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Strategies for Precision Cancer Therapy via Active Delivery Systems: Recent Progress in Protein, Peptide, and Small-Molecule Ligands

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Abstract. Malignant tumors are one of the major diseases threatening human health. Although traditional surgery, radiotherapy, and chemotherapy have improved patient survival to some extent, their efficacy is limited and accompanied by severe side effects. With the development of molecular biology and drug delivery technologies, active targeted delivery systems have gradually become an important direction for improving treatment precision and safety. This paper systematically reviews the research progress and applications of three main types of ligands in active delivery: firstly, protein-based ligands (such as monoclonal antibodies) are represented by T-DM1 and Brentuximab vedotin in antibody-drug conjugates (ADCs), demonstrating the dual advantages of precise targeting and potent killing; secondly, peptide-based ligands (such as iRGD and TAT peptides) show unique value in nanodrug delivery due to their permeability and low immunogenicity; thirdly, small molecule ligands (such as folic acid) achieve efficient and selective delivery by utilizing the differential overexpression of receptors. Finally, this paper summarizes the challenges and future development trends faced by current active delivery systems, including receptor recycling limitations, balancing bystander effects, and improving cell selectivity. In summary, the continuous optimization of active delivery technology will provide broader prospects for personalized tumor therapy.

Keywords: Active delivery, antibody-drug conjugate (ADC), iRGD, TAT peptide, folic acid, precise tumor therapy

1. Introduction

Malignant tumors are one of the major diseases globally threatening human health. Although traditional surgery, radiotherapy, and chemotherapy have improved patient survival to some extent, their efficacy is limited and often accompanied by severe toxic side effects. This predicament has prompted researchers to continuously explore more precise and efficient treatment strategies [1].

Since the mid-20th century, the concept of drug delivery systems (DDS) has gradually emerged. Its core objective is to precisely deliver drugs to diseased sites through appropriate carriers or modification methods, thereby improving efficacy and reducing damage to normal tissues [2]. The development of drug delivery has broadly gone through three stages: early passive delivery relied on

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the body's own pharmacokinetic processes, especially the EPR effect proposed in the 1970s, which allowed people to utilize tumor vascular permeability to promote drug accumulation in tumors, but with limited efficiency and significant individual differences [3]; subsequently, the active delivery stage emerged, achieving significantly improved uptake efficiency by modifying specific ligands on the surface of drugs or nanocarriers to bind to specific receptors on tumor cells or in the tumor microenvironment; in recent years, the introduction of intelligent and responsive delivery strategies has enabled drug delivery to react to tumor microenvironmental stimuli (such as acidic pH, enzymes, redox status), further promoting the development of personalized therapy [4].

Among these strategies, active delivery has become a research hotspot due to its high selectivity and designability, and the choice of ligands is crucial. According to the nature of the ligands, active delivery systems are mainly divided into three categories: protein-based ligands, represented by monoclonal antibodies, are widely used in the research and development and clinical application of antibody-drug conjugates (ADCs) due due to their specificity and mature industrial platform; peptide-based ligands such as iRGD and TAT peptides exhibit unique advantages in nanodrug delivery due to their small molecular weight, low immunogenicity, and strong permeability; small molecule ligands, with folic acid as a typical example, achieve precise delivery by binding to folate receptors overexpressed in various tumors [5]. Overall, the development of drug delivery systems has promoted the shift of tumor treatment from "broad-spectrum killing" to "precise targeting," and the continuous optimization of active delivery also provides new opportunities for future personalized tumor medicine and combination therapies.

2. Protein-based ligands

In active delivery systems, protein-based ligands are currently the most mature and widely used class. Their representative form is monoclonal antibodies, which can recognize cell surface antigens with high specificity, ensuring precise drug delivery to target cells [6]. Antibody ligands not only provide targeting capabilities but may also enhance immune responses through Fc-mediated effects. Therefore, ADCs with antibodies as the core have become an important direction in clinical oncology [6].

2.1. T-DM1

Among many antibody-based ADCs, T-DM1 is the earliest representative drug to successfully enter clinical trials and be approved for use [7]. It uses trastuzumab as a targeting ligand to recognize HER2 receptor-overexpressing tumor cells and precisely delivers the potent microtubule inhibitor DM1 into cancer cells via a linker (SMCC), thereby achieving the dual effects of antibody targeting + cytotoxic payload [8]. The emergence of T-DM1 not only validated the feasibility of protein-based ligands in the ADC field but also laid the foundation for the development of subsequent ADC drugs [7].

