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NANOTECHNOLOGY: AN EMERGING TOOL FOR EFFECTIVE CANCER TREATMENT

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ABSTRACT

Nanotechnology is rapidly progressing and is being implemented to solve the problems related to conventional chemotherapeutic agents such as low safety margin, poor water solubility, poor oral availability, normal tissue toxicity and tumor resistance. Nanotechnology promises targeted delivery of drugs and significant improvement in cancer diagnosis, treatment and management. Nanoparticle assisted combination therapies promotes synergism, enhances therapeutic effectiveness, improves pharmacokinetics and suppresses drug resistance. This review sheds light on various nanotechnological platforms as anticancer drug delivery vehicles, raises awareness of the advantages of therapeutic applications of anticancer agents using nanoparticles, minimizing the normal tissue toxicity, drug resistance and treatment of disseminated metastatic cells through targeted therapy.

INTRODUCTION

Cancer is a leading cause of death globally and remains one of the world's most devastating diseases, with more than 10 million new cases every year (WHO, 2015). Cancer can originate in various organs as its primary location in the body and becomes intractable when it spreads from the primary tumor site to various organs (such as bone, lung, liver, and then brain). Metastasis, the spread of cancer cells from a primary tumor to seed secondary tumors in distant sites, is one of the greatest challenges in cancer treatment today. For many patients, by the time cancer is detected, metastasis has already occurred and few patients with metastatic cancer are cured by surgical intervention (Sharp *et al*., 2011).

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Although cancer therapies are improving, many drugs are not reaching the sites of metastasis, and doubt remains over the efficacy of those that do. Methods that remain effective for treating large, well-vascularized tumors may be inadequate while dealing with small clusters of disseminated malignant cells and treatment of disseminated cells is also controversial, since they are to cancer stem-like cells, resistant to current therapies that consequently cannot be eradicated by conventional treatments (Chaffer and Weinberg, 2011; Anderson *et al*., 2011). Chemotherapy is a major therapeutic approach for the treatment of localized and metastasized cancers but the current clinical cancer treatments (either radiation therapy or chemotherapy) are "blind" as harmful chemicals and ionizing radiation affects the whole treated area regardless of whether the tissue in the area is benign or malignant because of lack of specificity they fail to differentiate between healthy and cancer cells leading to

severe adverse effects. Cell resistance, lack of specificity and severe adverse effects to conventional chemotherapeutic agents present an urgent need for innovative, more efficient and effective alternatives for cancer metastasis.

Nanomedicine is an emerging multidisciplinary field that offers unprecedented access to living cells and promises the state of the art in cancer detection and treatment. Nanoparticles have been of significant interest over the last decade as they offer great benefits for drug delivery to overcome limitations in conventional chemotherapy (Subbiah *et al*., 2010; Yoo *et al*., 2010). Over last two decades, a large number of nanoparticle delivery systems have been developed for cancer therapy and their use is attractive for several reasons: they have high surface-to-volume ratios enabling surface functional group modification to internalize or stabilize therapeutic agents for drug delivery; exhibit unique pharmacokinetics and minimal renal filtration; and may be used to encapsulate or solubilize the therapeutic agents for drug delivery. In this review, we will focus on types and character of nanoparticles and nanotechnological development as drug delivery systems for cancer therapy applications and to overcome drug resistance.

Types of Nanoparticles Used as Drug Delivery Systems for Cancer Therapy

The most common examples of nanoparticles applied as drug delivery systems for cancer therapy application can be made of variety of materials. The technology of nanocarrier drug delivery system includes polymeric nanoparticles, dendrimers, lipid nanoparticles, viral, bacterial, organometallic nanoparticles (nanotubes), hybrid, magnetic and inorganic/metallic nanoparticles. The diversity of delivery systems allows nanoparticles to be developed in diverse array of shapes, sizes, and components that enables them to be tailored for specific applications.

Polymer-based Nanoparticles

Polymer based nanoparticles are one of the most investigated types of nanocarriers and the drug is either physically entrapped in or covalently bound to the polymer matrix (Rawat *et al*., 2006). Polymer nanoparticles improve stability of the attached drug, improving intracellular penetration, preventing side effects, minimizing the non-specific uptake, address their low solubility and prolonging the circulation time (Duncan, 2006). Polymers used as drug conjugates can be divided into two groups of natural and synthetic polymers.

