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Mechanisms of Targeted Drug Delivery for Liver Cancer: Active, Passive, and Subcellular Strategies

Yang Tian, Yusheng Shi*

Department of Radiation Oncology, Zhuhai Clinical Medical College of Jinan University (Zhuhai People's Hospital, The Affiliated Hospital of Beijing Institute of Technology), Zhuhai, China
Email: *syszxm@hotmail.com

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Abstract

This article provides a comprehensive review of various approaches to targeted drug delivery for liver cancer, an area of significant need due to the limited effectiveness of current treatments. The article begins by highlighting the role of the liver in metabolism and discusses the high mortality associated with hepatocellular carcinoma (HCC). The shortcomings of traditional chemotherapy, such as multidrug resistance and off-target effects, necessitate the exploration of novel therapeutic strategies, with a focus on targeted approaches. The review details both passive and active targeting strategies. Passive targeting leverages the enhanced permeability and retention (EPR) effect and unique features of the tumor microenvironment, while active targeting employs specific ligands, such as peptides, antibodies, and proteins, to bind to overexpressed receptors on liver and tumor cells. The article further details many examples of active targeting using the asialoglycoprotein receptor (ASGPR), glycyrrhetinic acid (GA), transferrin receptor (TfR), and folate receptor (FR) on hepatocytes and tumor cells, demonstrating that there has been significant research effort put into this field. The importance of non-parenchymal cells in the liver is also discussed, and the article examines methods of targeting Kupffer cells, sinusoidal endothelial cells, and hepatic stellate cells for therapeutic benefit. The review goes on to cover the emerging field of subcellular targeting, including specific strategies to target the nucleus, mitochondria, and the endoplasmic reticulum/Golgi apparatus, noting that although there has been some progress, further research is needed in this area. The text finishes with a summary which acknowledges that while targeted therapies, including enzyme-activated prodrugs, such as Pradefovir, and other novel methods for drug delivery have shown significant promise, challenges remain in translating these therapies into clinical use due to limitations in understanding the

sequential transport and the mechanisms of action. Ultimately, the article emphasizes the need for in-depth research to fully realize the potential of precision cancer therapies for liver cancer.

Keywords

Targeted Drug Delivery, Hepatocellular Carcinoma (HCC), Active Targeting, Subcellular Targeting, Nanomedicine

1. Introduction

The liver is a vital metabolic organ in the human body, playing a crucial role in the metabolism of carbohydrates, fats, proteins, vitamins, and hormones [1]. Common clinical liver diseases include hepatitis, liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) [2]. In 2020, approximately 906,000 individuals were diagnosed with liver cancer worldwide, HCC is the sixth most common cancer and the fourth leading cause of cancer-related mortality [3]. HCC represents the most frequently encountered primary liver malignancy. Globally, HCC ranks as the third leading cause of cancer-related mortality, exhibiting a comparatively low 5-year survival rate of approximately 18%. The near equivalence of annual incidence and mortality rates (approximately 830,000 deaths per year) highlights the poor prognosis associated with this disease [4]. HCC is generally highly malignant with a poor prognosis, and in the majority of cases, it develops on a background of chronic hepatitis or cirrhosis. Symptoms are often subtle in the early stages; as the disease progresses, manifestations such as abdominal pain, abdominal masses, decreased appetite, fatigue, and progressive weight loss may gradually appear, making early diagnosis extremely challenging [5].

In the therapeutic landscape of hepatocellular carcinoma, efficacy data exhibit considerable heterogeneity. Surgical resection, for instance, yields an approximate 5-year overall survival rate of 70%; however, it is accompanied by a high recurrence rate of up to 80%. Liver transplantation demonstrates a 5-year survival rate ranging from 75% to 80%, with a recurrence risk of approximately 15%. Among non-surgical approaches, ablation therapies, intra-arterial treatments, and systemic therapies each contribute to varying degrees of therapeutic benefit. Radiofrequency ablation (RFA), for example, can achieve remission rates of 70%–90% for small tumors. Transarterial chemoembolization (TACE) can prolong median survival to 20 - 36 months [4]. Currently, surgical resection and liver transplantation are the primary treatment options for patients with early-stage HCC. However, due to the long latency period of HCC, most patients are diagnosed at intermediate or advanced stages at their initial presentation. Chemotherapy is a commonly used treatment for advanced and end-stage HCC. However, traditional chemotherapy for HCC is associated with several negative effects, such as multidrug resistance, high clearance rates, significant side effects, and unfavorable drug distribution [6]. In light of the numerous challenges associated with traditional

HCC chemotherapy, there is an urgent need to explore novel therapeutic approaches. Fortunately, the development and application of targeted therapies in medicine and human health have brought hope for achieving comprehensive diagnosis and treatment of HCC.