T-DM1 consists of three key components: the ligand (trastuzumab), the cytotoxic drug (DM1), and the linker. Trastuzumab is a specialized antibody that specifically recognizes the extracellular domain IV of the HER2 protein. Its Fab region is responsible for "lock-and-key" binding to HER2, highly selectively recognizing HER2-overexpressing cancer cells, while the Fc region can recruit immune effector cells to further kill tumor cells through ADCC [9]. DM1 is a highly effective microtubule inhibitor that blocks microtubule polymerization by binding to tubulin, causing cells to arrest in metaphase of mitosis and ultimately inducing apoptosis [11]. Due to the extremely high toxicity of DM1, its standalone use would severely damage normal cells, thus precise killing must

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rely on antibody delivery [11]. T-DM1 uses an SMCC linker, which is a non-cleavable linker that is highly stable in the blood, preventing premature release of DM1; DM1 metabolites containing lysine are only released when the antibody enters the cell and is degraded by proteases in the lysosome [8]. Its average drug-to-antibody ratio (DAR) is approximately 3.5, meaning each antibody molecule is conjugated to an average of 3-4 DM1 molecules.

In normal tissues, HER2 expression on the cell membrane is very limited, mainly used to maintain normal cell growth and differentiation signaling; however, in HER2-positive tumors, HER2 expression on the surface of cancer cells is significantly elevated, often tens or even hundreds of times higher than in normal cells [9]. This "overexpression" phenomenon not only drives the unlimited proliferation of tumor cells but also provides a highly specific "molecular target" for drug design. T-DM1 cleverly utilizes this differential feature by conjugating the anti-HER2 monoclonal antibody trastuzumab with the highly effective cytotoxic drug DM1 [8]. It possesses both immune and chemical toxicity mechanisms—its antibody component trastuzumab can block HER2-mediated oncogenic signals and trigger ADCC immune killing through the Fc region, while the cytotoxic component DM1, after endocytosis and release, binds to β-tubulin to inhibit spindle formation, leading to cell cycle arrest and apoptosis, thereby achieving highly specific, dual-pathway anti-tumor effects [10,11].

In this process, the Fab region of trastuzumab can highly specifically recognize and bind to the extracellular domain IV of the HER2 protein. This binding mechanism is similar to a "lock-and-key" model, ensuring that the drug primarily targets the cell membrane of HER2-overexpressing tumor cells. After binding, trastuzumab directly blocks the HER2 receptor from receiving and transmitting growth and survival signals into the cell, cutting off the activation of key signaling pathways including PI3K/AKT and MAPK/ERK, thereby inhibiting the unlimited proliferation and invasion capabilities of cells [9]. At the same time, the Fc region of the antibody is recognized by Fc receptors on the surface of immune effector cells (especially natural killer cells, NK cells). Once NK cells recognize the Fc region, they form an immune synapse and directionally release perforin to punch holes in the tumor cell membrane, allowing granzyme B to enter the cell, activating the caspase cascade, directly destroying cancer cell structures, and inducing apoptosis [10].

On the other hand, DM1 is conjugated to trastuzumab via a non-cleavable SMCC linker, remaining inactive during drug delivery. When T-DM1 binds to HER2 and is internalized by cells through receptor-mediated endocytosis, it is degraded in the lysosome, releasing DM1 metabolites. DM1 binds to specific sites on β-tubulin, blocking microtubule polymerization and preventing α/β tubulin dimers from adding to growing microtubules, leading to abnormal spindle formation. Chromosomes cannot be aligned and separated, causing cell cycle arrest in metaphase of mitosis. Prolonged metaphase arrest triggers multiple apoptotic signaling pathways, including the activation of caspase family proteins, thereby inducing programmed cell death [11]. This mechanism ensures that the cytotoxicity of DM1 is only activated within HER2-overexpressing tumor cells, achieving precise killing of cancer cells while minimizing damage to normal tissues.

2.2. BV

Following the success of T-DM1, another typical antibody-drug conjugate, Brentuximab vedotin (BV), further expanded the application of protein-based ligands in tumor therapy. BV uses the anti-CD30 monoclonal antibody CAC10 as a ligand, combined with the potent microtubule inhibitor MMAE, to deliver cytotoxic drugs to specific lymphoma cells via a cleavable linker (VC-linker) [12]. Compared to T-DM1, BV targets different tumor antigens and indications, demonstrating the broad application prospects of antibody-based ligands in various tumor types [12].

