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Advances in Lipid Nanoparticle Carriers for Cancer Therapy

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Abstract: Malignant tumors, featuring strong heterogeneity, innate immune escape and acquired drug resistance, is the top cause of disease-related death worldwide. Traditional treatments for these cancers have serious drawbacks in terms of therapeutic efficacy and safety. Lipid nanoparticle (LNP) is the most powerful nonviral nucleic acid delivery vector to date and can achieve efficient encapsulation, protection and intracellular delivery of nucleic acid molecules with a biomimetic nanostructure interlinked synergistically assembled by core components, has become a key research vehicle in the field of cancer gene therapy. In this review, we summarize the composition of core functions of the component of LNPs, molecular evolution trajectory, targeting optimization and so on, and system summarize the latest research progress of LNP in targeted delivery of traditional chemotherapeutic agents, specific gene regulation by nucleic acid therapy and combination cancer therapy etc. Collectively, these pieces of work provide a complete academic reference for future fundamental studies and clinical translation of LNP-mediated cancer gene therapy technologies, and lay the theoretical basis for further non-viral nucleic acid vectors used in cancer gene therapy in the wider biomedical field.

Keywords: Lipid Nanoparticles; mRNA Vaccines; Cancer Gene Therapy.

1. Introduction

High malignancy tumours are some of the major causes of mortality across the globe because of their complex biological properties, such as high heterogeneity, immune avoidance and developed drug resistance. Novel therapeutic strategies of tumours have always been a focus of biomedical research. Tumor vaccines as a form of active immunotherapy are designed to activate the immunity of host for specific recognition and deletion of tumour cells, a novel way of treating tumours. Here, messenger ribonucleic acid (mRNA) has emerged very rapidly as an ideal candidate for developing tumour vaccines because of its tremendous advantages: it does not require nuclear translocation, has a very short production cycle, and can encode multiple tumour antigens.However, intrinsically unstable mRNA, the nuclease instability of mRNA and low transmembrane deliverability, owing to the strong negative charge and hydrophilicity of mRNA itself make the clinical application of mRNA highly rely on safe and effective delivery systems.

Since the development of Lipid nanoparticles (LNPs), they have provided us with an essential strategy to overcome this problem. As one of the most developed types of nonviral nucleic acid carrier, LNPs have a capability of efficient encapsulation and protection of mRNA and function similar to biological membranes, thus mediating the cytoplasmic delivery of nucleic acid through endosomal membrane fusion to improve translation efficiency. Considering that LNP technology application in cancer therapy is moving from preclinical proof of concept to clinical translation, this paper summarizes the structure basis, mechanism and the latest advances in LNPs for different cancer treatment strategies.

2. Overview of Lipid Nanoparticles

The delivery efficacy of LNPs is owing to their multi-component, nanostructured nature. A typical LNP formulation contains four key lipid components: ionizable (or cationic) lipids, phospholipids, cholesterol and PEGylated lipids (PEG-lipids). Each component has a distinct and indispensable function in nanoparticle formation, cargo encapsulation, systemic circulation and intracellular delivery[1].

2.1. Core Functional Components and Their Evolution

2.1.1. Cationic Lipids and Ionizable Lipids

The cationic lipids are the core component of primitive LNPs, and the structure of the cationic lipid molecule can be abstracted into three segments: a positive charged hydrophilic segment (headed group), the hydrophobic alkyl chain segment, and a spacer group bridging the headed group and the hydrophobic chain segment. The positively charged group in the cationic lipid headed group can play electrostatic interactions with negatively charged phosphate backbone in the nucleic acid molecule, and promote the entry and uptake efficiency of cells by using the endocytosis pathway, and form the lipoplex stable structure. At the same time, the cationic lipids carry obvious risk of toxicity immunogenicity and initiate an immune response in the body, so it is necessary to chemically alter or adjust the composite ratio to reduce the immunostimulation, toxicity risk of the cationic lipid. In addition, the encapsulation efficiency of such lipid carriers is less than 40%, and their transfection efficiency and biocompatibility are insufficient [2]. These bottleneck factors have restricted their clinical translation and application.

Ionizable lipids offer enhanced safety profiles and prolonged circulation times compared to cationic lipids. In acidic buffer solutions, ionizable lipids carry a positive charge, enabling self-assembly with mRNA to form LNPs. Following cellular internalization of mRNA-containing LNPs, the acidic microenvironment within the endosome protonates the ionizable lipids once more, promoting fusion between the LNP and the negatively charged endosomal membrane, thereby enhancing the efficiency of mRNA escape from the

endosome. In the early 21st century, ionizable lipids such as 1,2-dioleoyl-3-dimethylammonium propane (DODAP) and 1,2-dioleyloxy-3-dimethylaminopropane (DODMA) were successfully employed for mRNA delivery [3]. Currently, the most widely used ionizable lipids include clinically validated molecules like DLin-MC3-DMA and SM-102, whose pH-sensitive molecular basis is critical for facilitating endosomal escape [4, 5].

