Chinese-German J Clin Oncol
DOI 10.1007/s10330-014-0039-7
October 2014, Vol. 13, No. 10, P489–P493

Research progress in nanoparticles as anticancer drug carrier*

Yingying Sun, Huaqing Lin (✉), Chuqin Yu, Suna Lin

Department of Guangdong Pharmacy College, Guangdong Key Laboratory for New Pharmaceutical Dosage Forms, Guangzhou 510006, China

Received: 28 July 2014 / Revised: 13 August 2014 / Accepted: 25 August 2014

Abstract Nanoparticles drug delivery system has sustained and controlled release features as well as targeted drug delivery, which can change the characteristics of drug distribution *in vivo*. It can increase the stability of the drug and enhance drug bioavailability. The selective targeting of nanoparticles can be achieved through enhanced permeability and retention effect and a conjugated specific ligand or through the effects of physiological conditions, such as pH and temperature. Nanoparticles can be prepared by using a wide range of materials and can be used to encapsulate chemotherapeutic agents to reduce toxicity, which can be used for imaging, therapy, and diagnosis. In this research, recent progress on nanoparticles as a targeted drug delivery system will be reviewed, including positive-targeting, negative-targeting, and physicochemical-targeting used as anticancer drug carriers.

Key words nanoparticles; anticancer drugs; drug carrier

Chemotherapy is one of the primary means of treatment of malignant tumors. However, many anticancer drugs not only have low therapeutic index, high toxicity, but also kill a large number of normal cells with killing cancer cells, produce larger side effects to the body. Therefore, it is necessary to find a targeted, partial concentrated delivery system that can improve efficacy and reduce toxicity. In 2004, Allen *et al* [1] titled in "Drug delivery systems are becoming mainstream medicine", published comments on application of nanotechnology in drug delivery in Science magazine: well-designed lipid nanoparticles or polymer nanoparticles can improve pharmacological and therapeutics properties of drugs. Many problems in the past influencing the clinical applications of drugs have been overcome by the fine particle carrier drug delivery system. Particle size and surface properties of nanoparticles in the body play an important role in the distribution of drugs whose surface has a large number of available modified groups and especially by use of special materials to achieve the purpose of targeting [2]. Nanoparticles can achieve tumor tissue targeting, tumor cell targeting and intracellular targeting. Therefore, nanoparticles as carriers of anticancer drugs in cancer therapy field have promising application prospects.

Correspondence to: Huaqing Lin. Email: huaqing_@vip.tom.com
* Supported by a grant from the foundation of Guangzhou Municipal Key Project for Special Scientific Plan (No. 2008A1-E4101).

Passive targeting drug delivery system

Passive targeting means reducing non-specific interactions to non-target organs, tissues and cells to increase the target site / non-target site ratio of drug levels. Tumor tissue riches in blood vessels, vascular wall gap is wider, structural integrity is poor, nanoparticles can penetrate the tumor capillary wall "gap" into the tumor. While the lymphatic system is imperfectly reflux, resulting in the accumulation of nanoparticles, this phenomenon is known as enhanced permeability and retention (EPR), passive targeting of nanoparticles is based on EPR effect to enrich in tumor tissue [3]. However, the nanoparticles are easy to be identified and swallowed as foreign material by phagocytic cells after intravenous injection. Macrophages mostly present in the bloodstream and more abundant reticuloendothelial system (RES), mainly in the liver, spleen, bone marrow, lungs and other organs [4]. Accordingly, the nanoparticles containing antineoplastic agents are more favorable to the tumor in the treatment of liver, spleen and other organs after intravenous injection, but the treatment of tumors in other organs are more difficult. To solve these problems, there have been long-circulation nanoparticles drugs loading with anticancer. Long-circulation nanoparticles have reduced

liver and spleen macrophages and other parts of the drugs to improve drug targeting and hinder conditioning of plasma protein particles, which play an important role in prolonging circulation time *in vivo*. Since polyethylene glycol (PEG) is non-toxic and non-immunogenic, it is used to achieve long-circulating nanoparticles by modifying nanoparticles' surface. Moghimi *et al* [5] pointed out that the half-life of PEG nanoparticles in mice and rats is 2–24 h *in vivo*, while 45 h in the human body. *In vitro* experiments showed a similar effect between PEG of paclitaxel nanoparticles and commercially available Taxol ® in inducing apoptosis. Tumor-bearing nude mice *in vivo* experimental results showed that, the survival time of tumor-bearing nude which were injected PEG of paclitaxel nanoparticles was longer than mice injected Taxol ®. This is due to the PEG of paclitaxel nanoparticles achieved by the EPR effect in tumor tissue and maintained effective therapeutic concentration [6].

