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Advances in liver-targeted nanodelivery systems based on lactobionic acid

Yaoyao Jiang, Yanxi Deng
Department of Pharmaceutical Engineering, College of Life Science and Agri-forestry, Southwest University of Science and Technology, Mianyang, Sichuan, China

Abstract
In order to improve the solubility, stability and bioavailability of drugs, targeted nano-delivery systems have become a major hotspot in research. And because of its targeted delivery and precise release of drugs, as well as improved efficacy and reduced adverse effects, it shows great potential in the development of precision medicine. Lactobionic acid, which contains galactose and gluconic acid, has efficient liver cancer targeting ability, and has various physiological activities such as antioxidant, free radical scavenging and good biocompatibility. Lactobionic acid-based nanodelivery systems for hepatocellular carcinoma have recognition specificity and high therapeutic efficiency, which helps in the delivery of chemotherapeutic agents or gene drugs. This paper focuses on the mechanism of action of lactobionic acid with hepatocellular carcinoma targeting ability and the research progress of lactobionic acid-based hepatocellular carcinoma-targeting nanosystems, and hopes to provide a reference for related researchers for the development of new delivery systems.

Keywords: Lactobionic acid; drug delivery system; nanocarriers; tumour targeting; hepatocellular carcinoma

Introduction

Primary liver cancer is a malignant tumour that mainly occurs in hepatocytes or intrahepatic bile duct epithelial cells. Primary hepatocellular carcinoma (HCC) is the main type of primary liver cancer, accounting for about 90% of the total incidence of liver cancer, with the sixth highest incidence rate and the fourth highest mortality rate among cancers in the world. [1]. HCC is one of the most common malignant tumours of high malignancy in our country, especially in regions with high prevalence of hepatitis virus infection. It is more prevalent [2, 3]. Early-stage liver cancer treatment options are mainly surgical resection, liver transplantation, local ablation, etc. The survival rate after treatment can reach 70%~80%, but up to 70% will still have recurrence and metastasis 5 years after surgery [4, 5]. Whereas, the middle and late stages of the disease are mainly treated by systemic systemic administration of drugs. Chemotherapy is the mainstay of advanced HCC treatment but with high side effects and limited efficacy [6, 7]. Therefore, there is an urgent need to develop new therapeutic options to improve the survival of HCC patients. Targeted nanodelivery system provides a new therapeutic option for liver cancer treatment by modifying liver cancer-specific ligands on the surface of nanoparticles to achieve targeted delivery to liver cancer cells [8]. Currently, desialylate glycoprotein receptor (ASGP-R), glycopyrrolate receptor (GA-R), transferrin receptor (TF-R), folate receptor (FA-R), epidermal growth factor receptor ((ECF-R), hyaluronic acid (HA) receptor, and mannose receptor (MR) have been found to be overexpressed in hepatocellular carcinoma cells [8, 9], and based on this feature, nanoparticles were modified to induce intracellular drug release via receptor-mediated endocytosis thereby reducing side effects and improving efficacy. However, GA-R is affected by blood circulation and drug extravasation, and the actual amount of drug reaching the site of action is not ideal. Mannose receptor has mannose component, which can stimulate phagocytes to enhance their phagocytosis and improve immunity significantly, but some studies believe that it cannot carry out signal transduction alone, and requires the participation of other receptors. And the nanocarriers modified by FA will be affected by immunoglobulin, hindering the recognition of FA receptor and accelerating the activation of complement *in vivo*, which will make reduce the targeting ability and insufficient stability of the targeting system [10].

Lactobionic acid (LA), chemically known as 4-O-β-galactopyranosyl-D-gluconic acid, is derived from one molecule of gluconic acid and one molecule of galactose linked by an ether bond (Fig.1), and the breakdown products are glucose and galactose. Lactobionic acid has a variety of physiological functions such as antioxidant, free radical scavenging, antibacterial, anti-aging, and anti-obesity. In current studies, LA is commonly used as a ligand for liver cancer targeting, and LA-modified nano drug delivery system (LA-TNDDS) was found to have excellent liver cancer targeting properties.

