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The Mechanism of Action and Clinical Research of Tumor-Targeted Nanomedicines in Cancer Treatment

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Abstract. Cancer remains a major global and national health burden, and clinical needs for effective therapies are urgent. The conventional chemotherapy is limited by its lack of specificity and a serious level of toxicity, which renders it difficult to address the requirements of precision medicine of patients. Tumor-targeted drugs are valuable in terms of providing support to precision therapy whereas nanomedicines have become an active research focus in the given area due to their specific physicochemical characteristics and delivery benefits. The review provides a summary of the mechanisms of action and clinical research of tumor-targeted nanomedicines, and describes three fundamental mechanisms, including passive targeting, active targeting, and trigger-release. It describes their principles, the characteristics of the drugs design, and those that have been successfully clinically validated and it also provides an overview of clinical research progress in common cancer types and also breaks down two key clinical challenge cases. Finally, the review shows new trends in the development of drugs and treatment methods. The aim of the review is to inform R&D and clinical translation in this direction in an attempt to increase the efficacy of cancer treatment.

Keywords: Nanomedicines, Tumor-Targeting, Clinical Treatment, Cancer

1. Introduction

Cancer is the major disease threatening human health worldwide, which is a highly concerning global health issue. In recent years, the death rate of cancers has been rising continuously; patients who died from non-communicable diseases (NCDs) have a three-tenths risk of dying from cancer [1]. In statistical data in 2022, there were 20 million cancer patients, of whom 10 million were dead patients [2]. Therefore, effective cancer treatment has an increasing demand around the world. Two cancer therapies in clinical medicine include radiotherapy and chemotherapy. Radiotherapy is a widely used cancer treatment method that is chosen by more than fifty percent of cancer patients. It delivers ionizing radiation to the tumor site by external or internal irradiation, causing the radiation to interact with seperate components of cells or create free radicals by ionizing intracellular molecules, then damaging DNA in order to control tumors and treat cancer. Through technological advancements, radiation therapy can now be used with imaging for more precise drug delivery and integrated with other treatment methods to enhance efficacy more. But traditional radiotherapy also has disadvantages. For instance, its low radiation absorption results in limited penetration depth, so

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it is hard to reach deep-seated tumors and thus cannot achieve the expected effect of therapy. The radiation from radiotherapy also disrupts the normal function of healthy tissues [3]. Chemotherapy includes the administration of cytotoxic drugs systemically. Its mechanisms involves directly interfering with tumor cell DNA strands and indirectly damaging tumor cells by generating reactive oxygen species (ROS) through interactions with water or oxygen [4]. Conventional chemotherapy is limited in dealing with cancer. As an illustration, it can hardly accumulate within the tumors and is normally preceded by noticeable side effects. As an illustration, it can merge with others with the healthy tissues and cause disturbances in the normal operations [5]. Based on this, a new type of drugs has emerged that is referred to as tumor-targeted nanomedicines. Such type of therapeutics utilizes nanomaterials to transport therapeutic agents to tumor sites specifically based on passive targeting, active targeting, or stimulus-responsive release to improve treatment efficacy. The clinical researches have proved that tumor-targeted nanomedicines is able to treat different cancers effectively like: non-small cell lung cancer, breast cancer, and prostate cancer [6]. This is the essence of the review. The following review is focused on offering the systematic review of the acting mechanisms and clinical research of tumor-targeting nanomedicines that can facilitate the definite cancer treatment and help advance its clinical use.

2. Characteristics and mechanisms of tumor-targeted nanomedicine targets

This part describes in detail passive and active form of targeting and trigger mechanism of tumor-targeted nanomedicines and presents in particular the mechanism and clinical trials with tumor-targeted nanomedicines.

2.1. The passive targeting mechanism relies on the EPR effect of the tumor microenvironment

2.1.1. Introduction to the passive targeting mechanism and EPR effect

The mechanism of passive targeting relies on the Enhanced Permeability and Retention Effect (EPR), which is a universal pathological phenomenon. Tumor vasculature exhibits large amounts of small abnormal pores in the endothelial lining and incomplete intercellular junctions, resulting in high permeability. The limited lymphatic drainage of tumor tissues stops effective clearance of nanomedicines entering the interstitium, allowing them to slowly accumulate inside the vascularized tumor regions. The EPR effect explains how macromolecular compounds or nanoscale drug carriers achieve targeted delivery to tumor tissues because of the hyperpermeability of tumor vasculature and the functional impairment of tumor tissue lymphatics, while being rapidly cleared from healthy tissues [7].

