Review

Nanotechnology in cancer therapeutics: bioconjugated nanoparticles for drug delivery

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Abstract

Nanotechnology refers to the interactions of cellular and molecular components and engineered materials—typically, clusters of atoms, molecules, and molecular fragments into incredibly small particles—between 1 and 100 nm. Nanometer-sized particles have novel optical, electronic, and structural properties that are not available either in individual molecules or bulk solids. The concept of nanoscale devices has led to the development of biodegradable self-assembled nanoparticles, which are being engineered for the targeted delivery of anticancer drugs and imaging contrast agents. Nanoconstructs such as these should serve as customizable, targeted drug delivery vehicles capable of ferrying large doses of chemotherapeutic agents or therapeutic genes into malignant cells while sparing healthy cells. Such ''smart'' multifunctional nanodevices hold out the possibility of radically changing the practice of oncology, allowing easy detection and then followed by effective targeted therapeutics at the earliest stages of the disease. In this article, we briefly discuss the use of bioconjugated nanoparticles for the delivery and targeting of anticancer drugs. [Mol Cancer Ther 2006;5(8):1909–17]

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. 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 if 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 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.

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 i.v. routes. There are several disadvantages to these methods; for example, oral administration of tablets or capsules could result in disorderly pharmocokinetics 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 i.v. routes are often even more problematic. The specificity of some conventional i.v. 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

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anticancer model (6). He proposed that the pharmacologic properties of a polymer-drug conjugate model could be manipulated by changing the physical and 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 (Fig. 1).

Passive Targeting

Passive targeting takes advantage of the permeability of tumor tissue. Rapid vascularization to serve fast-growing cancerous tissue lends itself to a leaky and defective architecture, which in turn, can be easily accessible to toxic chemotherapeutic drugs. Some drugs can be administered as prodrugs or inactive drugs, which once exposed to the tumor environment, can be switched on to become highly active. Passive targeting also incorporates the delivery of drug to the tumor bed through several invasive modalities.

Leaky Vasculature. Most polymer nanoparticles display the enhanced permeability and retention effect (Fig. 2). First described by Maeda (7), the enhanced permeability and retention phenomenon is based on two factors: (*a*) the capillary endothelium in malignant tissue is more disorderly and thus more permeable towards macromolecules than the capillary endothelium in normal tissues. This allows extravasation of circulating polymeric nanoparticle within the tumor interstitium, and (*b*) the lack of tumor lymphatic drainage in the tumor bed results in drug accumulation. If a chemotherapeutic agent is coupled to a suitable polymer or other molecular carrier via a degradable linker, then such carriers have the potential of increasing the concentration of the chemotherapeutic agent within the tumor tissue. As a result of these characteristics, concentrations of polymer-drug conjugates in tumor tissue can reach levels 10 to 100 times higher than that resulting from the administration of the free drug.

Tumor Microenvironment. This form of passive drug targeting takes advantage of the tumor environment. The drug is conjugated to a tumor-specific molecule and is administered in an active state, and once it reaches its destination, the tumor environment is able to convert it to an active and volatile substance, so-called tumor-activated prodrug therapy (ref. 8; Fig. 3A). The overexpression of matrix metalloproteinase-2 in melanoma has been shown in a number of preclinical as well as clinical investigations. Matrix metalloproteinase-2 plays a critical role in the degradation of basement membranes and the extracellular matrix. Mansour et al. (9) developed a water-soluble maleimide derivative of doxorubicin, incorporating a matrix metalloproteinase-2-specific peptide sequence. This polymer-drug conjugate had a high affinity for the cysteine-34 position of circulating albumin. The albumin-bound form was efficiently cleaved by the matrix metalloproteinase-2 liberating free doxorubicin. pH and redox potential have been also explored as drug release triggers at the tumor site (10).