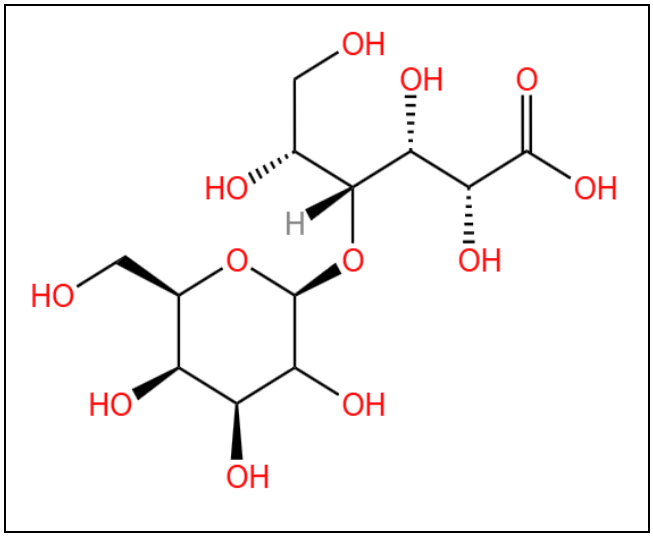

Fig 1: Chemical structure of lactobionic acid (LA)

1. Mechanism of action of LA with liver-targeting ability

The desialylate glycoprotein receptor (ASGPr) is a lectin that specifically binds desialylate glycoproteins. The salivary acid molecules in these glycoproteins have been removed, exposing the galactose site [11]. It has been found that the recognition of GalNAc and Gal by the glycan recognition structural domain (CRD) of ASGPr is dependent on Ca^{2+}.In the presence of PH>6 and Ca^{2+}, ASGPr first binds to ligands with GalNAc or Gal at the end to form a complex, which is rapidly internalised into hepatocytes mediated by the lattice proteins' receptor. Upon entry into the hepatocyte, the receptor-ligand polymer is dissociated, the glycoligand is delivered to the lysosome for degradation, and ASGPr is actively transported to the cell membrane surface, where it participates in a new round of ASGPR cycling [12, 13]. ASGPr is highly expressed on the surface of hepatocytes and various human HCC cell lines [14, 15]. In 15-week-old human foetal livers, ASGPr was predominantly present in the cytoplasm. As hepatoblasts differentiate into hepatocytes, the distribution of ASGP receptors gradually shifts to the cell surface [16].

Lactobionic acid contains a galactosyl group in its structure and therefore specifically recognises and binds to ASGPr. By modifying lactobionic acid onto the surface of proteins and polymers as well as various carriers, researchers have been able to deliver drugs specifically to hepatocytes in order to enhance drug efficacy and reduce side effects. For example, LA-modified mesoporous silica nanocarriers loaded with adriamycin (DOX/LA-MSN) were found in high levels in the vicinity of HepG2 hepatocellular carcinoma cells and inside the cytoplasm, whereas it was hardly found in 293T cells, which is an indication of high targeting of LA-MSN nanomedicine carriers. And based on the property that adriamycin has red fluorescence, it was found that the most red fluorescent substances contained in the cells were in the DOX/LA-MSN experimental group, which indicated a better drug uptake ability of the DOX/LA-MSN group [17]. Taken together with previous studies, LA-R has significant advantages in achieving efficient targeting in liver cancer.

LA as a nanodelivery system for liver cancer targets

Currently, LA has good research prospects for liver cancer targeted drug delivery systems. Researchers have made full use of the structural features of LA to design a variety of LA-modified drug delivery systems for hepatocellular carcinoma, including liposomes, micelles, inorganic nanoparticles, metal-organic frameworks, polymeric nanoparticles, LA-drug couplings, derivatives, gels, and so on.

1. Liposomes

Liposomes are widely used in the study of drug delivery systems due to their good biocompatibility, low toxicity, and ability to encapsulate a wide range of drugs, and are considered to have great potential for development. However, conventional liposomes suffer from problems such as non-specific distribution and imprecise drug release during drug delivery, limiting further enhancement of their efficacy [18, 19].

