Functionalized Nanoparticle Drug Delivery System Applied to the Diagnosis and Treatment of Tumor Cells

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Abstract. Chemotherapy is currently an important modality in the treatment of cancer and is widely used in the treatment of many cancers. However, the main problem with chemotherapy is the highly toxic side effects. How improve the efficacy of drugs and reduce their side effects has been a challenge for cancer treatment research. With the booming development of nanotechnology, functionalized nanomaterials are widely used for drug delivery and the treatment of tumors. Nanomaterials have unique physical, chemical, and optical properties, and the drug delivery system constructed by using multifunctional nanomaterials can not only precisely kill tumor cells to reduce damage to normal tissues, but also combine multiple therapeutic modalities simultaneously to improve the treatment effect of cancer. Therefore, the development of precise nano-targeted therapeutic techniques is of great importance for the treatment of cancer in clinical settings. In this thesis, we constructed various nano-drug delivery systems based on functionalized nanomaterials and applied them to drug delivery to tumors and multimodal therapy. These studies will help advance the development of nano-molecular drug delivery technologies to improve the therapeutic efficacy of drugs, reduce side effects and toxicity, and provide safer and more effective drug treatment options for clinical therapy.

1 Introduction

In recent years, with the rapid development of society and the increasing pressure on human life as well as environmental problems, the morbidity and mortality of tumors have remained high. Malignant tumors, also known as cancer, have become the number one cause of human death because of their rapid growth, infinite proliferation, strong infiltration, easy metastasis, easy spread, easy recurrence, and extremely difficult cure. The clinical treatment of tumors mainly includes surgery, radiotherapy, and chemotherapy. However, there are some shortcomings in these treatment methods, such as: although surgery can remove some tumors, it is difficult, incomplete, easy to metastasize and spread, and the success rate is low, which brings great pain to patients; although X-rays produced by radiation therapy can kill tumor cells, it also has certain radiation to surrounding normal tissues, which is harmful to human body; chemotherapy can use drugs to kill tumor cells and prevent their infiltration and metastasis. Chemotherapy can use drugs to kill tumor cells and prevent their infiltration and metastasis, but such drugs lack targeting and lead to great toxic side effects throughout the body. Since diagnosis and treatment are not integrated with each other, diagnosis and treatment cannot be carried out simultaneously, not only can the treatment process be monitored in real-time, but also the prognosis cannot be evaluated in time, resulting in poor tumor treatment effect. In recent years, with the rapid development of nanotechnology in the field of biochemistry, nanoparticle-based particle systems have provided new ideas for tumor diagnosis and treatment [1]. This paper outlines the application of nanoparticles in the diagnosis and treatment of tumors and explores their potential application as carriers of chemotherapeutic reagents.

2 Types and characteristics of nanoparticles

Nanoparticles, also known as milli-particles, are solid colloidal particles with a particle size of 0.1 to 100 nm and are composed of different types of materials. At present, nanoparticles used in brain tumor therapy can be mainly classified into three categories: particles composed of organic materials (such as liposomes, biodegradable polymers, solid lipid nanoparticles, nanospheres, etc.), particles composed of inorganic materials (such as iron oxide nanoparticles, metal nanoparticles, etc.) and nanoparticles of mixed materials. Magnetic nanoparticles: such as iron oxide and nickel oxide, have good magnetic properties and biocompatibility and can be used in biomedical imaging and tumor therapy. Magnetic Fe3O4, as the only magnetic nanomaterial currently approved by the Food and Dg Adm station (FDA) for clinical applications, has been attracting the interest of many researchers. However, the synthesized Fe3O4 nanoparticles are wrapped by hydrophobic substance oleophobic amine and can only be dispersed in non-polar or weakly polar organic solvents, and their solubility in water is extremely poor, so they cannot be used directly in living organisms [2]. To overcome this drawback, amphiphilic polymers (PEG) were modified on the surface

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of Fe3O4 [2]. nanoparticles, which not only reduced the absorption of plasma proteins by Fe3O4. nanoparticles but also greatly reduced the nonspecific absorption of the nanoparticles by macrophages, improving their circulation time and biocompatibility in blood. The PEGylated Fe nanoparticles were chemically loaded with the anticancer drug Chrmmone, which can effectively improve the circulation time and stability of Chrmmone in blood and is an ideal magnetic targeting drug carrier [4].