Local Drug Application. Direct local application allows the drug to be given directly to tumor tissue, avoiding systemic circulation. Various approaches have been taken to improve the tumor delivery of anticancer agents, such as intravesical injection and i.p. administration of various agents. These approaches require exposure to higher concentrations of antitumor agents, which is not always feasible. Localized drug delivery through intratumoral administration is an attractive approach that has been tried and tested (11). The administration of mitomycin directly into tumor tissue resulted in an increased concentration of the drug at the tumor site and decreased toxicity (12). Breast cancer cell lines transfected with wild-type p53 DNA-loaded nanoparticles have shown a sustained and significantly greater antiproliferative effect than those with naked wild-type p53 DNA or with wild-type p53 DNA complexed with commercially available transfecting agent (13). Onyx-0115 is a type 2/5 chimeric adenovirus that has been modified by attenuation of the E1B-55 kDa gene (14). E1B-55 kDa in complex with other proteins binds to and inactivates the p53 tumor suppressor gene. Onyx is a prime example of a therapeutic agent that has been administered in a variety of ways, most of which allow the drug to be given directly into tumor tissue. It has been used in clinical trials to treat head and neck cancer (intratumoral administration; ref. 15), pancreatic cancer (intratumoral via endoscopic ultrasound; ref. 16),

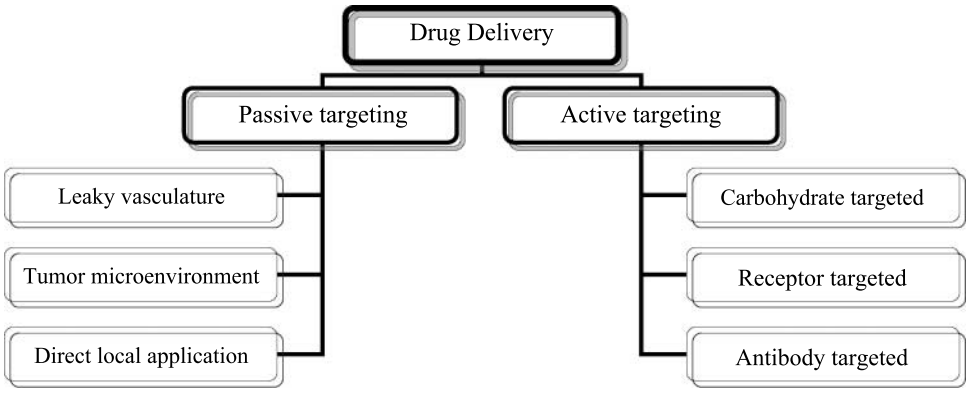

Figure 1. Mechanism of nanoparticle drug delivery via two main mechanisms—passive and active targeting.

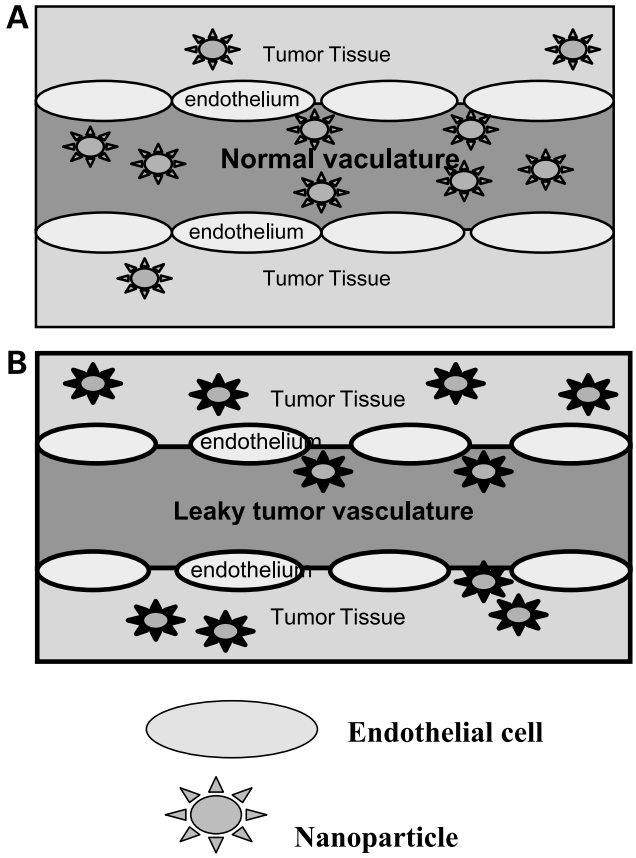

Figure 2. Enhanced permeability and retention affect. **A,** normal tissue vasculature is lined by tight endothelial cells thereby preventing nanoparticle drug-polymer micelle extravasation. **B,** tumor tissue vasculature is hyperpermeable allowing preferential accumulation of the drug in the tumor tissue, within individual cancer cells, intracellular organelles, or specific molecules in cancer cells.

