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REVIEW

Progress in the Application of Novel Nanomaterials in Targeted Therapy for Liver Cancer

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Abstract: In recent years, nanobiotechnology, widely used in hepatoma, holds great promise for improving targeted hepatocarcinoma therapy. On account of the unique properties of low toxicity, good tolerance, biocompatibility, and biodegradability of new nanomaterials, a targeted drug delivery system (TDDS) has been constructed, which can boost the therapeutic effect of hepatoma-targeted drugs, reduce drug toxicity, and minimize off target reactions by enhancing permeability retention effect (EPR) and active targeting, thus improving existing liver cancer targeted therapy strategies. Different nanoparticles have their own advantages and disadvantages. They can be loaded with multiple drugs on the same nanoparticle and can also be surface modified with each other to achieve synergistic anti-tumor effects. This essay provides a comprehensive overview of the current status of targeted therapy for hepatocarcinoma, nanoparticles' structure, advantages and disadvantages of each nanoparticle, and the application progress of nanoparticles in targeted therapy for liver cancer. We hope to provide a basis for the future clinical targeted therapy of hepatoma using nanotechnology.

Keywords: liver cancer, targeted therapy, nanotechnology, drug delivery, nanoparticles

Introduction

Hepatocellular carcinoma (HCC) is a major global burden, ranking as the third-leading cause of cancer-related mortality.[1] HCC, an aggressive, primary malignant liver tumor that usually occurs in the setting of chronic liver disease, particularly in patients with cirrhosis or chronic hepatitis B virus.[2] However, the epidemiology of hepatocellular carcinoma (HCC) has shifted significantly in the last 2 decades.[3] The changes are in the predisposing factors. Hepatitis B and hepatitis C as predisposing etiologies are decreasing while metabolic dysfunction-associated steatotic liver disease and alcohol-associated liver disease are increasing.[4]

Owing to the absence of conspicuous clinical manifestations in the incipient phase of liver cancer, most patients are already in the middle to late stages when diagnosed.[5] In the treatment of advanced liver cancer, systemic anti-tumor therapy plays an important role, which can control the progression of the disease, prolong the survival time of patients, and even achieve partial or complete remission of the tumor for some patients.[6] Systemic therapy mainly refers to anti-tumor therapy, including molecular targeted drug therapy, immune checkpoint inhibitor therapy and other traditional Chinese medicine therapies. However, these newly developed treatment strategies have not yet achieved widespread success, and liver cancer patients often show decreased sensitivity to these therapies.[7] And the validity of these therapies in improving the metastasis and treatment efficiency of liver cancer, controlling its targeting and release, as well as alleviating adverse reactions, remains inconclusive.[8] Therefore, we urgently need an improved or innovative systematic anti-tumor treatment method.

Recently, unprecedented progress has been achieved in the field of nanomedicine with the development of novel nanoparticles for cancer treatment and advancements in nanotechnology. Nanoparticles (NPs), with small sizes, large

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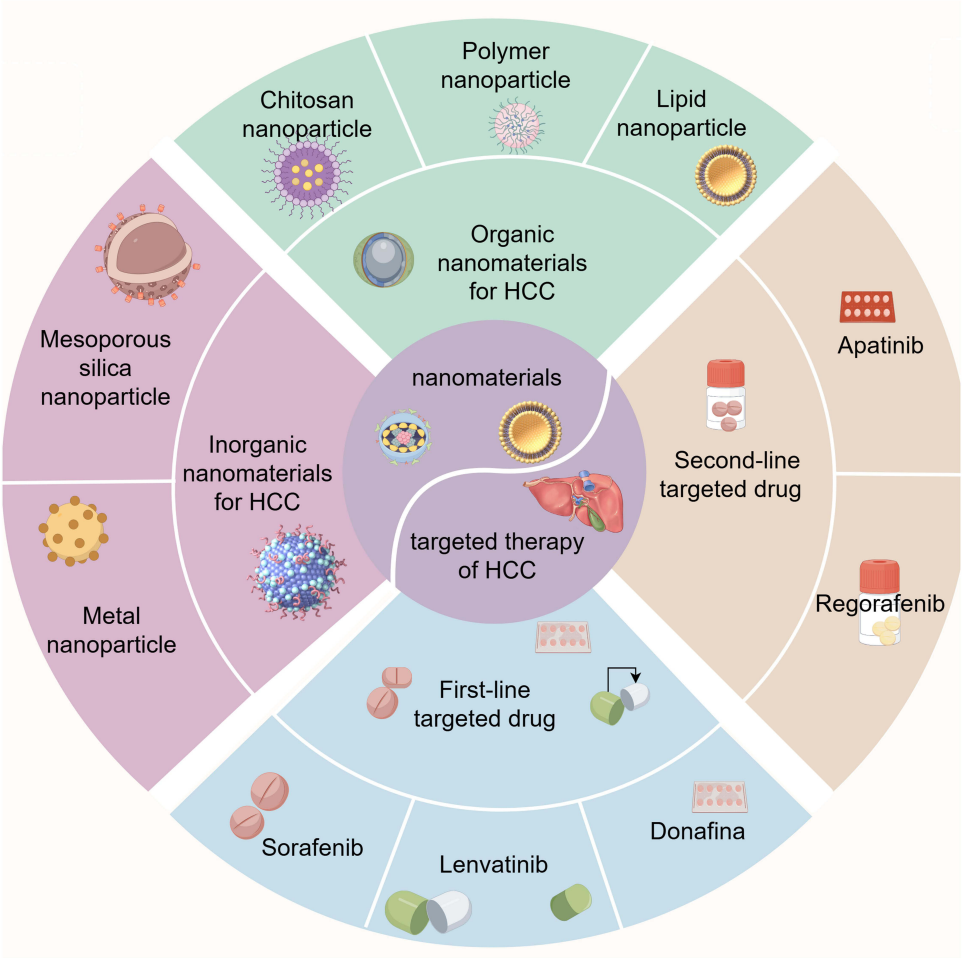
Graphical Abstract



specific surface areas, low toxicity, good tolerance, high sensitivity, biocompatibility, biodegradability and long duration of action, which can be used as a drug microcarrier to achieve targeted drug delivery, and reduce off target effects and adverse reactions.[9,10] Nano delivery systems can enhance anti-tumor efficacy by disrupting the stromal tumor microenvironment of liver cancer.[11] The nano delivery system also has the potential to increase local drug concentration in tumors, reduce systemic toxicity, and enhance the precision treatment effect of liver cancer.[8] Therefore, the utilization of nanomedicine delivery systems in HCC treatment holds great promise.