2. Mechanism of Action of Targeted Therapy

Targeted therapy works by identifying and binding to specific receptors on the surface of liver cancer cells, or to specific subcellular receptors, thereby blocking signaling pathways that promote cancer cell growth. This, in turn, aims to inhibit tumor cell proliferation, metastasis, and angiogenesis.

Currently, nanotechnology-based drug delivery systems for targeted cancer therapy have garnered increasing attention from researchers due to their ability to precisely deliver therapeutic agents to tumor sites [7]. Targeting strategies can be broadly categorized as either passive or active [8]. Active targeting is based on the use of specific ligands, such as peptides, proteins, and antibodies, that can specifically bind to overexpressed receptors on tumor cells. Passive targeting relies on the accumulation of nanoparticles with specific physicochemical properties (size, charge, etc.) within tumor tissue. This accumulation occurs due to the enhanced permeability and retention (EPR) effect and specific characteristics of the tumor microenvironment [9]. While active targeting exhibits high specificity, it can be limited by factors such as the high cost of ligands and potential immunogenicity. Passive targeting, on the other hand, is relatively simple to prepare and less expensive, but its targeting precision is comparatively limited.

3. Drug Targeting Mechanisms

3.1. Active Targeting

Active targeting relies on ligands that can specifically bind to overexpressed receptors on tumor cells, such as peptides, proteins, and antibodies. Receptors overexpressed on the surface of hepatocytes include asialoglycoprotein receptors (ASGPR), glycyrrhetinic acid receptors (GaR), transferrin receptors (TfR), and folate receptors (FR) [10]. Specific ligands developed against these receptors can be used to construct active targeted drug delivery systems, enhancing the targeting specificity of drugs for liver cancer cells. For example, conjugating nanoparticles containing ligands that recognize ASGPR with chemotherapeutic drugs can enable precise drug accumulation in liver cancer cells, thereby improving therapeutic efficacy. Active targeting strategies enable targeted drug delivery to hepatocytes, thereby increasing drug concentration within the target area and potentially enhancing efficacy while reducing toxicity. Numerous carrier materials are currently under investigation in preclinical studies; however, the attainment of their anticipated performance remains uncertain [11].

3.1.1. Hepatocytes

The liver is composed of hepatocytes and non-parenchymal cells, with hepatocytes

comprising approximately 60% to 70% of the total liver cell population [10] [12]. They are one of the fundamental structural units of the liver. Hepatocytes perform functions such as metabolism, bile production, and glycogen synthesis, and are associated with pathophysiological changes in conditions like acute hepatitis, cirrhosis, and liver abscess. Therefore, treatment of hepatocyte pathologies is particularly important.

1) Asialoglycoprotein Receptor (ASGPR)

ASGPR, also known as the galactose receptor, is the first identified mammalian lectin. It is predominantly expressed on the surface of hepatocytes and is rarely found on extrahepatic cells [12]. Negrete M. *et al.* developed two types of sugar-coated polydiacetylene nanomicelles-sorafenib carriers that target asialoglycoprotein receptor (ASGPR). These carriers induced apoptosis and reduced cell proliferation in liver cancer cells within the nanomolar (rather than micromolar) range [13]. Li T. designed and developed a novel asialoglycoprotein receptor (ASGPR)-targeted pegylated paclitaxel (PTX) nanoliposome for hepatocellular carcinoma (HCC). Their research demonstrated that this targeted liposome delivery system could not only alter the expression of cyclins but also enhance the killing effect of PTX on liver cancer cells [14].