Lactobionic acid (LA), as a ligand with liver-targeting properties, can modify liposomes and thus form targeted liposomes. Guo *et al*. synthesized a series of products by enzymatic catalysis of lactobionic acid and octadecylamine, during which the authors repeatedly optimized the reaction conditions (e.g., enzyme type, reaction medium, enzyme incorporation, substrate molar ratio, reaction temperature, etc.) in order to improve the conversion of octadecylamine, and employed techniques such as infrared spectroscopy (IR), mass spectrometry (ESI-MS) and nuclear magnetic resonance (1H-NMR) to structurally The structure of the synthesized product was confirmed by IR, mass spectrometry (ESI-MS) and nuclear magnetic resonance (1H-NMR), and the target product, N-octadecyl-4- [(D-galactopyranosyl)oxy]-2,3,5,6-tetrahydroxyhexanamide was finally screened, which provided an effective synthetic method for the development of novel liver-targeted liposomes [20].Bansal *et al*.Designed and prepared a lactobionic acid-coupled liposome (LA-LP) containing oxaliplatin (OX)) for targeted delivery of drugs to HCC cells [21]. The results of a series of experiments, including the characterisation of liposomes, cellular uptake assays, cytotoxicity assays and *in vivo* organ distribution studies, showed that LA-LP was able to efficiently deliver the drug to HCC cells by binding to ASGPR, increasing the efficacy of the drug and reducing the damage to normal cells.Dayani *et al*. developed a novel liposomal drug delivery system using a lactobionic acid-human serum albumin conjugate (LA- HAS conjugate) of SF-loaded ALNs for targeted therapy of HCC [22]. The results of *in vitro* drug study release studies showed that the release profiles of SF from targeted and non-targeted ALNs were similar and showed zero-grade kinetic release at a certain pH; the cumulative release rate of SF from ALNs was much higher than that from SF suspensions, which was about 100%, after 8 hours. The results of the *in vivo* experimental study showed that the cellular uptake and cytotoxicity of targeted ALNs were significantly higher than that of non-targeted ALNs, which is expected to improve the efficacy and reduce the side effects of SF in HCC treatment.

Lactobionic acid liposomes can also be used for multimodal imaging and therapy. Liu *et al*. provided a multifunctional nanoprobe suitable for magnetic resonance imaging (MRI), CT imaging, near-infrared fluorescence imaging, and targeted photothermal therapy of liver cancer [23]. The nanoprobe structure consists of a core (gold nanoparticles coated with a polydopamine (PDA) layer and adsorbed with indocyanine green (ICG)) and a shell (a DSPE-PEG liposome membrane coupled with lactobionic acid (LA) and integrated with Gd ions). It is proved that the nanoprobe can be used in MRI, CT imaging and near-infrared fluorescence imaging, which can improve the imaging sensitivity, reduce the dosage of contrast agent and alleviate the toxic side effects; under the irradiation of 808 nm near-infrared light, the adsorbed ICG molecules can convert the light energy into heat energy, generate a high temperature of 60-70 ℃, and thermally kill the hepatocellular carcinoma cells, which is a remarkable prospect for clinical application.

2. Micelles

Micelles are nanoscale (1-200 nm) spherical aggregates formed by self-assembly of amphiphilic copolymers with hydrophilic and hydrophobic blocks in aqueous medium [24], which have been widely used as drug aggregates for targeted delivery of chemotherapeutic drugs [25]. Wang *et al*. obtained a multifunctional supramolecular pre-drug micelles, which can be effectively enriched in tumour cells and also inhibit tumour proliferation, by using the targeting

property of lactobionic acid, which was prepared through the assembly of host-guest molecules [26].

To address the problems of low water solubility, short half-life, and severe side effects of chemotherapeutic drugs, Chen *et al*. coupled LA-modified hydroxyethyl starch (HES) with cisplatin pre-drugs to obtain LA-HES-Pt [27]. Quantitative flow cytometry measurements showed that the modification of LA molecules increased the cellular uptake of HES by HepG2 cells by 4.1-fold. And by measuring the platinum content, LA-HES-Pt was 15.6-fold higher than the uptake rate of cisplatin, resulting in a significant increase in anti-tumour activity. Shao *et al*. prepared an LA-modified baicalin self-assembled micellar drug-carrying system (LA-CMBC) by acylation reaction, which showed significantly higher *in vitro* antitumour effect than baicalin, and the cell growth inhibition rate of LA-CMBC loaded with adriamycin was significantly higher than that of pure adriamycin [28].