This review will discuss application of nanomaterials united with hepatic carcinoma targeted drugs. We will start by providing a brief introduction of current status of targeted therapy for hepatoma. Next, we will focus on introducing nanoparticles' structure, advantages and disadvantages of each nanoparticle, and the application progress of nanoparticles in targeted therapy for liver cancer. We aim to expeditiously integrate nanotechnology with targeted drug delivery for the clinical treatment of hepatoma, establish a foundation for improving the prognosis and living quality of patients with hepatic carcinoma (Figure 1, By Figdraw, www.figdraw.com).

Current Status of Targeted Therapy for Hepatoma

Most HCC patients are diagnosed in advanced stages and can only receive systemic treatment.[12] The whole-body therapy, also known as systemic therapy, primarily refers to anti-carcinoma treatments.[6] The systematic treatment of hepatic carcinoma can be divided into three phase: targeted therapy, immunotherapy, and target-free combination

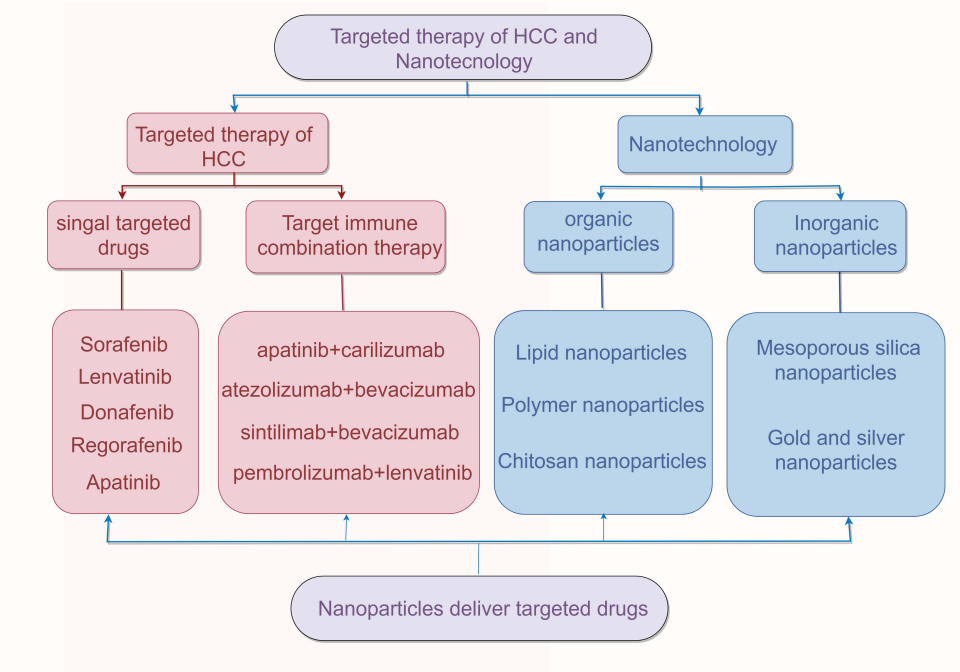


Figure 1 Mind map of the manuscript.

therapy.[13] Targeted therapy in combination with immune checkpoint inhibitors is considered as a front-line treatment option for patients with late-stage HCC.[14] In the past several years, a major breakthrough has been made in the systemic treatment of liver cancer, progressing from monotherapy targeted treatment to immune checkpoint inhibitor therapy, and further to combination therapy involving immune checkpoint inhibitors and targeted treatments.[12] Although these drugs are all suitable for treating advanced hepatic carcinoma, their mode of action, targets, and indications are different (Table 1).

First-Line Targeted Drug Therapy for Hepatoma

Sorafenib

In 2007, sorafenib was authorized as the frontline targeted medicine for treating unresectable or metastatic hepatocellular carcinoma.[20] Sorafenib (SOR) is a multi-kinase inhibitor that targets cell growth and angiogenesis,[30] targeting vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and Raf family kinases.[15] SOR can inhibit carcinoma cell multiplication, angiogenesis by targeting corresponding targets (Figure 2, by Figdraw, www.figdraw.com), thereby prolonging the overall median survival of patients.[31] SOR can promote the tripartite motif 54 (TRIM54) mediated ferroptosis suppressor protein 1 (FSP1) ubiquitination and induce ferroptosis in HCC cells through the extracellular signal-regulated kinase (ERK) pathway.[16] The induction of ferroptosis can enhance the anticancer effect of SOR, but it can also induce SOR resistance in the body.[32] Sorafenib is primarily indicated for patients with liver function ranked as Child-Pugh A and Child-Pugh B.[17] SOR may result in cardiovascular untoward reaction, including high blood pressure, myocardial ischemia, and left ventricular dysfunction.[33]

Lenvatinib

In 2018, lenvatinib was approved as the second frontline targeted drug for treating hepatocellular carcinoma in later period.[20] Lenvatinib is a multi-target tyrosine kinase inhibitor that targets VEGFR, PDGFR α, fibroblast growth factor receptor (FGFR), as well as the proto-oncogenes rearranged during transfection (RET) and receptor tyrosine kinase (KIT).[34] Lenvatinib has the effects of promoting cell apoptosis, inhibiting angiogenesis, and regulating immune response.[35] Lenvatinib can induce ferroptosis in HCC cells through fibroblast growth factor receptor-4,[21] promoting anti-tumor effects. Research indicates that lenvatinib is not inferior to sorafenib in terms of median survival time and overall

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Table 1 The Introduction of Targeted Drugs for Treating Hepatocellular Carcinoma

Drug	Approval Time	Mechanism	Target Site	Result	Adverse Reaction	Indication	References
Sorafenib	2007	Block the receptor. Inhibit the activity of RAF family kinases. Induce iron death in HCC cells	VEGFR, PDGFR, RAF	Inhibit tumor cell multiplication, angiogenesis. Promote tumor cell apoptosis	Hypertension, mucositis, hair loss, diarrhoea, weight loss, hand-foot skin reactions, and hypophosphatemia.	Liver function can be seen in ChildPugh A and ChildPugh B patients	[15–19]
Lenvatinib	2018	Block the receptor. Induce iron death in HCC cells	VEGFR, PDGFR, FGFR, KIT, RET	Inhibit tumor cell proliferation. Immune regulation	Inhibit tumor cell multiplication. Immune regulation.	Liver function ChildPughA grade advanced liver cancer patients	[6, 20, 21]
Donafenib	2021	Block the receptor. Induce iron allergy in HCC cells.	VEGFR, PDGFR, RAF, MEK, ERK	Restrain the spread of neoplasm cells. Help relieve pain.	Hand and foot skin reaction, elevated glutamic oxalacetic transaminase, elevated total bilirubin, decreased platelet and diarrhea	Patients with unresectable hepatocellular carcinoma who have not previously received systemic therapy	[6, 20, 22]
Regorafenib	2017	Block the receptor. Inhibit the activity of RAF family kinases.	VEGFR, PDGFR, RAF, FGFR, RET, TIE-2	Control the appreciation of cancer cells. Reduce blood vessels generate.	Hypertension, hand-foot derma responding, tiredness and diarrhea	Patients with advanced hepatocellular carcinoma who have previously received sorafenib	[6, 23, 24]
Apatinib	2020	Interdict VEGF and PI3K/AKT access.	VEGFR, AKT	Inhibit tumor growth, migration, invasion. Reduce angiogenesis.	Secondary hypertension, fatigue symptoms, hand-foot syndrome, vomiting, liver dysfunction, and proteinuria	The sick with liver cancer in late stage who have formerly undergone first-line treatment failure or are intolerable	[6, 25–29]