2.1.2. Design characteristics of nanomedicines based on the EPR effect

The optimal particle size range for nanomedicines based on the EPR effect is 10 nm to 400 nm, with 50 nm offering the best permeability. Particles that are too large or too small may be rapidly cleared or unable to penetrate tissues. The optimal shape is spherical or other regular forms to enhance macromolecular vascular penetration efficiency and interstitial diffusion. Irregularly shaped molecules may impair vascular penetration efficiency. Selecting softer drug particles (e.g., 10–40 kPa) can promote blood circulation. Nanoparticles with neutral or weakly negative surfaces reduce serum protein adsorption and prolong blood half-life [8,9].

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2.1.3. Drug examples and clinical validation

The following two examples of nanomedicines all belong to passively targeted nanocarriers. The first example is hydroxyapatite nanoparticles loaded with doxorubicin (DHAPNs), where the drug carrier type is an inorganic nanoparticle. Its passive targeting mechanism uses biocompatibility of hydroxyapatite and optimal size for accumulation within tumor tissues. It enhances doxorubicin retention in tumor cells by disrupting mitochondria and reducing ATP production in the same time, thereby inhibiting drug efflux pump activity. Clinical trials shows its efficacy in both in vitro and in vivo experiments for suppressing breast cancer cell growth, with no significant toxicity observed in normal cells. The second of these is Poly(styrene-maleic acid)-novocarbant (SMANCS) which is a polymer conjugated nanodrug. Its passive mode of targeting takes advantage of the properties of vascular endothelium of the tumors which are not fully developed, and have a defective lymphatic drainage, therefore tumor tissues can be enriched greatly through the effect of EPR. It has a significant higher concentration in tumor tissues than that of free novocarbant [8].

2.2. Active targeting mechanism

2.2.1. Mechanism of active targeting and common targets

Active targeting mechanism It entails the alteration of the surface of nanocarriers with unique recognition motifs that enable them to specifically aggregate into one another with receptors overexpressed on the tumor cell surface. This facilitates receptor mediated endocytosis including clathrin mediated endocytosis, and runs the purchase of nanocarriers into tumor cells. This enhances selective concentration of the drugs in tumor locations and increases the aptness of taking them by the cells. This can be done especially in cases where therapeutic drugs do not have the capacity to enter the cell membranes on their own. As stated earlier, active-targeted nanocarriers have to satisfy the design principles of the passive-targeted nanomedicines first. Once the initial tumor tissue enrichment is obtained due to the EPR effect, surface ligands can bind to receptors and, therefore, have an effect. Certain targeting ligands can also have synergistic anti-tumor activity with the carrier-loaded drug by intrinsic pharmacological effect, and again augment the therapeutic effect. Popular targets used in active targeting include small molecules, peptides, and proteins [10].

2.2.2. Clinical validation and examples of drugs

The PSMA-targeted docetaxel nanoparticle is an example of an active targeted nanomedicine. These inhibitors have a peptide structure similar to PSMA substrates and have surface modification of the small-molecule ligand ACUA. The specific ligand that attaches to prostate cancer cells or to the neovascular surface of most non-prostate solid tumours. This particular binding attains active targeting of tumor sites through the nanoparticles [11].

2.3. Set off the release mechanism

2.3.1. Newly developed mechanism of triggered drug release

The triggering mechanisms of tumor-targeted nanomedicines are classified into exogenous stimuluThe initiation of buoyancy of tumor-targeted nanomedicines is divided into exogenous stimulus-induced and endogenous stimulus-induced. Exogenous stimulus-eeek responses are, first of all, external physical responses, e.e. responsiveness of temperature and responsiveness to electric or

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magnetic fields. The main exploitations of the difference between tumor microenvironment and normal tissues method are the endogenous mechanisms of stimulation in which a controlled release of drugs is achieved through reacting to distinct physical signals or changes to the tumor microenvironment [12].

