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Ionizable Lipid Nanoparticles for Targeted Delivery of siRNA

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Abstract. Ionizable lipid nanoparticles (LNP)-mediated siRNA delivery provides a promising technological platform for cancer gene therapy. Traditional cancer treatment methods primarily focus on directly killing tumor cells, but RNA interference-based siRNA therapy can regulate the expression of genes related to disease, representing a therapeutic strategy shifting from "killing tumors" to "regulating genes." LNP, as one of the most mature non-viral nucleic acid delivery systems currently available, relies on its adjustable lipid composition, good biosafety and pH-responsive charge-conversion capability, and is able to protect siRNA from acid-enzyme degradation, promote cellular uptake, and achieve endosomal escape. Therefore, it overcomes key delivery barriers, such as the poor in vivo stability and low cellular uptake efficiency of naked siRNA. The successful approval of Onpattro fully verified the possibility of clinical translation of the LNP-siRNA delivery platform. However, the current LNP system still has issues, such as insufficient tumor targeting, accumulation in non-target tissues, and difficulty in precisely regulating them in vivo behavior. To overcome the above bottlenecks, researchers have been continuously improving the active tumour-targeting ability and delivery precision of LNPs through methods such as surface functionalization and modification of lipid composition. First, the composition and structure of ionizable LNPs and their targeted delivery mechanism are introduced in this review. then, various targeted modification strategies for tumor siRNA delivery are systematically listed, including peptides, antibodies, amino acids, and receptor-ligand systems, and finally, the current challenges and future directions are summarized.

Keywords: Ionizable lipid nanoparticles, siRNA, Targeted delivery, Peptide-targeted modification, Antibody-targeted modification

1. Introduction

Cancer is one of the most pressing issues of public health in the world. According to GLOBOCAN 2024 estimates, there are approximately 20.6 million new cancer cases and 9.8 million cancer deaths [1]. The new cancer cases in the world are expected to grow by 67 percent in the next 50 years to about 34.4 million [1]. This trend has increased expectations for more effective, durable and precise therapeutic strategies. Traditional measures of treatment, such as surgery, chemotherapy, radiotherapy, hormone therapy, and targeted therapy have enhanced patient survival, but also have numerous limitations, including poor performance in late disease, recurrence of the tumor, development of drug resistance, toxic effects of the treatment, and significant interpatient

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differences in treatment response [2]. These are mostly due to the heterogeneity and complexity of tumors.

Conventional cancer therapies mainly aim to eliminate tumor cells, rather than precisely regulating the molecular mechanisms underlying cancer initiation and progression. However, cancer is fundamentally a genetic disease driven by unregulated gene expression and abnormal signaling pathways. Therefore, more studies are focusing on nucleic acid drugs capable of directly regulating the expression of disease-related genes [3]. This represents an evolution in therapeutic strategy from killing tumors to regulating genes. Small interfering RNA (siRNA) is one of them that facilitates sequence-specific degradation of target mRNA via the RNA interference (RNAi) pathway. After entering cells, siRNA is incorporated into the RNA-induced silencing complex (RISC), in which the guide strand recognizes complementary target mRNA sequences and induces mRNA degradation, thus selectively silencing disease-related genes [3]. Owing to its high specificity and programmability, many preclinical studies of siRNA have demonstrated its huge therapeutic potential in suppressing tumor growth, angiogenesis, metastasis, and drug resistance [4]. However, the current deficiencies in the clinical application of siRNA for cancer treatment include poor biological stability, rapid degradation, low cellular uptake and insufficient tumour-specific accumulation [4]. The above barriers prevent naked siRNA from reaching the tumour cells and thus inhibiting their growth [4-6]. Therefore, the design of a safe, effective and tumour-targeted delivery system for the successful clinical application of siRNA therapy has been needed.

Among all non-viral nucleic acid delivery systems, ionizable lipid nanoparticles (LNPs) are now the most typical siRNA delivery systems. Ionizable LNPs are better than other non-viral gene delivery systems for delivering siRNA because they have high nucleic acid encapsulation efficiency, good biosafety and biodegradability, and can protect siRNA from nuclease degradation and overcome multiple biological barriers such as low cellular uptake and poor intracellular trafficking [4]. Ionizable LNPs are highly engineerable, and by modifying their composition and surface, their functions can be altered to achieve active targeting of diseased tissues or specific cells, increase the accumulation of siRNA at the lesion site, enhance tumour cell uptake, and reduce off-target effects and systemic toxicity [4].

