

Nanocarrier-Based Therapeutics and Theranostics Drug Delivery Systems for Next Generation of Liver Cancer Nanodrug Modalities

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Abstract: The development of therapeutics and theranostic nanodrug delivery systems have posed a challenging task for the current researchers due to the requirement of having various nanocarriers and active agents for better therapy, imaging, and controlled release of drugs efficiently in one platform. The conventional liver cancer chemotherapy has many negative effects such as multiple drug resistance (MDR), high clearance rate, severe side effects, unwanted drug distribution to the specific site of liver cancer and low concentration of drug that finally reaches liver cancer cells. Therefore, it is necessary to develop novel strategies and novel nanocarriers that will carry the drug molecules specific to the affected cancerous hepatocytes in an adequate amount and duration within the therapeutic window. Therapeutics and theranostic systems have advantages over conventional chemotherapy due to the high efficacy of drug loading or drug encapsulation efficiency, high cellular uptake, high drug release, and minimum side effects. These nanocarriers possess high drug accumulation in the tumor area while minimizing toxic effects on healthy tissues. This review focuses on the current research on nanocarrier-based therapeutics and theranostic drug delivery systems excluding the negative consequences of nanotechnology in the field of drug delivery systems. However, clinical developments of theranostics nanocarriers for liver cancer are considered outside of the scope of this article. This review discusses only the recent developments of nanocarrier-based drug delivery systems for liver cancer therapy and diagnosis. The negative consequences of individual nanocarrier in the drug delivery system will also not be covered in this review.

Keywords: nanocarrier, therapeutics, theranostics, drug delivery systems, liver cancer, nanodrug, modalities

Introduction

Recent statistical reports show that human liver cancer took place as the fifth most common type of cancer. The percentage of liver cancer patients is the highest in Asia and Africa and conversely the lowest prevalence in Europe.¹ The most common type of liver cancer is hepatocellular carcinoma (HCC).² Approximately 75% to 90% of liver cancer exists as hepatocellular carcinoma (HCC) or malignant hepatomas, and it is the most frequent liver cancer.¹ Liver transplantation and surgery are conventional treatment options in treating HCC patients at early stages, but at the advanced stage of the tumor, surgery is no longer feasible for most cases.

HCC or liver cancer can be treated clinically by chemotherapy besides surgery or transplant. Chemotherapy is the treatment of choice for most cases of liver

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cancer but due to drug toxicity, poor absorption in the tumor cell, multiple drug resistance limits the access of drug to liver cancer cells in chemotherapy.³ Most of the liver chemotherapeutics drugs are tyrosine kinase inhibitors which are anti-angiogenesis. This chemotherapeutic drug blocks the signaling pathways that lead to some extent to disrupt the normal cell functions. Eventhough, they primarily inhibit the liver cancer cell proliferation, but they also inhibit the normal cell growth such as hair follicles, bone marrow and gastrointestinal tract cells in the body.⁴ To overcome the limitations of drug toxicity of chemotherapeutics agents, developments of nanotechnology has transpired with therapeutics and theranostics nanocarrier based drug delivery system (DDS).

Nanocarriers (NCs) are nanomaterials of 10–200 nanometers in diameter. They consider as potential vehicles for DDS.⁵ NCs have potentially lowered the cytotoxicity and increase therapeutic efficiency for anti-tumor drugs.⁶ They can also be made to target specific surface receptors of cancer cells.⁷ Most of the chemotherapeutic anticancer drugs have low molecular weight, high toxicity and low specificity and less severe side effects on the patients. As a result, they are often cleared from the circulation before reaching the target site and thus do not accumulate in tumors region. In order to reduce the side effects of chemotherapeutic drugs on normal healthy tissues, nanodrug delivery therapies are required in order to achieve higher efficacy with negligible side effects. However, the designed NCs must have the properties of biodegradability and they must effectively entrap the drug molecules and circulate into the blood stream and target into the desired site with accurate dose.⁸ Nanocarrier-based drug delivery system (NDDS) is able to be tailor-made, by selectively delivering drugs to the cancerous regions and reducing the chances of unspecific delivery to the healthy tissues, thus reducing the side effects of the drugs. Therefore, nano drug delivery is the answer to recapitulate the new option for liver cancer cure.

Nanocarriers in Therapeutic Drug Delivery of Liver Cancer

NCs have emerged as one of the most powerful and promising tools for drug delivery, imaging and diagnosis due to their characteristics of being able to image the disease tissues, diagnose the condition or detecting the cancer cells at the earlier stage, and simulataneoutsly able to treat the disease. The system is proficiently known as theranostics nanocarriers which presentably

able to diagnose and treat the disease at the same time. The system must be biodegradable, having a small size with high surface area and surface modifying properties. They are rapidly evolving as an interesting and effective drug delivery system in liver cancer therapy.

Lately, many researchers have developed various NCs for liver tumor-targeted drug delivery and imaging. Figure 1 shows various nanocarriers used in liver cancer drug delivery system. For example, it was found that polymeric micelles-doxorubicin NC is effective for growth inhibition of HepG2 cell lines and a better survival rate in a HepG2 xenograft model.⁹

In addition, the theranostic strategy to treat liver cancer is becoming more prominent and in demand. Table 1 shows the list of NCs used for liver cancer therapeutics and diagnostic agents. Moreover, various NCs have been used in the treatment of liver cancer tumors including liposomes, micelles, dendrimers, metal oxide nanoparticles, nanocrystals, carbon nanotubes, magnetic nanoparticles, and nanogels which have been mentioned in Table 1.

Organic Nanocarriers for Therapeutics Applications in Liver Cancer

A wide range of nanostructures based on organic materials has been advanced for drug delivery systems. The first FDA approved nanodrug was based on nanocarrier liposome which is an organic nanocarrier utilizing doxorubicin as an anticancer agent.¹⁰ Polymeric nanocarriers are one of the most promising organic NCs for liver cancer.¹¹ They are biodegradable, biocompatible, non-toxicity and do not harm autogenous tissue even though it stays prolonged in circulation. The system also has a wide spectrum of therapeutic drugs of liver cancer that can easily be adsorbed, encapsulated or conjugated by the surface of the polymeric nanocarriers.¹² Tang et al, (2018) studied the biodegradable d-tocopherol polyethylene glycol 1000 succinatepolycaprolactone (TPGS-b-PCL) nanoparticles loaded with sorafenib (SFB) to evaluate the effectiveness of anti-tumor effect in HepG2 hepatoma cells and in HCC xenograft mouse model.¹³ They have successfully found that compared with free SFB, the SFB-loaded TPGS-b-PCL NPs are more effective in suppressing HepG2 cell growth and delayed tumor growth in the HCC xenograft model. Lee et al, (2016) had successfully developed a galactosylated-poly(lithocholic-acid based doxorubicin loaded nanocarrier for liver cancer therapy which suppresses the growth of hepatic tumor and metastasis in an orthotopic xenograft mouse model of liver

