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Role of Targeted Nanocarriers in Cancer Therapy

Boyuan Dou

School of Medicine and Bioinformatics, Northeastern University, Shenyang, China
2619896@dundee.ac.uk

Abstract. Due to the problems like not being specific enough for targets, having lots of toxic side effects, and the growth of resistance to medicine, traditional ways of treating cancer don't work very well. The appearance of targeted nanocarriers gives a major approach to beating these difficulties. These carriers accomplish exact drug delivery via a dual-targeting mechanism. And the passive targeting is mostly to improve the permeability of the vessel, and keep it, when you adjust the particle size that it can enter the gap of the tumor's blood vessel, plus ultrasonic physical method and other magnetic fields, the exact rate of the tumor can be achieved more. Active targeting is carried out by grafting specific ligands like antibodies, peptides onto the surface of the carrier, which bind to the receptor to achieve active targeting, bypassing tumor drug resistance. According to the carrier's core materials, SLNs of lipid-based carriers are suitable for thermosensitive therapy, PLGA of polymer-based carriers can achieve antibacterial and anticancer effects, silica nanoparticles of inorganic carriers are suitable for gene delivery, and heparin of bio-based carriers can reduce toxicity and side effects due to its inherent biological properties. Although there are still problems such as inter-individual variation in the EPR effect, safety issues, and barriers to clinical application in this field, the improvement of carrier design, safety regulations, and the combination of multiple carriers are expected to make targeted nanocarriers into an important tool for precise cancer therapy.

Keywords: Cancer, Nanocarriers, Passive target, Active target

1. Introduction

Cancer, also known as malignant tumor in medicine, is a kind of disease that is caused by the abnormality in genes of cells. Under normal regulation, cells grow, divide, and die in an orderly fashion. Cancer cells have lost the ability to do so, and they proliferate in an uncontrolled manner and differentiate abnormally. They not only invade the surrounding normal tissues but also metastasize to other parts of the body via blood and lymph, destroying the organ’s structure and function. These are caused by both genes and the environment. External carcinogenic factors are mainly divided into three types: physical carcinogens such as ultraviolet rays and ionizing rays; chemical carcinogens such as asbestos and the components of cigarette smoke; and biological carcinogens such as virus and bacterial infections or parasitic diseases, all of which have an impact on the development and differentiation of normal cells. It is estimated that in 2018 alone, there were

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9.6 million cancer-related deaths globally, accounting for one-sixth of the total number of deaths in that year, indicating that cancer is a significant threat to human life and health [1].

The main conventional treatments for cancer are surgery, radiotherapy, and chemotherapy. But each of them has its own limitations. Surgery is mainly used for patients in the early stage of cancer, and once the tumor cells have metastasized, surgery can no longer play a curative role. Radiation's action range in radiotherapy has limitations as well, it is mainly targeting localised tumors, hard to avoid healthy tissue and needs a long course of treatment. Chemotherapy is hard to send drugs accurately to a tumor, and the tumor cells may resist the drugs. This forces doctors to give more drugs, and this harms the patient's body a lot. Thus, targeted drug delivery has become more and more popular. With certain methods, medicines go directly to cancer cells and do not harm healthy ones. As the key delivery system, the size and long-circulation characteristics of nanocarriers in passive targeting can be tailored to take advantage of the tumor EPR effect for targeted release. In the active targeting process, the nanocarriers can be coated with a specific antibody to target the tumor site, achieving the purpose of active targeted delivery and precise drug transportation. Due to the paucity of systematic reviews and analysis of targeted nanocarriers in cancer therapy, this article aims to explain how nanomedicine delivery technologies are applied for targeted and precise delivery of drugs with high tumor selectivity and sustained release of the drug. Also discussed are existing advantages and smart release carrier technologies, which will give a better theoretical foundation for applying targeted nanocarriers in treating cancer.

2. Different targeted drug delivery strategies

Currently, the main targeted drug delivery strategy is to passively target or actively target [2].

