circulating in the blood.

In spite of being promising and having met with success so far, sensitivity and specificity need to be maximized while toxicity to be minimized before clinical trials can proceed.

5.4. Nanoparticles

Nanoparticles are submicronic colloidal systems. When nanoscale sizes are achieved (surface to area ratio is dramatically increased) the physical properties of known elements can vastly differ. The tuning of physical properties like colloidal properties, solubility and catalytic capacity can make possible great achievements in biomedicine. Their extremely small size allows them to penetrate cells and interact with cellular molecules. They also possess unique electrical properties that make them excellent semiconductors and ideal imaging agents. They are less toxic than quantum dots but their optical qualities are inferior. Utilizing surface modifications specific site targeting is made possible through biochemical interactions with the receptors expressed on target cells. Remarkable is their ability to cross several biological barriers, polisorbate coating can enable blood-brain barrier crossing. Biomedical applications in cancer treatment include effective drug delivery, imaging and photothermal therapy.
Nanoparticles being highly effective targeting agents can be loaded with a therapeutic agent encapsulated within their polymeric matrix or even conjugated onto the surface[28]. Gold nanoparticles have been investigated in a wide range of biomedical applications as they show remarkable biocompatibility and are easy to conjugate to biomolecules. Their applications in drug delivery include but are not limited to the following. The potent anticancer drug doxorubicin can be directly targeted to the nucleus of breast cancer cells by a nuclear localization sequence conjugated on the surface of nanoparticles[29]. The drug curcumin could be delivered in a more controlled manner through the use of a nanoparticulate delivery system consisting of glycerolmonoooleate and pluronic F-127[30]. TNF-α(tumor necrosis factor-alpha) is a cytokine, an excellent anticancer agent but has limited therapeutic applications due to being highly toxic. A PEG coated gold nanoparticle loaded with TNF was able to maximize tumor damage and greatly limit toxicity[31]. Finally, binding gold-based nanoparticles with breast-cancer receptor such as EGFR has been demonstrated to specifically trace and treat breast cancers[32].

The ability to absorb radiation at certain wavelengths have made Gold nanoparticles useful in photothermal therapy for the destruction of malignant cancerous cells. Irradiated with focused laser pulses of suitable wavelength gold nanoparticles heat up extensively and can kill bacteria and cancerous cells. Human breast cancer cells incubated with gold nanoshells and exposed to NIR laser light resulted in significant temperature increase and irreversible tissue damage[33].

New synthetic methods developed to control the size and shape of nanoparticles have made possible the control of tune absorption and emission properties[34]. Rapid advances in nanotechnology in the future will expand the entities of artificially engineered nanomaterials for cancer therapy and diagnosis.

![Single and Multiple Nanoparticle Drug Delivery](image)

**5.5. Carbon Nanotubes**

Carbon nanotubes are synthetic materials possessing unique electrical and mechanical properties. They are promising candidates for future applications such as building blocks for nanodevices like probes, electron field emission sources, chemical sensors and new nanomechanic materials due to their stiffness and high resistance to bending. Potential biological devices fabricated by integrating nanotubes with organic molecules can lead to new research fields and applications[35,36].
Organically modifying carbon nanotubes can generate multiple sites for the attachment of bioactive molecules. Thus modified nanotubes can be used as biosensors or novel delivery systems. They have seen use in vivo as drug delivery vehicles for the commonly used anticancer Drugs paclitaxel and doxorubicin to enhance efficacy and minimize side effects[37,38]. In addition, carbon cylinders composed of benzene rings have been applied as DNA and protein detection sensors, diagnostic devices for the discrimination of different proteins from serum samples and as drug, vaccine or protein delivery carriers[39].

Single walled nanotubes have very interesting structural, mechanical, electrical and optical properties that allow for great biomedical applications[8]. Their high optical absorbance in the near infrared regime causes heating under laser irradiation that can destroy cancerous cells selectively internalized with nanotubes. Also, other optical properties they possess including resonance Raman scattering and near-infrared photoluminance allow tracking and imaging in vitro and in vivo.

5.6. Nanocantilever

The ability of nanotechnology to yield advances in early cancer detection and therapy are based on multiplexing (real time detection of a broad range of molecular signals and biomarkers). Arrays of nanocantilevers, nanowires and nanotubes are primary examples of nanotechnology multiplexing detection[8]. Nanocantilevers are flexible beams forming a row of dividing boards coated with specific molecules that are capable of binding to cancer biomarkers. When biospecific interactions occur between the receptor on the one side of a nanocantilever and a ligand (biomarker tumor protein) then the nanocantilever bends (deflects). These deflections can be directly observed with lasers. Thus it is possible to detect early molecular events in cancer development. The breakthrough potential afforded by nanocantilevers resides in their extraordinary multiplexing capability [40,41].

6. CONCLUDING REMARKS

Nanotechnology is viewed as one of the greatest engineering advances and its applications in the field of cancer theragnostics has experienced extended growth especially in the last decade. Treatment for a variety of cancers is already on market and researchers are aiming to maximize the number of usable applications and minimize side effects from normal cell damage leading to better results and lengthening patient’s survival.

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