2.1.2. Auxiliary Lipids and PEG Lipids

Auxiliary lipids (phospholipids and cholesterol) also play an important role for the structural properties and the functional performance of LNPs. Phospholipids, because of their biologically inspired structural properties, not only aid the assembly and aggregation of LNPs but also favour the interaction between carrier and cell membrane, and therefore improve uptake into the cell.

Cholesterol, on the other hand, contributes to the structural characteristics of LNPs by controlling the fluidity and stability of the lipid membrane of the LNPs and prevents the release of encapsulated nucleic acids. In addition, cholesterol can also dampen recognition of the carrier by the clearance mechanism of the body and thus confer favourable properties on the circulation of the carrier.

PEG-lipids are located on the particle surfaces, preventing aggregation through steric hindrance effects. A typical representative is DMG-PEG2000, with its content controlled at 1.5-5% to balance stability and cellular uptake efficiency [6]. Polyethylene glycol (PEG)-modified lipids are formed by covalently linking hydrophilic PEG chains to hydrophobic lipid anchoring groups.

Their core function is to form a "hydrophilic protective layer" on the surface of liposomal nanoparticles (LNPs), thereby reducing the nonspecific adsorption of serum proteins and decreasing the phagocytic clearance of the carriers by the reticuloendothelial system, which significantly prolongs the in vivo circulation half-life of LNPs. Studies have shown that the use of low-molecular-weight PEG-modified lipids can maintain circulatory stability while minimizing adverse effects on nucleic acid delivery efficiency [7].

2.2. Targeting Optimization Strategies

However, unmodified lipid nanoparticles also have limitations as they tend to accumulate in the liver. Additional components can be incorporated into the LNP formulation to enhance targeting ability. Patel et al. developed amino acid-modified biodegradable lipids for the delivery of siRNA to cancer cells [8]. The prepared siRNA-LNPs exhibited extremely low cytotoxicity and high transfection efficiency, and could effectively silence IKKα and IKBKE in prostate cancer and pancreatic cancer cells. Jinjin Chen developed an endogenous lymph node-targeting lipid nanoparticle (LNP) 113-O12B without active targeting ligand modification, which showed significantly higher mRNA expression in lymph nodes and lower expression in the liver compared with ALC-0315 [9].

3. Advances in Lipid Nanoparticle Carriers for Cancer Gene Therapy

Benefiting from their excellent delivery performance and modifiability, LNPs have evolved from simple drug carriers to functional platforms integrating multiple therapeutic strategies. Their applications in cancer therapy mainly focus on three directions: delivery of traditional chemotherapeutic drugs, efficient introduction of nucleic acid drugs, and synergistic realization of multimodal combination therapy.

3.1. Traditional Drug Delivery Systems

Traditional chemotherapeutic drugs have limitations in the clinical application of cancer therapy such as non-specific biodistribution, a narrow therapeutic index and intrinsic or multiple drug resistance, which are the main sources of systemic toxicity and poor therapeutic effect. LNP dramatically improved the pharmacokinetic properties and tumour selectivity of chemotherapeutic drugs due to the two characteristics of passive targeting and active modification. Passive targeting is based on the enhanced permeability and retention (EPR) effect of the tumour tissue. The EPR effect is a phenomenon in which nanoparticles accumulate preferentially at a tumour site because of increased vascular permeability and impaired lymph drainage in tumour. Various teams designed an LNP formulation coencapsulating chemotherapeutic drug epirubicin and the active moiety of anti-angiogenesis—DPPA. This nanocarrier system not only enables targeted delivery of chemotherapeutic drugs but possesses inherent anti-angiogenic activity as well. its combination with PD-1 inhibitors significantly enhanced the anti-tumor immune response in animal models of breast and liver cancers [10].

Active targeting strategies improve the tumor accumulation efficiency of drugs by modifying specific ligands on the LNP surface to recognize receptors overexpressed on tumor cells. Folate receptors are highly expressed in ovarian and breast cancers, and folate-modified LNPs can increase drug uptake efficiency several-fold [11]; EGFR antibody-modified LNPs have demonstrated excellent tumor selectivity in colorectal cancer models [12]. In addition, tumor microenvironment-responsive LNPs achieve spatiotemporally controlled drug release by utilizing the characteristics of the tumor microenvironment such as acidic pH and specific enzyme activity.

