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CARRIERS FOR CANCER DRUG THERAPY

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ABSTRACT

Conventional chemotherapy drugs show lack of specificity, inducing reduced activity on the cancer treatment. They exhibit high toxicity and after a prolonged period of administration the cancer cells develop resistance (multiple\drugresistance,MDR).This situation leads to increasing the side effects of drugs and affect the quality of the patients life.In order to overcom ethe above mentioned problems, the recent research community is focused primarily on developing drug delivery systems which respond in different stimulus, in the range of nanometer. The scope of nanotechnology to develop target specific carriers to achieve higher therapeutic efficacy is gaining importance in the pharmaceutical and other industries. Specifically, the emergence of nanohybrid materials is posed to edge over chemotherapy and radiation therapy as cancer therapeutics. This is primarily because nanohybrid materials engage controlled production parameters in the making of engineered particles with specific size, shape, and other essential properties. It is widely expressed that these materials will significantly contribute to the next generation of medical care technology and pharmaceuticals in areas of disease diagnosis, disease prevention and many other treatment procedures. This review focuses on the currently used nanohybrid materials, polymeric nanoparticles and nanotubes, which show great potential as effective drug delivery systems for cancer therapy, as they can be grafted with cell-specific receptors and intracellular targeting molecules for the targeted delivery of therapeutics. Specifically, this article focuses on the current status, recent advancements, potentials and limitations of polymeric nanohybrids and functionalized carbon nanotubes as drug delivery carriers.

KEYWORDS: nanohybrid materials, polymeric nanoparticles and nanotubes.

INTRODUCTION[1]

What Is Cancer?

Cancer refers to a group of illnesses that result from cells in the body growing abnormally. These cells divide and produce new cells in an uncontrolled way that can spread throughout the body and cause damage to essential organs. When cancer spreads to other parts of the body, this is called metastasis. Metastases can occur when cancer cells enter the bloodstream or lymph system. These systems circulate all over the body and allow the cells to travel. Tumors are masses (or lumps) that can develop as abnormal cells accumulate. Not all tumors are cancer. Benign (non-cancerous or nonmalignant) tumors do not spread to other parts of the body and are rarely life-threatening. There are four main types of cancer:

1. Carcinomas – cancers of the organs
2. Sarcomas – cancers of the muscles, bone, cartilage, andconnective tissue
3. Lymphomas – cancers of the lymphatic system
4. Leukemias – cancers of the blood-making system

Cancer risk factors

- Tobacco use
- High fat diet and being overweight
- Excessive exposure to sunlight
- Drinking too much alcohol
- X-rays and other sources of radioactivity
- Geographic area
- Chemicals and other substances in theenvironment (carcinogens)
- Unsafe sexual practices (through acquiring certaininfections, such as HIV or genital warts)
- Family members who have cancer (certain types ofcancer are hereditary)

Common Symptoms of Cancer

It is important to know that these symptoms do not mean that the patient has cancer. Only a doctor can make a diagnosis.

Cancer symptoms

- Thickening or lump in the body
- Cough or hoarseness that does not go away

- Obvious change in a wart or mole
- Changes in bowel or bladder habits
- Unexplained bleeding or discharge
- Any sore that does not heal
- Unusual upset stomach or difficulty swallowing.

Diagnosing cancer

Doctors use various means to make a diagnosis:

- Physical examination
- Laboratory tests – such as blood and urine tests
- Imaging – x-ray, CT scan, and MRI are examples of imaging
- Biopsy.

Treatment for Cancer

The good news is that about half of all cancers diagnosed are now curable. Even with cancers that cannot be cured, symptoms are often greatly diminished by treatment. Treatment options, which depend on the stage and type of cancer, include:

- Surgery
- Radiation therapy
- Chemotherapy
- Biological therapy
- Hormone therapy.