2) Glycyrrhetinic Acid (GA)

Glycyrrhetinic acid (GA) is a glycosidic aglycone derived from the intestinal hydrolysis of glycyrrhizin. It has been reported to possess pharmacological activities such as hepatoprotective and antitumor effects [15]. Since GA receptors are expressed on the surface of mammalian hepatocytes, GA has been used as a ligand for liver targeting. Therefore, it can be used to modify drug delivery systems (DDS) and achieve improved drug uptake and therapeutic efficacy in the liver or hepatocytes [16]. Pan XW *et al.* investigated artemether-loaded and glycyrrhetinic acid-modified ART/GA-PEG-PLGA nanoparticles. The GA coating enhanced cellular uptake by liver tumor cells through endocytosis, exhibiting pro-apoptotic effects on HepG2 cells. These nanoparticles demonstrated high liver accumulation, prolonged retention, high bioavailability, promoted targeted drug distribution, and enhanced antitumor effects [17]. Sang *et al.* [18] incorporated glycyrrhetinic acid (GA) into their study on the preparation of chlorambucil (CLB)-chitosan prodrug micelles. GA was shown to improve the immunosuppressive microenvironment, target liver cancer cells, and synergize with CLB. Through interference with DNA replication and modulation of the tumor microenvironment, this approach effectively treated liver cancer. Qiu M. *et al.* [19] designed dual-ligand liposomes modified with both GA and cRGD, denoted GA/cRGD-LP, targeting GA receptors and $\alpha v\beta 3$ integrin, respectively, to enhance antitumor effects. Following a series of evaluations, these drug-loaded liposomes exhibited compliant particle size, potential, and morphology, as well as good cellular uptake, the ability to prolong drug circulation time in the blood, and the ability to inhibit tumor growth and improve liver tumor localization. This system has been demonstrated to be a promising targeted drug delivery system for liver cancer therapy.

In addition to the aforementioned liver-targeting drug delivery systems, bile acid receptor (BAR)- and scavenger receptor (SR)-mediated liver-targeting drug delivery systems also exist [20] [21].

3.1.2. Liver Tumor Cells

Liver cancer primarily comprises two major types: primary liver cancer and secondary liver cancer, with hepatocellular carcinoma (HCC) accounting for approximately 90% of primary liver cancers [22]. Liver tumor cell-targeted drug delivery systems can selectively deliver drugs to tumor cells, increasing drug concentration and effectively reducing adverse reactions and toxic side effects.

1) Folate Receptor (FR)

receptor (FR) is a potential solution for addressing the low tumor selectivity of conventional chemotherapeutic drugs [23]. In addition to antibody-drug conjugates, folate-functionalized nanoparticle drug delivery systems are also worth exploring due to their many advantages, though it seems they have not yet entered clinical trials [24]. Activated hepatic stellate cells (aHSCs) are a primary target for anti-fibrotic nanomedicines. Given that activated HSCs increase the expression of folate receptor α (FRα), Xiang L. *et al.* [25] explored the use of folate (FA) modification to target aHSCs and inhibit liver fibrosis. They synthesized FA-conjugated copolymers that self-assembled into spherical micelles with uniform size, good blood and cell compatibility, and pH-sensitive stability. FA-modified micelles were preferentially taken up by aHSCs and accumulated more in the livers of mice with acute liver injury. This contributed to a greater therapeutic effect of loaded camptothecin (CPT), inhibiting related genes in aHSCs. Encouragingly, free CPT and non-targeted CPT micelles showed poor efficacy, while FA-modified CPT micelles effectively improved the condition of mice with chronic liver fibrosis, marking the success of this targeting strategy.

2) Transferrin Receptor (TfR)

The transferrin receptor (TfR) is a type of transmembrane glycoprotein that is widely distributed in vertebrates. It is expressed at low levels in normal cells but is present at higher levels in tumor cells. Triptolide (TP) can inhibit the proliferation of liver cancer cells, but its application is limited by issues such as solubility, bioavailability, and adverse reactions. Researchers prepared transferrin-modified TP liposomes using the thin-film hydration method. Transferrin modification enhanced the tumor targeting ability and antitumor effects of the liposomes. The clinical application potential of transferrin-modified triptolide liposomes (TF-TP-LIP) warrants further investigation [26].

