A Review of Research Progress on Lipid Carriers for Tumor-Specific Targeted Drugs

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ABSTRACT

Malignant tumors represent a major global public health issue. Traditional cancer treatments lack selectivity between cancer cells and normal cells, leading to severe cytotoxicity and the development of drug resistance in cancer cells. To address these challenges, scientists have successfully designed a series of liposome modification strategies based on various tumor-specific targets and the unique advantage of lipid nanocarriers, which allow for easy multifunctional surface modification. This paper aims to systematically summarize modification strategies for lipid nanocarriers in the field of tumor-specific targeted drug delivery. Based on the literature, these strategies are categorized into three main approaches: ligand-mediated active targeting, stimulus-responsive carriers, and synergistic strategies. The results indicate that antibody- or peptide-modified liposomes significantly enhance tumor cell recognition and uptake; pH-sensitive and reduction-sensitive liposomes can utilize the tumor microenvironment (TME) to trigger spatiotemporally controlled release; and synergistic strategies, such as combining active targeting with stimulus-responsive or multi-ligand modification, can effectively overcome tumor heterogeneity and physiological barriers. The aim is to provide researchers with a structured framework for selecting and combining strategies, and to propose future directions (non-Enhanced Permeability and Retention effect (EPR) -dependent targeting, more realistic animal models, scalable production, etc.)

Keywords: Tumor-Specific Targeting, Lipid Carriers, Active Targeting, Stimuli-Responsive Liposomes, Synergistic Strategies.

1. INTRODUCTION

Malignant tumors remain a major threat to human health worldwide. According to the latest data released by the International Agency for Research on Cancer (IARC) of the World Health Organization, the global cancer burden is estimated to have risen to 19.3 million new cases [1]. Because traditional chemotherapy and radiation therapy lack cell selectivity, they can lead to severe toxic side effects and multidrug resistance; therefore, tumor-specific targeted therapy has become the focus of current cancer treatment research. Due to their excellent biocompatibility, biodegradability, ease of multifunctional modification, and ability to co-load both hydrophilic and hydrophobic drugs, lipid carriers have become a focal point of research in this field [2]. Therefore, a systematic review of design strategies for tumor-specific targeting using lipid carriers is of great significance.

The basic principles of tumor-specific targeting strategy with lipid collectors can be summarized into three categories. First of all, the targeting of active ligands includes attaching antibodies (such as anti-HER2[3]), various kinds (such as arginine-glycine-Aspartic (RGD) [4]), aptamers [5] or glycine molecules [6] to lipid carriers to identify special receptors that are highly present in tumor cells. Secondly, the stimulus-reactive lipid carrier uses tumor environment (such as acidic pH [7] and high concentration of glutathione [8]) to target, control the time and control the drug release [9]. Thirdly, collaborative strategies mix active targeting with stimulus-response mechanism, or use multiple ligands to overcome tumor heterogeneity and several physiological obstacles [10] [11]. At present, most published comments only talk about one strategy, or just list them without systematic comparison. It lacks a comprehensive framework to classify these three strategies, compare their mechanisms, advantages and limitations, and explain how they work together.

In order to fill this gap, this review would like to talk about the following points: (1) design principles and three important examples of oil transformation strategies; (2) Advantages and limitations of these three strategies; (3) How to use these strategies together for better carrier design.

This article is an unsystematic comment. We searched the Web of Science, PubMed and CNKI databases for articles on occupational fat, active targeting, stimulating response and collaborative strategies published between 2015 and 2026.

Section 2 (literary criticism) discusses the latest development of three editing strategies, as well as their advantages and limitations. Section 3 (Conclusion) summarizes the main findings of this review, explains the significance of research and practice, and provides insights for future research.

2. LITERATURE REVIEW

In this section, we look at three strategies to modify the blood lipid carriers used in tumor targeted therapy, as seen in recent articles. These strategies are: ligand-mediated activity targeting, stimulus-reactive lipid carriers, and synergistic targeting strategies. We summarized the main design principles, unique advantages and limitations of these three strategies.