CARRIERS USED IN CANCER

1.Oxygen carriers[2-5]

The potential to improve local control and survivalby hypoxia modification was demonstrated by a meta-analysisof 83 clinical trials3 and a number of therapeutic strategieshave also been established to overcome tumor hypoxiaby improving oxygen supply either by oxygen or carbogenbreathing or by increasing the hemoglobin level and oxygendelivery.4,5 The use of artificial oxygen carriers represents anew approach to the problem of hypoxia.For socio-economic reasons the development of safe andeffective synthetic oxygen carriers as an alternative tohomologous red blood cell transfusion was an important issue in perioperative medicine during the last decades.Currently, two types of artificial oxygen carriers areexperimentally and clinically investigated for their abilityto

replace red blood cells and to ensure adequate tissueoxygenation in case of acute anemia or infarction: cell-freehuman or bovine hemoglobin solutions and synthetic perflourocarboneemulsions.

Hemoglobin-based oxygen carriers and cancer therapy[6-16]

Most recent progress in blood substitute development has been in the area of hemoglobin-based oxygen carrying (HBOC) solutions, several of which are currently in advanced clinical trials. Intravenous administration of ultrapurified polymerized bovine hemoglobin solution was effective in increasing the oxygenation throughout experimental tumors under normal air breathing conditions.49–51 Therefore, an enhancement of tissue oxygenation (tpO2) in rodent tumors associated with an increased tumor growth delay was reported for purified bovine hemoglobin solutions combined with irradiation27,50,52,53 as well as with chemotherapeutic agents26,52–54 such as carmustine (BCNU), cyclophosphamide, ifosfamide, adriamycin, TNP-470, minocycline, melphalan, and cisplatin. When carbogen breathing was added to administration of the hemoglobin preparations, further increased therapeutic response and decreased tumor hypoxia were achieved. Various modified hemoglobin prepared from bovine, human, or mouse Hb, for example the PEGylated bovine hemoglobin (PEG-Hb), could also increase tumor oxygen content55,56 and improve the effectiveness of radiotherapy in rodent models.55 Perhaps spurred by these encouraging results, A clinical phase I/II study on the effect of polyethyleneglycol-conjugated hemoglobin (Enzon Corp., USA) for radiosensitization of tumors has been performed,57 but results are not published until now. However, more recent animal studies cast, at least in part, a shadow on the using of hemoglobin-based oxygen carriers as tumor radiotherapy sensitizer. In these experiments, a glutaraldehyde-polymerized bovine hemoglobin (Hb) solution HBOC-201 (Biopure; Cambridge, MA) was evaluated. Studies performed by Raabe et al. demonstrated that low-dose (0.3 g/kg) application of HBOC-201 did not improve the response of the rhabdomyosarcoma R1H of the rat to fractionated irradiation58 since the application of low-dose hemoglobin solution HBOC-201 (0.3 g/kg) alone failed to improve tumor tissue or healthy skeletal muscle oxygenation.59 Surprisingly, with the dosage of 0.3 g/kg HBOC-201, a plasmatic hemoglobin concentration of 0.5– 0.8 g/dl could be achieved. This concentration is high enough for improvement of tissue oxygenation according to previous isovolaemichemodilution study in dogs.6049. Teicher BA, Holden SA, Dupuis NP, et al. Oxygenation of the rat 9Lgliosarcoma and the rat 13672 mammary carcinoma with various doses of a hemoglobin solution.

Summary and future prospects[17-19]