Polymeric nanoparticles

Polymeric nanoparticles can be prepared from natural or synthesized polymers and may represent the most effective nanocarriers for prolonged drug delivery and materials of choice for the delivery of anticancer agents have been albumin, chitosan and heparin. Incorporation of antineoplastic agents into polymeric nanoparticles may significantly increase their cytotoxic effect and modify their release pattern. Paclitaxel loaded poly(lactic-co-glycolic acid) nanoparticle formulation *In vitro* exhibited a biphasic release pattern characterized by an initial fast release during the first 24 hours, followed by a slower and continuous release and significantly enhanced the cytotoxic effect of the drug against human small cell lung cancer cell line (NCI-H69 SCLC) as compared to free drug (Fonseca *et al*., 2002). Several polymeric nanoparticles are now in various stages of preclinical and clinical development for cancer therapy. Recently, albumin based nanoparticle formulation of paclitaxel (Abraxane) has been applied in the clinical treatment of metastatic breast cancer and has shown increased cancer cytotoxicity and therapeutic index as compared to paclitaxel cremophor-EL formulation (Gradishar *et al*., 2005).

Polymeric nanoparticles provide significant flexibility in design and can be made of biodegradable or nonbiodegredable materials. Biodegradable polymeric nanoparticles for anticancer drug therapy have attracted a great deal of interest in recent years since they could provide controlled, sustained and targeted drug delivery. The physicochemical properties of nanoparticles such as mechanical flexibility, shape and size contribute to their interactions with cell membranes and control their internalization pathways (Gratton *et al*., 2008a). The design and synthesis of precisely defined micro and nanoparticles has led to the foundation of "PRINT" technology (Particle Replication In Non-wetting Templates) for cancer therapy and other diseases.

Micelle Nanoparticles

Micelle nanoparticles are amphiphilic molecules and their functional properties are based on amphiphilic block copolymers such as poly (ethylene oxide)-poly(β-benzyl-L-aspartate) and poly (*N*-isopropylacrylamide)-polystyrene, that self-assembles in aqueous media to form nanoparticles composed of hydrophilic shell and hydrophobic core which acts as a reservoir for hydrophobic drugs. The hydrophilic shell stabilizes the core region in aqueous media and renders nanoparticles appropriate candidates for intravenous drug delivery (Adams *et al*., 2003; Aliabadi *et al*., 2008). Drug release from the micelles can be precisely controlled by altering the ambient environment by an external stimulus like pH, temperature, and also by ultrasound and enzymes (Rapoport, 2007).

Genexol-PM (PEG-poly (D,L-lactide)-paclitaxel), is a cremephor-free polymeric micelle-formulated paclitaxel and is the first non-targeted micellar formulation approved for cancer therapy (Kim *et al*., 2014). It has shown higher maximum tolerated dose, median lethal dose, differential tumor cytotoxicity and reduction in tumor volume as compared to free paclitaxel (Kim *et al*., 2001). Biocompatible and biodegradable formulation makes them excellent nanocarriers but low drug incorporation stability and low drug loading limits the targeting ability of polymeric micelles (Yamamoto *et al*., 2007).

Dendrimers

Dendrimers are highly branched synthetic globular macromolecules with tree like structures. They possess well defined branching architectures and these polymers are made of macromolecules such as poly (*N*-isopropylacrylamide)-polystyrene and poly (ethylene oxide)- poly (β-benzyl-L-

aspartate), with size ranging from between 5-15 nm (Ochekpe *et al*., 2009). Dendrimers are monodisperse, three dimensional molecules and offer enormous capability for solubulization of hydrophobic anticancer agents, and can be modified with guest agents (Cheng *et al*., 2008). The structure of dendrimers can be defined by an initiator core, layers of branching repeating units and functional eng groups on the outer most layer. The branches can provide vast amounts of surface area for anticancer drug delivery (Kim, 2008).

Dendrimers are one of the most advanced nanotechnological platforms for targeted drug delivery and address the controlled drug release by external stimuli. For example, co-encapsulation of methotraxate and all-trans retinoic acid, with methotraxate was loaded into the hydrophobic cavity and retinoic acids lodged into the voids between branching clefts, gave rise to a pH dependent drug-release profile. Acidic conditions accelerated the release while as neutral and alkaline conditions showed much slower drug release kinetics.