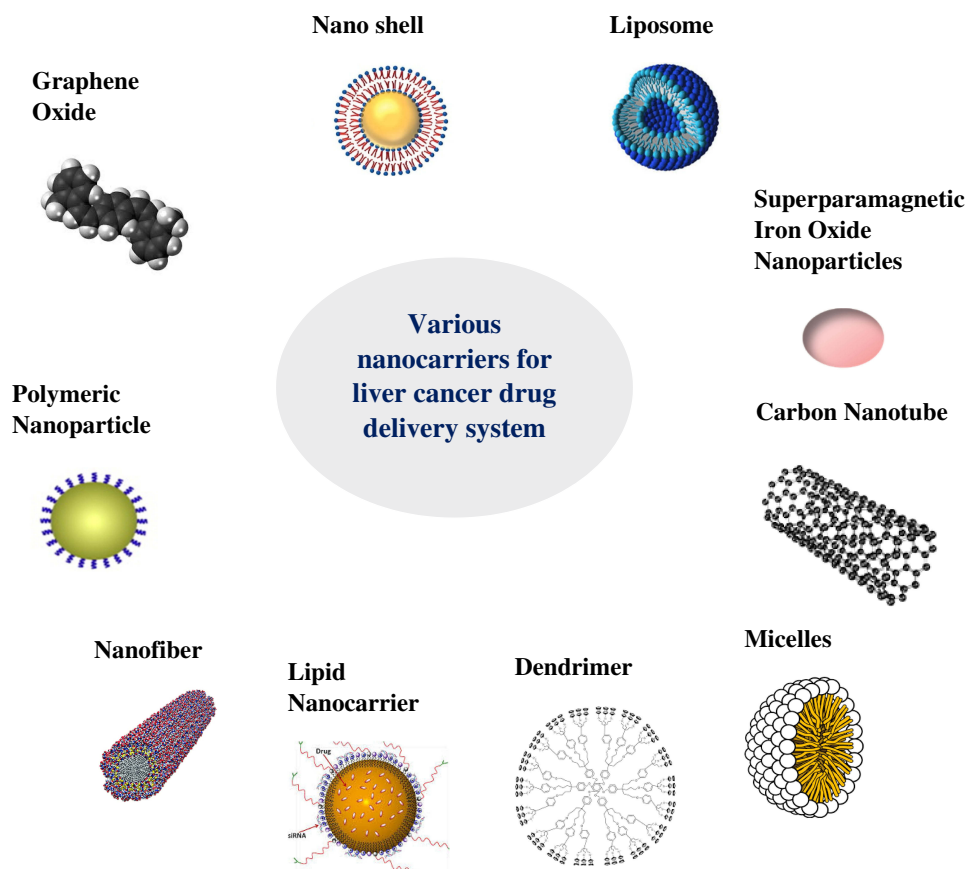


Figure 1 Various nanocarriers for liver cancer targeted drug delivery applications.

cancer.¹⁴ Several nanocarriers like chitosan nanoparticles, liposomes, micelle, dendrimer, lipid nanocarrier can be classified into organic nanocarrier.

Chitosan Nanoparticles

Chitosan (CS) is a biodegradable polymer of cationic polysaccharide generated by partial deacetylation of chitin. Many researchers have conducted studies on chitosan nanoparticles for liver cancer drug delivery for therapeutic purposes. Ye et al, (2018) evaluated the effect of chitosan coated doxorubicin loaded nanocarrier in liver cancer where it showed excellent inhibitions of cell growth of liver cancer.¹⁵ Loutfy et al, (2016) synthesized chitosan nanoparticle (CS-NPs) for evaluation of the in vitro human liver cancer cell model (HepG2). They investigated that the cytotoxic effect of CS-NPs towards liver cancer cells is relatively good and they suggested that CS-NPs are suitable for drug delivery proposes for liver cancer.¹⁶

Micelles

Polymeric micelles (PM) have been used for liver cancer drug delivery platform due to its core-shell structure, small

size and narrow size distribution.¹⁷ It can solubilize drugs and imaging agents which results in the advantages of diagnosis and therapy for liver cancer.¹⁸ PM has proven to be highly effective in drug delivery vehicles for liver cancer. Huang et al, (2010) synthesized glycyrrhetic acid (GA)-modified PM loaded with doxorubicin which has great potential in liver targeting therapy.¹⁷ Hanafy et al (2018) synthesized a novel PM (polyacrylic/poly-galacturonic acid hybrid) loaded with drug galunisertib (LY2157299) which acts as an inhibitor of TGF β to treat hepatocellular carcinoma.¹⁹ Yang et al, (2019) synthesized a nanocarrier of polyethylene glycol-derivatized glycyrrhizic acid (GA)-based PM loaded with doxorubicin which is delivered in HepG2 cell line.⁹ This PM demonstrated excellent therapeutic efficacy in vivo compared with free doxorubicin. It potentially inhibited the tumor growth and showed positive survival in a HepG2 xenograft model.

Liposome

In recent years, several studies have focused on liposomes for controlled drug delivery. Liposomes are relatively stable, consist of biodegradable materials. The drugs are

Table I List of Nanocarriers, Therapeutic and Diagnostic Agents for Liver Cancer

Nanocarriers	Drugs	Diagnostic Agent	Cell Lines	Outcomes	Reference
Micelles	Sorafenib	Polymeric micelles	HepG2-Luc tumor-bearing mice	Micelles show higher tumor growth inhibition in vivo systems.	[110]
Gadolinium co-loaded liposomes	Sorafenib	Gadolinium	HepG2 and mouse hepatocarcinomatous cells (H22)	The imaging time is long and signal enhancement is high, good inhibition of cells growth	[111]
Lipid-polymer hybrid nanoparticles	Sorafenib and doxorubicin	–	HepG2 HCC cells in xenograft mouse models	Significantly enhanced antitumor efficiency in HCC	[112]
Polymer nano-core shell	Hydrophobic drug (sorafenib), and hydrophilic drug (doxorubicin)	–	HepG2	Inhibits cell proliferation	[113]
Nanostructured lipid carriers (NLC)	Sorafenib	–	HepG2, Hep3B, Huh7	Enhanced anti-tumor activity of HCC	[32]
Silica coated Gold Nanoparticle	Doxorubicin	Gold Nanoparticle	SMMC-7721 tumor-bearing mice	Inhibit the tumor growth in vivo significantly and reduce the toxicity systematically	[114]
Polymer containing hydroxyapatite (HAp) shell and a magnetic core of iron oxide nanoparticles	Doxorubicin and/or curcumin	Iron xide	HEpG2	Effectively inhibit the growth HEpG2 (liver) cancer cells,	[115]
Zinc oxide quantum dots		–	HepG2	Induce the cytotoxicity and apoptosis in HepG2 cancer cells	[116]
Chitosan (CHI) modified single walled carbon nanotubes (SWNTs)	Doxorubicin	–	HCC SMMC-7721 cell lines	kill the HCC SMMC-7721 cell lines and depressed the growth of liver cancer compare to free doxorubicin.	[49]
Chitosan coated multiwall carbon nanotubes	Doxorubicin	–	HepG2, mice bearing the H22 tumor	higher antitumor activity and stronger fluorescent intensity have been shown in tumor tissue	[48]
Nanocomposite based on graphene oxide	Doxorubicin	Gadolinium	Human hepatoma cells	Exhibited cytotoxic effect upon liver cancer cells	[117]
Porous magnetic nanoclusters with iodinated Oil	Doxorubicin	Magnetic Nanoclusters	Liver tumors in rabbit model	Enhance the liver cancer cell death significantly	[118]
Silica nanoparticles	Cetuximab and Doxorubicin	–	HepG2 cells in vitro and in vivo	Better anticancer efficiency than free cetuximab and free doxorubicin	[119]

(Continued)

Table 1 (Continued).

Nanocarriers	Drugs	Diagnostic Agent	Cell Lines	Outcomes	Reference
Dextran	–	Super paramagnetic iron oxide nanoparticles (SPIONs)	Human hepatocellular cells, HepG2	Effective antitumor effect and magnetic resonance	[120]
Fe ₃ O ₄ /MnO hybrid nanocrystals	–	Mn ²⁺	Human hepatocellular carcinoma (HCC) in orthotopic xenograft model	Shows greater imaging effect by detecting the HCC with a high degree	[121]
Gadolinium-embedded iron oxide (GdIO)	–	Gd	Liver of BALB/c mice	Efficient tumor imaging	[122]
Nanofiber	Doxorubicin	–	H22, an aggressive murine liver cancer cell line SMMC7721 cell line	Provide good tumor-targeting activity.	[123]
Alginate/doxorubicin-modified alginate complex nanoparticles),	Doxorubicin	–	HepG2 Cells	The inhibition rate of tumor growth is high	[124]
Superparamagnetic iron oxide nanoshells	Doxorubicin	Superparamagnetic iron oxide	In vivo liver tumor model	Effective antitumor effect and imaging	[52]
Polyethylene glycol modified phospholipid micelles	Sorafenib	–	HepG2 Cells	Antitumor effectiveness is high	[3]
Dendrimer	Doxorubicin		HepG2 Cells	Inhibits the growth of liver cancer cells with a better efficiency.	[30]
Nanofiber	Cisplatin	–		Prevent tumor recurrence	[54]
Lipoprotein modified silica nanoparticles	Docetaxel and Thalidomide	–	HepG2 human hepatocellular liver carcinoma cell line	Achieve effective chemotherapy of liver cancer	[37]
Nanofiber	Doxorubicin	–	Mammary carcinoma EMT6 cells	Effective inhibition of cancer cells and in vivo release and biodistribution show greater outcome	[36]
Polymeric micelles	Doxorubicin	–	HCC cell line, HepG2	Good tumor growth inhibition and overall survival rate in a HepG2 xenograft model.	[9]
Folate-conjugated PEGylated PLGA nanoparticles	Sorafenib	SPION	BEL7402 cancer cells	Suppress the tumor cell proliferation effectively and improve the anticancer efficacy	[125]