3. Inorganic/metal nanoparticles

Lactobionic acid is also often combined with metal and inorganic nanomaterials for targeted drug delivery in hepatocellular carcinoma therapy, with mesoporous silica nanomaterials and graphene oxide being the main ones reported.

Mesoporous silica nanomaterials have stable physicochemical properties and are a class of non-toxic and biocompatible porous solid materials with a large specific surface area and high porosity [29]. In a study, Lactobionic acid (LA) was attached to the surface of the MSNs and CisPt (IV) to the pores of the MSNs by EDC/NHS chemistry, and MSNs with the ability to MSNs (MSN-P/LA-Pt) with the ability to target hepatocellular carcinoma cells [30]. The authors demonstrated through a series of *in vitro* and *in vivo* experiments that these nanoparticles are capable of rapid release of active platinum(II) in tumour cells with good targeting and low toxicity, which provides a new strategy for the chemotherapy of hepatocellular carcinoma.

NMOFs are a class of porous materials with highly ordered structure, large specific surface area and large pore volume, which are being also widely used in drug delivery [31, 32]. Fytory *et al*. developed a new type of doubly linked metal-organic frameworks (NMOFs) nanocarriers, and they used Zr(IV)-based NMOFs, which were synthesised by heating DMF containing ZrCl4 and 2-aminoterephthalic acid in DMF and HCL to synthesise the MOFs, and folic acid (FA), lactobionic acid (LA), glycyrrhetinic acid (GA), as well as bi-liganded LA and GA were successfully prepared as highly efficient and multifunctional drug delivery systems (DDSs) by forming amide bonds with the amino groups on the surface of the NMOFs via the EDC/NHS chemical method [33]. The results showed that the dual-ligand NMOFs exhibited higher efficiency in terms of cellular uptake and cytotoxicity behaviours. Samui *et al*. investigated an in situ synthesized lactobionic acid (LA)-coupled NH2-MIL-53(Al) nanometal-organic frameworks (NMOFs) to achieve the targeted delivery of the anticancer drug, adriamycin (DOX), to hepatocellular carcinoma (HepG2) cells [34]. The experimental results demonstrated that LA-targeted NMOFs were not cytotoxic in both normal and hepatocellular carcinoma cells, and showed greater cytotoxicity to HepG2 cells than normal cells; moreover, NH2-MIL-53 NMOFs possessed intrinsic fluorescence properties, and their fluorescence intensity remained unchanged after binding to lactobionic acid, which provided new ideas and methods for the design and development of novel NMOFs-based drug delivery systems. ideas and methods.

Graphene oxide (GO), as an emerging carbon-based nanomaterial with large specific surface area and abundant oxygen-containing functional groups, has great potential for drug delivery. Pan *et al*. reported a targeted anticancer drug delivery system based on lactobionic acid and carboxymethyl chitosan-functionalized graphene oxide nanocomposites [35]. The system loads adriamycin (DOX) onto the composites by adsorption. Lactobionic acid-modified GO has high drug loading efficiency, pH-sensitive release properties, and good biocompatibility, and has great potential as a targeted anticancer drug delivery system because of its ability to selectively deliver the drug to hepatocellular carcinoma cells.