3) Antibody-Drug Conjugates (ADCs)

Antibody-drug conjugates (ADCs) are a class of tumor cell-targeted drugs that have rapidly developed in recent years. Tian H. *et al.* [27] developed an antibody-modified prodrug nanoparticle based on the biopolymer dextran (DEX) for delivering the antitumor drug doxorubicin (DOX). First, oxidized dextran (ODEX) and DOX were linked through a Schiff base reaction to form ODEX-DOX, which could self-assemble into nanoparticles (NPs) with some aldehyde groups. Subsequently,

the amino groups of the CD147 monoclonal antibody were bound to the aldehyde groups on the surface of ODEX-DOX NPs, resulting in acid-responsive and antibody-modified CD147-ODEX-DOX NPs with a relatively small particle size and high DOX loading. The results showed that this acid-sensitive nanomedicine had higher safety and targeting effects. Gan *et al.* [28] developed a novel sorafenib-loaded polymeric nanoparticle (NP-SFB-Ab) that was linked to GPC-3. antitumor experiments showed that NP-SFB-Ab had a stronger killing ability against HepG2 cells than free SFB, SFB nanoparticles (NP-SFB), and non-drug-loaded nanoparticles (NP) at the same concentration. Furthermore, NP-SFB-Ab significantly inhibited tumor growth, outperforming both SFB and NP-SFB.

4) Low-Density Lipoprotein (LDL) Receptor

The low-density lipoprotein (LDL) receptor has been confirmed to be upregulated on the surface of many cancer cell lines, including liver cancer [29]. Ao *et al.* [30] prepared low-density lipoprotein-modified silica nanoparticles that co-delivered docetaxel (DTX) and thalidomide (TDD) (a docetaxel and thalidomide co-delivery system based on low-density lipoprotein-modified silica nanoparticles, LDL/SLN/DTX/TDD) analyses showed that LDL/SLN/DTX/TDD had a good drug-loading capacity and could enhance delivery efficiency by targeting the low-density lipoprotein receptor. It also exhibited higher cytotoxicity against HepG2 cells compared to unmodified silica nanoparticles and free drugs. Imaging and anticancer assays further confirmed that LDL/SLN/DTX/TDD had good tumor homing and synergistic anticancer effects.

3.1.3. Liver Non-Parenchymal Cells

Liver non-parenchymal cells include Kupffer cells (KCs), sinusoidal endothelial cells (SECs), and hepatic stellate cells (HSCs). These cells comprise approximately 30% of the total liver cell population and 8% of the liver volume [31] [32]. KCs are macrophages within liver sinusoids, accounting for over 80% of the body's total monocyte-macrophage population. They are key mediators of liver injury and repair, play an important defensive function, and can phagocytose and clear foreign substances from the blood. SECs are highly specialized endothelial cells that can play a role in the development of hepatocellular carcinoma and liver pathologies associated with inflammation and infection [31]. HSCs are the primary cells responsible for secreting the extracellular matrix in the liver and are a major driver of liver fibrosis [33]. Therefore, liver non-parenchymal cells are of significant importance for the treatment of liver diseases.

1) Macrophages Expressing the Mannose Receptor (MMR)

Macrophages expressing the mannose receptor (MMR) play important roles throughout the body. Anti-inflammatory macrophages expressing the mannose receptor (MMR) are involved in disease development. Zhou JE *et al.* [34] investigated the construction of a mannose-modified HMGB1-siRNA-loaded stable nucleic acid lipid particle delivery system (mLNP-siHMGB1) to target liver macrophages via the mannose receptor, thereby silencing HMGB1 protein expression and treating NASH. This system effectively silenced the HMGB1 gene, reduced

HMGB1 protein release in the liver, and modulated liver macrophages toward an anti-inflammatory M2 phenotype, effectively alleviating hepatic lobular inflammation and hepatic macrovesicular steatosis, and restoring liver function to normal levels in NASH model mice.

