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Research on Nano-based Targeted Delivery Systems for Anti-tumor Drugs

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Abstract: Tumor metastasis and recurrence are significant factors leading to patient death, and chemotherapy drugs can cause severe damage to normal cells while killing tumor cells. Therefore, improving the efficacy of chemotherapy drugs and reducing their toxic side effects has become a research hotspot in recent years. Nanotechnology enables efficient targeting of drugs to tumor sites, enhancing the therapeutic effect of anti-tumor drugs. This article reviews the design of nano-based targeted delivery systems for anti-tumor drugs, including nucleic acid aptamers, protein polypeptides, surface modifications, and other nano-carriers and their construction strategies. It introduces various targeting binding systems based on different biomolecules (such as folic acid, hyaluronic acid, sugar chains, etc.) and ligands. This article summarizes the retention behavior of nano-carriers in the body and anticipates future trends in nano-based drug targeting delivery systems.
Keywords: Nanotechnology; Anti-tumor; Targeted drug delivery

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1. Introduction

Cancer is one of the major diseases threatening human life and health today. According to statistics, in 2022, there were approximately 4.82 million new cases of malignant tumors in China, with lung cancer ranking first, and esophageal cancer and colon cancer also accounting for a considerable proportion [1]. Currently, cancer treatment primarily includes surgery, chemotherapy, radiotherapy, and targeted drug therapy. Chemotherapy, which involves using drugs to induce apoptosis or death in tumor cells, is the most widely used anti-cancer method. Commonly used anti-tumor drugs include anti-angiogenic drugs, cytotoxic drugs, and endocrine-disrupting drugs [2,3]. However, their therapeutic effects are often unsatisfactory, and they have significant toxic side effects. Therefore, developing novel targeted anti-tumor drug delivery systems is crucial. Traditional drug delivery methods find it difficult to deliver anti-tumor drugs to the tumor site due to physiological barriers (such as vascular endothelial cells and smooth muscle cells) between tumor tissue and normal cells, significantly reducing the therapeutic effect of chemotherapy drugs. Targeted drug delivery systems can precisely deliver drugs into tumor cells, improving drug efficacy and reducing damage to

normal tissues and organs. In recent years, targeted drug delivery systems based on monoclonal antibodies and nucleic acid aptamers have garnered significant attention due to their high specificity and efficiency. However, these two targeting systems rely on antigens or nucleic acid sequences for coordination recognition, making it impossible to achieve a one-to-one correspondence between the drug and specific targets. Therefore, designing functionalized nanomaterials for targeted drug delivery is particularly important.

Nanotechnology refers to a technical system consisting of artificial structural units and their assemblies with sizes ranging from 1 to 100 nm, applicable in drug delivery, diagnostic testing, and gene therapy. TiO2N is widely used in biomedicine due to its stable chemical properties, ease of synthesis, non-toxicity, good mechanical properties, and strong surface negativity. In recent years, researchers have used TiO2 nanoparticles in cell imaging, immune regulation, DNA carriers [4,5], and made some progress in anti-tumor research.

This article reviews the development status of nano-based targeted delivery systems for anti-tumor drugs from three aspects:

(1) Introducing different types of nano-carriers and their construction strategies, including drug-loaded liposomes, polymer micelles, DNA self-assembled nanospheres, and nucleic acid aptamers;

(2) Presenting targeting binding systems based on biomolecules and ligands, such as folic acid molecules, hyaluronic acid molecules, and sugar chain molecules;

(3) Summarizing the retention behavior and metabolic kinetics of nano-carriers in the body to provide references for subsequent related research.

2. Nanocarriers and their construction strategies

Nanocarriers refer to nanoparticles with a size below 10 nm. They primarily bind to cell membranes or intracellular receptors through various means such as electrostatic interactions, physical adsorption, Van der Waals forces, and hydrogen bonding, thereby achieving drug delivery and release [6]. Based on this, we refer to nanocarriers with targeting capabilities as drug-targeted delivery systems.

2.1. Aptamers

Nanoparticles are considered one of the most promising targeted delivery vehicles because they can specifically recognize specific sequences in proteins and elicit immune responses. As shown in **Figure 1**, a biological target can consist of one or multiple nucleic acid base pairs. These base pairs typically contain several complementary nucleotides (called complementary strands), and each base pair has a specific hydrophobic region. This conformational difference allows the two complementary strands to align in parallel but opposite directions, forming a “double-stranded lock” structure that is unstable and prone to breakage. Therefore, when aptamers specifically interact with target proteins, they can release a large number of amino acid residues, triggering protease cleavage or shearing reactions that lead to target protein inactivation [7].