2.1 Ligand-mediated active-targeting lipid carriers

The active targeting strategy of ligands aims at enabling lipid transporters to recognize special tumor cells. Its principle is to attach or place ligands (such as antibodies or dopamine) on the surface of lipid transporters. Therefore, they can identify a large number of receptors in tumor cells. It causes cells to swallow transporters through endocytosis and increases the amounts of drugs in cells. Therefore, the drug effect is better [12].

Today, ligands commonly used in these active targeting strategies, such as antibodies (such as anti-human epidermal growth factor receptor 2(HER2))., peptides (e.g., RGD), aptamers (e.g., AS1411), and glycans (e.g., hyaluronic acid), each with distinct characteristics: antibodies have high affinity but are highly immunogenic[13], while peptides are low-cost but have relatively weak affinity[14]; aptamers are chemically stable with minimal batch-to-batch variability, but their screening and optimization are complex[15]; carbohydrates exhibit excellent biocompatibility, but their binding strength is often insufficient[16].

A typical example is a representative study by Ahad et al. (2024), in which they conjugated trastuzumab with gold-containing compounds to prepare anti-HER2 immunoliposomes. In HER2-positive breast cancer cell lines (SK-BR-3, BT-474) and xenograft mouse models, these immunoliposomes demonstrated significantly higher tumor accumulation (an average increase of 3- to 5-fold compared to non-targeted liposomes) and reduced cardiotoxicity (as evidenced by lower cardiac troponin levels and preserved left ventricular function) [3]. Another classic example involves peptides; as summarized by Sheikh et al., RGD-modified liposomes can preferentially anchor to tumor blood vessels and deliver cytotoxic drugs directly to cancer cells that overexpress integrins [4]. Furthermore, the small molecular weight and low immunogenicity of peptides give them practical advantages over antibodies. The author also likens it to a multistage rocket: ligand-anchored liposomes are selectively recognized by target cells, accumulate at specific sites, and release the drug in a controlled and optimal manner.

A large body of literature on active targeting demonstrates that active targeting modification strategies can effectively enhance cellular uptake and tumor accumulation while reducing off-target toxicity [17]. A variety of ligands are available, and they can be flexibly selected based on their respective advantages and disadvantages to meet specific drug delivery requirements [18]. In addition, the density and orientation of the ligands on the surface of the carrier are critical to targeting efficiency. If the ligand density is too low, it will result in insufficient binding affinity and reduced activity; Excessively high density may cause steric hindrance or increase clearance efficiency [19].

However, ligand-mediated strategies for the active targeting of lipid carriers still have their limitations. (1) The timing of drug release cannot be controlled, which may result in premature leakage or slow release following endocytosis. This strategy fails to address the issues of controlled drug release and the instability of lipid carriers; the drug may be released too slowly after endocytosis to reach therapeutic concentrations, or it may leak prematurely into the systemic circulation, leading to off-target effects and systemic toxicity [7] [8]. (2) Tumor heterogeneity prevents a single ligand from targeting all cancer cells. Not all cancer cells within a solid tumor express the same receptor at the same level. As a result, monoligand-targeted drugs may select for receptor-negative subclones, which cannot be treated and lead to tumor recurrence [25] [26]. (3) Complex to produce, costly, and likely to trigger an immune response [13]. And most active targeting studies have been conducted in immunodeficient mouse models, using rapidly growing subcutaneous xenografts in the experimental procedures [17]. These models cannot fully replicate the complexity of the human tumor microenvironment, and the enhanced tumor accumulation observed in mouse models often does not translate equally to treatment outcomes in patients.

In summary, through repeated trials by researchers, active targeting modification strategies for lipid carriers have been clearly demonstrated to improve the recognition and uptake of tumor cells. However, as a standalone modification strategy, it still has many limitations (difficulty in achieving controlled release, tumor heterogeneity, manufacturing complexity, and poor translational relevance of related experiments). This tells us that the positive targeted strategy should be combined with other revised strategies to make up for its limitations and be used as a part of a multifunctional drug collector to better deliver drugs for use.

2.2 Stimulus-responsive lipid carriers

The design of stimulus-reactive lipid carriers involves the use of endogenous signals (microenvironment-specific differences between tumor cells and normal cells) to trigger the disintegration of the carrier structure at a specific time and place, thus allowing planned, targeted and controlled drug release. Its basic principle is to design the carrier to keep it stable in the circulation process, and trigger a specific signal only when it reaches the tumor site or enters the tumor cells, thus allowing the drug to be released quickly [7] [8].