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Brentuximab vedotin (BV) is an antibody-drug conjugate (ADC), with CAC10 as its ligand component. CD30 is highly expressed on the surface of tumor cells such as classical Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma (sALCL). However, under normal physiological conditions, CD30 expression is extremely low, only transiently induced on activated T and B cells, at levels far below those in tumor cells [13]. This unique expression pattern makes CD30 an ideal tumor-specific therapeutic target. The basic principle of ADCs is to introduce potent cytotoxic drugs while maintaining antibody targeting, thereby achieving "precision bombing" [6,12]. Brentuximab vedotin is designed based on this idea, and its mechanism of action can be summarized into two key aspects: first, the antibody component CAC10's interference with CD30 signaling and ADCC effect, and second, MMAE's microtubule toxicity.

Normally, CD30, as a member of the tumor necrosis factor receptor superfamily, recruits TRAF proteins upon ligand binding, thereby activating the NF-κB pathway and MAPK/ERK pathway, promoting the expression of downstream anti-apoptotic genes, and enhancing cell proliferation, giving tumor cells a survival advantage [14]. When the antibody component CAC10 of BV binds to CD30, it blocks the interaction between CD30 and its ligands, directly inhibiting NF-κB activation [14]. As NF-κB signaling is blocked, the expression of anti-apoptotic genes decreases, cell viability weakens, and tumor cells become more sensitive to apoptosis. In addition, similar to the antibody component of T-DM1, CAC10, as an IgG1 antibody, also possesses ADCC capability through its Fc region. When BV binds to CD30 on the surface of tumor cells, the Fc region can be recognized by Fc receptors on natural killer (NK) cells. NK cells then release perforin and granzyme B, activating the caspase cascade to directly induce target cell lysis and death, providing additional support for its anti-tumor effect [10].

Under antibody mediation, BV is specifically taken up by CD30-positive cells and enters lysosomes via endocytosis. At this point, the VC-linker is cleaved by cathepsin B, releasing MMAE. This molecule primarily binds to β-tubulin, and the basic structural unit of microtubules is a heterodimer composed of α- and β-tubulin. MMAE's binding site is on β-tubulin, and upon binding, it blocks the further polymerization of α/β dimers, thereby inhibiting microtubule polymerization, leading to the inability to form mitotic spindles, causing cells to arrest in metaphase of mitosis. The metaphase arrest triggers intracellular apoptotic signaling pathways, ultimately leading to programmed cell death [15]. Due to the extremely high toxicity of MMAE, targeted release via the ADC system allows for maximum tumor cell killing while avoiding systemic toxicity [12,15].

3. Peptide-based ligands

In active delivery systems, there are two other noteworthy types of ligands, one of which is peptides. Peptides, due to their small molecular weight, low immunogenicity, and ease of chemical modification, have become flexible and tunable molecular tools [16]. Through design and modification, peptide ligands can recognize specific receptors on the surface of cells or tissues, thereby enhancing drug cellular uptake efficiency and reducing non-targeted side effects [17]. In this context, two representative peptide ligands have received widespread attention: iRGD and TAT peptide.

3.1. iRGD

iRGD is a tumor-penetrating peptide that can recognize integrin receptors overexpressed in tumor vasculature and promote drug penetration into tumor tissue [18]. The iRGD sequence contains the classic RGD motif, which binds with high affinity to αvβ3/αvβ5 integrins overexpressed on tumor

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vascular endothelium and some tumor cell surfaces [19]. This binding allows iRGD to preferentially accumulate in the tumor microenvironment in blood circulation, preparing for subsequent penetration steps. In addition to the RGD motif, the iRGD sequence also contains a cryptic CendR motif, which is not exposed in blood circulation, avoiding non-specific binding and side effects. When iRGD targets the tumor microenvironment, local proteases recognize specific sites and cleave the peptide chain, exposing the CendR motif at the C-terminus [20]. This cryptic-exposure design ensures that penetrating activity is only activated at the tumor site, achieving high selectivity. The exposed CendR motif specifically binds to neuropilin-1 (NRP1) receptors on tumor vasculature and tumor cell surfaces [18,20]. Upon binding, a penetration pathway is activated, allowing peptides and drugs to be actively transported across the vascular wall into the tumor interstitium. This penetration mechanism far exceeds the drug permeability of traditional passive EPR effect-dependent methods, enabling drugs to rapidly enter deep tumor regions, cover the central area of the tumor, and improve overall drug efficacy [21].