metastatic colorectal cancer (via hepatic artery; ref. 17), ovarian cancer (i.p. administration; ref. 18), and advanced sarcomas (intratumoral under radiographic guidance; ref. 19). Lamprecht et al. (20) recently used Tacrolimus (FK506) loaded poly(lactic-co-glycolic acid) nanoparticles entrapped in pH-sensitive microspheres. The FK506 nanoparticles were administered orally or rectally to rats suffering from preexisting experimental colitis. Results showed successful incorporation of FK506 nanoparticle and release of both drug and nanoparticle into the tumor environment as opposed to the surrounding tissue. The relative drug penetration into inflamed tissue was 3-fold higher compared with healthy tissue when using nanoparticle as drug carrier. Direct delivery of drugs into the tumor tissue prevents the drug from circulating throughout the body and rendering itself to metabolism by various systems. The disadvantage of direct inoculation of drug into tumors is that this method can be highly invasive, tumor localization is not feasible, and accessibility to certain tumors, for example lung cancer, can be problematic.

Active Targeting

Active targeting is usually achieved by conjugating the nanoparticle to a targeting moiety, thereby allowing preferential accumulation of the drug in the tumor tissue, within individual cancer cells, intracellular organelles, or specific molecules in cancer cells. This approach is used to direct nanoparticles to cell surface carbohydrates, receptors, and antigens.

Carbohydrate-Directed Targeting. Lectin-carbohydrate is a classical example of active drug targeting. Cell surface carbohydrates affect tumor cell interactions with normal cells or with the extracellular matrix during metastatic spread and growth. These interactions can be mediated via tumor cell carbohydrates and their binding proteins known as lectins. The family of the discovered endogenous lectins is rapidly expanding. Some lectins recognize the ''foreign'' patterns of cell surface carbohydrates on tumor cells and play a role in innate and adaptive immunity. It has been shown that lectins affect tumor cell survival, adhesion to the endothelium, or extracellular matrix, as well as tumor vascularization and other processes that are crucial for metastatic spread and growth (21, 22). This ligand-carbohydrate interaction can be made use of by the development of nanoparticles containing carbohydrate moieties that are directed to certain lectins (direct lectin targeting) as well as incorporating lectins into nanoparticles that are directed to cell surface carbohydrates (reverse lectin targeting). Thus far, drug delivery systems that have been developed based on this novel interaction between carbohydrates and lectins are directed to whole organs (23), and could thus be harmful to normal tissues. Despite some of their problems, lectins are continuing to be studied for the development of ''smart carrier'' molecules for drug delivery and their unique affinity for sugar moieties on the surface of tumor tissue seems to be an attractive tool for further enhancement of nano-drug delivery.

Receptor- and Antigen-Directed Targeting. The overexpression of receptors or antigens in human cancers lends itself to efficient uptake via receptor-mediated endocytosis. This is a process whereby extracellular particles gain entry into the intracellular environment. In general, the drug bound to a polymer carrier is taken into the cell via ligand-receptor interactions. Once localized at the cell surface, the targeted drug-polymer carrier complexes may exert its cytosolic action either at the plasma membrane or following internalization. Dissociation of the drug from its polymer can occur at the extracellular space, at the cell surface, or more importantly, in lysosomes by lysosomal enzymes, resulting in the release of free drug into the cytosol (24). The receptors or antigens should be recycled and take their place on the cell surface after drug delivery is complete. This form of drug delivery incorporates three essential molecules: (*a*) polymers to which the drug can be conjugated, and to which (*b*) ligands or antibodies are linked, which in turn, bind with high affinity to the tumor cell surface, (*c*) receptors, or antigens, respectively (Fig. 3A).