In endogenous reaction systems, pH-sensitive liposomes are the most commonly used liposomes in designing modification strategies. PH-sensitive liposomes are designed to utilize the pH gradient between tumor microenvironment and acidic endosomes/lysosomes. PH-sensitive lipids (such as 1,2-diol-Sn-glycero-3-phosphothanolamine (Dope) and cholesterol-hemisuccinate (CHEMS)) were added to the lipid bilayer; When the pH value becomes too low, CHEMS becomes positively charged and no longer combines with DOPE. The destruction of lipid bilayer structure allows drugs to be released from the carrier quickly, ensuring accurate transport in cytoplasm and avoiding lysosomal degradation. A typical example is that pH-induced liposome cis-form preparation is used to treat lung cancer Demirbolat et al. (2025). Their experiments on A549 cells and subcutaneous mouse models showed that pH-sensitive liposomes selectively released cis-form in acidic tumor microenvironment. Compared with non-sensitive liposomes, the intracellular cis-form protein level was higher and the survival rate was higher [7].

Another type of endogenous reaction system is redox-sensitive liposomes. The design principle uses the concentration gradient of reduced glutamic acid (GSH) between the inside and outside of cells to release drugs in a very selective way. The classic strategy is to place disulfide bonds in the lipid structure. This keeps the molecules stable in the oxidative environment of blood, but decreases rapidly in the high GSH environment of cytoplasm. Disulfide disulfide bond breaks, the carrier structure is destroyed, and the drug is released quickly [20]. Mirhadi et al. (2022) designed liposomes containing adriamycin combined with lipids disulfide. In vitro experiments show that these redox-sensitive liposomes remain stable in simulated blood buffer with low GSH concentration, and there is almost no drug leakage, while they release drugs quickly in simulated cytoplasm buffer with high GSH concentration. In the mouse model with drug-resistant breast cancer, they improved the anti-tumor efficacy, performed better than insensitive liposomes, and also reduced the cardiotoxicity [8].

Other strategies include enzyme reaction methods [21] and [22] and reactive species reaction methods [23].

The literature of lipid carriers responding to stimuli clearly shows that these systems can solve the problem of controlled release in lipid carriers and show many benefits in cancer treatment. Firstly, pH-sensitive lipid systems are easy to prepare, and many studies have shown that this modification strategy can effectively reduce the non-target effects of drugs. Secondly, redox-sensitive liposomes allow highly selective intracellular release; Because multidrug-resistant cells usually have high GSH concentration, these liposomes may overcome multidrug resistance.

However, the strategy of changing the lipid carrier sensitive to stimulation still has its limitations. (1) A single trigger signal cannot explain the heterogeneity within the tumor (in some areas, the pH value is not low enough or the GSH level is not high enough). Tumor microenvironment is heterogeneous. In a single solid tumor, there are demethylation and hypoxia regions, regions with different pH levels, and differences in enzyme expression and GSH concentration. One-shot systems may not be able to deliver drugs to specific tumor areas with low stimulation. For example, in tumor areas with good infusion and pH close to normal cells, pH-sensitive liposomes may not release drugs effectively. On the contrary, in the hypoxia region with low GSH concentration, redox-sensitive liposomes may not be triggered, so drugs cannot be released effectively [24]. (2) Limited sensitivity; There is still background leakage under physiological conditions. There is little difference in pH between tumor cells and normal cells. Many pH-sensitive liposomes continue to leak some drugs at pH 7.4 within 24 hours, resulting in systemic toxicity. Similarly, even if the gradient of GSH is large enough, it may be small in some tumors or after chemotherapy [25]. (3) The reproducibility from one batch to another is poor, the long-term stability is poor, and it is difficult to mass produce. Because this liposome is difficult to manufacture, its poor repeatability from one batch to another and poor stability during long-term storage are obvious problems. Disulfide bonds in liposomes sensitive to pH and redox will degrade over time, resulting in their loss of reaction ability and inability to release drugs as

needed. In order to preserve them for a long time, it is usually necessary to freeze-dry them, but freezing and thawing them will destroy lipid droplets and change the way they release drugs [26].