An alternative to blood transfusion, based on oxygen-carryingsolutions, has been sought for over a century. So far, anumber of oxygen carriers (blood substitutes) based oneither hemoglobin or perfluorocarbon emulsions have beenand/or are being developed. These products mainly aim atreplacing the O2 carrying capacity of the blood to provideadequateO2 perfusion, and thus to resuscitate soldiers orpatients in hemorrhagic shock after traumatic injuries. Besidesthis, as the theme of the XIth International Symposiumon Blood Substitutes goes: ‘‘From blood substitutes to oxygentherapeutics’’, additional oxygen carriers uses can beenvisaged in a variety of diseases with compromised tissueoxygenation, such as heart infarct and stroke, in tumor oxygenation,sickle-cell anaemia, organ preservation, autoimmunehaemolysis or air embolism.Thomas Chang, a pioneer in blood substitute research atMcGill University, together with his co-workers has preparedtwo new generation of PolyHb.61 One is based on crosslinkingPolyHb with superoxide dismutase and catalase (Poly-Hb–SOD–CAT), This molecule could transport oxygen andsimultaneously remove oxygen radicals to lessen the effectsof ischemia reperfusion injuries. These benefit effects werealso exhibited by HBOC-201. The other is a soluble nanobiotechnology-based PolyHb–tyrosinase complex. This complexhas the dual function of supplying the oxygen neededfor optimal chemotherapy or radiation therapy and loweringsystemic levels of tyrosine. In vitro and animal studies indicatedthatPolyHb-tyrosinase was able to inhibit the growthof B16F10 cells and delay the growth of the melanoma withoutsacrificing its oxygen transport capacity.Taken together, both modified hemoglobin solutions andperfluorocarbon emulsions have shown expectable reoxygenationof solid hypoxic tumor in various animal tumormodels. Although clinical attempts using Fluosol to overcomehypoxia have met with some success and improved localcontrol have been reported in the Phase II studies, theresults have been far from satisfactory, and efforts are stillbeing made to find better methods. As mentioned above, inthe hemoglobin-based oxygen carrying solutions reachingadvanced clinical trials today, polymerized and conjugatedbovine hemoglobin solutions have been explored in rodenttumors to increase the effectiveness of anti-cancer treatments by irradiation or chemotherapy. To some extent, the seemingly controvertial results may be ascribed to different doses and schedules of the Hb solution administrated to different tumors. The scientific advances made in their development will, without doubt, advance the field of oxygen carriers towards eventual success and patient benefit.

2.Sonosensitizer liposome as a new drug carrier[20-56]

Conventional chemotherapy agents kill rapidly proliferating cells, tumor cells and normaltissue, creating some of the common side effects seen with chemotherapysuch as nausea and vomiting. Therefore, novel therapeuticstrategies, preferably consisting of noninvasive treatments, areurgently required. In addition, SDT is a noninvasive treatment withno adverse effects by ultrasound radiation. In the 1990s, SDT as anew approach to cancer therapy was firstly introduced by Umemuraand co-workers. In this study, SDT involving the administrationof a sonosensitizer, ultrasound sensitive material, producing aseries of chemical reactions activated by radiation to kill tumorcells, may be an optional treatment for localized tumors. Ithas advantages over surgery or radiotherapy, reducing long-termmorbidity and permitting alternative treatments to be selected inthe case of recurrent, residual, or second primary disease.However, the most widely used sonosensitizes are hematoporphyrin(Hp) and its derivatives (HpD), which have phototoxicityandlong-lasting skin sensitivity due to the retention of thesonosensitizer in subcutaneous tissues. Therefore, a large numberof methods are used to reduce these clinically significant toxiceffects. One of the most common methods is the use of a drug carrierto alter drug bio-distribution and increase drug concentrationin certain tumor cells. Examples of drug carriers include microspheres,nanoparticles, liposomes, and micelles.As a drug carrier, liposome can increase the drug concentrationin tumor cells by both passive and active targeting effects. Targeteddrug delivery, which can make the chemotherapeutic drugsdirectly concentrate on the target tumor sites, is one of the ultimategoals in drug delivery. However, the low targeting effectof liposomes seriously hinders their clinical application. To facilitatethe selective targeting of malignant cells, liposomes can becombined with SDT. Accordingly, we propose the use of sonosensitizersin combination with liposomes directly target to tumor cellswith ultrasound effect. A sonosensitizer–liposome complex, as anew drug carrier, combines the anti-tumor effect of chemotherapeuticdrugs and sonodynamic therapy. With ultrasound radiation,thesonosensitizers can more effectively guide the chemotherapeuticdrug to target tumor tissues, achieving the goal of killing cancercells and protecting normal cells at the same time, which providesa new treatment for cancer.