2.1. Passive targeting

Passive targeting is that drugs selectively accumulate at tumor sites according to the differences between tumors and normal tissues to achieve therapeutic effects. Its mechanism is the EPR effect [2]. The vascular system of the tumor is usually less regular than that of normal tissue, and has larger vessels and higher permeability. Unlike the tight connections between endothelial cells of regular blood vessels, the endothelial cells of tumor microvessels are not continuous and are easily permeable. Different tumor types are examined in anatomical studies, and it is seen that the gaps between endothelial cells vary between 100 and 780 nm. Moreover, growth factors such as vascular endothelial growth factor and basic fibroblast growth factor are also upregulated in tumor vasculature, leading to vasodilation and enhancing the extravasation of drug carriers out of vessels and into tumor tissues. At the same time, since the lymphatic drainage system of tumors is not well-developed and functional, macromolecular drugs are accumulated and retained in the tumor [3]. And this whole process is known as the EPR effect. Suitable for macromolecular drugs (molecular weight > 40 kDa) or small-molecule drugs encapsulated in nanocarriers. Small-molecule drugs like doxorubicin and paclitaxel may pass through the tumor's blood vessels but are quickly washed away by regular metabolism or diffusing into other places. Therefore, it is required to have a nanocarrier size which corresponds to vascular gap to prevent clearance. But EPR effect has shortcomings, which mainly acts on the peripheral areas of tumor, the drug diffuses hard, and residual cancer cells are easy to leave. In addition to using EPR, local drug delivery can be used as well, where the drug is directly injected at the site of the tumor to avoid any systemic toxicity, but only for localized solid tumors and not for a disseminated malignancy.

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Physical targeting is a special form of passive targeting using external stimuli to control drug release. For example, Ultrasound target is the application of focused ultrasound to a tumor area, and it can regulate the release mode of the drug by using both ultrasound energy and a magnetic field. First, ultrasound energy promotes the extravasation of the drug carriers and enhance the efficiency of the drug carrier to penetrate the tumor, for example, releasing the polymeric micelles, liposomes, and polymeric nanoparticles [4]. Polymeric micelles are self-assembled by amphiphilic block copolymers, with the hydrophobic core containing lipophilic drugs and the hydrophilic shell forming the outer corona, and their size can meet the permeability requirements of the tumor vascular gap [5]. Liposomes are vesicular structures formed from phospholipid bilayers, drugs are contained within their interior, PEG coating on the exterior can avoid clearance by macrophages, and they are appropriately sized for permeability requirements. Polymeric nanoparticles are generally made by first making an emulsion of the dispersed phase and then drying the emulsion to solidify the particles, so as to assemble polymers and drugs into nanosize particles. The differences of solubility in different solvents are mainly exploited. Ultrasound energy can act on these drug carriers, and it can expand the endothelial gaps of tumor blood vessels to promote extravasation by mechanical effects, which is periodic pressure changes in the medium causing changes in microstructure, or it can induce disassembly of the structure by thermal effects, which is converting ultrasonic energy into heat as it propagates, or it can cause disassembly by cavitation effects, which is forming microbubbles when the sound pressure exceeds a certain value, resulting in intense local physicochemical changes. In this way, the encapsulated drugs can be released at the tumor site to further increase the accumulation rate. For instance, the polymeric micelles based on PVP-b-PVAc (poly(N-vinylpyrrolidone)-block-poly(vinyl acetate), specifically PVP90-b-PVAc290) and PEGylated stealth liposomal doxorubicin both essentially depend on EPR effect to target tumor cells, but ultrasound energy can improve EPR by mechanical effect.

Second, in magnetic targeting, drugs are loaded into or conjugated with magnetic carriers. After intravenous injection, an external local magnetic field is applied to the tumor site, which can make the carriers accumulate in the tumor under the action of magnetic force, reduce the distribution of carriers in other non-target organs [6]. Magnetic carrier is a drug delivery system that incorporates or encapsulates magnetic materials, such as magnetite, iron, cobalt, and iron oxide nanoparticles, including magnetic nanoparticles and magnetic liposomes. For example, magnetic nanoparticles are generally synthesized using iron oxide nanoparticles as the core, and a polymer is coated on the surface to improve dispersion stability in aqueous solution, prevent aggregation after injection, reduce the amount taken up by the mononuclear phagocyte system, extend the circulation time of blood, and achieve high capacity for drug loading and controlled release, thus forming a drug-loading shell. Magnetic liposomes are formed by embedding iron oxide nanoparticles into the inner aqueous phase or the phospholipid bilayer of regular liposomes to form a composite material with a magnetic core and a liposomal shell that can encapsulate hydrophilic drugs in the core and lipophilic drugs in the bilayer [7].

2.2. Active targeting

Passive targeting takes advantage of the EPR effect to enrich drugs in tumors, but the targeting specificity is low. About 30% to 40% of nanocarriers still accumulate in normal tissues, thus, the drug concentration in tumors is only about 15% to 25% of the total dose that circulates through the body, resulting in both low therapeutic effect and systemic side effects. Because it depends on the tumor vascular permeability which will cause the EPR effect to be poor and ineffective. In such

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situations, active targeting makes up for the deficiencies of passive targeting and considerably improves the accuracy of targeting and the success of treatment [8].