entrapped by the inner core of the liposome.²⁰ It has been effectively used as a carrier system for delivering a variety of therapeutic agents due to its biocompatibility, low toxicity, biodegradability and capability of incorporating both hydrophilic and hydrophobic drugs.^{21,22} Wang et al, (2018) studied liposome decorated with antibodies of CD147, a polyclonal antibody highly presence in liver cancer cell lines and HCC tissues. In their study, CD147 was used as the target molecule to construct a new targeted liposome-based carrier loaded with doxorubicin. The result showed that this nanocarrier exhibit a higher cytotoxic effect on Huh-7 and HepG2 cells as well as the HCC3736 model.²³ Persico et al, (2018) investigated liposomes coated with chitosan and uncoated liposomes loaded with butyric acid (BA) to evaluate the anticancer effect of hepatoblastoma (HB) in HepG2 cell line.²⁴ They concluded that BA-loaded liposomes coated with chitosan showed higher cytotoxicity effect than both uncoated liposomes and free BA.²⁴ He et al, (2018) investigated in vitro and in vivo drug release studies on Sorafenib-loaded liposomes compared with free Sorafenib using Hep3B tumor-bearing xenograft nude mice. The experimental evidence suggested that biocompatibility, biotoxicity and anti-tumor effect were improved using sorafenib-loaded liposome compared with free sorafenib.²⁵ According to the results, liposome represents a novel and suitable nanocarrier-based treatment strategy for advanced HCC therapy in the future.

Dendrimer

Dendrimer-based drug delivery systems for antitumor therapy have a great advantage. The physico-chemical properties, such as structure and size, aqueous solubility, mono-dispersity and the high drug delivery ability make dendrimer a unique nanocarrier for drug delivery application.²⁶ Moreover, dendrimer has efficient renal filtration properties.²⁷ Wojnarowicz et al, (2018) synthesized a dendrimer based multifunctional NCs coated with polydopamine (PDA) and magnetite nanoparticles (Fe_3O_4). The synthesized nanocarriers were reported as non-toxic and it can load the drug photothermal and chemotherapeutic agents effectively to treat liver cancer cells at the solution of low nanoparticles.²⁸ Sharma et al, (2017) reported that the surface of dendrimers has water soluble functional groups that are responsible for the excellent water solubility.²⁹ Liver cancer drugs are hydrophobic, the inner core and branches of dendrimers have the characteristic of encapsulating hydrophobic drugs. Fu et al, (2014) had developed a multifunctional dendrimer-based nanocarrier conjugated with polyethylene glycol, modified with lactobionic

acid and encapsulated with doxorubicin for liver cancer therapy. They found that the nanocarrier effectively inhibits the growth of liver cancer cells.³⁰ Jain et al (2014) have carried out the synthesis of a nanoconjugate of glycyrrhizin-dendrimer modified with carbon nanotube.³¹ The liver cancer drug, doxorubicin was loaded and entrapped by the dendrimer and carbon nanotubes. The cytotoxicity, loading and release studies indicate that this dendrimer-based nanocarrier seems to be an effective vehicle for encapsulation of ionizable drugs of liver cancer.³¹

Lipid Nanocarriers

The lipid-based NCs provide an option in the development of a specific nanotherapeutics delivery system for different liver cancer drugs. A nanostructured lipid carrier was synthesized by Bondi et al, (2015) for the controlled release of sorafenib drug to see the anticancer activity compared to free drug. They suggest that lipid based nanocarrier can be a good delivery agent for liver cancer for therapeutic application.³² Furthermore, Zhao et al, (2015) developed a lipid nanocarrier that delivers the doxorubicin and curcumin drug in mice model and they found that lipid nanocarrier has the excellent inhibitory effect on tumor growth with its high encapsulation efficacy, uniform particle size and sustained release profile.³³

Organic Nanofiber

Organic nanofibers have been used as vectors for drug delivery for liver cancer. The chemotherapeutic drug-bearing nanofiber simultaneously inhibits metastasis and tumor growth of liver cancer cells. Ebara et al, (2015) constructed an organic nanofiber containing anticancer drug, paclitaxel and therapeutic gene, miRNA-145 to see the effect of both drug and gene delivery to liver cancer. It has shown that the reduction of growth of a liver tumor and prevents metastasis.³⁴ Ji et al, (2018) synthesized doxorubicin-conjugated nanofibers which have the property of sustained release drug for inhibiting tumor growth in an SMMC7721 cell line in the mouse model.³⁵ Liu et al (2013) investigated a doxorubicin-loaded nanofiber as a chemotherapeutic system against hepatic carcinoma. They observed significant anti-tumor efficacy in the resulting nanofiber.³⁶

Inorganic Nanocarriers

Inorganic nanocarriers are generally had physical properties, such as optical absorption, fluorescence (semiconductor QDs), and magnetic moment (e.g., iron oxides), useful

reactive groups for different biomolecules in order to achieve a biological functionality, such as active targeting of tissues or cells. Table 1 summarised various inorganic nanocarriers for the application of liver cancer nano drug delivery. For example, Ao et al, 2018 studied lipoprotein modified silica nanoparticles loaded with Docetaxel and Thalidomide to observe the cytotoxicity of HepG2 human hepatocellular liver carcinoma cell line and found effective tumor killing on liver cancer.³⁷

Graphene Oxide-Based Nanocarriers

Graphene oxide nanocarriers have excellent drug loading capacity. The property of high electron transfer of individual graphene sheets makes them a good carrier for drug delivery application.³⁸ Due to their high surface area, graphene-based nanocarriers can form specific interactions with various drug molecules.³⁹ Yang et al (2016) had indicated a targeted drug delivery system of graphene oxide with carboxymethyl chitosan, fluorescein isothiocyanate, lactobionic acid and anticancer drug doxorubicin. The nanocarrier has induced cell death after 24 hrs of incubation and shown higher biocompatibility with liver cancer cell lines.⁴⁰ Yuan et al, 2015 indicated that a combination of folic acid, monoclonal antibodies and gold nanoparticles-based graphene nanocomposites promoted HepG2 cell apoptosis with drug targeting and controlled release properties.⁴¹

Poly(lactic-Co-Glycolic Acid (PLGA) Nanoparticles

Poly(lactic-co-glycolic) acid PLGA nanoparticles are a copolymer of two monomers; lactic and glycolic acids. PLGA can be obtained as a synthetic polymer. Due to its biocompatibility, the US Food and Drug Administration and the European Medicine Agency has been approved PLGA for drug delivery.⁴² Recent studies have shown that PLGA nanoparticles have high drug loading capacity, good specificity, biocompatibility and efficacy in drug delivery of liver cancer. Gao et al, (2015) formulated poly(lactic-co-glycolic acid (PLGA) nanoparticles, coated with lipid and modified with a CXCR4 antagonist to deliver anticancer drugs sorafenib into HCC liver cancer. It was found that the sorafenib-loaded PLGA nanocarrier enhanced the anti-angiogenic effect, delayed the tumor progression and increased survival of the orthotopic HCC model mouse.⁴³ Li et al, 2015 formulated a poly(lactide-co-glycolide) conjugated with tocopheryl polyethylene glycol 1000 succinate (PLGA TPGS) nanoparticles loaded with oleanolic acid (OA) to improve the anticancer

efficacy of liver cancer treatments. They successfully found that PLGA nanoparticles loaded with OA shows the excellent anticancer effect on human liver cancer cell line HepG2 cells and in vivo model. In the work of Dangi et al, (2014), PLGA nanoparticles conjugated with lactobionic acid and loaded with 5-Fluorouracil (5-FU) showed a good anticancer efficacy on the human cancer cell line, HepG2 compared with free 5-FU.⁴⁴