4. Polymer nanoparticles

LA is now widely used to confer targeting capabilities to polymer nanoparticles. PLGA is an FDA-approved biodegradable and biocompatible copolymer widely used in drug delivery systems. It is capable of maintaining effective concentrations of drugs in the body by controlling the rate and duration of drug release, thereby improving therapeutic efficacy and reducing side effects [36]. Kabil *et al*. prepared a novel dual-targeted polymeric nanocapsules (NCs) with folic acid (FA) and lactobionic acid (LA) as the targeting ligands and polylactide-hydroxyglycolic acid copolymer (PLGA) as the matrix loaded with the resveratrol analogue, pterostilbene (PTN) [37]. The dual-targeted FA/LA-PTN-PLGA NC exhibited the highest cellular uptake efficiency compared to PTN alone and unmodified nanocapsules, and enhanced internalisation of PTN, which resulted in improved antitumour activity of the drug and showed good hepatoprotective and antioxidant activities in HCC-induced animal models. By combining the lactic acid, chitosan, gold nanoparticles and PLGA, a novel non-viral gene delivery vector, lactic acid-chitosan functionalized gold-coated polylactide-hydroxyacetic acid copolymer (PLGA) nanoparticles was constructed, and the expression of the loaded luciferase gene was significantly higher in HepG2 cells than in HEK293 cells, indicating that these nanocomplexes have high specificity for cancer cells [38]. complexes were highly specific for cancer cells, and effective gene delivery and expression to HepG2 cells was achieved by lactate-functionalized gold nanoparticles. This study not only provides a new design idea for non-viral gene delivery vectors, but also demonstrates its potential in targeting hepatocytes for gene therapy. Wang *et al*. prepared prepared thymine chitosan nanoparticles (Thy-Cs NPs), and LBA decoration on the surface of the thymine chitosan NPs increased specific uptake of methotrexate (MTX) into hepatocellular carcinoma cells and showed enhanced growth inhibition in 3D multicellular tumour spheroids, enabling efficient delivery of MTX [39].

Interventional therapies targeting free radicals are widely used in the prevention and treatment of different diseases, and a series of small molecule free radical-targeted drugs are approved by the FDA for the treatment of free radical metabolism-related diseases. Small molecule drugs have limitations such as rapid renal metabolism and low specificity in *in vivo* applications, resulting in often unsatisfactory therapeutic effects [40]. The therapeutic system of targeted nanotechnology provides new opportunities for

the development of free radical therapies. Li *et al*. successfully constructed LCP nanoparticles using lactobionic acid as a targeting ligand for hepatocellular carcinoma cells [41]. The nanoparticles could be activated by cobalt ions released from modified cobalt coordination polymers (Co-CP) *and* successfully induced apoptosis and iron death *via* inhibition of glutathione peroxidase 4 and caused lipid peroxidation accumulation, thus enhancing the efficacy of free radical therapy. *In vitro* cellular uptake and anti-tumour effect studies have shown that LCP has an efficient cellular uptake rate as well as the ability to differentiate between HepG2 cells and normal cells.

5. Other

LA drug couplers are complexes obtained by linking LA with drug molecules by chemical chemical or biological methods. Peptide nucleic acids (PNAs) are capable of regulating gene expression but suffer from non-specific biodistribution and fast elimination rate after administration. Kumar *et al*. achieved efficient targeted delivery of lactobionic acid to hepatocytes by coupling it with peptide nucleic acids (PNAs) [42]. In the study, lactobionic acid was co-conjugated with N-acetylgalactosamine (GalNAc) as a ligand to target the desialylate glycoprotein receptor (ASGP-R) on the surface of hepatocytes, which significantly improved the accumulation and retention time of PNA in the liver. It was demonstrated that lactobionic acid-conjugated PNA exhibited good biodistribution, gene silencing effect, and safety *in vivo*.

Based on the specificity shown by LA for ASGPR, Lu *et al*. designed a lactobionic acid derivative (LABO) capable of targeting ASGPR (desialylate glycoprotein receptor), which, after being specifically carried around the tumour, can penetrate the dense extracellular matrix (ECM) to reach the tumour much more easily than the pre-nano-engineered drug due to its small small molecular structure. Meanwhile, high ECM and tumour cell membrane viscosity could induce LABO to self-assemble in situ via J-aggregation to generate LABO-based nanoparticles (LABO NPs), which significantly prolonged its retention time in the tumour and enhanced photodynamic therapy effects. In addition this study constructed 18 F-labelled PET probe (18F-LABO) and developed a novel integrator agent for HCC diagnosis and treatment, which enables specific diagnosis and photodynamic therapy of HCC by LABO and 18F-LABO, and provides new strategies and tools for the clinical treatment of HCC [43].