Onpattro (patisiran) was the first approved LNP-siRNA drug that employs ionizable LNPs, and its successful delivery has fully validated the clinical applicability of LNP delivery platforms and advanced the development of siRNA delivery technology [4]. In short, ionisable LNP-mediated targeted siRNA delivery has shown excellent results in targeted cancer therapy.

Onpattro has shown in clinical trials that ionisable LNPs are suitable for nucleic acid delivery, and many studies have been carried out to optimise LNP design and tumour-targeting strategies. First, this paper will introduce the structure and targeted delivery mode of ionisable LNPs to provide a foundation for the following modification strategies. Then it will introduce the anti-tumour effects of peptides, antibodies, amino acids and receptor-ligand modifications in ionisable LNP-mediated siRNA delivery. Finally, the current problems and future directions of ionizable LNP-based siRNA therapeutics for cancer treatment are introduced.

2. Composition and structure of ionizable nanoparticles

The clinical applications of nucleic acid drugs are limited by insufficient delivery efficiency. The challenges not only come from instability of nucleic acid molecules but also include multiple biological barriers, such as systemic transport, cellular uptake, and intracellular release. Different from small-molecule drugs, nucleic acid molecules such as siRNA have large molecular size and hydrophilicity, making them difficult to pass through the cell membrane and enter the cytoplasm

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directly; meanwhile, they are susceptible to degradation by nucleases during circulation. Therefore, developing a delivery platform that can protect nucleic acid molecules and facilitate their effective release is becoming the key to promote clinical applications of RNA drugs. As one of the most mature non-viral nucleic acid delivery systems to date, LNPs serve as a key technology platform for siRNA therapies [5, 6].

Early nucleic acid delivery systems mainly rely on permanently cationic lipids. Although they can improve nucleic acid encapsulation capacity and cellular uptake efficiency, they also cause non-specific protein adsorption, immune responses, and high cytotoxicity [5]. To solve this contradiction, ionizable lipids have gradually become a core component of LNP design. Ionizable lipids can adjust their own charge state in response to changes in environmental ph. They maintain a near-neutral state in physiological environments, reducing toxicity and non-specific effects. Protonation occurs in the acidic endosomal environment, facilitating endosomal escape and nucleic acid release [5]. Accordingly, ionizable lipids meet the needs of different stages in nucleic acid delivery through pH-responsive charge transition, improving safety and delivery efficiency [5, 6].

Currently, LNP used for RNA delivery typically consist of four main classes of components, including ionizable lipid, helper phospholipid, cholesterol and PEG-lipid [5]. Among them, ionizable lipid is the most crucial factor that affects drug delivery efficiency; its chemical structure and apparent pK_a can influence protonation state of lipids, nucleic acid complexation, membrane interactions, and endosomal escape [5]. Helper phospholipid affects stability of membrane structures; cholesterol increases arrangement stability of lipids; PEG-lipid forms a hydrophilic protective layer that reduces particle aggregation and improves the stability of LNPs during circulation in the body [5].

LNP-mediated siRNA delivery requires the sequential crossing of multiple biological barriers. First, LNP protect siRNA within the core of lipids through encapsulation, preventing it from being degraded by nucleases during blood circulation and improving stability of nucleic acid drugs in the body. Next, LNP enter the circulatory system; their size, composition and surface properties would influence plasma protein adsorption, tissue distribution, and cellular uptake behavior [5, 6]. When LNP reach the target cell, they often enter the cell through endocytosis and form endosomal structure. However, cellular uptake does not equate to successful delivery. Endosomal escape is considered the primary rate-limiting step in RNA delivery, and its efficiency directly impacts the gene silencing outcome. In the acidic environment of the endosome, protonation of ionizable lipids enables interaction with the endosomal membrane and induces membrane destabilization, thereby facilitating the release of siRNA into the cytoplasm. So, the designs of ionizable lipids not only relate to encapsulation and stabilization, but also affect efficiency of this critical escape step [5]. The siRNA that successfully escapes the endosome subsequently mediates target gene silencing via the RNA interference pathway.