2) Hyaluronic Acid (HA)

Hyaluronic acid (HA) is a major component of the extracellular matrix and intercellular substance. It is primarily synthesized by hepatic stellate cells and degraded by sinusoidal endothelial cells. It possesses characteristics such as good biocompatibility and biodegradability, making it a commonly used drug delivery carrier [35]. Transforming growth factor-β1 (TGF-β1) plays a key role in promoting liver fibrosis. Pirfenidone (PFD) can inhibit the TGF-β1 signaling pathway, alleviating liver fibrosis mediated by activated hepatic stellate cells (HSCs). Yu F. *et al.* developed a targeted strategy to deliver PFD to HSCs by modifying DSPE-PEG_{2000}-coated extracellular vesicles (EVs) with hyaluronic acid (HA), which gave activated HSCs the ability to actively target PFD-loaded EVs via overexpressed CD44. In a liver fibrosis model, 4 weeks of HA@EVs-PFD treatment resulted in reduced liver collagen fibers, significantly improved hepatocyte morphology, and ameliorated liver fibrosis. HA@EVs-PFD holds promise as a potential therapeutic agent against liver fibrosis. Ashour AA *et al.* [36] used sodium hyaluronate or phosphatidylserine to modify novel modified lipid nanocapsules (LNCs), both blank and loaded with TSIIA. Biodistribution studies demonstrated the liver-targeting ability of the prepared modified LNCs, with a significant 1.5-fold increase in liver accumulation compared to the unmodified formulation ($p \leq 0.05$). Furthermore, the modified formulations showed better anti-fibrotic effects compared to unmodified LNCs and TSIIA suspensions. These modified TSIIA-LNCs can be considered promising novel targeted nanomedicines for the effective treatment of liver fibrosis.

3) Retinol-Binding Protein (RBP)

Retinol-binding protein (RBP) is a lipophilic carrier protein responsible for the uptake and storage of vitamin A (VA). Hepatic stellate cells (HSCs) store 80% of the body's VA [37]. The research aim of Xiong Y. *et al.* was to develop an anti-HF drug delivery system using retinoic acid (RA)-modified acrylic resin (Eudragit® RS100, Eud RS100) nanoparticles (NPs). This modification could enable the nanoparticles to bind to the retinol-binding protein reporter gene (RBPR) in HSCs, thus achieving targeted delivery to HSCs. Galangin (GA), a multi-potent flavonoid, has been shown to have anti-HF effects in previous studies. The results indicated that retinoic acid-modified GA NPs represent a promising candidate for developing drug delivery systems for the treatment of HF [38].

In addition to the aforementioned reports, studies have also shown that mannose-6-phosphate/insulin-like growth factor (M6P/IGFII) can activate HSCs, subsequently upregulating the levels of the M6P/IGFII receptor on their surface. Therefore, M6P/IGFII can serve as a specific target for the treatment of liver fibrosis [35] [39].

3.2. Passive Targeting

Passive targeting relies on the accumulation of nanoparticles with specific physicochemical properties (size, charge, etc.) within tumor tissue. This accumulation is due to the enhanced permeability and retention (EPR) effect and the specific tumor microenvironment, and it also depends on the physicochemical properties of the carrier (such as shape, size, and carrier surface) and important characteristics of cancer cells (such as temperature, pH, and tumor cell surface charge) [40]. Passive-targeting nanoparticles leverage the enhanced permeability and retention (EPR) effect within tumors to achieve targeted delivery. This approach offers the advantages of simplicity and broad applicability; however, due to limitations imposed by nanoparticle size, its targeting efficacy can be inconsistent, hindering precise target engagement [41].

3.2.1. Passive Liver Accumulation

Chimalakonda *et al.* [42] used a succinic acid linker to conjugate the antiviral drug lamivudine (3TC) with 25 kDa dextran, generating 3TCSD, which accumulated in the liver at levels 50 times greater than the parent drug. In addition, Chimalakonda *et al.* [42] used a succinic acid linker to conjugate methylprednisolone (MP) with 70 kDa dextran to generate DMP. The results showed that DMP could selectively deliver methylprednisolone (MP) to the liver.