In a word, lipid transporters that respond to stimuli successfully solve the problem of controlled drug release, and show that they can help overcome drug resistance in tumors in preclinical models. But they only rely on a trigger, their sensitivity is average, they are difficult to adapt to the heterogeneity of tumors, and they are difficult to manufacture, which limits their clinical use.

2.3 Synergistic Targeted Lipid Carriers

The modification of single function (only active targeting or only stimulating reaction) is not enough to deal with the complex tumor microenvironment and many cell barriers encountered in drug delivery. Therefore, the researchers put forward a new editing strategy, which combines positive goals and stimulus response modification. After a lot of experiments, they successfully created a coordinated targeting strategy, which put two or more functions in a single lipid carrier. The principle is that the physiological stages of drug delivery in cascade-circulation, extravasation, tumor penetration, cell funnel, escape from endosome and intracellular drug release-need special carrier characteristics to obtain good drug delivery: prolonged circulation time, passive accumulation, active recognition, efficient internalization, endosome lysis and triggered release [2]. No single change can meet all these needs. Therefore, lipid carriers that meet the drug delivery requirements are combined to obtain the best drug delivery.

At present, delivery strategies can be divided into two categories: (1) active targeting and the mixture of stimulus-response mechanisms; And (2) polyligand modification (bivalent or polyvalent). In addition, it is also a good way to improve the physical and chemical properties (particle size, charge and hydrophilicity/hydrophobicity) of the carrier, so as to better make passive accumulation and infiltration into tumors.

The reform strategy of combining active targeting with stimulating response is now one of the best ways to make the drug delivery system. The principle is that active targeting ligands are used to recognize and introduce receptors on the tumor surface, and then drugs are quickly discharged from the carrier through the stimulus-response mechanism in the tumor microenvironment. The design of this multifunctional lipid carrier is also helpful to solve the problems of special recognition of tumor cells and drug release control [3] [17].

A typical example is pH-sensitive liposomes modified with RGD. In this design, the circulating RGD polymorphism is attached to the surface of pH-sensitive liposomes (containing DOPE and CHEMS). RGD ligand can recognize and attach to integrin αvβ3 (produced in large quantities in many solid tumor cells and endothelial cells of new blood vessels). After endocytosis with the receptor, liposomes are transported to the endocytosis, and the acidic environment makes the carriers unstable, and they quickly release drugs into the cytoplasm. In the research of Wang et al. (2020), compared with RGD-modified non-sensitive liposomes or non-targeted pH-sensitive liposomes, RGD-modified pH-sensitive liposomes containing adriamycin showed stronger cytotoxicity and longer drug retention time in integrin glioma cells [11].

Another example of a modified strategy that combines active targeting and reduced sensitive release is the reduced sensitivity of liposomes to transfer proteins. This liposome can target the transfer protein receptor, and the transfer protein is produced in a large number of cancer cells. The disulfide bond in its lipid structure was cut off by the high concentration of GSH in tumor cells, which led to the instability and rupture of the carrier, and then the drug was quickly released into the cytoplasm [7] [17].

Multivariate (bivalent or multivalent) editing strategy is to help lipid carriers better deal with tumor heterogeneity. Carriers with a single ligand can grow cancer cells without the receptor, because all cells in the tumor do not have the same receptor at the same level. By placing two or more ligands on the surface of the same liposome, researchers have increased the number of receptors that the carrier can target, thus targeting cell groups with different receptors. A typical example of this multi-band strategy is the co-modification of dual-target liposomes with anti-HER2 antibodies and transfer proteins. The liposome was tested on HER2 positive breast cancer cells, which may also have transfer protein receptors. Compared with the carrier with a single ligand, bivalent drugs show higher absorption rate in cells with variable receptors [12] [27].

The study of cooperation strategy shows that this change strategy has great benefits. First of all, the combination of active localization and stimulus response method produces better anti-tumor effect than any single strategy. By combining the advantages of these two modified strategies, we created a drug delivery process of “recognition, internalization and release”, and we successfully achieved good drug delivery in several animal models. Secondly, multi-ligand modification expands the number of receptors that lipid collectors can target, and can help to overcome the problem of tumor

heterogeneity, especially when ligands target different types of receptors (for example, one targets tumor cells and the other targets tumor endothelial cells).