As research on LNP continues to develop, research focus has gradually shifted from enhancing efficiency of nucleic acid delivery to regulating their behavior in vivo. The emergence of the concept of programmable LNP means that researchers can proactively regulate its tissue distribution, cell selectivity and intracellular transport by material designs [6]. Research suggests that after LNP enter the body, their surface would interact with plasma protein and form protein corona. This process affects its organ tropism and cellular uptake efficiency [6]. For example, some LNP through apolipoprotein E (Apo E) express distinctive characteristics of hepatic accumulation [6]. However, for other therapies for tumor and extrahepatic diseases, solely relying on the natural distribution of tissues often fails to meet the requirements for precise delivery. Further redesign of the biological behavior of LNPs via materials engineering strategies is required [6].

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Currently, LNP targeted delivery strategies mainly include endogenous targeting based on lipid composition regulation and active targeting based on surface functionalization. The surface properties and tissue distribution of LNP can be adjusted by changing the ionizable lipid structure, lipid ratio, and adding specific functional lipids. For example, the selective organ targeting (SORT) strategy changes the biodistribution of LNP by introducing additional lipid components, enabling it to break through the limitation that traditional LNP is mainly enriched in the liver and achieve redistribution to other tissues [6]. Meanwhile, by connecting specific functional molecules on the surface of LNP, it can be endowed with the ability to recognize specific cells or tissues, improve the accumulation of therapeutic RNA in the target region, and reduce the toxicity caused by non-targeted tissue exposure [6]. Therefore, LNP functionalization modification based on different targeting molecules has gradually become an important research direction to improve the therapeutic effect of siRNA for tumor, which provides a theoretical basis for the subsequent targeted delivery strategy.

3. Anti-tumor efficacy of peptide-targeted modification

Although ionizable LNP can effectively protect siRNA and facilitate its entry into the cell, traditional LNP mainly rely on passive targeting to achieve tumor enrichment, lacking the ability to recognize specific tumor cells. It leads to accumulation of some nanoparticles in non-target tissues, limiting the therapeutic efficacy of siRNA [7-9]. Therefore, achieving active targeted delivery by introducing peptide ligands with specific recognition capabilities onto the surface of LNP has become a key strategy for enhancing the precision of siRNA therapy. Compared with macromolecular targeting molecules such as antibodies, peptides have the advantages of small size, easy structure modification and high biocompatibility, which can enhance the recognition ability of tumor cells while maintaining the delivery performance of LNP [7-9]. Currently, various peptide-modified LNP systems have been applied in research on siRNA-based cancer therapy; among them, peptides such as tLyp-1, Epi-1, and SP94 have demonstrated promising potential for application [7-9].

For KRAS-mutant tumors, Anthiya et al. developed a tLyp-1 peptide-modified siRNA-LNP delivery system for KRAS gene silencing therapy [7]. KRAS mutation is an important driving factor of many kinds of solid tumors, but it lacks effective drug-binding sites, making it a target that is difficult to intervene upon using conventional drugs. Directly reducing KRAS expression using siRNA has emerged as a promising therapeutic strategy. This study modified tLyp-1 polypeptide on the surface of c12-200 ionizable LNP to enable it to recognize the overexpressed neuropilin-1 receptor in tumor cells [7]. In vitro experiments demonstrate that the uptake efficiency of tLyp-1-modified LNPs in Nrp1-positive cells is approximately twice that of unmodified LNP. In the CFPAC-1 subcutaneous transplantation tumor model of pancreatic cancer, the tumor volume of tLyp-1 modified LNP was about 1.6 times that of the non-targeting group. The targeted LNP loaded with siKRAS-LNA combined with gemcitabine reduced the tumor volume by about 70%, while the non-targeting LNP combined with gemcitabine only reduced by about 40% [7]. These results suggest that tLyp-1-mediated active targeting can effectively enhance LNP accumulation and gene silencing efficiency in KRAS-mutant tumors.