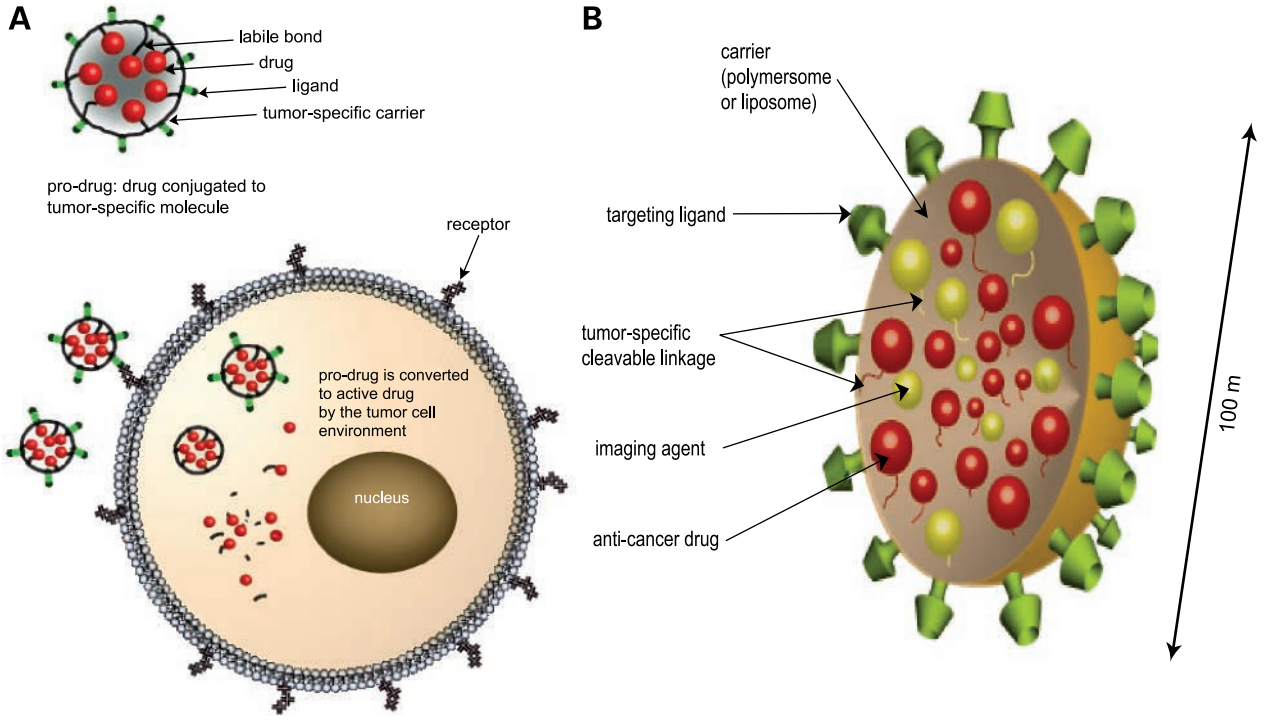

Figure 3. **A,** tumor-activated prodrug delivery and targeting. The anticancer agent is conjugated to a biocompatible polymer via an ester bond. The linkage is hydrolyzed by cancer-specific enzymes or by high or low pH at the tumor site, at which time, the nanoparticle releases the drug. **B,** self-assembled nanoparticles with both diagnostic and therapeutic functions. These nanoparticles allow drug delivery as well as imaging of tumor tissue.

Characteristics of Ligands and Antibodies

Ligands and antibodies used in receptor-mediated endocytosis should have high avidity and specificity for cell surface receptors. Kato et al. (25) calculated that for a ligand or antibody to be effective, they should have a high affinity for the receptor and markedly stimulate the internalization of polymeric particles. Other criteria to be considered when selecting a ligand/antibody to be incorporated into drug carrier systems include isotypes, rate of internalization, immunogenicity, physiochemical properties, biodegradability, and intracellular routing. Thus, the optimal ligand/antibody would be one that is easily incorporated into a nanoparticle, has a high affinity to cell surface receptors found only on tumor cells, has the ability to efficiently cause internalization of the drug, and most importantly, is biodegradable.