Carbon Nanotubes

Carbon nanotubes (CNTs) are needle-like shape materials that able to carry therapeutic drugs to the cellular component.⁴⁵ According to the study of He et al (2017), CNTs are potentially considered excellent nano-vehicles for the delivery of different therapeutic agents due to their small size and mass, high electrical, strong mechanical potency and thermal conductivity.⁴⁶ CNTs exhibit biocompatibility, low toxicity, fewer side effects, high treatment efficacy with low drug doses in tumor-targeted drug delivery.⁴⁷ Qi et al (2015) had used CNTs as a carrier to deliver the doxorubicin drug in vivo liver tumor model and found excellent antitumor activity in the Hep2 cell lines.⁴⁸ Ji et al (2012) studied doxorubicin-loaded chitosan folic acid conjugate single walled CNTs for controlled release in HCC cell lines. They successfully found that CNTs-based nanocarrier can effectively kill the HCC cells and depress the liver cancer growth than free doxorubicin in nude mice.⁴⁹ Elsayed et al (2019) has designed sorafenib-loaded carbon nanotubes (CNTs) that showed the therapeutic efficacy against HCC.⁵⁰

Superparamagnetic Iron-Oxide Nanoparticles

Superparamagnetic iron-oxide nanoparticles (SPIONs) have shown significant performance in the field of liver cancer therapy and diagnosis. Azzariti et al (2017) had synthesized polyethylene-glycol modified micelles loaded with SPIONs and sorafenib to test the liver cancer inhibition effect. Due to the impact of the magnetic field, SPIONs have made potential targeting ability to specific sites in liver cancer. They administered SPIONs in the human hepatocellular carcinoma (HepG2) cells in an in vitro system to evaluate tumor cell targeting efficacy of the sorafenib-loaded superparamagnetic micelles and they found that this nanocarrier had controlled drug loading efficacy and better inhibition effect.³

Nanoshell

Nanoshells have attracted tremendous attention over the past few decades as a promising tool for liver cancer therapy.⁵¹ It is a self-assembled polymer forming a core

or shell structure and has been used for liver imaging as well.⁵² One of the most useful nanoshells is gold nanoshells. According to Liu et al, (2010), gold nanoshell showed good targeting ability to liver cancer cells, for example, BEL7404 and BEL-7402 without affecting the normal healthy liver cell like HL-7702.⁵³

Inorganic Nanofiber

Both organic and inorganic nanofibers are considered as good carriers for drug delivery of liver cancer. Zhang et al, (2014) investigate cisplatin-loaded, multilayered polylactide electrospun nanofiber in liver cancer in mice. They evaluate the inhibitory effect of cisplatin-loaded nanofiber in the H22 cell lines. The nanofiber improved tumor cytotoxicity and prolonged drug release and prevent tumor recurrence following HCC surgery.⁵⁴

Various Nanocarriers for Theranostic Drug Delivery for Liver Cancer

The theranostic delivery literally means putting together diagnostic and therapeutic agents on a carrier to cure and diagnose cancer. Theranostic nanocarriers have emerged to diagnose and treat the diseases at the cellular and molecular level. Figure 2 represents the theranostic model of nanocarriers. Currently, the theranostic delivery-based approach has been explored effectively for treating liver cancer. The therapeutic agents in theranostic nanocarriers include chemotherapeutics drugs, proteins, peptides, gene

and genetic materials. Diagnostic agents that are commonly used in theranostic nanocarriers include gadolinium, fluorescent dyes, quantum dots, superparamagnetic iron oxides, radionuclides, heavy elements, such as iodine for optical imaging, magnetic resonance imaging (MRI), nuclear imaging and computed tomography.⁵⁵ Table 2 shows the list of nanocarriers used for liver cancer theranostic drug delivery. For example, Zhang et al, (2016) used lipid-micelles as nanocarrier and used gadolinium as a contrast agent for MRI/photoacoustic imaging (PAI) in HepG2 tumor-bearing mice.⁵⁶

Gadolinium as a Diagnostic Agent for Liver Cancer

FDA approves gadolinium (Gd) as a diagnostic agent for magnetic resonance imaging (MRI) of the liver to detect and characterize the tumors in liver cancer. Liu et al (2011) had designed novel multifunctional polymeric nanoparticles modified with gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA) to deliver Gd-DTPA to the tumor area and achieve the early diagnosis of hepatocellular carcinoma (HCC).⁵⁷ Luo et al (2011) had carried out the synthesis, characterization and imaging of gadolinium-based multifunctional peptide dendritic MRI probes for liver imaging. The properties and targeting effect of gadolinium containing dendritic have shown a strong impact on their behavior in vitro and in vivo as MRI contrast agents to detect the tumors.⁵⁸

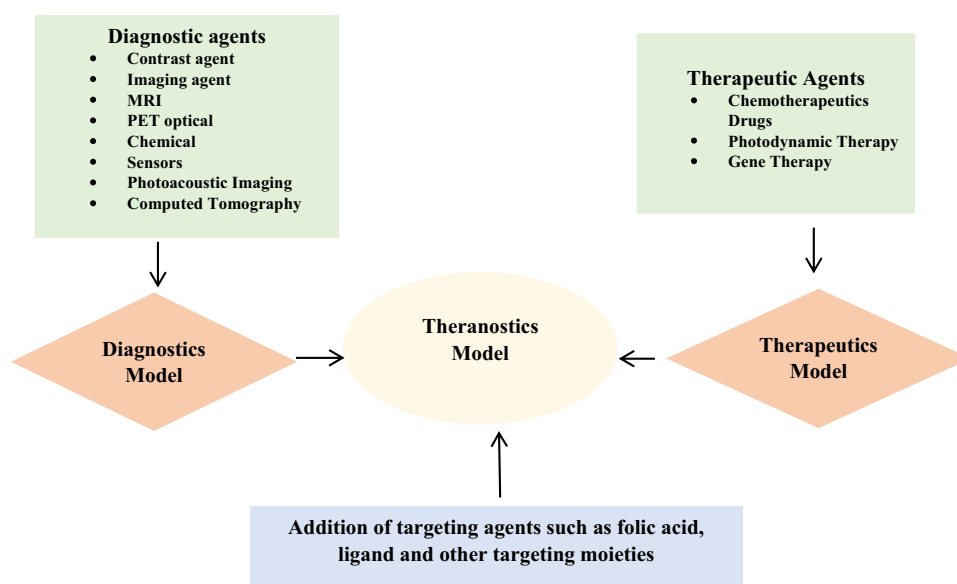


Figure 2 Theranostics nanocarrier model.

Table 2 Theranostics Nanocarriers Delivery Agents for Liver Cancer

Nanocarriers	Drug	Diagnostic Agent	Technique	Target	References
SPION	Doxorubicin	Iron oxide	MRI	Liver cancer of rabbit bearing orthotopic tumor	[126]
Micelle	Sorafenib	SPION	MRI	Cancer of subcutaneous H22 cells bearing mice	[127]
Polymeric nanoparticles	Doxorubicin	SPION	MRI	Rabbits bearing VX2 rabbit tumor	[128]
Lipid-micelles	–	Gadolinium	MRI/photoacoustic imaging (PAI)	HepG2 tumor-bearing 80 nude mice (22–24 g)	[56]
Micelles	Mitoxantrone (MX)	Micelles	MRI/upconversion luminescence (MRI/UCL)	Human hepatocellular carcinoma cell line BEL-7404	[59]
Dendrimer	–	Polydopamine	CT (chemotherapy) and PTT (photothermal therapy)	HepG2	[129]
Polymeric nanoparticle	–	Gadolinium	MRI	HCC	[57]
Gadolinium-based silica-coated nanocrystals	–	Gadolinium	PDT and MRI	BNL I ME A. 7R.1 cell	[130]
Dextran	–	Iron oxide nanoparticles	–	HepG2	[120]
Micelles	Doxorubicin	Super magnetic iron oxide	Targeted therapeutic and imaging strategy against liver cancer.	HepG2	[131]
Calcium phosphate nanoparticles	Doxorubicin	Diethylenetriaminepentaacetic acid gadolinium	MRI	BEL-7402 and HepG2 cell lines	[132]

Abbreviations: SPION, Superparamagnetic iron oxide nanoparticle; MRI, magnetic resonance imaging; PDT, photodynamic therapy.