Active targeting drug delivery system

The limitation of passive targeting nanoparticles is that the specificity is low for tumor tissue. Unlike passive targeting drug delivery system, initiative targeting drug administration is designed with specially and carefully biometrics, which specifically directed drugs to the identification of targets. Tumor tissue over-expresses some receptor or presents some specific antigen. Ligands of targeting receptor bind receptor over-expressed on tumor cell surface, this combination has several characteristics, such as specificity, selectivity, saturation, strong affinity and significant biological effects. Targeting ligand antigen could achieve active targeting through binding targeted by tumor-associated antigens present on the tumor cells surface (TAA), tumor-specific antigens (TSA) or tumor angiogenesis-associated antigen, therefore active targeting of nanoparticles having high specificity to tumor tissue is better to achieve the purpose of targeted therapy [7]. The commonly used targeting molecules include folic acid, transferrin proteins, peptides, monoclonal antibodies (MAbs) and etc.

Folic acid

Folate receptor (FR) is over-expressed in human tumors cell surface, such as ovarian cancer, breast cancer, cervical cancer, colon cancer, nasopharyngeal carcinoma, whereas it is highly conserved in normal tissue [8]. Human cervical carcinoma cells HeLa's surface receptor over-express FR, Shen *et al* [9] prepared a folate binding doxorubicin-loaded folic acid-conjugated albumin nanospheres (FA-DOX-AN), compared with doxorubicin-loaded albumin nanospheres (DOX-AN), FA-DOX-AN interacted by receptor-ligand, and got into HeLa cells quickly, HeLa cell viability was low. The survival of non over-expressed FR of aortic smooth muscle cells surface is higher than in HeLa cells, suggesting that the cytotoxicity of FA-DOX-AN in normal cells is low, thus could reduce side effects of doxorubicin. Drugs bind to cell surface receptors after making to targeted nanoparticles, entering into cells by endocytosis, avoiding identification P-glycoprotein to overcome resistance. Wang *et al* [10] found that heparin-folate-paclitaxel (HFT-T) can significantly reduce the resistant cell line KB-8-5 activity, the killing effects are stronger than free paclitaxel and non-target nanoparticles to tumor cells with resistance. The *in vivo* experiments showed that mice tumor volume injected HFT-T was significantly smaller than injecting free paclitaxel. These results showed that, HFT-T nanoparticles could reduce P-glycoprotein associated with drug resistance compared with free paclitaxel, and improve efficacy. In addition, studies [11] showed that the folic acid modification of nanoparticles could not only be used for drug delivery but also tumor imaging.

Transferrin (Tf)

Transferrin receptor (TfR) is a transmembrane glycoprotein, and its function is mediating the absorption of iron by interacting with transferrin. The receptor expression level is low in normal cells, as the demand for iron due to the rapid growth of tumor cells, in the tumor cells (such as liver cancer, breast cancer, pancreatic cancer, glioma, lung adenocarcinoma, chronic lymphocytic leukemia and non-hodgkin's tumor), the expression of transferrin receptor increased significantly [12]. Xu *et al* [13] prepared paclitaxel-loaded nanoparticles with transferring (PTX-Tf-NPs), that the killing effect of PTX-Tf-NP on HeLa cells over-expressing TfR is 1.34 times higher than PTX-NPs, while the cell cytotoxicity of without TfR human umbilical vein endothelial cells (HUVECs) is consistent with the PTX-NPs. Furthermore, long-term use of doxorubicin is easy to produce drug resistance of tumor cells, but the conjugates combined with Tf could enter the cell by TfR-mediating endocytosis and overcome the low intracellular drug concentration caused by the drain pump and increase tumor cells doxorubicin sensitivity. For other drugs such as cisplatin, chlorambucil, mitomycin C, gemcitabine, daunorubicin and other covalent couple Tf, selectivity and sensitivity of tumor cells significantly enhance [14].