The decrease in premature drug release during the circulation period, by pH-triggered drug-release, could reduce the systemic toxicity (Tekade *et al*., 2009). Dendrimers may be used for therapeutic as well as for imaging purposes. In one study, dendrimers conjugated with fluoresein and folic acid, and linked with complimentary DNA oligonucleotides to produce molecules that target cancer cells over expressing high affinity for foliate receptors (Choi *et al*., 2005). The modifiable surface characteristics of dendrimers makes them elegant nanoparticles for anticancer drug delivery but because of limited number of clinical and preclinical studies of dendrimers as drug delivery agents, it is not possible to make any conclusions about their safety and efficacy for human use.

Liposomes

Liposomes are the one of the most established and used drug-delivery vehicle. Liposomes consist of amphiphilic lipid molecules that assemble into bi-layered spherical vesicles through self-reorganization of amphiphilic lipids and excipients (Kim, 2007). Phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine and phosphatidylglycerol are common building blocks of liposomes and other molecules such as cholesterol are incorporated into the liposomal membrane to enhance their stability and rigidity (Couvreur and Vauthier, 2006). Owing to their unique structure, hydrophilic molecules can be encapsulated in the inner aqueous phase while hydrophobic molecules can be carried in the hydrophobic domains of the of the lipid bilayer (Zhang *et al*., 2009).

Lipid-based vesicles pose several challenges such as instability in the blood stream and a rapid, burst release of the drug but emergence of poly-ethyleneglycol-coated liposomes, revolutionized the liposomal drug delivery as they increased the circulation half life of liposomes from a few hours to approximately 45 hours and reduce the recognition by macrophages (Couvreur and Vauthier, 2006). Currently, liposomal-drug formulations used for cancer treatment include DaunoXome (liposomal daunorubicin) (Guaglianone *et al*., 1994), for blood tumors and Doxil (PEGylated liposomal doxorubicin) for ovarian and breast cancers (Judson *et al*., 2001). Other anticancer liposomal formulations are currently in different clinical trials. For example, SPI-077 (liposomal cisplatin) for solid tumors, Thermodox (thermosensitive liposomal doxorubicin) for hepatocellular carcinoma, CPX-351 (liposomal cytarabine-doxorubicin) for acute myloid leukemia, lipoplatin (liposomal cisplatin) for NSCLC and Stimulax (liposomal-anti-MCU1 cancer vaccine) for NSCLC (Judson *et al*., 2001; Prados, 2015).

Fullerenes

Fullerenes include buckyball clusters and nanotubes, entirely composed of carbon atoms linked with each other via sp^2 hybridized bonds (Kim, 2007; Tardi *et al*., 2009). Conceptually, carbon nanotubes are described as well ordered carbon coaxial graphite sheets of less than 100 nm rolled up into cylinders (Tran *et al*., 2009). Based on their structure, two forms of carbon nanotubes are single- and multi-walled nanotubes. They can be used as biosensors for proteins and DNA and also as carriers. Apart from acting as a novel tool for anticancer drug delivery, carbon nanotubes can be used to immobilize molecules such as anticancer drugs, in order to penetrate the cell membranes. For example, delivery across the membrane was studied in case of doxorubicin linked to an oxidized SWCNT covalently linked to FITC and a monoclonal antibody at non-competing binding sites (Heister *et al*., 2009). There is a striking evidence that fullerenes especially MWCNTs can induce cell cytotoxicity, DNA damage and inflammation and *in vivo* safety and efficacy of fullerenes require further studies (Yamashita *et al*., 2009).

Metal-Based Nanoparticles

Metal-based nanoparticles have been extensively studied as diagnostic and drug delivery systems. Most of these nanoparticles have been studied for imaging using magnetic resonance and high-resolution superconducting quantum interference devices. Metallic nanoparticles upon monochromatic infrared light excitation or oscillating magnetic field stimulation, are able to convert energy into heat to kill cancer cells (Cheng *et al*., 2008). For example, silica nanoparticles coated with gold upon near-infrared excitation produce heat to kill tumors and are currently under study for head and neck cancer therapy (Johannsen *et al*., 2005).