survival (OS), and it even demonstrates advantages in objective response rate (ORR) and progression-free survival (PFS).[36,37] Lenvatinib is suitable for advanced liver cancer patients with Child-Pugh A liver function who are unresectable.[6]

Donafenib

In June 2021, donafenib was authorized in China for the treatment of unresectable HCC patients who had not formerly received the whole-body therapy.[22] Donafenib is a tritiated derivative of sorafenib that utilizes deuterium exchange to increase its bioavailability and targets VEGFR, PDGFR and Raf kinase.[38] Through screening the CRISPR library, it was observed that the combined use of donafenib and GSK-J4 can synergistically induce iron allergy in HCC cells, thus demonstrating a significant therapeutic effect on stage Ia and Ib hepatocellular carcinoma.[20] Among advanced hepatocellular carcinoma patients in China, donafenib is superior to sorafenib for better overall survival.[6] In the multicenter, randomized, controlled Phase II–III trial ZGDH3, donafenib showed good safety and tolerability, and was superior to sorafenib in overall survival.[23] Common adverse reactions of donafenib include cutaneous manifestations of the extremities, elevated alanine aminotransferase, elevated total bilirubin, thrombocytopenia, and diarrhea.[6]

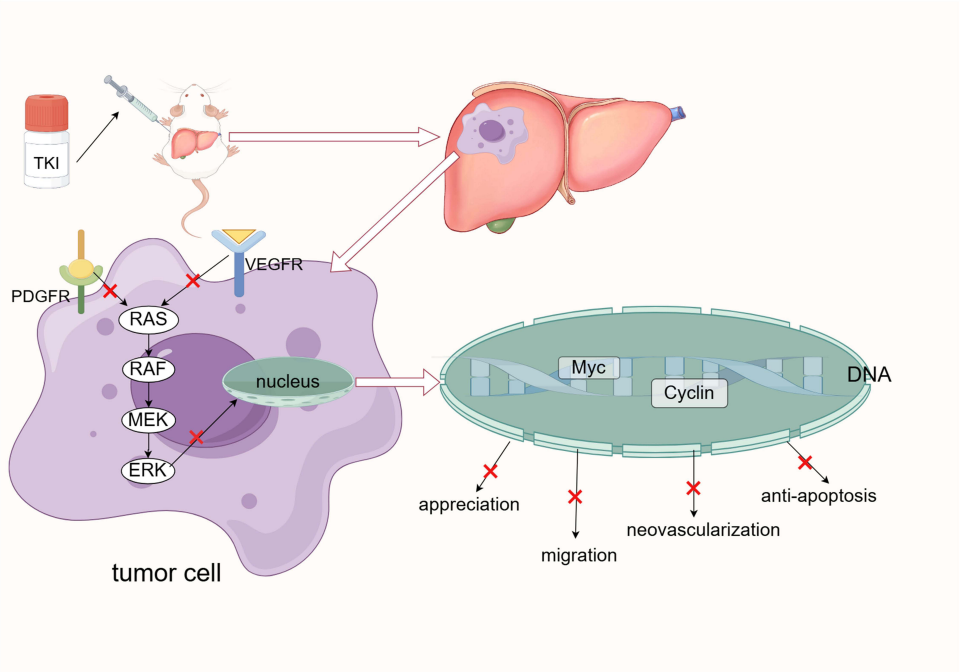

Figure 2 Map of mechanism of action of Tyrosine kinase inhibitors for HCC.

Second Line Targeted Drug Therapy for Liver Cancer

Regorafenib

In 2017, regorafenib was ratified by the Food and Drug Administration (FDA) for treating late-stage HCC patients who had been previously treated with sorafenib.[23] Regorafenib is a fluorinated derivative of sorafenib.[39] Regorafenib is an orally active inhibitor of diphenylurea multi kinase, targeting VEGFR1-3, c-KIT, TIE-2, PDGFR - β, FGFR-1, RET, RAF-1, BRAF, and p38 MAP kinases.[40] Regorafenib represents a pioneering medication authorized for the treatment of patients with hepatocellular carcinoma exhibiting progression during or following sorafenib therapy.[24] The approval of this therapy is based on the results of a randomized, double-blind, placebo-controlled, multi-country Phase III RESORCE trial in HCC sufferers who have progressed during sorafenib treatment.[41] Current evidence suggests that regorafenib can remarkably increase the survival rate of patients who have progressed with sorafenib treatment.[42] However, the adverse reactions of regorafenib are similar to those of sorafenib and cannot be used in patients who are intolerant to sorafenib.[6]

Apatinib

In December 2020, following the results of the AHAL trial, the National Medical Products Administration (NMPA) ratified apatinib as a second-line treatment for terminal hepatocellular carcinoma sufferers.[25] Compared with sorafenib, apatinib exhibits higher selective inhibition of VEGFR-2.[26] Apatinib can target tumor blood vessels by interdicting the VEGF and Phosphatidylinositol 3-Kinase/Protein Kinase B (PI3K/AKT) pathways, reducing tumor angiogenesis, inhibiting tumor growth, migration, and invasion.[43] The Phase III clinical research of apatinib second-line treatment for terminal hepatic carcinoma in China has demonstrated that, compared with placebo, apatinib can remarkably prolong the median survival time of terminal hepatic carcinoma sufferers.[25] The most common adverse reactions of apatinib are secondary hypertension, fatigue, vomiting, liver dysfunction, and proteinuria.[27] But these adverse reactions are relatively mild, and patients can tolerate or alleviate them through symptomatic treatment.[27]

Target Immune Combination Therapy for Liver Cancer

Immunotherapy for HCC mainly includes immune checkpoint inhibitor therapy, vaccine therapy, and adaptive cell therapy. Among them, monoclonal antibodies (mAbs) against immune checkpoint inhibitors (ICIs), the cytotoxic T lymphocyte-associated protein 4 (CTLA-4) or the programmed cell death-1/programmed cell death ligand 1 (PD-1/PD-L1), have always