3.2.2. Transporter-Mediated Uptake

Bile acids (BAs) have a planar amphipathic structure, and drugs can be conjugated to different positions on the BA molecule through various chemical bonds, such as ester, ether, and amide bonds. Bile acid conjugates or bile acid mimics can target organs involved in enterohepatic circulation [43] [44]. As a bile acid transporter, NTCP facilitates liver targeting using bile acid conjugates or bile acid mimics due to its expression in hepatocytes. To reduce potential hemolytic anemia caused by ribavirin treatment for hepatitis C, Dong *et al.* [45] conjugated ribavirin to a bile acid using an amino acid linker. This conjugate could release ribavirin in the liver S9 fraction of mice, with exposure in the liver S9 fraction being nearly the same as when ribavirin is administered directly. However, exposure in erythrocytes, plasma, and kidneys was approximately 1.8 times lower. Xiao *et al.* [46] synthesized a series of CPT-bile acid analogs and screened out a deoxycholic acid-CPT conjugate, which improved the liver targeting index and stability.

3.2.3. Enzyme-Activated Prodrugs

HepDirect prodrugs are a class of novel cyclic phosphate or phosphonate prodrugs discovered by Erion *et al.* that can be activated by CYP450. Pradefovir, a HepDirect prodrug of adefovir, has entered Phase III clinical trials [47]. NQO1 is overexpressed in HCC, and this characteristic can be utilized for the enzyme-directed reductive activation design of anti-hepatocellular carcinoma prodrugs. For example, the quinone moiety of CX-23 binds to the residues of the NQO1 active site and the FAD required for NQO1 catalytic activity. This approach can not only

inhibit the progression of hepatocellular carcinoma but also reduce hepatorenal toxicity [48].

3.2.4. Environment-Responsive

Structures such as amide bonds, ester bonds, anhydride bonds, and hydrazone bonds are readily hydrolyzed in acidic environments, and they are therefore commonly used in pH-responsive prodrugs. Li *et al.* [49] condensed doxorubicin (DOX) modified with *cis*-aconitic anhydride with dextran, establishing a self-targeting drug delivery system (Dex-g-DOX) for the treatment of orthotopic hepatocellular carcinoma. Dex-g-DOX could self-assemble into micellar nanoparticles under physiological conditions. The inherent targeting properties of dextran enabled a high accumulation of the nanoparticles in the liver, followed by selective release of DOX in acidic endosomes or lysosomes, exhibiting high antitumor efficacy.

3.3. Subcellular Targeting

Non-specific distribution of drugs in the body can lead to limited efficacy and the occurrence of side effects, making targeted drug delivery a focus of attention. Currently, targeted drug delivery has evolved from the tissue and cellular levels to the subcellular level. The precise delivery of drugs to specific organelles can improve therapeutic efficacy and reduce toxicity, making it an important direction for drug delivery. Certain therapeutic agents exhibit the capacity for specific localization within particular organelles. Even subtle structural modifications to drug molecules can fundamentally alter their subcellular distribution, thereby influencing both efficacy and safety profiles. Current delivery systems are predominantly evaluated in vitro, presenting a significant disparity with *in vivo* environment, thus raising concerns regarding their in vivo relevance and therapeutic effectiveness. Further in-depth investigations are warranted to provide a robust foundation for clinical translation [50].

3.3.1. Nuclear Targeting

Many anticancer drugs are designed to disrupt the genes of cancer cells in order to inhibit their proliferation, which means that these drugs must act after entering the nucleus of cancer cells [51]. However, the delivery of drugs to the nucleus faces barriers presented by the cell membrane and nuclear membrane, resulting in lower-than-ideal efficiency. For example, engineered modular DNA carrier (MDC) proteins have been used as protein-DNA nanoparticle carriers, which include sperm chromatin component protamine for cell-level targeting, the endosomal translocation domain of diphtheria toxin, and sequences for optimized nuclear localization. Inside cancer cells, MDCs interact with nuclear transport proteins and are actively transported to the nucleus to exert their effects [51]. pH-responsive core-shell nanoparticles (CSNPs) utilize TAT peptides to deliver drugs to the nucleus under specific conditions [52]

Small molecules such as dexamethasone and 10-hydroxycamptothecin (HCPT) can be used to modify nuclear-targeted drug delivery systems. For example,

multifunctional shell cross-linked nanoparticles (SCNPs) that combine RGD peptides with a super-pH-sensitive PDPA core can deliver doxorubicin (DOX) to the nucleus. Hyaluronic acid (HA)-modified mesoporous silica nanoparticles (MSNs), when combined with folate (FA) and dexamethasone (DEX), can achieve tumor cell targeting and nuclear targeting [53] [54].