Active targeting is done by adding special stuff called tumor-targeting ligands, like antibodies, peptides, or hormones, to the outside of drug carriers. In terms of the principle of specific binding between ligands and receptors, these ligands can actively target the biomarkers expressed by tumor cells or tumor vascular endothelial cells, delivering drugs accurately and increasing the amount of drug that reaches tumors to 60%-80% of the total amount of the drug given to the whole body [2]. Antibodies bind specifically to the tumor-associated antigens overexpressed on the surface of tumor cells via the antigen-binding fragment, which initiates the receptor-mediated endocytosis (a type of cell-specific uptake mechanism), and enables the intracellular drug delivery. Peptides are small molecules consisting of a limited number of amino acids and are characterized by small size, good tissue penetration, low cost, and represent an important complement to antibody-based targeting and overcome several shortcomings of antibodies. By specific amino acid sequences, peptides attach to receptors on cancer cells or the blood vessels feeding into tumors. Though not as high affinity as an antibody, they have a much greater permeability and the possibility of multivalent presentation (each carrier can display dozens or hundreds of peptide copies). Hormone ligands are able to target hormone-dependent tumors as these tumors express more receptors for that specific hormone. As endogenous molecules, hormones bind with high affinity to specific receptors on the surface of tumor cells, inducing receptor-mediated endocytosis, and bringing drugs into the cells.

The target of tumor vascular endothelial cells is more advantageous than others, because it is easy to access and has no gene mutation and drug resistance, and it can provide nutrition for cancer cells. To target tumor vasculature would starve the tumor of its nutrients and it is unlikely for resistance to occur as the tumor evolves [9]. Targeting the tumor cell exploits the presence of tumor-associated antigens, these are specific markers on the surface that are expressed or over-expressed as a result of the malignant transformation. Ligand – receptor interactions are then utilized to precisely deliver the drugs. And conjugation technology can also be used to couple the carrier and drug to the ligand with a linker, forming ligand-carrier-drug complexes that maintain both ligand-specificity and drug activity while controlling intracellular drug release. Stable complexes are formed by chemical bonds or linkers, the carriers are responsible for drug loading and circulation prolongation, the targeting ligands are responsible for recognizing the tumor cell surface target, and the linkers ensure that these components are combined without mutual interference.

3. Applications of targeted nanocarriers in cancer

Targeted nanocarriers, whose physicochemical properties and different functionalizations are controllable, have a great future in cancer treatment. According to the main components of their core materials, they can generally be divided into four major categories. There are various kinds of carriers, each with their own distinct characteristics and playing essential roles in particular applications.

3.1. Lipid-based targeted nanocarriers

Lipid-based targeted carriers are made up of natural or artificial lipids (like phospholipids, cholesterol, and solid lipids) that can self-assemble into nanostructures that have the ability to carry both water-soluble and fat-soluble drugs and that can be safely used in the body. Solid lipid nanoparticles (SLNs), e.g., use solid lipids as a carrier matrix. SLNs have some advantages for encapsulating hydrophobic drugs and controlling drug release, they can efficiently encapsulate and

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release hydrophobic drugs, slow the diffusion of drugs, and can be used for multiple therapies (hydrophilic drugs, hydrophobic drugs, proteins, peptides) [10]. SLNs are also stable platform for thermosensitive drugs. In the treatment of cancer by hyperthermia, paclitaxel loaded SLNs made from stearic acid as the matrix can accumulate in the lung cancer lesion, and combined with microwave hyperthermia to achieve a tumor drug concentration 6 times higher than that of free drugs, which is clearly superior. In addition, studies have also shown that using PC as a ligand, and taking advantage of the PLTP-mediated transport for targeted internalization in pancreatic cancer cells. Researchers have designed and synthesized PC-modified multiarm PEG (PC-8-PEG) and PC-PIC/m (polymeric micelles), and the results show that it can be rapidly and highly absorbed into human pancreatic cancer BxPC3 cells, with a 4-20 times higher than the non-PC modified one. This uptake was energy dependent and could be markedly inhibited at low temperatures or in the presence of added free PC to compete with it; inhibition of PLTP also reduced internalization [11].

3.2. Polymer-based targeted nanocarriers

Polymer-based targeted nanocarriers are made of natural polymers, synthetic polymers, or stimuli-responsive polymers as matrices with suitable degradation rates and biocompatibility. For example, PLGA (poly (lactic-co-glycolic acid)) can be chosen as the core material for co-encapsulation of metronidazole and oxaliplatin, and then these nanoparticles can be covered with neutrophil membranes [12]. This system can achieve drug enrichment by synergistic effect of passive targeting, active targeting and microenvironment-responsive. At the passive targeting level, EPR effect can make PLGA nanoparticles pass through blood vessels and stay in tumor. Active targeting is done by special interactions made through membrane proteins or extra changes, microenvironment responsiveness is made by making the system fit the tumor's acid and other features, so that it builds up more in the place. A paper published in Nature Communications in 2024 reported a pH-sensitive triblock copolymer nanosystem that targets mitochondria and regulates cell metabolism and ER stress directly causing ICD in cancer cells. The platform can be sequentially modified with cRGD and mannose ligands, so that it could simultaneously target the melanoma cells and TAMs. The adjuvant R848 is loaded after which it functions as an in-situ tumor vaccine that reprograms TAMs to an M1 phenotype. In vivo experiments showed that the dendritic cells were successfully activated, T-cell infiltration was enhanced, and tumor growth was significantly inhibited, and when combined with immune checkpoint blockade, it greatly increased the survival time of tumor-bearing mice [13].