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been the center of HCC immunotherapy.[44] However, the percentage of patients who achieved a lasting response to anti-CTLA-4 and anti-PD-1/PDL-1 monotherapy was lower. The combination of different types of drugs can exert a synergistic effect and enhance the efficacy of anti-HCC,[45] for example, combination of ICIs with TKIs, combination of ICIs with TKI and combination of different ICIs.[46]

The combination therapy of apatinib and carilizumab monoclonal antibodies has been ratified in China for front-line treatment of unresectable or metastatic hepatic carcinoma sufferers.[6] The findings of the CARES-310 international multicenter phase III study showed that compared with sorafenib monotherapy, the combination therapy of apatinib mesylate and carilizumab reduced the risk of death by 38%.[47] The combination therapy of apatinib mesylate and carilizumab has shown better efficacy and controlled virulence in resectable HCC patients.[48] Compared with monotherapy with carilizumab, the common skin toxicity (RCCEP) caused by the combination therapy of apatinib and carilizumab was significantly reduced (29.5% vs 66.8%).[49] The common adverse reactions of this combination therapy are hypertension, hand foot syndrome, and elevated aminotransferase.[6]

The combination of atezolizumab and bevacizumab is the first regimen to show superiority over sorafenib and has been used as the preferred systemic therapy for patients with HCC in stage C of Barcelona liver cancer.[50] The results of the global multi-center phase III study of IMbrave150 showed that for patients with advanced unresectable HCC who had not received systematic treatment before, the overall survival (OS) and progression-free survival (PFS) of atezolizumab combined with bevacizumab were significantly better than those of sorafenib.[51]

The results of the ORIENT-32 national multicenter phase III study by Ren et al showed that in previously untreated Chinese patients with HBV-related HCC, compared with sorafenib, sintilimab combined with bevacizumab analogues showed significant over-survival and progression-free survival benefits, with tolerable and controllable safety.[52] For the treatment of patients with unresectable HCC, compared with other first-line treatment options for HCC, sintilimab combined with bevacizumab biosimilar is a more cost-effective first-line treatment drug.[53]

The combination therapy of pembrolizumab and lenvatinib has been applied to the actual first-line treatment of advanced HCC in China.[54] Hu et al showed that the median OS of the combination of pembrolizumab and lenvatinib was longer than that of lenvatinib alone (21.1 months and 19.0 months, respectively).[55] However, the combination of pembrolizumab and lenvatinib may increase the overall incidence of adverse drug reactions (ADRs).[56] The most common adverse reactions were gastrointestinal diseases and hepatobiliary diseases, among which hepatic encephalopathy was the most common adverse event (AE).[57]

Organic Nanomaterials for Targeted Therapy of Hepatic Carcinoma

On the basis of the current status of targeted therapy for liver cancer, there are still many problems with the current targeted therapy strategies for hepatoma. Therefore, a novel type of material is urgently needed to solve these problems. In recent years, researchers have extensively studied nanomaterials and integrated them into the treatment of HCC. Although nanoparticles are small, they can be used to make drug delivery systems with tremendous effects.[58] In addition, research indicates that nanoparticles have significant effects on specific drug targets of existing experimental drugs for treating HCC.[59]

Nanoparticles, which can be applied for targeted therapy of liver cancer, can generally be divided into two categories: organic nanoparticles and inorganic nano-particle. Organic nanoparticles include lipid nanoparticles, polymer nanoparticles, chitosan nanoparticles, etc. Inorganic nanoparticles include silicon-based nanoparticles and metal nanoparticles. These nanoparticles have both similarities and their own advantages (Table 2).

Lipid Nanoparticles and Their Adhibition in Targeted Therapy for Liver Cancer

Lipid nanoparticles are characterized by their biocompatibility, non-poisonous, and excellent tolerance.[83] Lipid nanoparticles have the following advantages: stronger physical stability, easy scalability, and relatively lower production costs.[84] Furthermore, lipid nanoparticles can accumulate in areas with increased vascular permeability due to inflammation, infection, a phenomenon called the enhanced permeability and retention effect.[85] Lipid nanoparticles come in various forms, involving liposomes, solid lipid nanoparticles, exosomes, and so on.[60]

Table 2 The Introduction of Nanoparticles for the Treatment of Hepatocellular Carcinoma

Nanoparticle	Loading of Medicine			Biodegradable	Biocompatibility	Target Cell	Advantage	Result	Influencing Factor	References
	Lipophilic Drugs	Hydrophilic Drug	Nucleic Acids							
Liposome	√	√	—	√	√	HepG2, H22	Strong physical stability, easy to expand, and low production costs.	Improve directional delivery ability. Prolong drug action time.	Structure, size and surfactants.	[60–63]
Solid lipid nanoparticles	√	√		√	√	HepG2	High stability. Free functional groups that can bind to particular ligands.	Increase drug accumulation in tumor cells. Increase drug bioavailability.	Composition, particle size, surface charge and surfactant.	[60–62, 64, 65]
Polymer nanoparticles	√	√	√	√ Synthetic polymers to prepare nanoparticles are not biodegradable	√	HCC cell line	Various types. Strong operability. Drug high encapsulation rate. High stability.	Improve the selectivity of tumor cells. Boost the anti-tumor effect. Reduce the adverse effects of drugs.	Particle size, drug loading and drug encapsulation rate.	[66–69]
Chitosan nanoparticles	—	—	—	√	√	HepG2, H22, SMMC-7721	Low toxicity, Mucous adhesion.	Improve drug effect and induce cell apoptosis.	Particle size, surface charge, surface properties.	[70–74]
Gold and silver nanoparticles	—	—	—	—	√	HT29, HepG2 and resistant to HepG2	Strong chemical stability. Structural stability and dimensional variability.	Produces higher antitumor activity. Affect cell respiration and produce reactive oxygen species. Inhibit tumor angiogenesis.	Particle size, shape and spatial arrangement.	[75–77]
Mesoporous silica nanoparticles	√		—	√	√	BNL 1 ME A. 7R.1 cell	Can be loaded with a great deal of different drugs. Chemical and thermal stability is good.	Increase the solubility and bioavailability of the medicine. Prolong the action time of the medicine.	Particle size, shape, surface chemical characteristics and surface charge.	[78–82]

Some pathways of sorafenib action may exhibit selective downregulation during the treatment process, known as sorafenib resistance.[86] To overcome sorafenib resistance in HCC, researchers have developed many novel nano delivery systems for delivering sorafenib.[86] Among them, lipid nano delivery systems are the most widely used.[60] The nano delivery system can assist sorafenib in actively or passively targeting tumor tissues in vivo,[87] resulting in higher release efficiency and bioavailability.[88]