Mechanism of SDT on cancer

Ultrasound can effectively increase the affinity and clustering ability of a drug focusing in a specific tumor location and employing to release drugs at that site, thereby minimizing damage tosurrounding normal tissues. Numerous experiments indicate that ultrasound, as a

mechanical wave, can strongly penetrate biological tissues. In addition, High intensity focused ultrasound (HIFU) can non-invasively concentrate acoustic energy into deep tissues. The ultrasound-induced increase in drug penetration into cells is believed to result from oscillations in gas bubbles in media. These oscillations cause cavitations and disruptions close to the cell surface and membrane that allows increased drug diffusion. Compared with chemotherapy and radiationtherapy, Ultrasound can decrease damage to normal tissues therapy, Ultrasound can decrease damage to normal tissues with ultrasound. Hence, it can be used to treat tumor cells resistant to chemotherapy or radiation therapy. Recently, the use of ultrasound has drawn considerable attention as a new method for cancer therapy because of it also inducing apoptosis. In addition, some researchers explored that ultrasound radiation with a sonosensitize could obviously increased cell membrane lipid peroxidation. In order to verify the mentioned above mechanism, Tsuru et al. established a mouse xenograft mode and studied on SDT with a novel sonosensitizer (a porphyrin derivative) in vitro and in vivo. The results suggested that SDT with a sonosensitizer could increase cell membrane lipid peroxidation and damage tumor cells, resulting in necrosis and prevention of tumor growth. On the other hand, during the spread of an ultrasound wave in a tissue, part of the mechanical energy is absorbed and the remaining part is transformed into thermal energy, which increases the tissue temperature. The thermal destruction of tumor tissue is one of the mechanisms of ultrasound-mediated tumor treatment. Generally speaking, ultrasound emission on the focused point creates a strong sound field that is used to make the tumor temperature reach its critical level for tumor necrosis, achieving the clinical goal. The critical temperature for tumor necrosis is about 42.5–43 _C. Therefore, the rationale for the use of hyperthermia is that sustained temperatures above 42.5 _C directly kill living cells. In general, ultrasound enhances drug transport through tissues and across cell membranes by different mechanisms, and low-intensity ultrasound radiation has been used for drug or gene delivery in recent years. Thus SDT can effectively increase chemotherapeutic drug concentration in tumor sites and reduce toxicity to normal tissues, improving therapeutic effects by using ultrasound.

3. Carrier-mediated delivery of peptidic drugs[57-65]

Proteins and peptides are increasingly being recognized as worthwhile leads for the development of newer therapeutics for a broad spectrum of diseases including but not limited to cancer, hepatitis and rheumatism. Their usually specific mode of action requires that, theoretically at least, only low doses are needed, thus lowering the risk of side effects caused

by small molecule drugs and larger charged ones such as oligonucleotides.carriers have certain significant advantages if used properly, as summarized aptly by Allen and Cullis. These factors include enhancement of drug solubility, controlled release of drug avoiding substantial side effects, better biodistribution of the drug molecules, and with certain carriers, the ability to target the diseased tissue in vivo. In terms of costs, according to analysts such as Peters et al.and Smith et al., When a drug molecule is administered with a carrier, drug clearance decreases (half-life increases), volume of distribution decreases, and the area under the time versus concentration curve increases. For larger diameter particulate carriers, the size of the carrier (normally within 50–200 nm, but sometimes reaching several microns) confines it to the bloodcompartment, and the volume of distribution will approachthat of the plasma volume if the drug release rate is low. Inessence the carrier has to bind the drug molecule, hold it for anadequate period of time till it reaches its required site of action, and then release it in a controlled (non-burst) fashion. The maximum tolerated dose (MTD) of the carried drug is directly affected by the carrier, as determined by the rate of release of the drug molecules from the associated state. This attenuates the drug's pharmacokinetic (PK) and biodistribution(BD) features, and will determine what dose of drugs can be administered. Certain pathological conditions such as tumors and inflammation, may actually accentuate the efficiency of the carrier including the ability to selectively deliver its payload to the diseased tissues. The enhanced permeability and retention (EPR) phenomenon, sometimes referred to as passive targeting, has been the lifeline of such carriers as stealth liposomes and microspheres. While a 10-fold increase in tumor drug concentration can be achieved using DDSs, delivery of drug from the entrapped state often tends to be focal (localized around the vehicle) rather than homogeneously distributed throughout the target tissue. Thus, smarter options for DDSs are needed.