Most common metallic nanoparticles used as anticancer drug delivery systems are gold, silver, iron oxide, silicon, titanium dioxide and gadolinium particles (Doria *et al*., 2012). The large surface area of metallic nanoparticles has been used for the delivery of surface-bound therapeutics. Aurimune (TNF-alpha bound to PEG-coated nanoparticles) requires incorporation into a nanocarrier formulation to reduce systemic cytotoxicity and results show that nanoparticles formulations delayed tumor growth with local heating (42^{o} C for 1 hour) using a SCK mammary tumor xenograft of mouse model (Visaria *et al*., 2007; Paciotti *et al*., 2004). Metallic nanoparticles may be inert vehicles and biocompatible but after drug administration they can exhibit cumulative toxicity, have no controlled release properties and they may not provide advantageous over other types of nanoparticles (Wang *et al*., 2012) so the use of metallic nanoparticles is a concern for anticancer drug delivery.

Hybrid Nanoparticles

The growing interest in nanotechnology has produced a variety of nanoparticulate systems in addition to the aforementioned types of nanoparticles. Hybrid nanoparticles are composed of polymeric materials forming the core surrounded by a single or multiple lipid layers forming a protective membrane (corona) (Chan *et al*., 2009). In a study involving, melanoma and Lewis Lung carcinoma models, a significant delay in tumor growth and increased survival time was observed upon exposure to doxorubicin and combrestatin. Doxorubicin conjugated with PLGA to form core and combrestatin mixed with phospholipids and encapsulated in the lipid bi-layer to form nanoparticles described as "nanoshells". Drugs were released over a period of three days with combrestatin released first to reduce the vascular density followed by doxorubicin to kill the cancer cells (Sengupta *et al*., 2005).

Nanoparticles as Anticancer Drug Delivery System

The physicochemical properties of a drug determines the *in vivo* fate of a drug i.e., absorption, distribution, metabolism and elimination, when given orally or distribution, metabolism and elimination, when given intravenously. Numerous biological factors especially associated with tumors influence the delivery of the drugs inside the tumor cells. Physiological barriers at the tumor level such as poorly vascularized regions, acidic environment etc, as well as at the cellular level such as alteration in the enzyme systems, altered apoptosis etc, and in the body such as distribution, biotransformation and clearance of the agent, must be overcome to deliver anticancer agents inside the tumor cell *in vivo* (Brigger *et al*., 2002).

Nanoparticles loaded with anticancer agents can successfully increase the drug concentration in cancer tissues enhancing antitumor potency. The size and surface characteristics greatly influence the distribution pattern of nanoparticles. For example, conventional nanoparticles (surface non-modified nanoparticles) are rapidly opsonized and cleared by macrophages. Nanoparticles with modified surface properties (stealth carriers) have been developed to reduce recognition by macrophages, predisposition of plasma proteins and to prolong the half-life in the blood compartment as well as in the extra-vascular tissues, since the usefulness of conventional nanoparticles is limited because of macrophage clearance (Shenoy *et al*., 2005).

Strategies for cancer therapy using Nanoparticles

Metastasis, the spread of cancer cells from a primary tumor to seed secondary tumors in distant sites, is one of the greatest challenges in cancer treatment today. Despite significant increase in understanding of metastatic cancer pathogenesis, metastasis evolution, early diagnosis, tumor microenvironment, signaling pathways and irradiation treatment, most cancer deaths are due to metastasis. Reasons for this include resistance to chemotherapeutic agents, tumor microenvironment, and difficulty in removing all cancer cells by surgery or physiological barriers hindering access of drugs to the tumor (Brigger *et al*., 2002).

Multiple therapeutic approaches have been approved or are in clinical development but improving therapy for metastatic cancer is still a challenge.

Non-Targeted Nanoparticles

The enhanced permeability and retention effect (EPR) significantly increases the bioavailability and improves the accumulation of non-targeted nanoparticles in tumors due to passive diffusion from blood to tumors because of pathological abnormalities in tumor vasculature such as inter-endothelial gap defects, allowing extravasation of nanoparticles and due to subsequent poor lymphatic drainage, accumulation of nanoparticles is enhanced in the tumor environment (Maeda, 2001). The nanoparticle shape, size, surface charge and stealth properties are the critical factors affecting the pharmacokinetic properties. Smaller nanoparticles (70nm) have higher surface curvature reducing the protein adsorption of the surface while as particles with size of 200nm adsorbed more albumin on the surface (Lundqvist *et al*., 2008).