The Structure and Advantages of Liposomes

Liposomes are a nano scale capsule system with a surface lipid layer enclosing an aqueous core (Figure 3, by Figdraw, www.figdraw.com).[89] Liposomes have capacity to capture hydrophobic medicine in the bilayer region and hydrophilic drugs in the internal water space.[90] The preparation methods of liposomes include thin-film hydration,[91] reverse-phase evaporation,[92] and microfluidic mixing.[93] According to the quantity of lipid bilayers, lipid vesicles can fall into three types: multimicelles, small single micelles, and large single micelles.[61] Multi-micelle vesicles are composed of multiple lipid bilayers, separated from each other by water space.[61] Multiple drugs could be loaded into the lipid and water layers or multiple-water layers of multi-micelle liposomes to produce synergistic anti-tumor effects.[94] Liposomes can dissolve hydrophobic drugs in lipid membranes and encapsulate hydrophilic drugs in aqueous cores.[62]

The structure and compositional characteristics of liposomes make them suitable as drug delivery carriers. There are two main approaches for stowing drugs into liposomes: passive embarkation and active embarkation.[63] Passive loading refers to loading drugs while forming liposomes.[63] Active loading, also referred as remote loading, first generates liposomes containing transmembrane gradients, and then uses concentration gradients to load drugs into pre-made empty liposomes.[63] Because active loading typically achieves higher drug lipid ratios and generates stable particles.[63] Therefore, liposomes are more suitable for loading drugs through active loading methods. Compared with unmodified large liposomes, neutral or electropositive small liposomes have a longer circulating time in vivo.[61] In addition, the surface modification of liposomes can also be done by coating chitosan or polyethylene glycol (PEG) chains to improve the stability of liposomes and reduce aggregation, thus prolonging circulation time of drugs in the body.[61] Chitosan coated drug loaded liposomes can induce higher anti-inflammatory effects in human hepatocellular carcinoma cell line (HepG2) cells.[95]

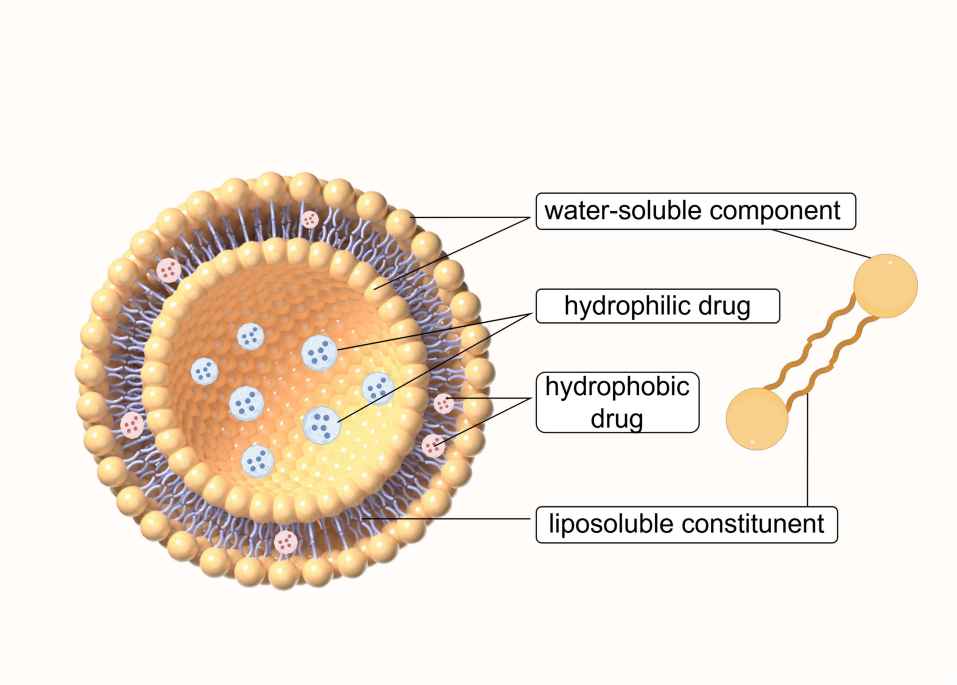

Figure 3 Schematic diagram of liposome structure.

Structure and Advantages of Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLNs) are typically composed of medicine, solid lipids, and surfactants.[64] The composition of Solid lipid nanoparticle (SLN) not only affects particle dimension, surface characteristic, packaging efficiency, drug absorption mediation, and intercellular release, but also enhances the internalization of nanoparticles (NPs) within cells and affects specific targeted cell regions.[62] In addition, SLN also has the ability to connect specific ligands to surfaces containing free functional groups.[64] Based on the above characteristics of SLN, it is believed that SLN is a promising nanomaterial that can be used for high-efficiency delivery of various active pharmaceutical component.[64]

SLN is an efficient, non-toxic, and multifunctional drug delivery carrier that can encapsulate lipophilic and hydrophilic drugs as well as nucleic acids, regulating targeted drug delivery and stimulus responsive drug release.[61] According to different surface charges, SLN can be divided into anionic SLN and cationic SLN.[96] Surface charge plays a vital role in the stability of drug delivery systems (DDS) and the adsorption range of nanoparticles on biofilms.[97] Cationic lipids exhibit dose-dependent toxicity, leading to hepatocyte necrosis and exhibiting genetic toxicity at concentrations that affect cell viability.[98,99] Therefore, when utilizing cationic solid lipid nanoparticles for drug loading, it is imperative to carefully consider the dosage in order to mitigate potential toxic effects. The animal model study of diethylnitrosamine (DEN) showed that compared with free drugs, drug loaded SLN can significantly lessen the amount and size of liver nodules, enhance the activity of endogenous antioxidants, and eliminate destructive free radicals.[60]

Surfactants not only enhance the physicochemical stability of lipid nanoparticles, but also affect particle size and the crystallization and polymorphic transformation process of lipids within the particles.[65] The physicochemical stability of SLN can be improved by converting solid lipid nanosuspension into dry powder, which solves the problem of low oral utilization of large-sized SLN.[65]

Application of Sorafenib United With Magnetic Lipid Nanoparticles in the Treatment of Liver Cancer