Based on this principle, researchers have developed various methods to design aptamers with high affinity and selectivity, including:

(1) Artificial screening using known protein sequences [8];

(2) Synthesizing peptide chains containing multiple amino acids through protein engineering techniques [9];

(3) Screening nucleic acid fragments with high affinity for target proteins through phage display technology [10];

(4) Utilizing computer-aided molecular simulation techniques to predict aptamers with high affinity [11].

In recent years, with the rapid development of sequencing technology, it has become possible to determine the complete genome information of any given species through genetic sequencing, thereby accelerating the research process of nano-targeted drugs. Currently, a large number of different types of aptamers have been reported, such as aptamers derived from human immunoglobulin G, neutrophil elastase, hemoglobin, etc. [12] Among them, some aptamers have been proven to effectively mediate tumor chemotherapy, gene therapy, and gene editing, making them one of the hot research directions in the current field of nanotechnology.

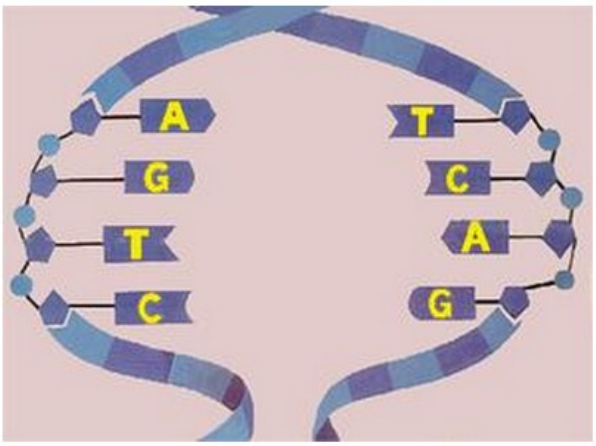

Figure 1. Nucleic acid base pairing.

2.2. Protein polypeptides

The surface of nanoparticles can achieve encapsulation of drug molecules through physical adsorption or chemical modification. Proteins themselves have good biocompatibility and biodegradability, so they are often used as drug carriers for drug delivery. For example, based on the reversible degradation characteristics of the tumor microenvironment, polyethylene glycol (PEG) can be grafted onto the cell membrane of tumor-associated fibroblasts and then encapsulated with chemotherapy drugs such as doxorubicin [13]. Some researchers have also designed and synthesized a new type of magnetic polymer microspheres using the electrostatic interaction between positively charged butylamine ions (NH4+) and negatively charged benzothiazole anions (BzS) to carry the anticancer drug paclitaxel [14]. These examples illustrate that using protein polypeptides to construct nanocarriers can not only reduce the residence time of drugs in the bloodstream but also significantly improve the retention efficiency of drugs at tumor sites.

2.3. Surface modification

To increase the stability of nanocarriers in organisms, surface modification is necessary. Common surface modification methods include lipidization, chemical modification, etc. For instance, lipidization can protect nanoparticles from damage by the body's enzyme system while reducing the risk of systemic exposure [15]. Additionally, by adding various functional molecules, the physicochemical properties of nanoparticles can be further improved, enhancing their stability in organisms and targeting effects [16]. Moreover, surface modification of nanocarriers helps address the issue of nanoparticles easily disintegrating under acidic conditions, ensuring long-term drug retention in tumor tissue.

3. Construction of target binding system

Dai *et al.* reported a nanosystem composed of folic acid and polymer carriers. This system covalently binds folic acid to polyethylene glycol (PEG) or hyaluronic acid with hydrophobic groups and attaches them to the surface of copper nanoparticles [17]. In the tumor microenvironment, tumor-associated fibroblasts abundantly express the folate receptor FFR1, enabling them to specifically recognize and ingest nanoparticles modified with folic acid, thereby facilitating drug release.

Yang proposed a carbohydrate-based targeting strategy, which utilizes the sugar chains in the tumor microenvironment for targeted binding [18]. Firstly, degradable carbohydrates such as glucose, galactose, and fucose are synthesized. These are then combined with cationic liposomes containing carboxyl or hydroxyl groups to prepare a targeted drug delivery system. These cationic liposomes can be modified using various methods to adapt to different types of cell surface receptors, such as membrane proteins or ion channels. Subsequently, cationic liposomes with different ligands are coated onto specific nanocarriers, ultimately obtaining nanocarriers with tumor-targeting properties.