For single, limited hepatocellular carcinoma, hepatic resection is the treatment of choice. However, the rapid reduction in liver volume after surgery increases the risk of liver failure and postoperative mortality. Zheng *et al*. successfully developed a hydrogel based on carboxymethyl chitosan (CMCS), oxidised hyaluronic acid (OHA), and lactobionic acid (LA) as a means of loading umbilical cord mesenchymal stem cell (hucMSC)-derived exosomes (Exos) for liver liver regeneration after resection [44]. The introduction of hepatic adhesion of the hydrogel in this study of LA solved the problem of poor targeting of intravenously injected Exos to some extent.

Dendrimers are synthetic macromolecules with precise structures and functionalized surfaces [45], which have attracted much attention in the field of drug delivery due to their multifunctionality and efficient loading ability, making them ideal nanocarriers. Among them, polyamide-amine (PAMAM) dendrimers are the most widely studied and are commonly used for loading imaging and therapeutic agents for the integration of diagnostic, therapeutic and diagnostic treatment of tumours [46]. Fu *et al*. performed a series of chemical modifications on the fifth-generation (G5) PAMAMs using fluorescein isothiocyanate (FITC) and LA (or PEG-conjugated LA, PEG-LA), G5. NHAc-FI-LA and G5.NHAc-FI-PEG-LA affixes were synthesised for encapsulation of the model anticancer drug adriamycin (DOX) [47]. Flow cytometry and CLSM observations showed that the LA-modified dendrimer/DOX complexes were able to specifically target ASGPR-overexpressing HepG2 cells. Interestingly, the PEG spacer arm further enhanced this targeting specificity as well as the anti-tumour effect, providing a new drug delivery system and new ideas for targeted liver cancer therapy.

Conclusion and prospect

The application of precision medicine in chemotherapy and cancer treatment is gradually changing the paradigm of traditional cancer treatment and has become a major trend in the future development of medicine. Through accurate diagnosis and personalised treatment plans, precision medicine can significantly improve the effectiveness of chemotherapy, reduce unnecessary side effects and provide more effective treatment options for cancer patients.

By combining with a variety of nanomaterials (e.g. liposomes, micelles, inorganic nanoparticles, polymer nanoparticles, etc.), LA-modified nano-delivery systems can not only significantly improve drug solubility, stability and bioavailability, but also carry out specific diagnosis and reduce the distribution of the drug in non-target tissues through targeted delivery, reducing the side-effects and enhancing therapeutic efficacy. This also contributes to the development of precision medicine, and it is believed that LA-TNDDS can make greater breakthroughs in the field of precision treatment of liver cancer after more in-depth research.

Although LA-based targeted nanodelivery systems for hepatocellular carcinoma have made remarkable progress, there are still some challenges that need to be addressed. Firstly, the *in vivo* stability and long-term safety of LA-modified nano-delivery systems still need to be further investigated. Although *in vitro* experiments and preliminary *in vivo* studies have demonstrated good biocompatibility, long-term *in vivo* metabolism and potential immune responses in clinical applications still need to be thoroughly explored. Secondly, the targeting efficiency and drug release mechanism of LA-modified nano-delivery systems need to be further optimised. Current studies have mostly focused on improving the binding ability of LA to the receptor, but there are still relatively few studies on the release mechanism and kinetics of the drug in the tumour microenvironment. Future studies could explore smarter responsive nano-delivery systems for precise drug release.

In terms of clinical translation, the development of LA-based nano-delivery systems still requires more detailed and profound studies to provide stronger evidence for the safety, efficacy and feasibility of LA nano-delivery systems, to better understand the actual needs of patients with hepatocellular carcinoma, and to optimise the therapeutic regimen of nano-delivery systems.

In summary, lactobionic acid-based targeted nanodelivery systems for hepatocellular carcinoma show great potential

for drug delivery and therapy. Future studies need to further optimise its targeting efficiency, drug release mechanism and *in vivo* stability. Through interdisciplinary collaboration and clinical translational research, it is expected that the LA nano-delivery system will be promoted to clinical applications and provide more effective treatment options for liver cancer patients.

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