Although peptide modification enhances the targeting ability of LNPs, ligand introduction may also change the surface properties of nanoparticles and reduce their stability. To solve this problem, Sakurai et al. developed an EPI-1 peptide modified siRNA delivery system, and optimized the LNP structural stability using PEG monoaryl fatty acid [8]. The Epi-1 peptide is capable of recognizing EpCAM on the surface of tumor cells. Research has shown that the incorporation of PEG-monoacyl

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fatty acids enhances nanoparticle stability and prevents LNP aggregation while preserving EpCAM-mediated targeting capabilities, thereby reducing the half-maximal effective concentration from over 10 nM to less than 1 nM [8]. In an ovarian cancer peritoneal dissemination model, the optimized delivery system achieved approximately 50% and 40% PLK1 gene silencing in free-floating peritoneal cancer cells and mesenteric solid tumors, respectively, whereas no significant effect was observed with unmodified LNPs [8]. The above results show that the reasonable selection of PEG lipid type can maintain the targeting function while ensuring the stability of the delivery system.

In addition, the complex tissue barriers within solid tumors are also significant factors limiting siRNA therapy. Aiming at the difficulty in the treatment of sorafenib resistant hepatocellular carcinoma, Younis et al. [9] designed ultra-small lipid nanoparticles modified with SP94 polypeptide to achieve the combined delivery of sorafenib and midkine siRNA. SP94 peptide can specifically recognize hepatocellular carcinoma cells. Meanwhile, using microfluidic technology, the LNP particle size was optimized from 160 nm to approximately 60 nm, extending the blood circulation half-life from less than 20 minutes to over 9 hours [9]. Gene silencing experiments showed that the half-maximal effective dose of usLNPs loaded with MK-siRNA in tumor tissues was about 0.1 mg/kg, and had no obvious effect on healthy liver. In the treatment experiment, usLNPs delivering sorafenib and MK-siRNA reduced the tumor volume by about 85%, while sorafenib single agent and MK-siRNA single agent reduced the tumor volume by only 40% and 18%, respectively. In the sorafenib resistance model, the combination of sorafenib and MK siRNA delivered by usLNPs still reduced the tumor by about 70% [9]. The above results indicate that SP94 targeted modification combined with nanoparticle size optimization can improve the therapeutic effect of siRNA in drug-resistant hepatocellular carcinoma.

Overall, peptide-based targeted modification enhances the precision of siRNA delivery by endowing LNP with the ability to actively recognize tumor cells. These studies indicate that peptide selection, receptor recognition, and LNP stability require comprehensive optimization to fully realize the therapeutic potential of the targeted delivery system (see Table 1).

Table 1. Summary of research on peptide-targeted LNPs for tumor siRNA delivery

Drug	Modification strategies	Targets	Effects	Ref.
siKRAS-LNA + Gemcitabine	tLyp-1 peptide modification	neuropilin-1	Tumor accumulation increased 1.6-fold, and combination therapy reduced tumor size by approximately 70%.	[7]
siPLK1	Epi-1 peptide + PEG-monoacyl fatty acid	EpCAM	The EC_{50} dropped to <1 nM, and gene silencing efficiency was approximately 40%–50%.	[8]
Sorafenib + siMK	SP94 peptide + 60 nm particle size optimization	Hepatocellular carcinoma	The half-life was extended to >9 h, and the tumor shrank by approximately 85%.	[9]

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4. Anti-tumor efficacy of antibody-targeted modification

In addition to polypeptide ligands, antibodies, with their higher antigen binding affinity, have also become an important research direction for the surface functionalization of LNP. For a long time, antibody-targeted modification of LNPs for in vivo delivery has been limited by the weak specific recognition ability of cell types. Traditionally, LNPs are employed for passive targeting of tumours; however, as they cannot distinguish between cancer cells and normal cells effectively, the therapeutic RNA accumulates in non-target organs and is thus less effective in treating the disease and may cause off-target toxicity. Therefore, by attaching antibodies to the surface of LNPs as high-affinity targeting ligands, specific antigen-antibody recognition can be used to enhance the binding, uptake and internalisation of nanoparticles by target cells and improve delivery accuracy. Due to their good surface functionalisation properties and flexible, tunable lipid compositions, antibody conjugation can be used to achieve active targeting of LNPs. Among them, anti-EGFR antibodies have received much attention due to the high expression of EGFR in many tumours of epithelial origin [10, 11].