Wei designed an amino-based lipophilic drug delivery system. This involves grafting a hydrophobic compound containing an amino group (such as tetrafluoroboric acid) onto polyethyleneimine. It is then introduced into polyethylene glycol through electrostatic interactions. Finally, mannose side chains are grafted onto the polyethylene glycol-tetrafluoroboric acid block copolymer [19]. Since the amino groups on the mannose side chains can specifically bind to mannose receptors on the surface of tumor cells, the mannose side chains can serve as a “molecular switch.” When ingested by tumor-infiltrating macrophages, the nanodrug carrier detaches from the polyethylene glycol backbone, releasing the previously enclosed drug and achieving efficient tumor treatment.

Additionally, researchers have designed a nucleic acid aptamer-based targeted binding system to enhance the specificity of drug targeting [20]. Nucleic acid aptamers select corresponding targets based on the affinity between their base sequences and tumor-related antigens, thus avoiding unnecessary toxic side effects caused by nonspecific binding. Simultaneously, nucleic acid aptamers can bind to a higher density of nucleic acid sequences, improving the accuracy of targeting tumor sites. Currently, several DNA-based nucleic acid aptamers have been successfully applied in clinical trials, such as Aptamer 437, which has shown significant therapeutic effects in the treatment of colorectal cancer.

4. Retention behavior of nanocarriers in the body

4.1. Passive targeting retention in tumor tissues

The retention behavior of nanocarriers in the body is primarily based on some special physiological and pathological characteristics of tumor tissues, among which the most typical is the Enhanced Permeability and Retention (EPR) effect. Due to rapid proliferation, tumor tissues are rich in neovascularization, have larger gaps between vascular endothelial cells, and lack an effective lymphatic drainage system. Nanocarriers with particle sizes in the range of 10–200 nm can penetrate tumor tissues through these enlarged vascular endothelial gaps and remain in the tumor site for a long time. For example, polylactic-co-glycolic acid (PLGA) nanoparticles, as commonly used nanocarriers, can passively accumulate in tumor tissues through the EPR effect when their particle size is within the appropriate range [21]. Studies have shown that doxorubicin loaded into PLGA nanoparticles has a significantly higher drug concentration in tumor tissues after intravenous injection compared to free drugs, and can maintain a higher concentration at the tumor site for a longer time, effectively improving the killing effect of the drug on tumor cells.

4.2. Active targeting retention

To further improve the retention efficiency of nanocarriers in tumor tissues, surface modification of nanocarriers can be performed to carry targeting ligands that can bind to specific receptors or antigens on the surface of tumor cells, achieving active targeting retention. Common targeting ligands include folate, transferrin, monoclonal antibodies, etc. Folate receptors are highly expressed on the surface of various tumor cells, and folate-modified nanocarriers can be efficiently taken up by tumor cells through specific binding to folate receptors [22]. For example, folate-modified liposomes encapsulating paclitaxel have significantly increased uptake in tumor tissues and prolonged retention time in tumor cells compared to unmodified liposomes, enhancing the inhibitory effect on tumor cells. Transferrin receptors are also overexpressed on the surface of many tumor cells, and transferrin-modified nanocarriers can also achieve active targeting and retention of tumor cells through receptor-mediated endocytosis [23]. Monoclonal antibodies have high specificity and can accurately recognize specific antigens on the surface of tumor cells. Connecting them to the surface of nanocarriers can significantly improve the targeting and retention time of nanocarriers at the tumor site. For example, trastuzumab-modified nanoparticles have good targeting and retention effects on HER2-positive breast cancer cells [24].

5. Conclusion

In the field of anti-tumor drug delivery, nanomaterials have attracted significant attention due to their unique physicochemical properties. However, designing nanocarriers with high targeting specificity, high drug loading capacity, and good biocompatibility remains a considerable challenge. Currently reported targeted carriers are mostly homogeneous systems that form stable encapsulated structures by wrapping ligands within the carrier after specific binding. As a result, these carriers often require dissolution with the assistance of organic solvents or other polymeric solvents. Nevertheless, organic solvents may cause severe adverse reactions in patients, while polymeric solvents may not achieve the desired targeting effect. Therefore, it is imperative to develop novel nanocarriers capable of achieving targeted delivery. This article primarily focuses on constructing drug targeting systems by exploiting interactions between different types of biomolecules and various target molecules. These molecules include folate receptors, hyaluronic acid receptors, sugar chains, proteins, and more. Among them, nucleic acid aptamer-based targeting systems are the most common. However, their development is limited by drawbacks such as susceptibility to degradation by host cells and the inability to penetrate the blood-brain barrier.

In future research, it is essential to delve deeper into the synergistic effects among different types of biomolecules and optimize their structures and properties for better application in drug targeting. Additionally, beyond drug targeting systems based on target molecules, there is potential to develop targeting peptides and drug delivery systems based on protein-ligand coupling strategies to further enhance the accumulation efficiency of drugs in the body.

Disclosure statement

The author declares no conflict of interest.

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