In addition to mechanistic studies, iRGD has also been successfully applied in specific drug delivery systems. For example, Zhang et al. designed iRGD-modified lipid-polymer hybrid nanoparticles co-loaded with paclitaxel (PTX) and tetrandrine (TET) [22]. In this system, TET is directly encapsulated within the nanoparticles and is preferentially released after entering tumor cells to inhibit the P-glycoprotein (P-gp) efflux pump, thereby overcoming multidrug resistance; PTX, on the other hand, is linked to the polymer backbone via a reducible disulfide bond, cleaving and releasing inside tumor cells to exert microtubule inhibitory effects and induce apoptosis [22]. The iRGD modification not only allows nanoparticles to preferentially accumulate in tumor tissue in blood circulation but also promotes particle crossing of the vascular barrier and deep penetration into the tumor core by exposing the CendR motif and binding to NRP-1 [23]. Experimental results showed that this system significantly increased tumor uptake and therapeutic efficacy of drugs in drug-resistant ovarian cancer cells and mouse tumor models, while reducing side effects on normal tissues [23].

3.2. TAT peptide

TAT peptide is a short-chain cell-penetrating peptide (CPP) [24]. Since its discovery in the late 1980s, TAT peptide has attracted widespread attention due to its unique ability to cross cell membranes and deliver various molecular cargoes into cells [25]. Typically, TAT peptide consists of 11 amino acids (sequence YGRKKRRQRRR) and carries a positive charge. These positive charges enable TAT peptide to interact strongly with negatively charged cell membranes, thereby achieving drug delivery [26]. TAT peptide enters cells mainly in two ways: direct translocation and endocytosis [27].

3.3. Direct translocation

When TAT peptide approaches a negatively charged cell membrane, the positive charges of the peptide interact with the negative charges of the membrane, while hydrophobic residues insert into the membrane lipid bilayer, disrupting lipid arrangement and forming transient pores. TAT peptide can then directly pass through the membrane into the cytoplasm [28]. This process does not depend on receptors on the cell membrane, nor does it require active cellular participation, and the membrane can rapidly self-repair after pore formation [29].

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3.4. Endocytosis

When TAT peptide approaches a negatively charged cell membrane, it first interacts with the negative charges on the membrane surface through electrostatic attraction, thus approaching the membrane surface. Subsequently, TAT peptide binds to GAGs on the membrane. This binding not only stabilizes the peptide's localization on the membrane surface but also causes a large accumulation of positive charges in the local area, forming what is called positive charge accumulation [30]. This local concentration of positive charges disrupts the arrangement of the lipid bilayer, changing the physical state of the membrane. Small G proteins within the membrane can sense these local membrane structural changes and activate downstream signaling pathways. Under the action of these signals, the cell membrane undergoes local invagination, forming vesicles (endosomes), which internalize TAT peptide and its carried molecules together into the cell [27,30]. In this process, the local curvature of the membrane also changes.

In specific active delivery research, TAT peptide has been successfully applied in various drug delivery systems [31]. Torchilin et al. conjugated TAT to the surface of liposomes and encapsulated doxorubicin (DOX) within them, constructing TAT-modified doxorubicin liposomes (TAT-DOX-Liposomes) [32]. Doxorubicin in blood circulation is often rapidly degraded or cleared, reducing therapeutic efficacy, while liposomal encapsulation can effectively protect the drug, improving its stability and in vivo half-life [32]. Furthermore, the introduction of TAT significantly enhanced the binding and endocytosis of liposomes with cell membranes, allowing doxorubicin to enter tumor cell nuclei more efficiently [33]. Doxorubicin induces cell apoptosis by intercalating into the DNA double helix and inhibiting topoisomerase II activity, leading to DNA breaks and replication arrest [34]. Compared to unmodified control groups, TAT-DOX-Liposomes showed higher cellular uptake efficiency and killing activity in vitro; in animal models, they also demonstrated stronger anti-tumor effects and lower toxic side effects [32,33]. This study clearly demonstrated the advantages of TAT peptide in active delivery: not only actively transporting drugs to the site of action through cell-penetrating properties but also effectively protecting drugs in combination with liposomal carriers, thereby significantly improving therapeutic efficacy [31].

4. Small molecule ligands

In active delivery, another relatively important type of ligand is small biological molecules. Among many small molecule ligands, folic acid (Folic acid) has almost dominated this field due to its advantage of highly expressed folate receptors (FR) in various cancer cells, thus demonstrating excellent targeting capabilities [35].