Magnetic lipid nanoparticles encapsulate magnetic nanoparticles with different electron densities in a lipid matrix.[100] The preparation method is as follows:[100] using hexadecyl palmitate as the lipid matrix, sorafenib and superparamagnetic iron oxide nanoparticles (SPIONs) are loaded onto hexadecyl palmitate SLNs using thermal homogenization technology. Sorafenib-loaded magnetic solid lipid nanoparticles (Sor Mag-SLNs) have good colloidal stability and cell compatibility in aqueous environments, which can prevent nanoparticle aggregation.[100] The Sor Mag-SLNs have a sorafenib loading efficiency of about 90% and are very stable in an aqueous environment.[100] The Sor-Mag-SLNs can increase the phosphorylation of extracellular signal-regulated kinase in HepG2 cells through the release of sorafenib, thereby inhibiting the proliferation of HepG2 cancer cells.[100] Additionally, the superparamagnetic iron oxide nanoparticles (SPIONs) in Sor Mag-SLNs provide a magnetic moment that enables Sor Mag-SLNs to selectively target sorafenib to HCC tumor cells in the presence of a long-rage quiescent magnetic field, producing cytotoxic effects without entering surrounding normal tissues and organs.[101] Sor Mag-SLNs can also utilize the relaxation properties of their magnetic lipid nanoparticles as negative contrast agents for MRI tracking.[100]

Therefore, we believed that compared to sorafenib monotherapy, magnetic lipid nanoparticle loaded sorafenib has the following advantages: More significant therapeutic effect, less adverse reactions and side effects. It can target HCC tumor cells more specifically without affecting surrounding normal tissues.

Application of Sorafenib, siRNA United With Ultra Small Lipid Nanoparticles in the Treatment of Liver Cancer

Ultra-small lipid nanoparticles (us-LNPs) are composed of novel pH sensitive lipids, various phospholipids, and highly selective targeting peptides.[102] Us-LNPs can selectively deliver the cytotoxic drug sorafenib in combination with siRNA against the midkine gene (MK-siRNA) to HCC tumor cells.[103] Kimura, N. et al developed a baffle mixer device named the invasive lipid nanoparticle production device, or iLiNP device for short.[104] It can improve the drug metabolism, biodistribution, stability, tumor penetration, and cell delivery of sorafenib loaded with us-LNPs by modulating the size and physicochemical peculiarities of nanoparticles.[104] Younis, M. A. et al drew a conclusion, selective simultaneous delivery of SOR and MK-siRNA to liver cancer cells by us-LNPs enhances the cytotoxicity of low-dose sorafenib and the SOR-resistant HCC established in mice can be eradicated by 70%.[103] Us-LNPs can enhance the bioavailability of sorafenib in vivo, its ability to specifically target HCC tumor sites, and tumor penetration efficiency.[102]

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Thus, we think that the simultaneous delivery of SOR and MK-siRNA by ultra-small lipid nanoparticles (us-LNPs) can enhance drug efficacy and delay sorafenib resistance while reducing the dosage of sorafenib.

Application of Sorafenib or Lenvatinib United With Lipid Nanoparticles in the Treatment of Liver Cancer

YTH N6-methyladenosine RNA binding protein 1 (YTHDF1) is a pivotal N6-Methyladenosine (m6A) " reader " protein.[105] YTHDF1 is highly expressed in liver cancer stem cells (CSC).[106] YTHDF1 promotes the proliferation, migration and invasion of HCC cells by activating the PI3K/AKT / mTOR signaling pathway.[105] YTHDF1 also makes patients more likely to develop resistance to multiple tyrosine kinase inhibitors such as lenvatinib and sorafenib.[106] Zhang et al believed that lipid nanoparticles can reduce the expression of YTHDF1 by targeting YTHDF1, thereby inhibiting the renewal of CSC and reducing the proliferation of HCC cells. Furthermore, the sensitivity of HCC cells to targeted drugs was enhanced, and the anti-HCC efficacy of targeted drugs (lenvatinib and sorafenib) was improved.[106] In addition, lipid nanoparticles can also deliver microRNAs and small interfering RNAs into HCC cells, thereby altering these genetic networks to affect cell behavior.[107]

In summary, we believe that the application prospect of lipid nanoparticles is very broad. Lipid nanoparticles can be used for targeted drug delivery and nucleic acid delivery. Targeted drugs and nucleic acids can be simultaneously delivered to HCC cells to regulate gene expression and inhibit the production of HCC cells from the source. It may eventually achieve the effect of curing HCC in the future.

Polymer Nanoparticles and Their Application in Targeted Treatment for Hepatoma

Polymer nanoparticles are a colloidal system that refers to a collective term for various types of nanoparticles based on polymers.[66] Polymer nanoparticles mainly refer to polymer nanospheres and nanocapsules.[66] Among them, polymer nanospheres are solid matrix particles, while polymer nanocapsules are a capsule like system.[66] On account of the distinctive character of polymer nanosystems, researchers have suggested that both natural and artificial polymers can be used to create targeted DDS to improve the curative effect of hepatic carcinoma.[108]

Physicochemical Properties and Preparation of Polymer Nanoparticles

The preparation methods of polymer nanoparticle drug delivery systems include emulsification solvent diffusion technology,[109] condensation of lipophilic and hydrophilic polymer monomers.[110] Polymer nanoparticles can serve as carriers for bioactive molecules such as medicine, genes, nucleic acids, and fluorescence.[66] These bioactive molecules may adsorb on the facade of the sphere or be encased inside the particles.[66] Compared with other particle drug delivery systems, the merits of polymer nanoparticles as active substance delivery systems involve high drug encapsulation rate, high intracellular uptake rate, high stability, high biocompatibility, wide variety, and strong operability.[111,112] In addition, different polymer nanoparticles can be designed to improve selectivity towards HCC tumor cells, effectively delivering various drugs to targeted tumor cells.[66]

Merits and Shortcomings of Polymer Nanoparticles

Polymer nanoparticles load molecular-targeted drugs onto the interior or exterior of nanoparticles through envelopment, adsorption, aggregation, condensation, or coupled reactions.[67] There are mainly two loading methods:[66] Add drugs during the production of polymer nanoparticles; Prepare polymer nanoparticles in drug solution to adsorb drugs. Compared with traditional targeted therapy, polymer nanoparticles loaded with anti-tumor drugs have the following advantages:[66,67] The encapsulation of polymerid nano-particle can increase the plasma half-life and bioavailability of drugs by preventing rapid clearance by the kidneys and recognition by the reticuloendothelial system.[113] Polymer nanoparticles can achieve higher drug cumulation in HCC tumor cells through enhanced EPR or active targeting effects.[114] Drugs with different anti-tumor mechanisms can be encapsulated in carefully designed polymer nanoparticles for synergistic therapy, improving anti-tumor efficacy.[115] Polymer nanoparticles loaded with anti-tumor drugs can cross biological barriers and even escape from autophagic cells to prevent self attack.[116] In addition, polymer nanoparticles are suitable for almost all routes of administration: intravenous or intramuscular injection, skin or nasal absorption, oral administration, etc.[66] However, polymer nanoparticles also have drawbacks such as fragility, high preparation costs, and residual toxic solvents.[66]