To address the problem of a lack of effective targeted therapy for HPV-positive head and neck cancer, Kampel et al. have used the Anchored Secondary Scaffolding for Efficient Targeting (ASSET) platform to engineer anti-EGFR antibody-modified LNPs for the delivery of siRNA targeting HPV16 E6/E7 oncogenes [11]. HPV16 E6 and E7 proteins are required for the development and spread of tumours.

The ASSET technology adds a lipidation group to link targeting antibodies with LNPs and keeps the antibody-binding part free for antigen recognition. Researchers constructed targeted LNPs loaded with siE6 or siE7 and evaluated their gene silencing efficiency and anti-tumor effects in an HPV16-positive head and neck cancer model. siE6-tLNP significantly reduced E6/E7 mRNA expression and induced apoptosis in tumour cells. In the UMSCC-104 xenograft model, intravenous injection of siE6-tLNP reduced the size of the tumours by about 50% compared with the control group, and a stronger inhibitory effect on E6/E7 was observed in the tumour tissue. Anti-EGFR antibodies can also inhibit the EGFR signalling pathway to suppress tumours, and this effect may be in cooperation with that of siRNA-mediated gene silencing [11].

Geisler et al. used Strain-Promoted Azide–Alkyne Cycloaddition (SPAAC) click chemistry to conjugate anti-EGFR antibodies on the surface of LNPs and studied how the density of antibodies affected delivery efficiency [10]. aEGFR-LNP were prepared by adjusting the ratio of DSPE-PEG-azide. In vitro experiments have shown that LNPs modified with a high density of antibodies induce more luciferase expression in JEG-3 cells; however, in vivo results show that LNPs with a moderate antibody density achieved the best mRNA delivery performance, and excessively high modification density actually reduced delivery efficiency. Antibody density is not always positively correlated with the efficiency of in vivo delivery; excessively high levels of antibodies may be cleared by the mononuclear phagocyte system (MPS) or inhibit antigen binding through steric hindrance.

In short, antibody-targeted modification improves the selectivity of LNP for EGFR-positive cells and thus enhances their uptake. Delivery efficiency is also affected by other factors, such as the type of antibody, conjugation method and density of antibodies, and the microenvironment in vivo. Optimize antibody conjugation methods and surface modification parameters for all disease models in future work to enhance the clinical applicability of targeted LNPs (see Table 2).

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Table 2. Summary of research on antibody-targeted LNP for tumor RNA delivery

Drug	Modification strategies	Targets	Effects	Ref.
siE6/siE7	ASSET technology; anti-EGFR antibody modification	EGFR / HPV16 positive head and neck cancer	E6/E7 mRNA levels were significantly reduced, and tumor volume decreased by approximately 50%, acting synergistically with the antibody's intrinsic EGFR-inhibitory effect.	[10]
mRNA	SPAAC click chemistry; different antibody densities	EGFR	Moderate density yields the best in vivo delivery results, while excessively high density diminishes effectiveness.	[11]

5. Anti-tumor efficacy of amino acid-targeted modification

In addition to targeting ligands such as peptides and antibodies, the delivery performance of LNPs can also be modulated by functionalizing the head groups of the lipid molecules themselves. As natural endogenous molecules, amino acids possess excellent biocompatibility and biodegradability; incorporating them into lipid structures holds promise for reducing the toxicity risks associated with synthetic lipid carriers [12].