Superparamagnetic Iron Oxide Nanoparticles as a Diagnostic Agent for Liver Cancer

Superparamagnetic iron oxide nanoparticles (SPIONs) are important in the field of theranostic delivery because of their magnetic property. SPIONs have been used as diagnostic agents for magnetic resonance imaging (MRI) to detect liver cancer as they can be targeted to specific sites of liver cancer through the effect of the magnetic field. SPION can be used as a therapeutic agent, as well as an MRI contrast agent in liver cancer cell line. It was found that SPION was degraded into a soluble form of iron or non-toxic ions in the body and cleared from the blood by phagocytosis. They are metabolized in cell lysosomes.⁵⁹ There are a few types of superparamagnetic iron oxide (SPIO) in the market such as

Ferumoxytol, Ferumoxides, Ferucarbotran, Ferumoxtran-10, and Ferropharm. They have been designed and clinically tested as MRI contrast agents. Ferumoxytol comprised of iron oxide nanoparticles surrounded by a carbohydrate coat. It is a potential imaging approach for evaluating certain liver tumors.⁶⁰ Ferumoxide (dextran-coated SPION) and Ferucarbotran (carboxydextran-coated SPION) are the two SPIONs clinically approved for liver cancer imaging.⁶¹ SPIONs and sorafenib loaded nanoformulation were prepared by Azzariti et al, (2017) based on polyethylene glycol-modified phospholipid micelles. They investigate their drug delivery for hepatocellular carcinoma and found that SPION could enhance imaging by magnetic targeting.³ However, iron oxide nanoparticles had limited clinical use in imaging liver, spleen and lymph nodes, due to the passive

accumulation in these organs. Therefore, FDA has withdrawn the approval of iron oxide nanoparticles and the usage was discontinued as MRI contrast agents in the US. Meanwhile, other SPIONs, namely ferumoxsil (Lumirems/Gastromarks) for oral administration and ferumoxide (Endorems/Feridexs) are available as intravenous injection, were also discontinued for economic and safety issues reasons.^{62–65}

Quantum Dots as a Diagnostic Agent for Liver Cancer

Quantum dots (QDs) are one of the most efficient diagnostic agents used in theranostic applications for diagnosis and therapy of liver cancer due to their unique physico-chemical characteristics, especially photoluminescence characteristics. Olerile et al, (2017) showed that HepG2 cells of liver tumors were detected by the NLC nanostructured lipid carrier-loaded QDs.⁶⁶ Das & Mohapatra (2017) found QDs are suitable for targeted imaging of liver cancer cells, where QDs are incorporated as a platform of bioimaging systems for liver cancer detection and imaging.⁶⁷ Shao et al (2015) applied QDs-based liposomes carrier for liver cancer imaging of suicide gene therapy.⁶⁸ Al-Jamal et al (2009) demonstrated that the near-infrared fluorescence imaging accumulated efficiently in liver cancer cells of mice via QD fluorescence. In addition to their findings, QDs can be encapsulated within the lipid bilayers of liposomes to form

nanoscale vesicles and perform as a contrast agent to identify liver cancer imaging.⁶⁹

Nanocarriers Interaction with Liver, Cellular Uptake, Biodistribution and Clearance

The liver consists of two types of major cells: parenchymal cells and non-parenchymal cells. Parenchymal cells can be further subcategorized into hepatocytes and cholangiocytes, while non-parenchymal cells include Kupffer cells (KCs), liver sinusoidal endothelial cells (LSECs) and hepatic stellate cells (HSCs).⁷⁰ KCs, LSECs, HSCs and hepatocytes are responsible for various physiological functions of the liver including cellular uptake of the nanocarrier. The huge portion of NCs are taken by KCs, followed by LSECs, HSCs and less by hepatocytes cells.⁷¹ Figure 3 shows nanocarriers uptake by different liver cells. The liver metabolizes the drugs and NCs. The administered NCs should be eliminated from the body by degradation or excretion. However, some NCs are very stable and difficult to be broken down, while some NCs are biodegradable and easy to be metabolized (Kang & Song, 2018).⁷² After administration, NCs which are less than 6 nm in size can be excreted by renal within hours to days. The non-degradable nanocarriers which are larger than 6 nm in size are taken up by the mononuclear phagocyte system (MPS). Hepatobiliary excretion of nanocarrier (> 6 nm) is a route for NCs removal through the liver. The liver is the

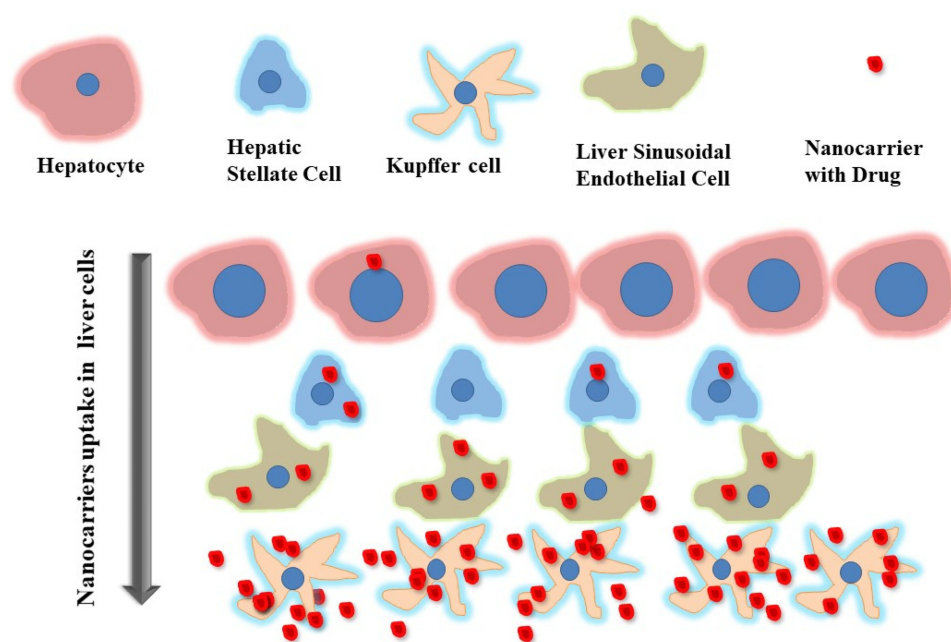


Figure 3 Nanocarriers (NCs) uptake in different liver cells.

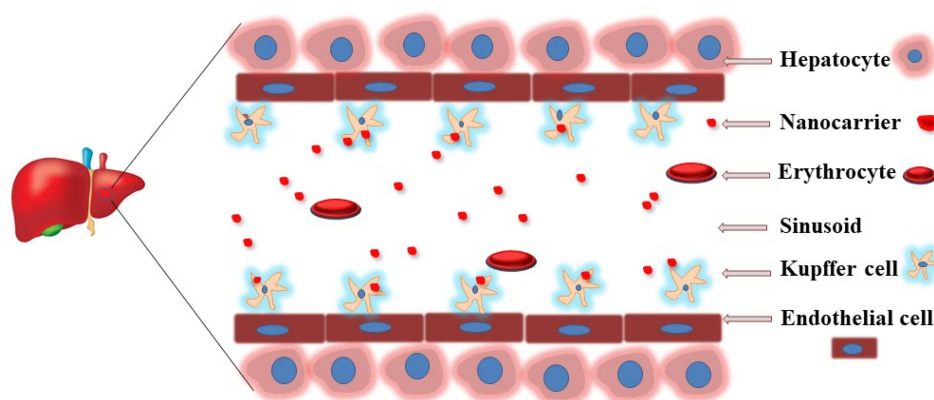


Figure 4 Nanocarriers elimination in liver from the bloodstream.