Fullerenes and their derivatives as a new type of carbon-containing nanomaterials have antioxidant activity and cytoprotection, antibacterial activity, antiviral [5], drug delivery, and tumor therapy. Fullerenes as drug carriers can be effectively loaded with anticancer drugs such as PXL and DOX. However, the strong hydrophobicity of fullerenes and the residual organic solvents in the preparation process have become major obstacles to their biomedical applications. Carbon Nano Tubes (CNTs for short) is a kind of inorganic carbon nanomaterials of great importance. They not only have a unique hollow structure and inner and outer tube diameters but also have good cell penetration ability and can be used as drug carriers. (WCNTs). In vitro experiments on both SWCNTs and MWCNTs have shown that they have significant cytotoxicity, which limits their application in the field of drug carriers. Other studies have shown that surface modification of CNTs can reduce their toxicity and improve their biocompatibility, which has led to increasing research on surface modified CNTs in the field of drug carriers [7].

3 Nano drug delivery system in tumor diagnosis and treatment

3.1 Targeting lymphoid tissue

Nanomedicine carriers can effectively target vaccines to lymphatic tissues, prolong the retention time of vaccines in lymphatic tissues, and control the release of vaccines and adjuvants. It facilitates antigen delivery and induces T-cell activation, enhancing the effect of tumor vaccines. The particle size of the nano-drug delivery system is a major factor in determining lymphatic targeting. In addition, the lymphatic targeting of nanocarriers depends on the composition of nanomaterials, particle morphology [3], surface chemistry, etc. Swartz et al. showed that nanoparticles with a particle size of 10-100 nm can effectively target lymph nodes and can be retained by lymph nodes [6], increasing the chance of antigen uptake and delivery in nanocarriers. The effect of different particle sizes on the immunogenicity of antigens was compared. Muraoka et al. subcutaneously injected self-assembled nanogels targeting myeloid macrophages into experimental mice for the delivery of tumor peptide vaccines. The results showed that nanogels with an average particle size of 60 nm could better activate the immune response of CD8+ T cells and exert preventive and therapeutic anti-tumor effects [figure 1 [8]].

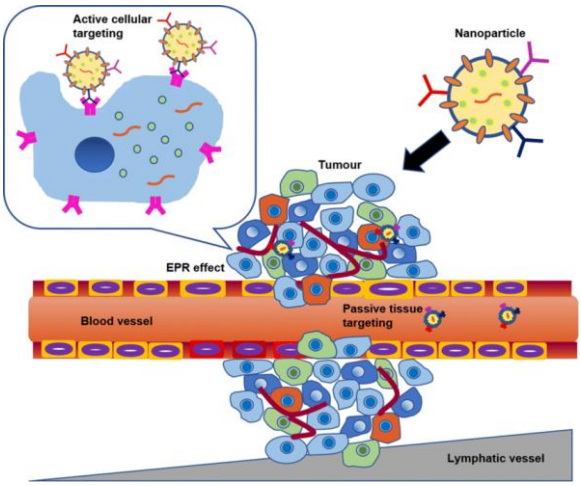

Figure 1 Schematic diagram of active targeting of nanoparticles at tumors

3.2 Phospholipid Nanoparticle Transport Systems

Liposomes in the size range of 80-100 nm have been considered as promising drug delivery carriers because of their ability to encapsulate water-soluble compounds more than other nanoparticles. Some liposome-based drug delivery systems have been used in clinical applications. Doxorubicin and erythromycin were the first liposomal drugs used to treat brain tumors, with disappointing results due to their low distribution capacity within the tumor. Enhanced convection delivery (CED) may improve the efficacy of liposomal drugs in the treatment of brain tumors. Topotecan and irinotecan (CPT-11), both inhibitors of topoisomerase I, which induces DNA damage, have not been used as primary therapeutic agents for brain tumors because of their high systemic toxicity. Injection of topotecan liposomes into experimental animals with U87MG glioma by CED was able to prolong survival time [4]. Topotec-an liposomes were able to aggregate in tumor cells at high concentrations while reduc-ing systemic toxicity. Liposomes encapsulating a camptothecin derivative and iri-notecan are a new oncology drug delivery system undergoing clinical trials. Its safety, pharmacokinetics, maximum tolerated dose, and other properties are currently being tested [8]. Nanoparticles composed of low-density lipoproteins (LDL) have the poten-tial to be used as a new drug introduction vehicle in the treatment of gliomas. LDL receptors are usually overexpressed in tumor cells due to their metabolic demand for phospholipids. In vitro, studies have shown that LDL nanoparticles can be rapidly taken up by glioma cells through LDL-dependent mechanisms.