Patel and others have designed a series of ionizable lipids based on histidine and lysine for the tumour delivery of siRNA [12]. The researchers have verified the feasibility of this Design for the selected LHHK lipid in both vitro and animal models. Using 2-(aminomethyl)butanedioic acid as the backbone, they prepared lipids with eight different head-group combinations and conducted an initial screening in PC3-Luc cells. Among all the tested lipids, the LHHK lipid, which contains two histidine residues and one lysine residue, had the highest silencing efficiency (70%) and was comparable to that of the positive control Lipofectamine 2000; however, it showed significantly lower cytotoxicity than Lipofectamine 2000 [12]. Further characterization of LHHK LNP showed that its pK_a was 6.08, which falls within the optimal range (pK_a 6-7) for promoting endosomal escape, and a higher pK_a is more favourable for gene silencing activity [12]. In a serum stability assay, LHHK LNPs protected siRNA for as long as 24 hours in 50% human serum; a hemolysis assay showed strong membrane-disrupting activity at pH 5.6 but no hemolytic activity at pH 7.4, indicating that the LNP is capable of pH-responsive endosomal escape [12]. In the cellular uptake experiment, LHHK-LNP showed a higher uptake in PC3 cells compared with other lysine-modified lipids and had the lowest degree of colocalization with lysosomes (indicated by a lower Pearson correlation coefficient), thus demonstrating superior endosomal escape ability [12]. Functional validation of gene silencing has also been carried out; LHHK-siRNA-loaded LNPs showed significant gene silencing in PC3 and DU145 prostate cancer cells, and similarly, LHHK-siRNA-loaded LNPs targeted against the Inhibitor of Nuclear Factor Kappa B Kinase Subunit Epsilon (IKBKE) achieved substantial silencing in PANC-1 and PANC02 pancreatic cancer cells and inhibited cell proliferation [12]. In the PANC02 subcutaneous pancreatic cancer xenograft model, peritumoral injection of 0.4 mg/kg IKBKE siRNA-LNP effectively suppressed tumour proliferation;

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both tumour mass and volume were reduced by approximately 40%, and there were no corresponding increases in mouse body weight or elevated plasma ALT and AST levels. The above results show that LHHK LNP has good efficacy and safety at therapeutic doses [12].

Overall, amino acid-modified ionizable lipids leverage the excellent biocompatibility of endogenous molecules; by modulating the LNP's pK_a and endosomal escape capability through headgroup composition, they offer a regulatory pathway for siRNA delivery that differs from external ligand modification. Current research primarily focuses on the screening of lipid structures and in vitro validation, with relatively limited data from animal experiments; future studies could further explore the effects of different amino acid combinations on delivery efficiency and targeting capabilities.

6. Receptor-ligand targeted modification

Receptor-ligand interaction is a fundamental mechanism for molecular recognition and transport in biological systems; applying this principle to the design of nanodelivery systems enables the precise delivery of siRNA. By modifying the carrier surface with specific ligands that recognize receptors overexpressed on target cells, active targeted delivery of nucleic acid drugs can be achieved.

Wang et al. used a lentiviral vector to deliver the mini-dystrophin gene for the gene therapy of Duchenne muscular dystrophy (DMD) [13]. They constructed four types of lentiviral vectors encoding mini-dystrophin and delivered them via local injection into the tibialis anterior muscle of mdx mice. The results demonstrated an in vitro transfection efficiency of 83.99%; in the treated group, dystrophin expression was restored and maintained for at least 26 weeks, the proportion of centrally nucleated muscle fibers was significantly reduced, and grip strength showed marked improvement compared to the untreated group [13].

Zhou et al. designed a reversible camouflaged biomimetic nanocomposite to deliver siSav1 in order to treat myocardial ischemia-reperfusion injury [14]. Its structure includes a membrane penetrating helical polypeptide/siSav1 core, a charge reversal middle layer, and a platelet macrophage hybrid membrane as the shell. Following intravenous injection, this complex effectively reduces Sav1 expression levels and promotes myocardial regeneration to restore cardiac function in rat and pig models [14].

Currently, research on receptor-ligand targeted modification for tumor siRNA-LNP delivery remains insufficient; this may be attributed to the heterogeneity of target receptor expression in solid tumors, the complex barriers of the tumor microenvironment, and the dynamic changes in receptor expression levels during the course of treatment. Nevertheless, the regulatory strategies associated with tissue-specific promoters and the delivery concept of biomimetic membrane camouflage remain highly valuable for reference. Future research could explore incorporating the regulatory logic of tissue-specific promoters into the screening and application of tumor-specific promoters; meanwhile, the biomimetic membrane camouflage strategy holds promise for integration with LNP platforms to enhance nanoparticle penetration within the tumor microenvironment and improve cellular selectivity. With the deepening understanding of tumor receptor profiles, the potential for receptor-ligand targeted modification in tumor siRNA delivery warrants further exploration (see Table 3).