3.2. Nucleic Acid Drug Delivery Systems

Unlike the direct killing effect of chemotherapeutic drugs, LNP-mediated nucleic acid therapy focuses on the reprogramming of tumor biological behavior. Nucleic acid drugs (siRNA, mRNA, etc.) hold great potential in tumor therapy, but their in vivo delivery is hindered by poor stability, low cellular uptake efficiency, and difficulty in endosomal escape. The successful application of SM-102 in COVID-19 mRNA vaccines has provided an optimized formulation basis for tumor mRNA delivery [7].

Targeting the intrinsic oncogenic pathway of the tumour cell is the most straightforward application scenario of RNAi therapy. For transcription factors that cannot be intervened by small-molecule drugs, the LNP-siRNA system also provides a promising alternative strategy. Quick et al. reported an LNP-siRNA system targeting androgen receptor splice variants (AR-V7) and found a tumour accumulation of up to 4.4% ID/g in a prostate cancer model. By the transcription factor-specific silencing AR-V7, the formulation can greatly delay progression of castration-resistant prostate cancer, providing a viable therapeutic strategy for therapeutic transcription factors that are difficult to handle [13].

However, targeting only tumor cells is insufficient to overcome solid tumors, since growth and progression of the solid tumor largely depends on the tumor's immunosuppressive microenvironment. Such insight has

induced the paradigm shift of RNAi therapy to target the tumor immune microenvironment (TME). Bai et al. reported peptidomimetic LNPs for siRNA delivery against STAT3, which successfully silenced STAT3 expression in melanoma cells and immune cells in the TME with systemic delivery, resulting in silencing PD-L1 expression and remodeling TME, showing a profound antitumor activity as monotherapy [14]. Liu et al. entrap siRNA targeting fragile X mental retardation protein (FMRP) in LNPs and combined it with PD-1 antibodies, achieving almost 80% inhibition of tumor growth in a triple-negative breast cancer model [15].

From these mechanistic studies, it was seen that silencing FMRP was able to remodel the immune cells' structure within the TME, increase the infiltration and function of CD8+ T cells, thus improving the response rate of the treatment of immune checkpoint blockade therapy dramatically. On this basis, researchers have further explored the strategy of combination therapy between RNAi and immune checkpoint blockade. Liu et al. reported an LNP-siRNA targeting immune response gene 1 (IRG1), which is active in TAMs, specifically. By silencing the expression of IRG1 to remodel the morphology and function of TAMs, this formulation enhanced intratumoral infiltration of CD8+ T cells, reestablished anti-tumor immunity in many solid tumour models and induced an effective immune response in the TME [16], which effectively avoided the difficulty of modifying tumor cells directly, and achieved "indirect" long-term anti-tumor effect by regulating key immune cells in the TME.

There has also been breakthrough development of tumor vaccine technology based on mRNA-LNP. Personalized cancer vaccine mRNA-4157 encodes for tumor neoantigens, which is delivered by LNPs to induce specific T cell response. In clinical trials of melanoma and head and neck cancer, mRNA-4157 plus pembrolizumab decreased the risk of relapse or death by 44% at 18-month follow-up, indicating its efficacy and safety [17]. In addition to protecting mRNA, LNPs can also considerably enhance expression levels of the antigen via its endosomal escape function. An LNP combined with pHLIP (mRNA@LNP-pHLIP) improved the endosomal escape efficiency by making use of pH-dependent membrane insertion property of pHLIP, increasing mRNA expression levels by 3–5 times in different cells; mRNA could express protein at sustained and higher expression levels in vivo mouse experiments [18].

3.3. LNP-Mediated Cancer Combination Therapy Systems

LNP-mediated cancer combination therapy systems significantly improve cancer treatment efficacy by integrating multiple therapeutic modalities. The co-delivery of chemotherapeutic drugs and nucleic acid drugs is a typical application. Guo et al. constructed prostate-specific membrane antigen aptamer-functionalized core-shell nanoparticles co-encapsulating paclitaxel and pooled siRNAs targeting drug resistance-related genes, achieving a synergistic anti-tumor effect in a drug-resistant prostate cancer model through a sequential release mechanism [19]. Wang et al. developed lipid-coated albumin nanoparticles co-encapsulating paclitaxel and sorcin-siRNA for paclitaxel-resistant ovarian cancer, which effectively reversed chemoresistance by restoring intracellular calcium homeostasis to induce apoptosis [20]. Chen et al. used folate-modified LNPs to co-encapsulate si-cPKM and paclitaxel, and confirmed in an intrahepatic cholangiocarcinoma organoid model that this system could enhance drug penetration and efficacy by remodeling the fibrotic microenvironment [21].