Polymer Nanoparticles for Drug Delivery and Release

The ways in which polymer nanoparticles deliver drugs include: Delivering drugs to appropriate organelles in tumor cells through clathrin mediated endocytosis (*ie* cellular internalization);[117] Guided delivery of drugs loaded with polymer nanoparticles to tumor cells through passive and active targeting strategies.[68] In addition, targeting ligands can be modified to bind to receptors overexpressed by cancer cells, thereby enhancing the selectivity of polymer nanoparticles towards cancer cells.[118] Due to the superior biocompatibility of the albumin shell, dual modified albumin polymer nanocomposites can be prepared by encapsulating polymer nanoparticles with albumin.[69] Compared to polymer nanoparticles, this nanocomposites have superior drug loading performance, higher stability, and excellent tumor targeting.[69] The stability of polymer nanoparticles is influenced by the preparation method, particle size, drug loading capacity, drug encapsulation efficiency, drug formulation, and administration route.[66] Currently, adding stabilizers is the preferred and most commonly used method to enhance the stability of polymer nanoparticle suspensions.[66]

Application of Sorafenib United With Polymer Nanoparticles in Treating Liver Cancer

Gan et al prepared a novel polymer nanoparticle loaded with sorafenib (NP-SOR-Ab).[119] NP-SOR Ab is assembled from the copolymer TPGS-b-caprolactone (TPGS-bPCL), as the copolymer of PCL and D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS), and P123 with the drug sorafenib, and then coupled with anti-GPC3 antibodies using nanoprecipitation method.[119] TPGS is a water-soluble form of vitamin E, which has the characteristics of prolonging circulation time and synergistic effects with other anti-HCC drugs.[120] In HepG2 human liver cancer cells, NP-SOR Ab exhibited higher cellular uptake and stronger cytotoxicity than free SOR.[119] Furthermore, NP-SOR Ab can enhance the bioavailability of sorafenib,[121] resulting in more significant anti-HCC efficacy. In addition to the above advantages, NP-SFB Ab has good sorafenib release in cell culture medium, which can significantly inhibit tumor growth while reducing some of the adverse reaction of sorafenib drugs themselves.[119]

TOM et al synthesized Fe3O4 nanoparticles using co-precipitation method, and then loaded sorafenib and coated polyvinyl alcohol (PVA) to prepare a sorafenib polymer magnetic nanoparticle (PVA-SPION) delivery system.[122] PVA can enhance the solubility of hydrophobic Fe3O4 nanoparticles in aqueous solution.[122] Compared with free sorafenib, the PVA-SPION delivery system loaded with sorafenib has the following advantages:[122] It has a smaller size, which produces stronger penetration and retention effects and enhances anti-cancer activity. It has biocompatibility and biodegradability. It has high stability and bioavailability. Tumor cell death can be induced through apoptosis and autophagy mechanisms, then disrupting the tumor microenvironment (Figure 4, by Figdraw, www.figdraw.com). It can evade the biological clearance mechanism of endothelial cells or macrophages, protecting drugs from being destroyed before reaching the target site.

In summary, compared to free sorafenib, NP-SOR-Ab and PVA-SPION delivery systems loaded with sorafenib have more significant anti HCC effects.

Application of Lenvatinib United With Polymer Nanoparticles in Treating Hepatic Carcinoma

Nano delivery carriers are undoubtedly the most feasible method to enhance the curative effect of Lenvatinib.[123] In addition to delivering sorafenib, polymer nanoparticles can also serve as nano delivery systems for lenvatinib. Wu et al constructed a polymer biomimetic nanomedicine delivery platform consisting of a pH susceptive polymer, poly(β-amino ester)-polyethylene glycol-amine (PAE-PEG-NH_2), and a shell composed by tumor cytomembrane, encapsulating the core of Lenvatinib.[124] The pH-responsive characteristics of PAE-PEG-NH2 and the specific targeting effect on cancer cell membrane (CCM) enable this novel nanomedicine to achieve precise targeting of cancer cells and pH-responsive release in the tumor microenvironment.[124] Wu et al suggested that the nanomedicine can effectively eliminate tumors in mice in 21 days, exhibiting excellent tumor accumulation and therapeutic effects.[124] Based on the physicochemical properties and applications of polymer nano-particle introduced above, polymer nanoparticles can also be used for the encapsulation of other liver cancer targeted drugs.

Therefore, this nanomedicine can open up a novel path to decrease the adverse effects of lenvatinib and boost the first-line clinical drug treatment efficacy for liver cancer.

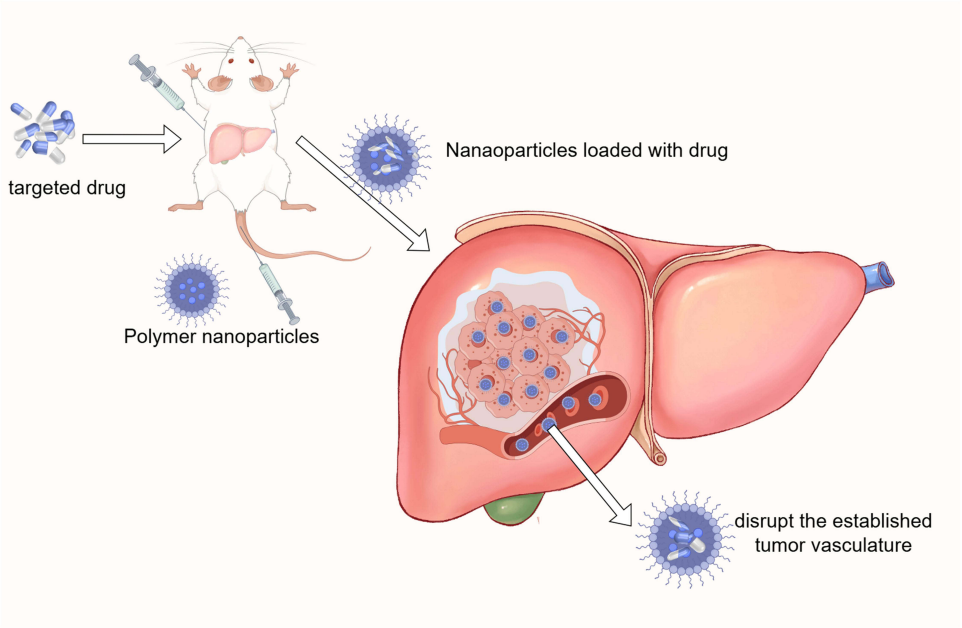

Figure 4 Sorafenib are loaded by polymer nanoparticles and delivered to HCC tumor cells.