3.3 Nanoparticles as a Carrier for tumor Targeted X-Ray CT contrast agent

Computed tomography (CT) is one of the most widely used non-invasive diagnostic imaging techniques in clinical practice and has been in use for most of the century. A variety of CT contrast agents have been developed to enhance the contrast of soft tissues. Currently, the water-

soluble contrast agents widely used in clinical practice are all derivatives of triiodo phenyl rings, such as iodophor sol, iodamide, tiropramide, and pantothenic glucosamine. However, because these CT contrast agents are small iodine-containing molecules, they have short circulation time in the body, are non-selective, and their use in large doses can lead to serious adverse reactions and aller-gies in some patients, thus greatly limiting their use for targeted imaging and angi-ography in some sites such as tumors, liver, and lymph nodes [5]. Over the past dec-ade or so, researchers have addressed this problem by exploiting the unique properties of nanoparticles such as long in vivo circulation, high permeability and retention effects in solid tumor tissues (EPR effect), easy surface modification, and integration of multiple functions in one. A large amount of research has focused on the devel-opment of clinically applied iodine-substituted small molecules into iodine-substituted nanoparticles, including emulsions, liposomes, lipoproteins, polymeric nanoparticles, and insoluble nanomaterials. The main objective of these nano-materials is to increase the concentration of iodine and to achieve a particle size that allows for a higher contrast than conventional water-soluble CT contrast agents and to achieve different in vivo kinetics than clinically used iodine-substituted small molecule contrast agents. In addition, some studies have introduced metallic and inor-ganic nanoparticles with high X-ray absorption properties into iodine contrast agents to increase their contrast performance. For example, gold has received much atten-tion due to its higher atomic number than iodine and its greater contribution to X-ray attenuation, and many Au nanoparticle-based contrast agents have been used for In vivo X-ray CT imaging. When gold and iodine, two highly X-ray impermeable ele-ments, are combined together, they have a synergistic effect and show a significantly enhanced X-ray attenuation effect. To target nanoparticles to tumor tissues for tu-mor-targeted drug delivery and bioimaging, active targeting is usually achieved using ligand-receptor binding systems or antibody-antigen binding systems. Folic acid (FA) is an early applied tumor-targeting molecule, and compared to its expression level in normal tissues, FA receptors are overexpressed in epithelial malignancies such as colorectal, ovarian and breast cancers [9]. It has been shown that FA is a high-affinity ligand for FA receptors (Kd ≈ 10-10 mol/L) [7] and FA-modified carriers can be efficiently taken up by cells with high FA receptor expression through receptor-mediated endocytosis. In this study, iodine-containing polymeric nanoparticles P (MATIB) were prepared by precipitation polymerization. (MATIB-co-MBA-co-GMA) by precipitation polymerization, and FA molecules were modified onto the surface of this nanoparticle, and then gold nanoparticles (Au) were deposited inside and on the surface of this nanoparticle. gold nanoparticles (AuNP) were deposited on the surface, resulting in P(MATIBco-co MBA-co-GMA)-FA-AuNP nanoparticles, which were used as tumor targeting X-ray CT contrast agent, while using the nanopar-ticles as a carrier for The nanoparticles were also used as a carrier for the antitumor drug Adriamycin hydrochloride (DOX) as a drug model to study The performance of this nanoparticle as an antitumor drug delivery vehicle was investigated, in order to obtain a nanoparticle system that can simultaneously achieve tumor-targeted imag-ing and drug delivery for tumor diagnosis [10]. The performance of the nanoparticles as anti-tumor drug delivery carriers was investigated, with the aim of obtaining nano-particle systems that can simultaneously achieve tumor-targeted imaging and drug delivery and realize the integration of tumor diagnosis and treatment.