4. Liposomes[68]

Liposomes generally have a large carrying capacity, but usually not large enough to ferry large molecules such as proteins. For liposomes, hydrophilic drugs can be readily entrapped within the aneutral and/hydrophobic moleculesmay be carried within the hydrophobic bilayers of the vesicles. There are various types of liposome formulations available, some of which have arisen due to a marriage of the ideas for specific types of liposomes.[6] The liposome field is over 3 decades old now, with the commercialization of a handful of anti-cancer therapeutic agents, all non-peptidic. Such small molecule drugs that are used to treat certain types of neoplasms include the nucleic acid synthesis-interfering agents doxorubicin

(available as Caelyx1) and daunorubicin (available as Daunoxome1queous interior of the vesicles).

5.Microparticles[67]

Microparticles are carriers from 1 to 100 mmin diameter. These have been used classically for ferrying small molecule drugs such as doxorubicin or Therasphere1 used for selective delivering yttrium-90 radiotherapy to hepatic tumor nodules. However, other disease indications can benefit from such delivery and include inflammatory bowel disease, Parkinson's disease, arthritis and peripheral vascular disease. The potential for peptide and protein delivery with this class of carriers was proposed almost a decade ago. While not much has been realized as for liposomes above, human growth hormone Biosphere1, Technosphere1 insulin and Technosphere1 PTH microspheres, as well as starch microspheres loaded with interferon-a 2B being tested clinically reinforces the applicability of this technology.2–5. Treatment of tumor-bearing mice with a single intratumoralinjection of biodegradable polylactic acid microspheres loaded with recombinant interleukin-12 (IL-12) promoted complete regression of the primary tumor as well as prevented pulmonary metastases from establishing. Mice that experienced tumor regression after being treated rejected a subsequent challenge with live tumor cells, which indicatedthe development of systemic antitumor immunity, possibly animportant finding for patients that have undergone surgerybut may have remnant cancerous cells within that need to be entirely eradicated. The sustained release of IL-12 from the microspheres was superior to bolus injection of free IL-12, and intratumoral delivery of microspheres was more effective than other routes of administration.

6.Cell-penetrating peptides[68-69]

In the past decade, a number of cell-penetrating peptides (CPPs) have emerged, facilitating the intracellular delivery of polar biomolecules in vitro and in vivo. While these individual peptides differ in length and sequence, they share a few common features. These include theoretical hydrophobicity and helical moment, the ability to interact with lipidicmembranes, and to adopt a distinct secondary structure upon association with lipids. The major dogma has been that CPPs enter cells by a receptor-independent process, although the exact mechanism(s) remain to be elucidated. In any case, the ability of these short peptides to cross plasma membranes even when associated with hydrophilic cargoes, makes them a worthwhile technology for further study and development. There is increasing recognition of the

capability of these membrane-permeating peptides especially for protein and peptide delivery.