In addition to the aforementioned, Aptamers are also used for nuclear targeting. Aptamers are synthetically produced short single-stranded RNA or DNA molecules that exhibit high specificity and affinity, with low immunogenicity and toxicity [55].

3.3.2. Mitochondrial Targeting

Mitochondria are double-membrane-bound organelles and are among the most important organelles for energy production and metabolic regulation in eukaryotes [56]. Cancer cells have an abnormal mitochondrial function, which can serve as a target for cancer therapy. Drugs must bind to active components, be transported to the mitochondria, and accumulate there to exert their therapeutic effects.

1) Lipophilic Cations

The composition and membrane potential of the mitochondria give it the characteristic of accumulating cations [57]. For example, TPP-modified silica nanoparticles, when combined with HA, can deliver DOX to the mitochondria of cancer cells. DQA-modified paclitaxel-loaded liposomes, when combined with HA, can enhance drug accumulation in the mitochondria, exhibiting a higher inhibitory effect on cancer cells [58].

2) Mitochondrial-Penetrating Peptides

Mitochondrial-penetrating peptides (MPPs) can be effectively taken up by a variety of cells. By considering specific chemical properties, peptide sequences can be synthesized that specifically bind to different organelles. MPPs are designed to be cationic and lipophilic, and they can be targeted to mitochondria by rationally controlling their lipophilicity and charge [58]. Nanoparticle systems that combine mitochondrial localization sequence (MLS) peptides and FA can achieve sequential targeting of cancer cells, enhancing cellular uptake of DOX [59].

3.3.3. Endoplasmic Reticulum and Golgi Apparatus

The endoplasmic reticulum and Golgi apparatus are involved in protein synthesis, processing, and transport [60]. Dysfunction of these organelles can trigger cell death, making them potential targets for cancer therapy. Nanoparticles can deliver drugs to tumor cells via endocytosis. For example, cell-penetrating peptide (CPP)-conjugated lipid/polymer hybrid nanovesicles (LPNVs) can achieve endoplasmic reticulum-targeted delivery, inducing apoptosis in cancer cells [61]. However, there is currently limited research on sequential delivery systems targeting the endoplasmic reticulum/Golgi apparatus, mainly due to an unclear targeting mechanism.

4. Summary

Passive targeting utilizes the physiological characteristics of the liver to achieve

drug accumulation, but it is limited by uneven drug distribution and non-specific uptake. Notably, active targeting overcomes these issues through specific interactions, improving targeting specificity and efficacy. Future research efforts must prioritize addressing the challenges impeding the translation of nanomedicine delivery systems from bench to bedside. On the one hand, it is imperative to resolve the complexities associated with the large-scale production of nanoformulations. This entails optimizing manufacturing processes to achieve stable, reproducible production, coupled with rigorous control of their physicochemical properties. On the other hand, in-depth assessments of nanomedicine safety and efficacy are crucial, necessitating the selection of disease models that more closely recapitulate the pathogenetic mechanisms of hepatic disorders. This strategy aims to minimize discrepancies between preclinical and clinical findings. Research on liver-targeted prodrugs has made progress, as seen in the development of drugs such as Pepaxto and Pradefovir, and it is hoped that future developments will provide more effective and safe treatment options for patients with liver disease. However, several challenges remain, such as an insufficient understanding of sequential transport and treatment mechanisms, which hinder clinical translation. Furthermore, liver-targeting drug carriers can be engineered to incorporate stimuli-responsive moieties, such as those sensitive to pH, temperature, light, or oxidative stress, to facilitate drug accumulation and selective release within the hepatic environment. However, to enhance the translational value of current nanomedicine research, continuous exploration and further in-depth investigations are warranted to propel the advancement of precision oncology. The translation of targeting nanoformulations from bench to bedside presents substantial challenges, a critical consideration that warrants careful attention throughout the research process.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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