3.3. Inorganic targeted nanocarriers

Inorganic targeted nanocarriers adopt inorganic materials such as metals, metal oxides, and carbon-based materials as cores and utilize their unique physicochemical characteristics for targeted therapy. For instance, poly(L-lysine) can be utilized to functionally coat the surface of silica nanoparticles, which can enhance the delivery of antisense oligonucleotides to human nasopharyngeal carcinoma and epithelioid carcinoma cell lines. The in vitro experiment found that the antisense oligonucleotide delivery of serum-free medium was 20 times and the serum-containing medium was 6 times more than the free oligonucleotide. It effectively enriched the drug [14]. Iron oxide (Fe3O4) nanoparticle, furthermore, it can be used not only as a contrast agent for magnetic resonance imaging (MRI), but also as magnetically targeted carriers that are concentrated on the tumor site when subjected to an external magnetic field and generate heat when exposed to an alternating magnetic field for magnetic hyperthermia. The surfaces of the particles can be further functionalized with PDA or PEG

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to load chemotherapeutic drugs, such as DOX, which can be combined with hyperthermia. Gold nanoparticles (Au NPs) that have a strong surface plasmon resonance, can change near-infrared light into heat for PTT. Conjugate targeting ligands like folic acid and RGD peptides to Au-S bonds to improve the tumor targeting specificity of these systems [15].

3.4. Bio-based targeted nanocarriers

Bio-based targeted nanocarriers are made of biological substances like cells' membranes, exosomes, virus-like particles, natural proteins, and polysaccharides. Utilize the internal targeting characteristics and minimal immunogenicity of biomolecules to reach a specific location. For example, Heparin not only has anticoagulant effects, but also disrupts tumor-initiating factors, inhibiting the growth and metastasis of tumors. Anticancer drugs can be functionally modified to heparin, or incorporated into heparin-based nanodelivery systems. Heparin can also bind to anticancer prodrugs, and it has been shown to provide a safe and effective means of drug delivery [16]. A research was published in 2025, in which scientists managed to build up a pH-sensitive targeted nanodrug delivery system dependent upon a bio-sourced metal – organic framework (Bio - MOF) for carrying the chemotherapeutic substance 5 - fluorouracil (5 - FU). The results indicated that there was more swelling, degradation, and 5-FU release under acidic condition (pH 5.5) which simulates tumor environment. After an additional surface coating the system was highly biosafe for normal 3T3 cells and cytotoxic for SH-SY5Y cancer cells. The uncoated formulation gave off more powerful anticancer effect but less controlled-release ability. These results suggest that this bio-based nanocarrier might have some good chances for combining targeted chemotherapy and how well it is not harmful to the body [17].

4. Conclusion

Targeted nanocarriers bring in new ideas for cancer treatment with a mix of passive and active targeting, and they step up the accuracy of targeting using physical targeting, which gets over important restrictions of old chemotherapy. Passive targeting mainly relies on EPR effect and adopts suitable-sized, surface-modified carriers for the first tumor accumulation. Active targeting uses specific ligand-receptor interactions to improve targeting accuracy and tackle challenges like weak EPR in some tumors and the emergence of drug resistance, whereas physical targeting uses the physical characteristics of carriers to strengthen the EPR effect and overall targeting efficiency. Different kinds of carriers all have their own advantages: lipid-based carriers have good biocompatibility and low leakage of drugs, polymer-based carriers can achieve "antibacterial–anticancer" combined therapy, inorganic carriers are suitable for gene delivery and integrated diagnosis and therapy, and bio-based carriers can reduce side effects and degrade quickly, which meet different needs in the treatment of cancer. Although there are still some challenges, such as a large inter-patient variation in EPR effects, biosafety concerns for some carriers, and a low rate of clinical translation, these problems may be solved by improving the design of carriers, enhancing the regulatory safety of carriers, and rationally combining multiple carriers and targeting methods. Targeted nanocarriers are bound to find ever increasing use for precise cancer therapy in the future, they will play a big role in fighting cancer.

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