primary organ of the MPS that entraps majority of the administered NCs. The MPS and renal system compete with the tumor for circulating NCs and eliminate 99% of the administered NCs. The MPS contains phagocytic cells such as macrophages which consist of the liver, spleen, lymph nodes, bone marrow and skin. Most administered NCs are sequestered by the liver and the spleen. Macrophages in the liver include KCs and liver sinusoids along with endothelial cells (Wilhelm et al, 2016).⁷³ Figure 4 shows the elimination of nanocarriers in the liver from the bloodstream. NCs sequester from the body through macrophage. The mechanism of NCs sequestration by macrophages is phagocytosis, macropinocytosis, caveolin-mediated endocytosis, clathrin-mediated and endocytic pathways.⁷⁴ NCs can enter liver cells via several endocytic pathways. Passive penetration may occur through the plasma membrane while active penetration occurs mainly via endocytosis.⁷⁵ The process of NCs uptake into cells begins with the nanocarriers being enclosed within the early endocytic vesicles and thus not directly carried into the cytosol. Endocytosis can occur through pinocytosis or phagocytosis pathways.⁷⁶ In pinocytosis, NCs are internalized by small vesicles while in phagocytosis the cells such as monocytes/macrophages, neutrophils and dendritic cells engulf the NCs and form intracellular phagosomes.⁷⁵ Pinocytosis further subdivided into four different categories; macropinocytosis, clathrin-mediated endocytosis, caveolin-mediated endocytosis and clathrin- and caveolin-independent endocytosis.⁷⁷ It was reported that graphene oxide (GO) NCs could be internalized by HepG2 cells but reduced GO (rGO) or adsorbed onto the cell surface without internalization.⁷⁸ Phagocytosis occurs mainly in liver KCs.⁷⁹ For instance, polyalkyl cyanoacrylate nanoparticles loaded with an anticancer agent, doxorubicin into 200–300 nm size

substantially accumulated in hepatic KCs, which then acted as a reservoir, slowly releasing doxorubicin as the particles degraded.⁸⁰ Li et al, 2014, synthesized cholesteryl pullulan nanoparticles (CHP) which enhanced the efficiency of drug delivery in human hepatocellular carcinoma by clathrin-mediated endocytosis and micropinocytosis pathways. These pathways were involved in the uptake of CHP nanoparticles.⁸¹ However, HepG2 cells have no endogenous caveolin, so they are unable to mediate the nanocarriers uptake by caveolae mediated endocytosis.⁸² Figure 5 shows the clearance of nanocarriers from the liver. According to the study by Zhang et al, (2016), NCs enter the liver via the portal vein and traverse into the hepatic sinusoid and sequestered in KCs. Based on their physico-chemical properties, NCs are filtered into the space of diseases and endocytosed by hepatocytes, followed by the NCs enter the bile duct and travel through the hepatic ducts. After that according to the state of the digestive system and bile production, NCs may first collect inside the gallbladder and enter inside the common bile duct. From there, NCs are excreted into the duodenum and eventually traverse into the gastrointestinal tract and eliminate from the body.⁸³

Targeting Approaches for Nanocarrier Based Drug Delivery in Liver Cancer

Nanocarrier drug delivery targeted to a tumor cell is based on active and passive targeting interactions. In active targeting, ligands are attached on the surface of each nanocarrier which is complementary to the tumor target sites. In passive targeting, the nanocarrier surface is coated with stabilizing agents which help to cross the tumor vascular barrier through intercellular gaps. This is

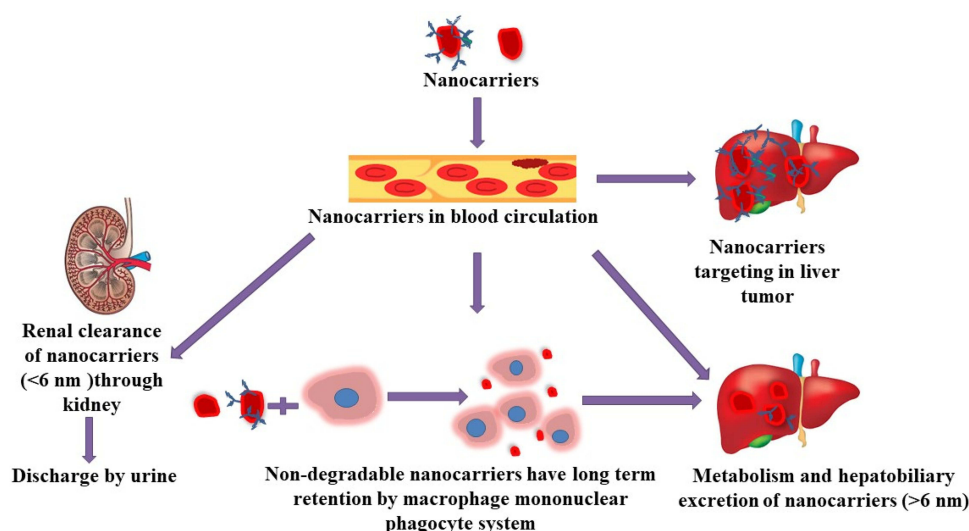


Figure 5 Schematic diagram showing possible nanocarriers clearance.

termed as “enhanced permeability and retention” (EPR). Accumulation of drugs loaded in NCs by passive targeting usually occurs via the EPR effect.⁸⁴ Nowadays scientists are focusing on development and design of NCs system that can deliver drug molecules directly to liver cancer cells either via passive targeting pathway based on the EPR effect or via active targeting mediated by tumor-specific targeting ligands. Both passive and active targeting can potentially accumulate chemotherapeutic drugs into the targeted liver cells and decrease the accumulation of drug into healthy tissues.⁸⁵ NCs rapidly pass from the systemic circulation to the vessels after injected and cross the vascular barrier to enter the tumor region. Once NCs have crossed the vascular barrier, they must interact with the tumor microenvironment.

Strategies for Passive Targeting to Liver

Passive targeting refers to the nanocarriers uptake or transport to the cancer region through leaky vasculature that makes a pathway for the nanosized carrier to enter tumorous cells by passive diffusion. According to Bae & Park (2011), the tumor tissue has abnormal leaky vasculature which helps nanocarrier to enter it. This phenomenon is called enhanced permeation and retention (EPR) effect.⁸⁶ The EPR effect was first written by Matsumura and Maeda in 1986 which helps in the accumulation of nanocarrier passively which can be taken up in the liver for therapeutics drug delivery.⁸⁷ Figure 6 shows the passive targeting of nanocarriers to the liver cells. The passive targeting approach usually depends on the physico-chemical properties of the nanocarrier such as size, the surface of the drug as

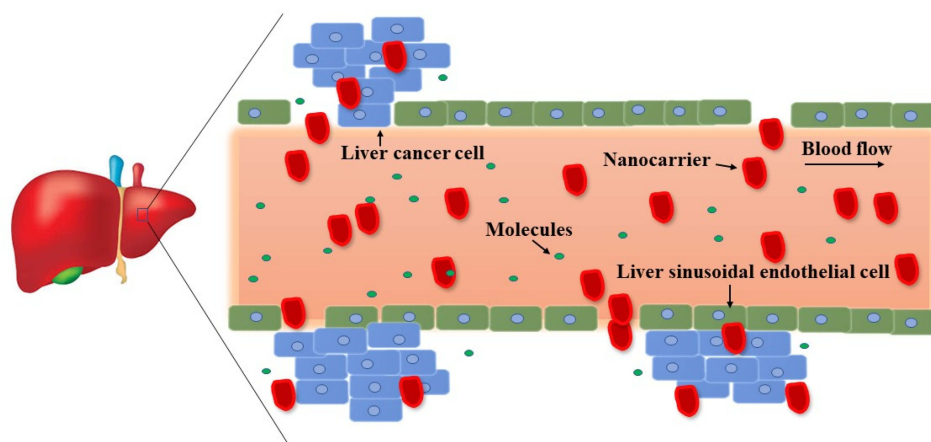


Figure 6 Passive targeting of nanocarriers to the liver cells.