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Table 3. Summary of research on receptor-ligand targeted LNP for tumor RNA delivery

Drug	Modification strategies	Targets	Effects	Ref.
mini-dystrophin gene (lentiviral vector)	Expression driven by the muscle-specific promoter Spc-5-12	DMD	In vitro transfection efficiency was 84%; dystrophin expression was restored and maintained for ≥26 weeks, the proportion of centrally nucleated fibers decreased, and grip strength improved significantly.	[13]
siSav1	Reversible camouflage biomimetic nanocomposite	Myocardial ischemia-reperfusion injury	Reduced Sav1 expression promotes cardiomyocyte regeneration and the recovery of cardiac function.	[14]

7. Conclusion

Given that cancer is a serious problem of public health, new methods for treating it are constantly being developed by doctors and scientists around the world. Although siRNA therapy can inhibit the growth of tumours by silencing cancer-related genes at the genetic level, its application in clinical practice and translation have been limited by poor in vivo delivery efficiency. By functionalising the surface of LNPs or modifying their lipid composition, various active targeting strategies have been developed; as a result, different degrees of improvement in the precision and safety of siRNA delivery have been achieved, and enhanced efficacy in inhibiting tumour growth and metastasis has also been demonstrated.

Peptide-targeted modification strategies that use ligands such as tLyp-1, Epi-1 and SP94 to target receptors on the surface of tumor cells have shown better anti-tumor effects than non-targeted agents in models of KRAS-mutant tumours, ovarian cancer with peritoneal dissemination and drug-resistant hepatocellular carcinoma. The ASSET platform and SPAAC click chemistry were used to conjugate an anti-EGFR antibody on the surface of LNPs. In a head and neck cancer model, they have confirmed the synergistic effect of the antibody's intrinsic anti-tumor activity and siRNA-mediated gene silencing, and found that the relationship between antibody density and in vivo delivery efficiency is not a simple positive correlation. Amino acid-targeted modification optimised the lipid composition of LNPs; the LHHK lipid enhanced endosomal escape efficiency by altering the pK_a and achieved safer and more effective gene silencing in a pancreatic cancer model. Receptor-ligand targeted modification approaches, such as lentiviral vectors encoding mini-dystrophin and biomimetic nanocomplexes, have shown good results in treating DMD and myocardial ischemia-reperfusion injury. Although no advantages of this kind of delivery for cancer treatment have been found so far, it is still worth studying. These studies have shown that the active targeting efficiency and safety of LNP-siRNA delivery systems are influenced by many factors, such as the affinity of the ligand, ligand density, conjugation method, LNP particle size, and lipid composition, in addition to the affinity of the ligand itself.

Although there have been many improvements in active targeting modification strategies, some problems remain. Tumor heterogeneity results in different expressions of target receptors among

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various cells, and thus, a single ligand cannot target all the cancer cells. Ligands are added to enhance targeting, but they may also change the surface characteristics of LNPs and cause particle aggregation; thus, delivery efficiency will be reduced. Ligand Density does not directly affect the efficiency of in vivo delivery, and a relatively high density may be harmful to this efficiency. A dense stromal barrier in the tumour and an adverse tumour microenvironment also limit the diffusion of nanoparticles.

In light of the aforementioned challenges, future research could focus on the following aspects. A multi-ligand cooperative targeting strategy may address the issue of insufficient coverage by a single ligand—caused by tumor heterogeneity—through the simultaneous recognition of multiple receptors. Combination therapy strategies integrating LNP-siRNA delivery with chemotherapeutic agents or immune checkpoint inhibitors have demonstrated synergistic potential in some studies. Furthermore, targeting strategies developed in other fields—such as tissue-specific promoters and biomimetic membrane camouflage—hold promise for adaptation in the development of delivery systems responsive to the tumor microenvironment. Pharmacological studies focusing on ligand density and LNP surface properties should also be conducted in depth to better optimize modification strategies. The clinical translation of actively targeted LNP requires more systematic design optimization to achieve a better match between ligand selection and the physicochemical properties of the LNP themselves. With the continuous development of biotechnology, active-targeting LNP-siRNA delivery holds promise for playing a greater role in the field of cancer therapy.

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