Peptides

RGD peptide is a kind of arginine-glycine-aspartic acid (Arg-Gly-Asp) short peptide. RGD peptides could bind integrated receptors (mainly αvβ3 protein) and over-express in endothelial cell of tumor angiogenesis [15]. Studies [16] showed that RGD peptides could inhibit the adhesion and migration of tumor cells, induct apoptosis, inhibit neovascularization of a tumor tissue, increase the target-

ing effect of the drug on the tumor, and therefore, the coupling of RGD peptide of nanoparticles can enhance targeting effect on tumor vascular. RGD peptide coupling gemcitabine albumin nanoparticles (RGD-BSANP-GEM) can enhance BxPC-3 cell line's inhibition, this cell line is from human pancreatic cancer over-expressed of αvβ3 receptor, while the inhibition in PANC-1 cell lines is low expression of αvβ3 receptor in human pancreatic cancer, and showed no significant difference when compared to unconjugated with the RGD peptide nanoparticles. Injected by the tail vein which belonged to nude mice inoculated with melanoma cells with fluorouracil nanoparticles conjugated RGD peptide, fluorouracil nanoparticles, and fluorouracil, Dubey *et al* [17] found that fluorouracil nanoparticles conjugated RGD peptide in the tumor concentration is 1.54 times higher than fluorouracil nanoparticles, 9.1 times higher than fluorouracil, respectively. RGD peptide coupling of fluorouracil nanoparticles can significantly slow tumor growth rate. In recent years, receptor imaging technology is more and more popular as an important tool for biological research, integrin αvβ3 receptor is expected to become the target of new radiopharmaceuticals, radioactive nuclide labeled RGD peptides may be used clinically as a potential tumor receptor imaging agent [18].

Monoclonal antibodies (MAbs)

Tumor cell's growth, proliferation and differentiation require continuous stimulation of various growth factors, and these growth factors are also involved in tumor's invasion, metastasis and angiogenesis. Monoclonal antibody competitively binding to its receptor can inhibit ligand-receptor interaction, so that tumor cells die themselves as the lack of growth factors stimulation. Currently, there have been three monoclonal antibody of drugs against human epidermal growth factor receptor (HER), cell differentiation antigens (CD) 20, vascular endothelial growth factor (VEGF) have been formally approved in clinical application, including trastuzumab antibody, rituximab and bevacizumab. But the application of monoclonal antibodies were also been found resistance and side effects, while this antineoplastic with larger molecular weight is not easy to enter solid tumors and affect the internal efficacy [19]. What conventional anticancer drugs ubiquitously exist a serious flaw is that they also have greater toxicity in normal cells. Therefore, the cytotoxic drugs conjugated with monoclonal antibody by chemical and biological method, using antigen-antibody specific binding capacity, cytotoxic drugs were transported into a target cell accurately and effectively improved the local drug concentration in the tumor, which greatly reduced the drug concentration of other body organizations and organs, as to achieve a synergistic attenuated role [20]. Treatment of paclitaxel nanoparticles were studied by Cirstoiu-Hapca *et al* [21] which were conjugated trastuzumab of ovarian cancer effect and distribution in the body of the nude mice vaccinated SKOV-3 cells. The results showed that paclitaxel nanoparticles have higher anti-tumor effect compared with free paclitaxel, conjugated trastuzumab of paclitaxel nanoparticles could effectively inhibited tumor growth and improve survival of tumor-bearing mice. The reason was that the SKOV-3 cells over-express HER receptors conjugated trastuzumab could make drugs selectively stronger distributed and higher paclitaxel gathered in cells.

Physical chemistry targeted drug delivery systems

Magnetic Nanoparticles as drug carriers in most studies tend to treat and diagnosis of cancer. In terms of disease treatment, under an action of an external magnetic field, paramagnetic or super paramagnetic iron oxide nanoparticles with temperature rising to 40–45 ℃ can achieve the purpose of killing the tumor. Fix magnetic particles of drugs with directional orientation of a magnetic field, use an alternating magnetic field to heat magnetrons to destroy cancer cells. In terms of disease diagnosis, magnetic nanometer materials are used for magnetic resonance imaging to track the drug delivery process and its distribution in biological body after surface coating and other processing, super paramagnetic iron oxide nanometer materials [22].