However, there are still limitations in modifying the cooperative targeting strategy of lipid collectors. (1) The manufacture of multifunctional quarrying machine is complicated, and it is difficult to control the density and orientation of ligands well. When two different ligands are placed on the same liposome surface, it is necessary to control their molar ratio and surface orientation well and avoid cross-reaction. Too large ligand surface density may lead to stereoscopic hindrances, less binding affinity, and more clearance rates. In addition, the optimal density of each ligand can be different, which makes it difficult to distribute evenly over the whole surface. In addition, when the formula has multiple matching steps, the repeatability from one batch to another becomes difficult, and the requirements for regulatory approval are stricter, which greatly increases the production time and cost. (2) Different functional components can interfere with each other (for example, membrane permeation of various substances can increase non-specific capture). For example, aiming at improving the trapping of cells can increase the trapping in normal tissues, if they are not well covered. If the composition of pH-sensitive lipids helps to release the imbalance of contents, they may also lead to premature leakage to physiological pH. (3) Synergistic strategy still depends on EPR effect, which is quite different in human tumors. Most of the cooperative studies are carried out by xenotransplantation subcutaneous tumor models of immunodeficient mice, which cannot well represent human cancer. Human tumors usually show lower permeability (lower EPR effect), more fibrosis and higher interstitial pressure, all of which prevent the penetration of nanoparticles. The promising results observed in mice may not be completely transformed in clinical trials.

3. CONCLUSION

This review systematically summarizes three main lipid carrier editing strategies for the delivery of tumor-targeted drugs: ligand-mediated active targeting, stimulus-reactive lipid carriers and collaborative targeting strategies. After reading, analyzing and thinking a lot about the article, we put forward the following views.

3.1 Key Findings

The literature provides a large number of correct and wrong three main revision strategies of experimental evidence (active positioning, stimulus response and collaborative strategy). Active localization is a good way to identify and capture cells, but it can't control the release, and it is easily disturbed by differences. Stimulus response allows drugs to be released at the right time, but it usually uses only one signal, which may not be enough in a complex tumor microenvironment. Combinatorial strategy puts multiple functions together, which is more effective in preclinical research, but they are more complicated and difficult to manufacture, and depend on the EPR effect under discussion.

3.2 Common issues

At the same time, there are several common limitations in the three modification strategies. First of all, there is a lack of systematic head-to-head comparison. Most studies evaluate a single carrier in a single model, so it is impossible to compare the relative effectiveness of different strategies under the same conditions. Secondly, subcutaneous xenotransplantation model is often used in immunocompromised mice. These models cannot reproduce the variability found in human tumor biology, especially in immune microenvironment, matrix composition and EPR effect. Thirdly, the lack of a well-designed unified integration framework leads to the ligand design completely relying on trial and error, which complicates the carrier design and slows down the development process.

3.3 Future Research Directions

Based on the discussion on the common limitations of the three carrier modification strategies in this review, we creatively put forward the following potential future research directions:

Targeted strategy, independent of EPR. Because EPR effect is unreliable in human beings, we need a strategy that does not rely on passive accumulation. This includes, for example, active endocytosis (e.g., using ligands that bind to receptors that mediate cell transport), magnetic targeting (where an external magnet guides the carrier), or ultrasonic delivery. In addition, the wearer can design patient stratification for blood biomarker guidance, rather than directly targeting the wearer.

Improved preclinical model: standardized use of orthotopic xenotransplantation model and patient-derived model, as well as transgenic mouse model that more accurately reproduces human tumor biology. A complete immune function model was included to evaluate the influence of immunotoxicity and immune system on the performance of the vector.

Simplified and scalable production. We develop a modular synthesis method that allows the exchange of ligands or reactive groups as "plug and play" without re-optimizing the whole formula. We use microfluidic mixing platform to produce lipid nanoparticles stably and expansively. The conveyor designed by us can be freeze-dried without losing its function to improve the shelf life.

Designed for clinical use. We must consider regulatory considerations, such as compliance with good manufacturing practices (GMP), quality control parameters and safety pharmacology, from the beginning of the design process to ensure that each step meets regulatory requirements, so as to obtain the most feasible clinical design.

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