The co-delivery of immune checkpoint inhibitors and tumor vaccines aims to simultaneously address two core obstacles: the functional inhibition of effector T cells and the scarcity of tumor-specific T cells. Yang et al. prepared LNPs co-encapsulating OVA mRNA and siRNA targeting PD-L1 (LNP/mOVA/siPD-L1) using microfluidic technology, which were used to transfect bone marrow-derived dendritic cells to construct dual-engineered DC vaccines. The combination of this vaccine with anti-PD-L1 antibodies achieved complete tumor suppression in a colorectal cancer model and induced a long-lasting immune memory effect [22]. Lin et al. developed a tumor-targeting nanoformulation RSLNP/siPD-L1 co-encapsulating the SN38 prodrug and siPD-L1, and its combination with mRNA vaccines increased the tumor inhibition rate by 47.7% in a melanoma model and 26.1% in a breast cancer model by inducing immunogenic cell death combined with immune checkpoint blockade [23]. Zhou et al. encapsulated MC38 tumor total RNA and siPD-L1 in cationic liposomes, which synergistically amplified the cytotoxic activity of CD8+ T cells by enhancing dendritic cell antigen presentation and simultaneously inhibiting PD-L1 expression [24]. In addition, the combination of epigenetic regulatory drugs and traditional chemotherapy has also shown potential. Studies have indicated that chemotherapeutic drugs such as oxaliplatin can induce immunogenic cell death, and their combination with epigenetic regulatory drugs such as DNMT inhibitors is expected to produce a synergistic anti-tumor effect.

In recent years, strategies for on-demand drug release using external physical energy have also attracted considerable attention. Uzel et al. reported a lipid-gold hybrid nanoparticle loaded with 5 nm gold nanoparticles and doxorubicin, which utilized the plasmon resonance effect of gold nanoparticles induced by 527 nm nanosecond pulsed laser to transiently disrupt the lipid bilayer membrane through single-pulse irradiation, triggering rapid drug release. Compared with conventional liposomes, this strategy increased the intracellular accumulation of doxorubicin in target cells by up to 11 times, significantly enhancing the killing effect on cancer cells in vitro [25].

4. Future Perspectives

LNP carriers have certainly made impressive strides in tumor gene therapy. But when it comes to bringing them into the clinic, several hurdles remain.First and foremost, targeted delivery isn't nearly precise enough yet. At present, most intravenously injected LNPs end up in the liver – a long-standing problem that makes it difficult to reach other organs, especially the tumor tissue itself.

So how might we fix this in the coming years? A few promising avenues are already on the table. One is to screen through new libraries of ionizable lipids. Another is to fine-tune the density and 3D arrangement of ligands on the particle surface. We could also design smarter, multi-stage targeting systems that respond specifically to cues from the tumor microenvironment. With these approaches combined, the current bottleneck stands a good chance of being broken.

Where is LNP technology heading in the fight against cancer? The outlook is highly promising. Drawing on what we have learned so far, the coming years are likely to see

innovation happening on multiple fronts.First, precise targeting is a top priority. By designing new ligand modifications and building LNPs that can sense and respond to the tumor microenvironment, we expect to achieve both active tumor homing and controlled drug release.Second, multifunctional LNPs are set to become a game-changer. Instead of just delivering drugs, these next-generation carriers can be equipped with imaging probes and real-time monitoring modules – all in one single platform. This integration will greatly accelerate the development of theranostics, where diagnosis and therapy go hand in hand.

In terms of material innovation, the application of biodegradable materials and biomimetic membrane materials will improve the biocompatibility of LNPs. Artificial intelligence-assisted LNP design platforms will accelerate the development process of novel carriers by using machine learning algorithms to predict optimal formulation combinations. Breakthroughs in large-scale production technology will solve the bottlenecks of current preparation processes, and the application of microfluidic technology and continuous production processes is expected to realize the standardized production of high-quality LNPs.

In the direction of clinical translation, the development of personalized treatment regimens will be the focus, with LNP drug-loading systems customized based on the tumor characteristics of patients. In-depth exploration of combination therapy strategies will promote the synergistic application of LNPs with emerging technologies such as immunotherapy and gene editing. The establishment and standardization of a long-term toxicity evaluation system will advance the clinical translation process of LNP formulations, and a well-established pharmacokinetic research model will help accurately evaluate the safety of carriers.

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