The shape of nanoparticles may dramatically affect the internalization pathways. Rod shaped were internalized more efficiently than spherical shapes in Hela cell line suggesting that nanoparticles geometry is an important factor determining the rate of internalization (Chithrani and Chan, 2007). The stealth property of nanoparticles (sterically stabilized carriers) significantly increase circulation half-life as it reduces the protein predisposition and renders them passive for macrophage phagocytosis hence decreasing the clearance rate. So, such long acting nanoparticles are supposed to act efficiently on tumors located outside the mononuclear phagocyte system (Moghimi *et al*., 2001).

For example, Paclitaxel loaded poly(lactic-co-glycolic acid) coated nanoparticle formulation *in vitro* exhibited a biphasic release pattern characterized by an initial fast release during the first 24 hours, followed by a slower and continuous release and significantly enhanced the cytotoxic effect of the drug against human small cell lung cancer cell line (NCI-H69 SCLC) as compared to free drug (Fonseca *et al*., 2002). The surface structure of a nanoparticles can also affect its cellular uptake and recent studies have shown that nanoparticles coated with sub-nanometer striations demonstrate enhanced cellular uptake as compared with random surface structures (Verma *et al*., 2008).

Targeted Nanoparticles

Nanoparticle delivery has provided an enormous level of control over the pharmacokinetics of chemotherapeutic agents. Co-encapsulation of many drugs in nanoparticles makes them more potent against cancer cells but there is always possibility of normal tissue damage by these particles. Paul Erlich introduced the concept of "magic bullets"-targeted therapy, referring to surface modification or surface functionalized with biological agents for specific cell targeting (Strebhardt and Ullrich, 2008). Non-targeted nanoparticles can passively accumulate at the tumor site through EPR effects but targeting can enhance the process and reduce the collateral damage to the normal tissue.

Nanoparticles can be targeted to concentrate drug within a particular organ and diffuse into a specific target tissue. For example, nanoparticles can be targeted for foliate receptors as it is overexpressed in many tumor cells (Stella *et al*., 2000). Receptor-mediated targeting can be approached by targeting the surface receptors of endothelial cells of tumor blood vessels, extracellular matrix i.e. tumor microenvironment or by targeting the tumor cell surface receptor for signal-pathway inhibitors or cytotoxic drugs. Doxorubicin showed enhanced accumulation in cancer cells and decreased tumor weight in primary and metastatic sites of hepatic lymph nodes upon employing integrin receptor mediated delivery of doxorubicin nanoparticles (Murphy *et al*., 2008). Targeting tumor environment is efficient for the delivery of anti-angiogenesis agents while as tumor cell receptors can be targeted for the delivery of therapeutic concentrations of anti cancer agents, intracellularly.

Polymeric nanoparticles, dendrimers, liposomes all contain surface functional groups that can be employed to target receptors or ligands specific to tumor cells. Examples of targeting ligands for nanoparticles delivery include peptides, aptamers (oligonucleotides), antibodies, diabodies and single-chain variable fragments (antibody variants) and can be directed against specific surface receptor on tumor cells to achieve precise killing, minimizing the normal tissue toxicity, optimum intracellular therapeutic concentrations of anticancer agents and reducing the drug resistance.

Conclusions

Cancer is an extremely complex disease with many challenges still remaining. The hope for fighting cancer is still sustained because of enormous development in anticancer therapy with more than 50 new agents approved in past 10 years and many more in clinical development. This review has shown liposomes, polymeric nanoparticles, dendrimers etc to encapsulate and act as a vehicle for variety of anticancer and antiangiogenic agents.

Precise control over formulation and release of combination of drugs from nanoparticles can lead to significant tumor reduction with minimal cytotoxic effects on normal cells upon targeted delivery and can provide approaches to overcome cancer resistance. Nanoparticle drug delivery has provided the gift of unprecedented control over the pharmacokinetics and drug combinations can now be optimized and delivered in a more effective way. By the improvement of knowledge of tumor microenvironment, signaling-pathways, proto-oncogenes, tumor suppressor genes i.e. cancer biology, nanoparticles can be produced with improved efficacy. Nanoparticle drug delivery against cancer has already produced some exciting results and holds even greater promise in the future but there is still an increasing need in evaluating the toxicity inflicted by these nanoparticles on various tissues of the body.

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