2.3.2. Relevant clinical trials

The trial was a clinical trial involving thermosensitive liposomes (Dox-TSL, loaded with doxorubicin), whose triggering mechanism is release of doxorubicin in tumor vasculature under the influence of localized hyperthermia. This design also not only increases drug-tumor cell attach time but also achieves a penetration depth of 78m DNA which is twice that of traditional Doxil liposomes, this has successfully overcome penetration barriers of traditional nanomedicines. By exploiting this better Figure of speech, clinical trials are going on. During a Phase I trial in treating primary and metastatic liver cancer, investigators used a combination of Dox-TSL and radiofrequency ablation (RFA) treatment regimen which used the drug intravenously 15 minutes before the ablation. The findings indicated that patients who were treated with the maximum tolerated dose (MTD) had a treatment failure time of 374 days which is much higher as compared to 80 days of those who were treated with sub-MTD dose. The combination therapy, as opposed to RFA alone also exhibited good safety and a significant improvement in efficacy. Besides, due to a wide antitumor spectrum of doxorubicin, Dox-TSL is also being tested in Phase I in other indications, such as bone metastases, pancreatic cancer, as well as metastatic liver cancer, indicating a promising range of possibilities in clinical practice [13].

3. Clinical research progress of tumor-targeted nanomedicines in common cancer types

This section mainly focuses on clinical research related to tumor-targeted nanomedicines, and focusing on their applications in treating non-small cell lung cancer (NSCLC), breast cancer, and prostate cancer.

3.1. Clinical research in Non-Small Cell Lung Cancer (NSCLC)

Non-small cell lung cancer (NSCLC) is a subtype of lung cancer. The epidermal growth factor receptor (EGFR) plays a key role in NSCLC development. Its abnormal activation stimulates tumor cell reproduction, making it a potent therapeutic target in clinical treatment. The pharmacodynamic design of nanomedicines targets various EGFR mutations present in NSCLC patients, such as exon 19 deletions and L858R. Based on the type of nanocarriers, targeted drugs are chiefly categorized into three groups: organic nanomaterials, inorganic nanomaterials, and siRNA delivery systems.

Organic nanomaterial drugs, owing to their excellent biodegradability and drug-loading capacity, have become the primary carriers for nanotargeted drugs in NSCLC. They are categorized into polymer-based and lipid-based types. Taking chitosan-coated osimertinib nanoparticles as an example, this drug targets the EGFR T790M resistance mutation.This nanoparticles showed 2.4- to 2.6-fold improvements in antitumor effects in mouse xenograft model of H1975 with a rate of about 81.59 of accumulating the drug in the tumor intratumorally. They also caused G2/M phase arrest in tumor cells, and a massive decrease in tumor volume. Multimodal therapies can be adapted in Organic nanomaterials drugs. Using the example of cetuximab-modified gold nanoparticles (C225-AuNPs), 14 nm gold nanoparticles conjugated with cetuximab may be taken into the A549 cells by EGFR-mediated endocytosis. The therapy is more effective than free cetuximab since it increases

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cytotoxicity by 1.8-fold, blocks the EGFR signaling pathway, and induces targeted therapeutic effects. The siRNA delivery mechanism is aimed at the efforts to tackle the resistance mechanisms in EGFR and to be able to restore the susceptibility of the tumor cells to treatment. Indicatively, siMad2 nanoparticles were used to interfere in one of the proteins (cell cycle checkpoint protein). These nanoparticles gain access to A549 cells through endocytosis through EGFR. Following the silencing of Mad2 gene, cisplatin resistant cells are seen to be four times more sensitive to the cisplatin. Targeting of nanoparticles is sixfold greater than non-targeted nanoparticles with a duration of drug retention in tumors up to 96 hours. Therefore, this method is effective in producing good local therapeutic effects on tumor cells. Altogether, EPGR-directed medicines show great promise to the clinical management of NSCLC [14].

3.2. Clinical studies on breast cancer

There have been clinical demonstrations of the usefulness of tumor-targeted nanomedicines in various breast cancer subtypes. Use breast cancer of HER2 as an example and triple-negative as an example.