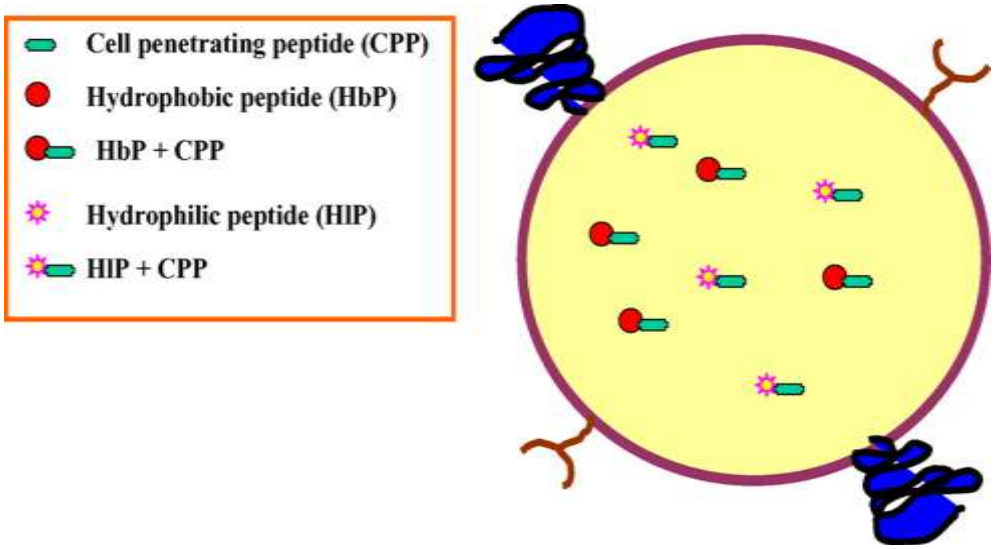

Fig. 1: An ideal peptide carrier. A vesicle capable of targeting tumour cells in vivo with two types of peptidic molecules.

Antibody (or ligand) attached to surface for targeting. PEGylated lipid, blue attachment to vehicle surface. Yellow aqueous or matrix allows hydrophobic drug(s) (red dots) and hydrophilic drug(s) (pink stars) to be delivered. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

ADVANTAGES[70-81]

1. The oxygen transport model was used to evaluate mixtures of red blood cells and six types of HBOCs that consisted of two polymerized hemoglobins, two liposome-encapsulated hemoglobins, and two hydrogel-encapsulated hemoglobins.
2. Sufficient oxygen must be delivered to both normoxic and cancerous tissues to maintain normal tissue functions when oxygenating the tumor.
3. An enhancement of tissue oxygenation (tpO2) in rodent tumorsassociated with an increased tumor growth delay was reportedfor purified bovine hemoglobin solutions combinedwith irradiation.
4. The greatest tumor growth delays were obtained with Oxygentlevels between 4 and 12 g PFC/kg.
5. Inhaled aerosols are effective as therapeutic carriers for the treatment of pulmonary ailments such as CF.

6. SDT involving the administrationof a sonosensitizer, ultrasound sensitive material, producing aseries of chemical reactions activated by radiation to kill tumorcells
7. SDT is a promising therapeutic method to treat certain cancers.With ultrasound, sonosensitizer drugs can be activated in deepertumors.
8. Doxorubicin (DOX) liposome can increase drugdeposition and retention with tumors to improve the therapeuticefficacy while reducing toxic off-target effects.
9. The use ofspheres as potential carrier for anticancer drug delivery has attractedmuch attention due to their wide applications.

APPLICATIONS[82-85]

1. To improve the biodistribution of cancer drugs, nanoparticles have been designed for optimal size and surface characteristics to increase their circulation time in the bloodstream.
2. They are also able to carry their loaded active drugs to cancer cells by selectively using the unique pathophysiology of tumors, such as their enhanced permeability and retention effect and the tumor microenvironment.
3. Nanoparticles have the ability to accumulate in cells without being recognized by P-glycoprotein, one of the main mediators of multidrug resistance, resulting in the increased intracellular concentration of drugs.
4. Steric stabilization, remote loading of drugs by pH and ion gradients, and lipoplexes based on complexes of cationic liposomes with anionic nucleic acids or proteins extended research toward liposome application and opened the way for development of a large spectrum of products.
5. Hemoglobin-based oxygen carriers theoretically investigates the possibility of supplementing human blood with hemoglobin-based oxygen carriers (HBOCs) in an attempt to target oxygen delivery specifically to the low oxygen tension regions present in tumors.
6. Penetratin, a short peptide fragment from the third helix of the Antennapedia protein homeodomain, is able to penetrate into a variety of cells.
7. Hollow polymeric spheres have spurred increasing interest due to their potential applications such as drug delivery systems.

CONCLUSION

The carriers are used in the cancer drug therapy. There are different types of carriers are used,for different types of cancer. They are biocompatible, have little toxicity, a good degree of tissue specific action, be easily prepared and administered.

A lot of work remains to be done in general and specifically in the fight against cancer.However, the presence of such agents in clinical trials and on the market attest to the applicability of this mode of treatment against various disease indications including cancer.

SDT can effectively increase chemotherapeutic drug concentration in tumor sites and reduce toxicity to normal tissues, improving therapeutic effects by using ultrasound. The Hb solution administrated to different tumors. In these way different carriers are used in different types of cancer.

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