well as carriers which increase the nanocarriers accumulation in the liver tissues.⁸⁸ The study of Prabhu et al, (2015) had reported that passive targeting also depends on some significant features of cancer cells such as temperature, abnormal vasculature, pH, permeability and surface charge of tumor cells.⁸⁹ Furthermore, Ferreira et al, (2013) had illustrated that some physico-chemical properties of nanocarriers such as size, molecular weight, surface charge, hydrophobicity, a hydrophilic feature which are significant for passive targeting of drug delivery.⁹⁰ The liver endothelial wall has sinusoids capillaries which present 100–200 nm fenestrations to facilitate the passive accumulation of nanocarrier to targeted cancerous tissues. Nanocarriers less than 200 nm facilitate passive targeting into the liver because these particles can easily be removed through larger sinusoidal fenestrations.⁹¹ Bae & Park (2011) have reported that the advantage of passive targeting drug delivery systems is that drugs in nanocarriers stay for a longer period in the blood circulation. Prolonged duration in the circulation gives the EPR effect and therefore the significant level of drug carrier in the blood to accumulate the nanocarriers in the targeted area in the liver cells.⁸⁶ When nanocarriers enter the bloodstream, they have a non-specific interaction with serum proteins to form a “protein corona”. After interaction with the biological fluid, it may cause the aggregation of nanocarriers and change the functionality of the carriers influenced by the physico-chemical properties of the nanocarriers.⁷³ Protein corona leads to low accumulation of the drug in the cancer cell due to the EPR effect. In addition, due to the large size of NCs, the carriers cannot slip between the endothelial cells lining and normal blood vessels in the EPR effect. It was found that the size, diameter and surface properties of protein corona influence the

outcome of passive targeting.⁹² The liver KCs uptake these NCs while they arrive on the wall of the sinusoids and thus accumulate in the liver.⁹³ The drug is then released adequately into the liver cancer cells. Therefore, the surface of the NCs may need to be modified by polymers, stabilizer or proteins for enhancement of their affinity to cells and reduce protein corona.⁹⁴

Strategies for Active Targeting to Liver

Active targeting occurs when nanocarriers conjugate with ligands or targeting moieties. Specific receptors or antigens molecules are attached on the surface of nanocarriers, which target the active site of the tumor followed by the accumulation of drug nanocarriers uptake at the site of action. Liver cells such as Kupffer cells, endothelial cells, hepatocytes, hepatocellular carcinoma cells have various specific receptors which bind to specific surface ligands on nanocarriers.⁷ These ligands can be recognized by their receptors presents on liver cancer cells, which allowed the binding of the nanodelivery system to the cell surface, triggering drug released into tumor cells. For example, HCC cell has asialoglycoprotein (ASGP) receptor where ligands from nanocarrier like galactoside, galactosamine, lactose, sterylglucoside, pullulan, lactobionic acid complementarily bind to ASGP receptor.⁹⁵ Bioactive moieties such as chemotherapeutic drug or specific gene will be released into the liver cancer specific site after the nanocarriers bind to the surface. Figure 7 shows the active targeting strategies of nanocarrier for liver. After administration, the modified nanocarriers with specific ligands on the surface can be recognized by their receptors presents on a specific type of liver cells. As shown in Figure 8, there are five different liver cells; hepatocyte, hepatocellular carcinoma cell, hepatic

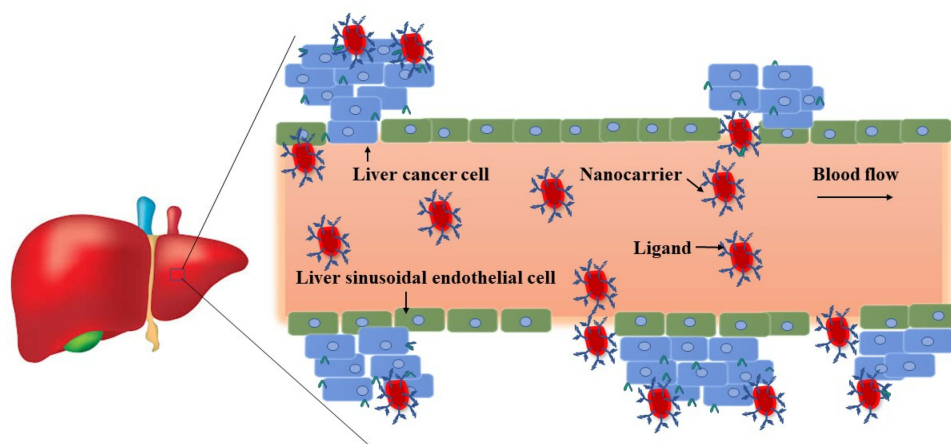


Figure 7 Active targeting of nanocarriers to the liver.

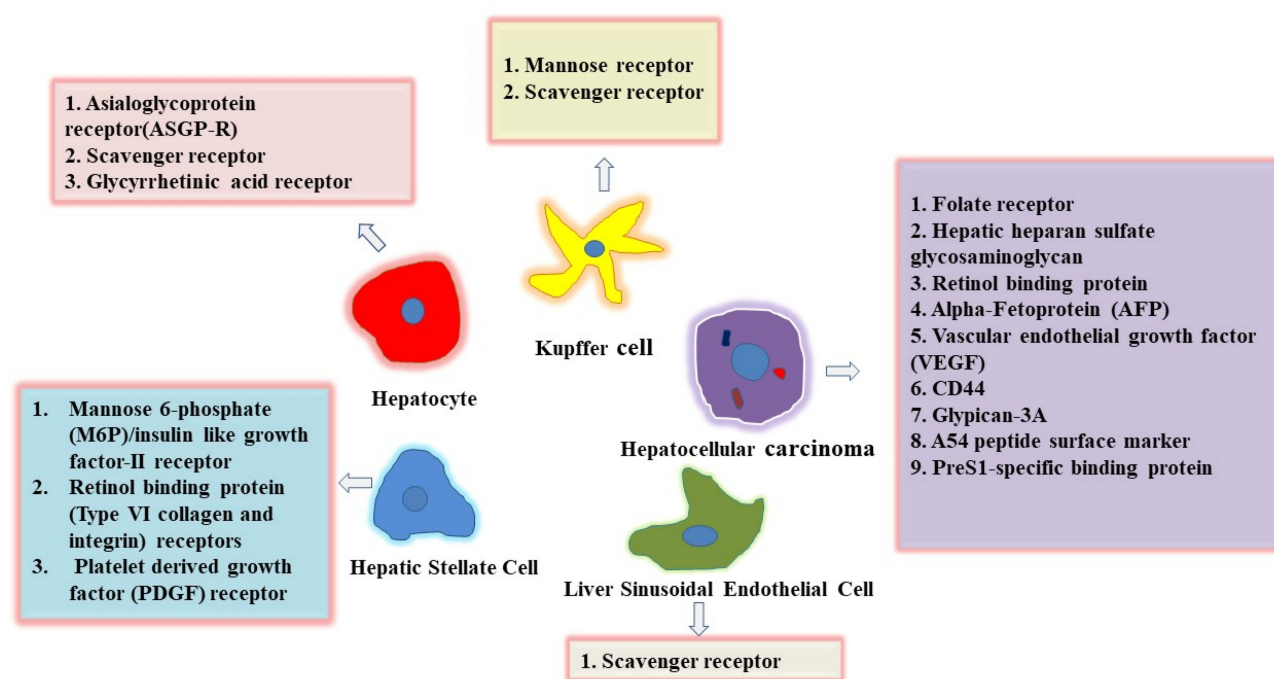


Figure 8 Receptors present on liver cells for nanocarriers binding via active targeting to the liver cells.

stellate cell (HSC), Kupffer cell and endothelial cell.⁹⁶ Each hepatic cell expressed different types of receptors that allowed the binding of the nanocarriers. Nanocarrier with active targeting moieties must be in physical contact with the receptor present on liver cancer cells. The carrier molecules must be capable of penetrating the stomach and intestine as well as recognized by the receptor present on liver cells. Glypican-3A is recently reported as a promising biomarker for hepatocellular carcinoma.⁹⁵

In active targeting, scientists developed different gene silencing technologies such as antisense technologies, small activating RNAs (saRNAs) for liver tumor targeting. The development of a saRNAs upregulates the enhancer binding protein α (CEBPA). The CEBPA gene encodes C/EBP- α which is described as a transcription factor for liver function. The upregulation of C/EBP- α activity limits HCC growth. The C/EBP- α pathway activation is a therapeutic target for saRNA, to inhibit liver tumor growth. The CEBPA gene identified a saRNA sequence that upregulates CEBPA mRNA in human hepatocellular carcinoma cells. This saRNA activates the CEBPA mRNA and inhibits the growth of liver cancer cell lines in vitro.⁹⁷ Kim et al (2019) evaluated N-acetylgalactosamine (GalNAc) conjugation to antisense oligonucleotides (ASO) as a novel therapeutic approach that enhanced the antitumor activity in the HCC tumor model. ADP-ribosylation 4C (ARL4C) is a small

GTP-binding protein that is highly expressed in primary HCC tumors.⁹⁸ Harada et al (2019) have modified antisense oligonucleotide (ASO) which effectively reduced ARL4C expression in HCC. They suggested that ARL4C ASO can be used as a novel targeted nucleic acid for the treatment of primary liver cancer.⁹⁹

The Design of Drug Delivery System for Liver Cancer, Its Clinical Success and Limitations

Nanocarrier-based drug delivery systems (DDS) will be the future generation of DDS of liver diseases such as hepatitis, liver fibrosis, hepatocellular carcinoma due to few side effects, low drug distribution in normal cells and high drug distribution in target tumor cells. Nanocarriers must be nontoxic, biodegradable, biocompatible and physico-chemically stable. The uptake and interaction of nanocarriers must be suitable for liver cells.⁷ Figure 9 shows a schematic diagram of targeted drug delivery to the hepatocellular carcinoma orthotopic model. However, the clinical phases are still slow, and more studies need to be done for the sake of the benefit of the human.