First is the HER2-positive breast cancer. HER2 is a crucial oncogene in breast cancers that promotes the proliferation of the tumor cells. The overexpression of HER2 in breast cancer can be used in the diagnosis of the disease as also targeted therapy using HER2 has a great impact on patient survival. An example of this is the use of trastuzumab that extends the median survival to 56 months in patients with breast cancer that has invaded and is HER2-positive. The conventional targeted drugs fall into organic and inorganic nanocarriers. Organonic nanocarrier offers the use of surface modification with HER2-reactive ligands, such as trastuzumab, GE11 peptide, which results in precise delivery.Inorganic nanocarriers, such as gold nanoparticles, combine therapeutic and imaging functions. Trastuzumab-modified nanoparticles can deposit high radiation doses (e.g., 60.5 Gy) in HER2-positive breast cancer xenografts when locally injected, suppressing tumor growth for 70 days without large amount of normal tissue toxicity. Furthermore, single target drug avoidance is the cause of resistance issues, which can be overcome through the use of two-to-target nanosystems, which detect HER2 and other target simultaneously. An example is that gold nanoparticles with trastuzumab and panitumumab, when loaded with 177Lu expelled nuclear radiation dosage of 36119Gy in breast cells that overexpressed both HER2 and EGFR and were much more cytotoxic than unimodal systems [15].

The other peculiar subtype of the breast cancer is the triple-negative breast cancer (TNBC). There are mainly three types of nanoscale targeted drugs which are lipid-based carriers, polymer-based nanocarriers as well as carbon-based nanocarriers. Dual-drug co-loaded liposomes are considered to represent one of the lipid-based carriers. These incorporate 1:10 ratio encapsulating paclitaxel and doxorubicin which reduces cardiac toxicity when used in 4T1 mouse breast cancer model. Also, the integrin 3 liposomes loaded with rapamycin-doxorubicin showed synergistic antitumor activity against triple-negative breast cancer (TNBC), in in vitro and in vivo models. Nanocarriers composed of polymers include bio-inspirational peptide-modified PLGA-PEG micelles. This carrier has the ability to interact with collagen IV-derived peptide AXT050 in order to bind tumor-related integrins which can enhance targeted delivery of peptides to stimulate TNBC cells in mouse simulated models twice. In terms of carbon-based nanocarrier, the most important type of application is multi-walled carbon nanotubes (MWCNTs). When combined with collagen, they recap the extra cellular matrix, virtually inhibiting the contraction, proliferation, and mobility of TNBC cells as well as suppressing the levels of MMP-9 expression [16].

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3.3. Clinical research in prostate cancer

Prostate cancer cells have a high level of prostate-specific membrane antigen (PSMA) on their surface. It has been a perfect choice to treat prostate cancer specific therapy because of its striking tumor specificity. One of the examples in the area is the PSMA-targeted 2-deoxyglucose (2DG)-functionalized dendrimeric (PSMA-2DG-D) nanoplatform. It applies the glucose transporter (GLUT) which is highly expressed in tumor cells as its core carrier, and it uses a 2DG-modified mixed-layer dendrimer as its core carrier to further target the tumor through the mediation of 2DG. At the same time, the surface of this nanocarrier is conjugated with an irreversible PSMA ligand (CTT1298), and it aids PSMA-mediated endocytosis, which promotes drug internalization efficiency in tumor cells to a considerable degree. PSMA-2DG-D nanomedicine features an impressive prostate cancer targeted adhesion in both in vitro and in vivo preclinical investigations. The released drugs on its surfaces are loaded on the effective way which reduces the off-target toxicity by achieving controlled release in the tumor microenvironment. Today, PSMA-targeted radiopharmaceuticals are approved to be used in a clinical environment. 177Lu-PSMA-617 (Pluvicto) in metastatic castration-resistant prostate cancer (mCRPC), a radiopharmaceutical, and 68Ga-labeled Locametz in diagnosing prostate cancer. It is noteworthy that the PSMA-2DG-D nanoplatform is able to deliver the chemotherapy drug cabozantinib to the target site with high accuracy thereby decreasing systemic toxicity of the drug, as well as increasing its water solubility with a concentration of 150 mg/mL. It also enhances tumor selectivity that counters the limitations inherent in the conventional chemotherapy drugs such as particularity, dissolvency and toxicity limit. This advancement holds a new nanoparticle product with a clinical translation potential in the treatment of mCRPC with accuracy [17].

4. Pivotal issues in clinical practice and countermeasures

The current section deals with one of the greatest issues in clinical oncology: tumor drug resistance evaluating the mechanisms and providing related management. There is the issue of drug resistance to targeted drugs.