Characteristics of Cell Surface Receptors and Antigens

Receptors and antigens on cell surfaces can be targeted to aid in the delivery of chemotherapeutic drugs. For optimum delivery of drugs, receptor and antigen should be present in abundance on the surface of the tumor tissue (26, 27), and the ligand/antibody should have a high affinity for these cell surface molecules. Ideally, up-regulation of receptors should occur following exposure to the targeting ligand, the rate of endocytosis should be high, and there should be a mechanism by which, once active drug is released into the cell, the receptors or antigens are recycled back onto the surface of the cancer cells. Unfortunately, many of the receptors useful for tumor targeting are often found on a wide variety of cell types, for example, epidermal growth factor or low-density lipoprotein receptors. There are a few receptors that seem to be partially tumor-specific, for example, folate receptors are highly overexpressed on the surface of various cancers, including ovary, brain, kidney, breast, and lung cancers. For this reason, several nanoparticles with high affinity for folate receptors are currently in development.

Characteristics of Polymers for Drug Delivery

To be successfully used in controlled drug delivery formulations, a material must be chemically inert and free of leachable impurities. Some of the materials that are currently being used or studied for drug delivery include poly(vinyl alcohol), poly(*N*-vinyl pyrrolidone), and polyacrylamide. Several synthetic and natural polymers with a linear, random-coil structure have been introduced into clinical practice, including polyethylene glycol, polystyrene maleic anhydride co-polymer, [*N*-(2)hydroxypropyl]-methacrylamide copolymer (HPMA), and poly(α,1-glutanic acid; PG; ref. 28, 29). Most commonly, the polymer is an inert structural component of a conjugate, polymeric micelle, or a nonviral vector. Another crucial factor is that a polymer being used for drug delivery should be biodegradable. Polymers should be able to be broken down into biologically acceptable molecules that can be metabolized and eliminated from the body via normal metabolic

pathways. There are a number of factors that will affect the biodegradation of the original material. These factors include aspects of chemical composition such as molecular structure, chemical structure, diffusion capacity, morphology, shape, molecular weight, and the presence of ionic groups.

One of the most commonly used polymers in drug delivery has been PG, which is composed of naturally occurring L-glutamic acid linked together through amide bonds. The free γ-carboxyl group in each repeating unit of L-glutamic acid is negatively charged at a neutral acid, thus accounting for its water solubility. Several drugs can be attached to the carboxyl groups. Polymers can be used by themselves for drug delivery but most research has been on the conjugation of biodegradable polymers to proteins and drugs or to drugs and ligands (Fig. 3B).

Polymer-Drug Conjugates

Among the new drug delivery systems, polymeric nanoparticles have been considered as promising carriers for anticancer agents. To promote optimal targeting of cancer cells, several strategies for conjugation of drugs into polymer carriers have been developed. In one approach, drugs are directly conjugated to the targeting ligand. However, problems arise with the inactivation of the cell-binding domains during the conjugation process and decreased antitumor activity (30–32). In another approach, drugs are conjugated to polymers as a means of allowing drugs to accumulate at the tumor site by the enhanced permeability and retention effect. Several synthetic polymer-based drug conjugates have entered clinical trials. The first HPMA-based chemotherapeutic drug to enter clinical trials was an HPMA-doxorubicin conjugate named PKI (33). Doxorubicin is linked to the HPMA copolymer via a tetrapeptide chain comprised of Gly-Phe-Leu-Glycine; the doxorubicin content was 7 to 9 wt.% and the molecular weight was 300,000 g mol^{-1}. A total of 36 patients with a variety of primary tumors were enrolled in the study. The mean age of the patients was 58.3 years. Most patients had received prior therapy with chemotherapy and or radiation therapy. Prior exposure to anthracyclines was allowed. Tumor imaging was done at baseline and after three cycles of chemotherapy. Twenty-one patients also had studies done with ^{131}I-radiolabeled analogue of PKI in an attempt to confirm tumor localization of the polymer. The drug-polymer was infused once every 3 weeks. The maximum tolerated dose was 320 mg doxorubicin-equivalent/m^2. The dose-limiting toxicities were febrile neutropenia and mucositis. The pharmacokinetic behavior of PKI was markedly different from native doxorubicin, with a distribution half-life of 2.7 hours and an elimination half-life of 49 hours compared with 0.13 and 85 hours, respectively. This was in agreement with preclinical animal data, and supported the possibility of the enhanced permeability and retention effect. In contrast, phase I trials using HPMA conjugates of paclitaxel and camptothecin have been disappointing. The conjugates displayed toxicities little or no better than the free drug. It is believed that these conjugates were unsuccessful because of the rapid release of free drug into the systemic circulation, probably due to the use of a fragile ester linkage between the drug and the polymer (34). Drugs conjugated to PG are also being extensively studied. Doxorubicin and daunorubicin have also been attached to PG and have shown activity *in vivo* against L1210 leukemia and B16 melanoma cells, although the cytotoxic effect was weaker than the free drug (35–37). Similar results *in vivo* have been reported when PG was conjugated with Ara-C, cyclophosphamide, and melphalan (38, 39). However, the cytotoxic effect *in vivo* has been shown to be better than the free drug for all these three drug-PG conjugates. Wosikowski et al. were able to show that methotrexate bound to human serum albumin enters cells by albumin-mediated endocytosis. They also observed that thymidylate synthesis was inhibited when KB cells expressing folate receptors were exposed to this conjugate. *In vivo*, this conjugate drug showed activity in 9 out of 14 tumors (40).