The nanomedicines have marketed at a slow phase as the clinical phase needs to be recapitulated. The poor survival rate of nanomedicines demands its improvement

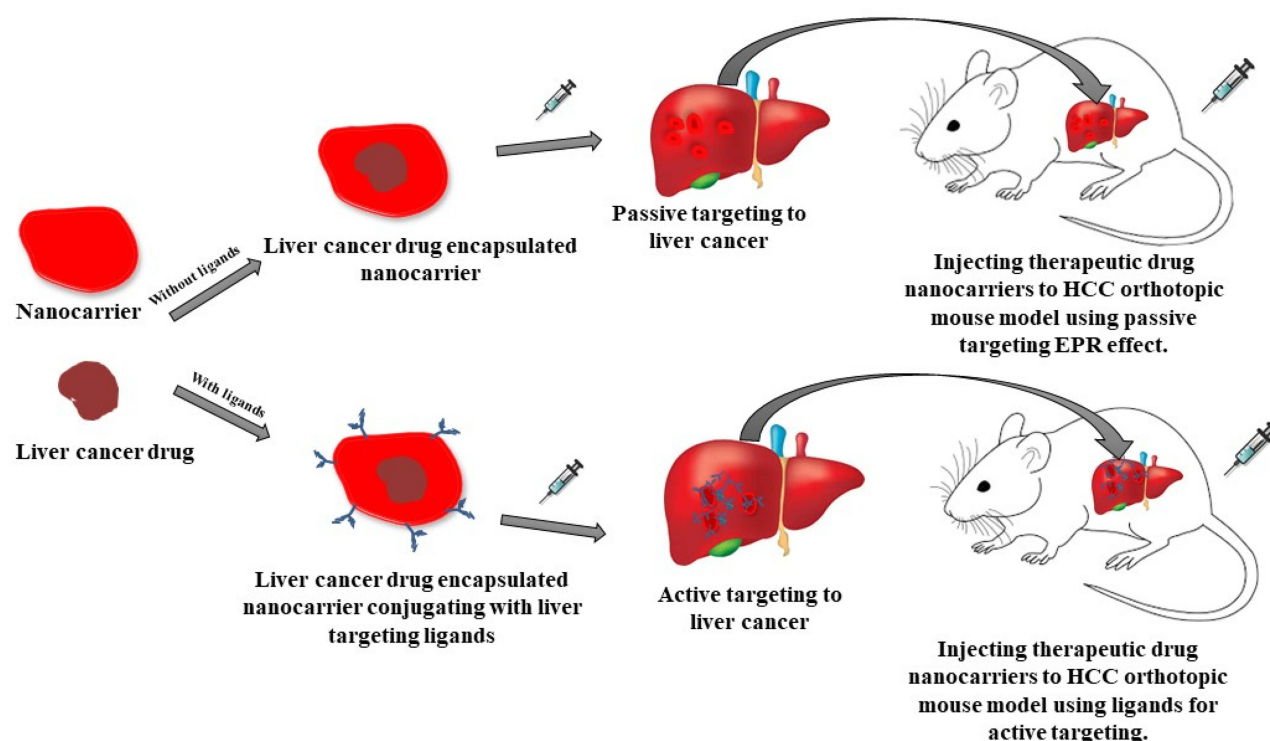


Figure 9 Nanocarrier encapsulated liver cancer drug for drug delivery to the hepatocellular carcinoma (HCC) orthotopic model.

in therapeutic and diagnostic fields for better survival of patients.¹⁰⁰

In 2009, Zhou et al, (2009) evaluated the Phase II clinical trial to test the activity and toxicity of mitoxantrone (di-hydroxy-anthracenedione, DHAD)-loaded poly-butyl-cyanacrylate nanoparticles (DHAD-PBCA-NPs) and DHAD. They injected both nanoparticles and DHAD in Chinese patients with unresected HCC. The response rate of DHAD-PBCA-NPs was 10.5%, 28.1% of patients had progression compared to 61.4% of patients with stable disease. DHAD injection showed no response, 54.9% of patients had progression and 45.1% of patients had stable disease.¹⁰¹ Preclinical studies showed that DHAD-PBCA-NPs showed better tumor-inhibiting effect than DHAD injection in HCC nude mice.¹⁰²

There are many reasons for the limitations of nanocarrier systems. The designed nanocarriers cannot function effectively if they access at disease specific sites in an insufficient dose. As a result, the clinical translation of nanocarriers with the drug has been limited.^{86,103} The biological environment such as pH, protein, and enzyme often creates hostile conditions for nanocarriers.¹⁰⁴ The injected nanocarriers often face many physical and biological barriers such as protein adsorption, diffusion,

aggregation, shear forces, renal clearance, phagocytic sequestration, etc. These barriers have a negative effect on reaching the target diseased tissue or cells.^{105–108} According to the analysis by Wilhelm et al, (2016), only 0.7% (median) of the administered nanoparticles dose was found to be delivered to a solid tumor. This means that 7 out of 1000 administered nanoparticles capable of entering a solid tumor mouse model.⁷³ According to Park (2013), less than 95% of nanocarriers are ended up at the non-targeted sites, the rest 5% of administered nanocarriers can end up at the tumor site. In addition, most of the tumor cells express receptors but in the period of nanocarriers' arrival to the tumor cells, it may not have overexpressed receptors.¹⁰⁹ As a result, only limited outcomes were found for nanomedicine. Although there are some challenges in nanotechnology fields for the development of nanocarrier systems, these nanocarriers for drug delivery for the purpose of liver anticancer therapy and imaging have been evolved significantly.

Conclusion

There are many limitations to conventional approaches for liver cancer therapy. Due to the non-specific interaction with cells, side effects, lack of drug targeting, the

resistance of the liver cancer cells, problems with the permeability, solubility and stability of anticancer drugs, chemotherapy does not provide holistic treatment for liver cancer. In contrast, nanocarrier for liver cancer has shown significant prospects for solving problems in liver cancer chemotherapy. Nanocarriers are capable of high drug loading capacity, high stability, excellent tolerability, drug degradation, reduce multidrug resistance, controlled release and sustained delivery of anticancer drugs. Therefore, therapeutics and theranostics drug delivery nanocarrier systems have important advantages over conventional treatment methods. The development of a variety of nanotechnology platforms such as theranostic nanocarriers has considerable promise as the next generation of medicine that enables the early detection of disease, simultaneous monitoring and treatment, and targeted therapy with minimal toxicity to diagnose and treat liver cancer.

Nanomedicine. in particulur nanocarriers have a huge potential in future liver cancer holistic management. However, there are many challenges needed to be solved in drug delivery systems, such as excessive accumulation of the carriers in the liver, low therapeutic efficacy on the cancer cells and some barriers near the tumor areas or in vasculature area that create obstacles to penetration into liver cancer cells needed to be overcome. The ligands or targeting moieties need to translocate the nanocarriers to a specific region of tumors to achieve the site-specific delivery of nanodrugs. The current nanotherapeutic systems have developed only a limited number of clinically approved nanodrugs for liver cancer. There are many new therapeutic drugs with diverse physico-chemical properties of nanocarriers need to be invented to achieve adequate therapeutic payload and imaging sensitivity. Moreover, the controlled release of various drugs from its nanocarrier in liver cancer is another challenge in the development of nanomaterials that need further studies.

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Disclosure

The authors report no conflicts of interest in this work.

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