3.4 Experimental materials

Name of experimental materials reagents	Manufacturer
N-Isopropylacrylamide (NIPAM)	Shanghai Maclean's Biochemicals
1, 3-Diphenylisobenzofuran (DPBF)	Shanghai Maclean's Biochemicals
5-Fluorouracil (5-Fu)	Shanghai Maclean's Biochemistry
Methylenebisacrylamide (MBA)	Shanghai Aladdin Biotech
Indocyanine Green (ICG)	Shanghai Aladdin Biotech
Dimethyl Sulfoxide (DMSO)	Shanghai Aladdin Biochemical Technology
Potassium persulfate (KPS)	Beringia
DMEM high sugar medium	Zhejiang Senry Biotechnology
Phosphate Buffer Solution (PBS)	Zhejiang Senry Biotechnology
Fetal Bovine Serum (FBS)	Zhejiang Tianhang Biotechnology
Penicillin-Streptomycin solution	Hangzhou Geno Biotechnology
Trypsin	Hangzhou Norsend Biotechnology
Tetramethylazole Blue (MTT)	Solebro Technology
Acridine Orange (AO)	Shanghai Biotechnology
Ethidium bromide (EB)	Shanghai Biotechnology
4',6-Diamidino-2-phenylindole (DAPI)	Shanghai Biotron Biotechnology
Dichlorodihydrofluorescein-acetoacetate (DCFH-DA)	Shanghai Biotron Biotechnology
Annexin V-FITC/PI kit	Shanghai Biotron Biotechnology

Figure 2 List of Experimental Reagents and Materials with Manufacturers

3.5 Preparation of PNIPAM nanogels

As shown in Figure 2 PNIPAM nanogels were prepared by soap less emulsion polymerisation as follows: 1.0 g of NIPAM and 0.5 g of MBA were weighed and dissolved in 60 mL of deionised water, nitrogen was introduced into the solution and the solution was stirred at 70°C for 0.5 hours. Then, aqueous KPS (2 mg/mL, 10 mL) was slowly added dropwise to the solution to initiate soap-free emulsion polymerization, and the reaction was stirred continuously under nitrogen for 6 hours. Finally, the product was allowed to cool and then transferred to a dialysis bag, where deionised water was selected as the dialysis solution and dialysed for 2 days [9].

3.6 In vitro release of PNA-DOX drug

The in vitro release of DOX was determined by dialysis. 1 L of PBS solution at a concentration of 2 mg/mL PNA-DOX nanogel was placed in a dialysis bag, which was then placed in 5 mL of PBS solution at various pHs (7.4, 6.5 or 5.0) or pH 7.4 with or without 4 mM DTTPBS solution in a water bath at 25, 37 or 42C. At regular intervals, 4 mL of the solution was removed from the release system for UV-Vis spectrometry analysis and supplemented with 0.5 mL of fresh PBS solution. The DOX versus time equation for cumulative release (C_r) (1) [10]:

$$C_r(\%) = \frac{Abs_t}{Abs_{tot}} \times 100 \quad (1)$$

Where Abs_t and Abs_{tot} respectively represent the total absorbance of the solution at time t and the absorbance of the total DOX amount contained in the gel used for release.

4 Conclusion

Inorganic nanomaterials have made great progress in recent years as drug carriers due to their unique physicochemical properties, but their biosafety has been a con-troversial issue that requires long-term in-depth research. In addition, the current re-search direction of nano-drug carriers is along the direction of multi-functionalization, such as the combination of magnetic nanoparticles and mesoporous materials to make it have a magnetic targeting function while increasing the drug loading capaci-ty; the combination of quantum dots and magnetic nanoparticles to target drug load-ing while being able to trace the distribution of drugs in the body; the combination of inorganic quantum dots, magnetic nanoparticles, and Smart Polymer can not only achieve multiple targeting and fluorescence imaging but also achieve multi-targeting and fluorescence imaging. The combination of inorganic quantum dots, magnetic nanoparticles, and Smart Polymer can not only achieve multi-targeting and fluores-cence imaging but also easily realize the intelligent controlled release of drugs. It is reasonable to believe that multifunctional drug carriers with fluorescence detection, multi-targeting, efficient drug delivery, quantitative and timed drug release, and non-toxic side effects are important for the diagnosis and treatment of major diseases such as cancer.

In summary, we present a simple method for the synthesis of P(NIPAM-AA) nanogels with good biocompatibility in terms of drug release, high drug encapsulation rate and temperature/pH/redox multi-responsiveness. When internalised, the drug encapsulated in the nanogels can be effectively released and exert its therapeutic effects. The good bioactivity of the nanogels and their smart drug release controllability (temperature/pH/reduction multi-responsiveness) make them an ideal nano-drug delivery platform for various cationic anticancer therapeutics, including DOX. In addition, the nanogels were prepared without any organic solvents, making the preparation method green and environmentally friendly, and this study provides new implications for the effective intracellular delivery of a wide range of drugs and the design of novel drug platforms.

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