The Food and Drug Administration recently approved Abraxane (ABI-007). ABI-007 is a cremophor-free, protein-stabilized nanoparticle formulation of paclitaxel. Paclitaxel is an anticancer agent used in the treatment of breast, lung, ovarian, and head and neck cancers (41).To enhance drug solubility, paclitaxel is formulated with the micelle-forming vehicle cremophor EL (polyxyethylated castor oil) and ethanol (42). Cremophor may, however, add to the toxic effects of paclitaxel by producing or contributing to the well-described hypersensitivity reactions that commonly occur during infusion, affecting 25% to 30% of treated patients, and also contribute to chronic paclitaxel toxic effects, such as peripheral neuropathy (43). A phase I clinical trial determined that the maximum tolerated dose of single-agent albumin-bound paclitaxel every 3 weeks was 300 mg/m^2 in patients with solid tumors (breast cancer and melanoma). No hypersensitivity reactions were observed during the infusion period (44). Two partial responses were seen among 19 treated patients, both in breast cancer. A second phase I trial, reported at the 2004 American Society of Clinical Oncology Annual meeting, showed five responses among 39 pretreated patients with advanced solid tumors, including one response in a patient with non–small cell lung cancer, three responses in patients with ovarian cancer, and one in breast cancer (45). Similar results were reported by Damascelli et al. (46) ABI-007 was infused every 4 weeks for three cycles in 43 patients (31 with advanced head and neck cancer and 12 with recurrent anal canal squamous cell carcinoma). The dose-limiting toxicity was myelosuppression, the maximum tolerated dose was 270 mg/m^2 and premedication was not required. Subsequent use of ABI-007 in both phase II and phase III trails proved that this new formulation was far superior to taxol. In a randomized, open-labeled trial of 454 patients with metastatic breast cancer, the overall response rate for ABI-007 was 33% compared with 19% for taxol. Median time to progression was 21.9 weeks for ABI-007 versus 16.1 weeks for taxol. Overall side effects were fewer ABI-007, even though it delivered a 50% higher dose of the active agent paclitaxel.

Several other taxane formulations that do not require cremophor EL as a solubilizer are under development. Genexol-PM is a polymeric micelle-loaded paclitaxel without cremophor EL. Genexol-PM was found to have a three times higher maximum tolerated dose in nude mice, and the biodistribution of Genexol-PM showed 2- to 3-fold higher levels in various tissues, including liver, spleen, kidney, and lung, and more importantly, in tumors. The *in vivo* antitumor efficacy of Genexol-PM was also found to be greater than that of taxol (47). Kim et al. did a phase I trial to determine the maximum tolerated dosage, dose-limiting toxicities, and pharmacokinetic profile of Genexol-PM in patients with advanced refractory malignancies. The main dose-limiting toxicities were neuropathy, myalgia, and neutropenia, and the recommended dosage for further phase II studies was 300 mg/m^2. Again, the conclusion was that Genexol-PM was superior to conventional paclitaxel in terms of the obviation of premedication and the delivery of higher paclitaxel doses without additional toxicity (48).