4.1. The problem of resistance to targeted drugs

Drug resistance occurs when the tumor slowly becomes insensible to proposed therapy. Its fundamental principle lies on the heterogeneity of tumors: subpopulations of cells with specific driver mutations are present within tumors and even a single biopsy might not be in a position to represent the entire molecular phenotype of a tumor.As a result, targeted therapy can only eliminate drug-sensitive tumor clones, while rest subclones with unique molecular profiles proliferate under therapeutic pressure to become dominant populations, then finally become triggering resistance. As a major precursor to resistance, minimal residual disease cells can survive through subclonal evolution and signal pathway reprogramming, then develop resistance capabilities. In addition, some initially sensitive tumor cells undergo transcriptional and epigenetic reprogramming under therapeutic pressure to activate survival signals, such as the BCL-2/BCL-xL mitochondrial pathway, entering a reversible quiescent state. These cells may regain drug sensitivity after treatment cessation but exhibit pronounced resistance during ongoing therapy [18].

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4.2. Adverse reaction management issues

Even though targeted therapies offer new strategies to overcome tumor drug resistance, drug-induced adverse reactions remain a major issue in clinical research. On the one hand, the cumulative toxicity resulting from combination therapy strategies is a significant manifestation of adverse reactions. In the field of nanomedicine, to overcome resistance limitations, clinical studies often implement combination regimens where nanocarriers co-deliver chemotherapy drugs with sensitizers. Commonly used sensitizers include verapamil, curcumin, and tetrahydrobromantidine, while such combination therapies can synergistically enhance antitumor efficacy, they also cause a synergistic improvement in toxic reactions. As an illustration, the emergence of such phenotypes as tumor cell resistance was reversed with co-encapsulating vincristine in PLGA nanoparticles with an addition of the P-glycoprotein inhibitor verapamil. However, neurotoxicity and gastrointestinal discomfort were higher in patients receiving nanoparticle monotherapy than in monotherapy nanoparticle groups. Similarly, folate-functionalized chitosan nanoparticles co-loaded with doxorubicin and the NF- -blocker PDTC enhanced antitumoral effects but caused hepatic and renal toxicity in mice test systems.

Conversely, Specific toxicities inherent in nanocarriers per se also should not be ignored.

Certain nanomaterials have the tendency to cause inflammation or tissue destruction due to their intrinsic stimulatory effect on the body. As an example, quantum dot-modified PLGA nanoparticles allow both imaging and drug delivery to be performed and have caused local inflammatory response in preclinical models because of their heavy-metal constituents. Besides, in spite of accumulation of nanomedicines in tumor tissues through EPR effect or function of active targeting ligands, off-target distribution of carriers is not totally avoidable and may result in the destruction of normal tissues. An example is that folate-modified nanoparticles may specifically target the folate receptors that are significantly high on tumor cell surfaces, whereas it is still possible to have low amounts of such receptors be present on normal tissues (such as bone marrow and kidneys) resulting in non-specific accumulation of drug, thereby causing adverse effects [19,20].

5. Conclusion

Tumor-targeted nanomedicines have a great impact in improving the pharmacokinetics of chemotherapeutic agents by passive targeting, active targeting and trigger-release approaches thereby increasing tumor-specific accumulation and decreasing toxic side effects. Personalized therapy can be provided through the use of imaging technology and nanomedicines. Additionally, nanomedicines targeting tumors undergo through several clinical trials and have proven fruitful clinical research developments in several prevalent tumors including non-small cell lung cancer, breast cancer, and prostate cancer. There are however two challenges in clinical application, the first is in the case of the drug resistance and management of the adverse reactions. The future will see the optimal drug design and combination therapy schemes employed to correct these problems. To sum it up, the targeted nanomedicines of the tumors have reached the maturity process in the mechanism-of-action analysis and clinical transfer which would enable novel therapeutic avenues in the specific treatment of tumors and cancers. Future studies of tumor-targeted nanomedicines should address fundamental toxicity-related challenges and improve the physicochemical characteristics, efficacy of targeted delivery, and discuss low-toxicity combination regimens in an attempt to enhance antitumor therapy. Such bi-focus ensures safety and effectiveness as a means of therapy.

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