Folic acid is a water-soluble vitamin involved in DNA synthesis and cell metabolism in the body [36]. Many cancer cells overexpress folate receptors (FR) on their surface, while normal cells have low expression of folate receptors [37]. This difference makes folic acid a natural targeting ligand that can selectively deliver drugs to cells with high FR expression. GPI-FR is the main folate receptor, enriched in lipid raft microdomains of the cell membrane [38]. Folic acid, as a ligand, first binds to GPI-FR with structural specificity [39]. GPI-FR is enriched in lipid raft microdomains. When folic acid binds to the receptor, these receptor-ligand complexes aggregate within the lipid rafts, providing space and structural basis for the formation of endocytic vesicles [38]. During vesicle formation, actin, as a cytoskeleton, supports membrane invagination, while myosin pushes the vesicles along actin fibers into the cytoplasm [40]. Unlike classical receptor-mediated endocytosis (dependent on clathrin and dynamin), which forms vesicles via Clathrin and Dynamin, GPI-FR endocytosis relies entirely on actin and myosin dynamics, thus belonging to non-classical

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receptor-mediated endocytosis [41]. The formed endocytic vesicles then fuse into early endosomes. Early endosomes act as sorting centers, determining the fate of folic acid-drug complexes. Most GPI-FRs are recycled back to the membrane surface for the next round of folate capture, while folic acid-conjugated drugs or carriers are further transported to late endosomes, and then to lysosomes for release [42]. Most GPI-FRs also return to the membrane surface. This entire mechanism makes the folic acid-GPI-FR system a highly efficient, reusable, and specific targeting strategy in the active delivery of nanodrugs and small molecule drugs [39,42].

In specific active delivery research, folic acid (FA) has also been successfully applied in various drug delivery systems [43]. Researchers conjugated folic acid to the surface of liposomes and encapsulated paclitaxel (PTX) within them, constructing folic acid-modified paclitaxel liposomes (FA-PTX-Liposomes) [44]. Paclitaxel, a clinically common anti-tumor drug, often requires organic solvents for dissolution in vivo due to its strong hydrophobicity, which often leads to significant toxic side effects [45]. Liposomal encapsulation can significantly improve its water solubility and stability, extending the drug's in vivo circulation time [43,44]. Furthermore, the introduction of folic acid enables liposomes to achieve receptor-mediated endocytosis by specifically binding to highly expressed folate receptors (FR) on cancer cell membranes, thereby improving the efficiency of active targeted drug delivery to tumor cells [44]. After entering the cell, FA-PTX liposomes first bind to FR and enter early endosomes, then are transported to late endosomes and lysosomes, gradually releasing paclitaxel [44,46]. The released PTX binds to microtubules, stabilizing their polymerized state and preventing normal depolymerization of the spindle, leading to cell cycle arrest in the G2/M phase. Cells are unable to complete division, ultimately triggering apoptotic signaling pathways [47]. Compared to unmodified control groups, FA-PTX-Liposomes showed higher uptake efficiency and stronger cytotoxicity in in vitro experiments; in animal models, they also demonstrated significantly enhanced anti-tumor effects and reduced systemic toxic side effects [44,46].

5. Conclusion

Despite significant progress in basic research and clinical applications of active delivery strategies represented by T-DM1, BV, and cell-penetrating peptides in recent years, some urgent challenges remain. Future development trends are mainly reflected in the following aspects:

Firstly, in receptor-mediated drug conjugates, the efficacy of T-DM1 is limited by receptor recycling pathways, leading to insufficient intracellular drug release. Future improvements could involve combining Hsp90 inhibitors, regulating endocytosis-recycling balance, or designing novel linkers and carriers to enhance drug delivery efficiency to lysosomes, thereby strengthening killing effects. Secondly, for BV and other ADCs with bystander effects, how to balance efficacy and safety will be a key issue. Future research should focus more on optimizing linkers and cytotoxic drugs to control the distribution range of toxicity, and through precise patient stratification and individualized dosing strategies, reduce non-specific toxic side effects and drug-drug interaction risks. Thirdly, for cell-penetrating peptides (such as TAT), their main limitation lies in the lack of cell selectivity, which can lead to non-specific uptake. Future improvements will involve introducing tumor microenvironment-responsive elements or combining them with specific ligands (such as antibodies, folic acid, etc.) to achieve multiple recognition, thereby balancing efficient penetration with precise targeting. In summary, the future development of active delivery systems needs to seek the optimal balance between efficacy and safety. Through the continuous integration of molecular engineering, intelligent responsive materials, and combination therapy strategies, it is expected to build more

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precise, efficient, and clinically feasible drug delivery platforms, providing new breakthroughs for the treatment of major diseases such as cancer.

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