Clinical results evaluating a polyglutamic acid-paclitaxel conjugate (CT-2103, XYOTAX) are also exciting. CT-2103, also known as paclitaxel polyglumex, is a nanoparticle formed by an ester linkage between γ-carboxylation acid moiety of glutamic acid and the paclitaxel 2′-hydroxyl group (49). It has shown promising results in phase I and II trials. Major responses have been observed in a variety of solid tumors, including gastric cancer, colorectal cancer, non–small cell lung cancer, ovarian cancer, and breast cancer (50–53). Its side effect profile is limited to fatigue, uncomplicated neutropenia, nausea, and vomiting. These adverse events were uncommon and routine premedications were not required. Hypersensitivity reactions were also rarely observed. The results of three phase III trials (STELLAR 2, 3, and 4) in patients with non–small cell lung cancer are eagerly awaited.

Polymer-Drug-Ligand Conjugate

The major shortcoming of polymer-drug conjugates is the lack of specificity for cancer cells. Although one of the well known water-soluble paclitaxel conjugates, poly(L-glutamic acid)-paclitaxel has shown both tumor effect and improved index *in vivo*, this ''binary nanoparticle,'' also binds to the proteins and enzymes of normal cells. The development of ternary biomolecules is under way to overcome the problem of nonspecific binding and to allow a drug to reach tumor cells only. Ternary nanomolecules are composed of three elements: (*a*) drug carrier—in most cases, a polymer, (*b*) a drug, and (*c*) a ligand. Many researchers have studied several targeting ligands such as antibodies, cytokines, and homing peptides to improve the tumor selectivity of polymeric drug carriers (54, 55). However, the attachment of an antibody or a homing peptide to polymeric drugs has not been very successful in animal studies. The reasons may be either changes of chemical properties due to functional group modification or decreased interaction with receptors due to embedding of target moieties in polymeric carriers (56, 57). The first clinical study of ternary biomolecules involved polymer carrier, targeting ligands and anticancer drugs. The anticancer drug doxorubicin was conjugated to HPMA and the target ligand was galactosamine. Seymour et al. conducted phase I/II trials in patients with primary hepatocellular carcinoma and the compound was given by i.v. infusion every 3 weeks. The conjugated drug accumulated at liver cells effectively and achieved a greater drug concentration in tumors than when administering nontarget polymer or ligand used in this study. However, galactosamine fell short of expectations as a specific targeting moiety, as it had a high affinity for binding to receptors on the normal as well as those on cancerous cells (58).

To address the specificity issue, researchers have turned their attention to the unique traits of tumor cells. Many human cancers overexpress receptors or antigens that lend themselves to efficient drug uptake via receptor-mediated endocytosis. Because glycoproteins cannot remove polymer-drug conjugates that have entered the cells via endocytosis, such active drug targeting has the potential advantage of overcoming multiple drug resistance. For example, the cell surface of folic acid is a water-soluble vitamin and a ligand used for tumor targeting via folate receptor–mediated endocytosis. The membrane-bound folate receptor is overexpressed on a wide range of human cancers, such as those originating in ovary, lung, breast, endometrium, kidney, and brain (59, 60). Therefore, the folate receptor serves as an excellent tumor marker as well as a functional tumor-specific receptor (61). Ternary nanoparticles encompassing camptothecin, poly(ethylene glycol), and folate have shown high affinity for folate receptor-positive KB cells (62). Similar results have been seen employing doxorubicin-poly(ethylene glycol)-folate conjugates (63). Both these nanoconstructs exhibited more potent cytotoxic effects on KB cells than the free drug. Results from both studies suggest that folate-targeted nanoaggregates could be a potentially useful delivery system for folate receptor–positive cancer cells.