Folic acid and Cyclodextrin-functionalized super paramagnetic iron oxide nanoparticles (FA-CD-SPIONs) were prepared by Hayashi *et al* [23]. The CD has a good inclusiveness for drugs, FA as a breast tumor targeting ligand gave FA-CD-SPIONs cancer targeting function. The analysis results showed that FA-CD-SPIONs with particle size of 12.4 nm could be stable in the water. Under a particular low frequency alternating magnetic field (230 kHz, 1000e) effect, FA-CD-SPIONs showed specific absorptivity (132 W/g) and can induce magnetic force vibration heat and release the drug from the CD by changing the magnetic field. Meanwhile, FA-CD-SPIONs have no toxicity effects on cell, which could be used for drug delivery and magnetic hyperthermia.

As magnetic resonance imaging (MRI) can be used to carry out rapid nondestructive testing for the internal organs and soft tissues of the organism, it has become one of the most effective clinical diagnosis methods of soft tissue lesions, especially in detection of tumor. MRI with super paramagnetic iron oxide particles as a probe utilizes imaging methods to noninvasively measure and characterize biological processes at the cellular level *in vivo* conditions, including cell proliferation, differentiation, migration, aggregation, and so on, which have advantages of completely noninvasive and high spatial resolution, and

so on. What's more, super paramagnetic iron oxide particles contrast agents can be used for magnetic resonance molecular imaging. Single/polyclonal antibody can couple super paramagnetic iron oxide particles to form molecular probes, which can be used to identify antibodies corresponding to coupled antigen in biological body, and display the location (the site of deposition of the probe) and concentration of specific antigens by changing the relaxation times of protons around [24]. The technology seeks to disease-specific biomarkers visualization at the molecular and cellular level. Ling *et al* [25] researched a series about theragnostics polymer nanoparticles simultaneously loaded with anticancer drug docetaxel and super paramagnetic iron oxide with prostate stem cell antigen antibodies (scAbPSCA-Dtxl/SPIO-NPs) for the treatment of prostate cancer. The results indicated that, scAbPSCA-Dtxl/SPIO-NPs not only specifically targeted prostate cancer cells and inhibited their growth, but also could be used as MRI contrast agents, due to the specificity and aggregation effect of scAbPSCA-Dtxl/SPIO-NPs. There have attractive prospects on drug delivery and real-time monitoring of therapeutic effect of the treatment of prostate cancer and other diseases. In addition, pH-sensitive and temperature-sensitive nanoparticles have more researches.

Problems and prospects

With the deepening of clinical researches, nanoparticles for cancer treatment will be further improved and developed. Efflux pump for multidrug resistance may be overcome, providing better efficacy without the side effects of the emergence, significantly reducing. The drug made from the targeted nanoparticles bind to cell surface receptors, get into the cell through endocytosis, avoid recognizing by P-glycoprotein and overcome the resistance. Practice shows that targeted drugs in clinical application are only effective in some patients. It was pointed out that we must firstly screen patients who are appropriate to a sort of targeted drug, to judge whether she/he can obtained efficacy through drug. In addition, we should monitor whether the targeted drug fail or not during treatment, if it is found that efficacy significantly reduced, can be promptly disable or switch to other drugs, the traditional pathology biopsy specimens were obtained from tumor tissue before treatment, various target molecules' growth and decline situation can not be reflected during treatment. To solve these problems, the composite functional nanoparticles a set of angiography and treatment or imaging nanoparticles and treatment nanoparticles can be prepared, to use imaging nanoparticles for targeted localization of the disease, and then use nanoparticles for targeted therapy treatment. As the size and surface properties of them are very similar, so that treatment nanoparticles can reach target molecular of disease, and subsequent contrast imaging can also confirm whether the nanoparticles reach the target molecular for the treatment and treatment is effective. Nano-drugs as a new class of pharmaceutical preparations in nanotechnology research and development, its security issues can not be ignored in the present attractive nano-biological effects. Whether nanomaterials will lead to specific biological effect or not, whether generate path physiological and toxicological effects and other issues after entering the living body, all of which require further evaluation of nano-drugs' biological safety.

Confilcts of interest

The authors indicated no potential conflicts of interest.

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DOI 10.1007/s10330-014-0039-7
Cite this article as: Sun YY, Lin HQ, Yu CQ, *et al*. Research progress in nanoparticles as anticancer drug carrier. Chinese-German J Clin Oncol, 2014, 13: 489–493.