Alternatively, the tumor vasculature can be targeted to allow targeted delivery to a wide range of tumor types. Vascular endothelial growth factor is expressed in many solid tumors (64). In binary systems, vascular endothelial growth factor has been used in liposomes and polymeric nanospheres to deliver angiostatin and endostatin (65, 66). The $\alpha_v\beta_3$ integrin is one of the most specific biomarkers that can differentiate newly formed capillaries from their mature counterparts (67). High-affinity $\alpha_v\beta_3$-selective ligands, Arg-Gly-Asp (RGD) in its conformationally constrained cyclic form has a higher binding affinity than in its linear form (68). Ternary doxorubicin-loaded poly(ethylene glycol) nanoparticles conjugated to cyclic RGD (69) and paclitaxel-cyclic RGD nanoparticles have recently been reported.

Future Perspectives of Nanotherapeutics in Cancer

Nanotechnology is beginning to change the scale and methods of drug delivery. For decades, researchers have

been developing new anticancer agents and new formulations for delivering existing and new agents. The entry of binary and ternary nanoparticles that combine synthetic polymers with proteins or drugs, as well as polymer micelles that incorporate covalently bound drug, into clinical development, has established polymer therapeutics as an expanding and credible role in cancer therapeutics. The Food and Drug Administration approval of Abraxane has led to the strong belief that the nanoparticle, protein-bound technology has become a key aspect for the development of anticancer agents. The simple idea that eliminating cremophor from the taxol formulation and producing a compound that produces no hypersensitivity reactions and obviates the need for premedication has led to this new agent being incorporated into various breast cancer adjuvant trials. Several binary molecules have been formulated and some of their pitfalls have led to the development of even more sophisticated ''ternary biomolecules'' that incorporate a complex understanding of chemistry, biology, and medicine. For specific targeting, the differences between cancerous cells and normal cells, which include uncontrolled proliferation, insensitivity to negative growth regulation and antigrowth signals, angiogenesis, and metastasis can be exploited. There is a growing body of knowledge of unique cancer markers thanks to recent advances in proteomics and genomics. They form the basis of complex interactions between bioconjugated nanoparticles and cancer cells. Carrier design and targeting strategies may vary according to the type, developmental stage, and location of the cancer.

A number of tumor-specific antibodies (MDX-010, Avastin, Rituxan, Herceptin, Pertuzumab, Mylotarg, Erbitux, and Cetuximab), angiogenesis inhibitors (vascular growth factor–trap, IMC-1C11, SU5416, SU668, angiostatins, endostatins, and ZD6126), and drugs targeting specific proteins and small molecules (TP38, EM164, NVP-ADW742, PX-748, Gossypol, Oblimerson, Bortezomib, Celecoxib, Refecoxib, BAY43-9006, Rapamycin, UCN-01, and Bryostatin) are undergoing both preclinical and clinical trials. If these tumor-specific inhibitors can be conjugated to fit the model of a biodegradable nanoparticle, then the differences between cancerous cells and normal cells can be exploited.

There is much synergy between imaging and nanotechnology in biomedical applications. Many of the principles used to target the delivery of drugs to cancer may also be applied to target imaging and diagnostic agents. Multifunctional nanoparticles that can serve as both diagnostic and therapeutic tools are currently being engineered (Fig. 3B). Researchers are continuing to look into nanoparticles that are conjugated to ligands targeting various receptors, such as the folate receptor, epidermal growth factor receptor, estrogen and progesterone receptors, low-density lipoprotein receptors as well as to ligands that target various antigens, such as prostate-specific antigen. The use of more ''biologically friendly'' carrier molecules is another area in which more research is needed to help combat the side effects of some of the synthetic polymers. With continuous efforts by multidisciplinary team approaches, nanotechnology will clearly shed new light on diagnostics and therapeutics in cancer research.

Conclusion

Nanotechnology is a fast-expanding area of science. This area of research is anticipated to lead to the development of novel, sophisticated, multifunctional applications which can recognize cancer cells, deliver drugs to target tissue, aid in reporting outcome of therapy, provide real-time assessment of therapeutic and surgical efficacy, and most importantly, monitor intracellular changes to help prevent precancerous cells from becoming malignant. On-going efforts by scientists, researchers, and medical personnel can sincerely ensure to ''do big things using the very small.''

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