Chitosan Nano-Particles and Their Application in Targeted Therapy for Hepatic Carcinoma

Chitosan is a biocompatible and biodegradable mucosal adhesive polymer.[125] Chitosan nanoparticles can increase the curative effect of HCC by improving the pharmacokinetic characteristics of targeted drugs,[70] and are a well-known and widely used delivery system in the area of nanomedicine.[71]

Physicochemical Properties, Advantages of Chitosan Nanoparticles

Chitosan can be easily made into various forms, including nanospheres, fibers, gel and films.[126] Chitosan can also be modified through the coupling of its active amino groups on the d-glucosamine residues with other molecules.[127] Moreover, due to the easy alteration of the primary amine chemical structure on the chitosan skeleton, chitosan is more prone to derive derivatives than other nanoparticles.[127]

Nanoparticles of chitosan have the following characteristics:[128] It has high biocompatibility and biodegradability, and its biological compatibility and degradability can be adjusted by changing its molecular weight and degree of deacetylation.[129] Mucous adhesion and this feature are beneficial for directing drug delivery to organs covered by mucus, prolonging the duration of drug action.[127] It has high targeting specificity and this characteristic is due to the positive charge on the surface of chitosan, which can generate greater attraction to negatively charged biofilms, thereby exerting effects on specific parts of the body.[72] Nanoparticles are small and can escape from macrophage uptake through capillaries, enhancing drug efficacy and reducing side effects.[71] Chitosan can be administered through multiple routes, involving oral, parenteral, mucosal, and intravenous injection.[130]

Application of Chitosan Nanoparticles in Targeted Therapy for Liver Cancer

Chitosan nanoparticles can generate EPR effect and interact specifically with liver tumors through passive and active targeting.[131] Chitosan nanoparticles can exert synergistic anti-tumor effects by delivering various drugs to the liver.[70]

Chitosan can protect stem liver cells by inhibiting lipid peroxidation, counteracting free radicals, regulating pro-inflammatory cytokines, and inducing apoptosis.[73] Chitosan nanoparticles have strong cytotoxic effects on tumor cells both in vitro and in vivo.[71] In vitro, the main method is to destroy the cell membrane of HepG2 cells, reduce the negative charge on the membrane surface, and lower the survival rate of HCC cells.[132] In the body, it induces intracellular reactive oxygen species (ROS), which then induces mitochondrial rupture and endoplasmic reticulum stress, directly leading to

tumor cell apoptosis.[133] The size and surface character of the polymer have influence on the hepatic targeting ability of chitosan nano-particles.[73] Chitosan nanoparticles with smaller particle size and positively charged surface have higher liver targeting ability and anti-tumor activity.[132] Chitosan nanoparticles have the potential to enhance macrophage phenotypic stability, inhibit tumor growth and metastasis, and facilitate to cure liver damage, tumors, and other related diseases.[74]

ROS and pH sensitive chitosan nano-particles have been developed for the purpose of targeted drug delivery and release at tumor sites, with the aim of enhancing the hepatic carcinoma curative effect.[70] Varshosaz et al utilized an emulsion evaporation method to conjugate polyethylene glycol-modified trimethyl chitosan (TMC) emulsions with octreotide for the purpose of loading and delivering sorafenib.[134] The optimized sorafenib exhibits stronger cytotoxicity and more drug accumulation in HepG2 cells.[135] Yao et al indicate that pH susceptive carboxymethyl chitosan embellished liposomes can be used for joint delivery of sorafenib and siRNA, enhancing the efficacy of sorafenib and decreasing its side-effects.[136]

To sum up, Organic NPs have great advantages in delivering targeted drugs. Organic NPs can better produce EPR effect at the tumor site and specifically interact with liver tumors through passive and active targeting. Organic NPs, such as chitosan nanoparticles, have strong cytotoxicity to tumor cells and play an anti-HCC role. Organic NPs have excellent biocompatibility and degradability, and are more suitable for human delivery of targeted drugs. Organic NPs are small in size and can escape from macrophage uptake through capillaries, enhancing the efficacy of drug delivery and reducing side effects.

Inorganic Nanoparticles for Targeted Therapy of Hepatoma

Inorganic nanoparticles encompass quantum dots, metal nano-particles, nanodiamonds, iron oxide nanoparticles, and silica nanoparticles.[137]

Silicon Dioxide Nanoparticles and Their Application in Targeted Therapy for Hepatoma

Silicon dioxide nanoparticles (SiNPs) are highly ordered crystalline particles made of silicon dioxide, with a surface composed of siloxane constructions and silicon hydroxyl groups.[138] Compared with solid silica nano-particles (SSN), mesoporous silica nanoparticles (MSN) have an internal nano network with highly ordered channels, which is more suitable for preparing drug carriers.[139]

Physicochemical Peculiarities and Advantages of Silica Nanoparticles

Silica nanoparticles can not only serve as delivery vehicles for small antiviral molecules, drugs, and other macromolecules,[139] but can also exert antiviral effects by preventing direct interactions between surface viral proteins and cells through specific regulation.[140] Based on the sustained release payload characteristics of silica nanoparticles, they can be used to shape virus-like particles to gradually release viral antigens in host cells and induce long-lasting immunogenic responses.[141] Furthermore, silica nanoparticles are well tolerated and safe when administered via oral, intradermal, intravenous, and topical administration.[139] Among them, silica nano-particles with a diameter of ≤10 nm could be rapidly excreted through the kidneys and hepatobiliary system within 72 hours after intravenous administration.[142] Silica nanoparticles with diameters in the range of 50–300nm are more easily endocytosed by cells and have no significant cytotoxicity.[143] Therefore, silica nanoparticles in the range of 50–300 nm are more suitable for preparing drug delivery systems.

Mesoporous Silica Nanoparticles Physical and Chemical Properties, Preparation Methods, Advantages

Mesoporous silica nanoparticles (MSN) possess a honeycomb-like porous structure, which can encapsulate a large amount of drugs.[144] MSN includes two functional surfaces: the inner surface of cylindrical pores and the outer surface of particles,[145] which enable the internal and outside surfaces of MSN to produce different types of functionalization and play multiple roles.[78] MSN has the following characteristics: high drug loading capacity, acceptable biocompatibility, and distinctive form.[146] Usually, elevating the efficacy of MSNs can be achieved by surficial decoration of MSN or co-

assembly with other nanoparticles.[79] MSN can also serve as a carrier for biological imaging agents (*ie* biosensors) to assist in the diagnosis of hepatocellular carcinoma.[147] Additionally, the EPR effect of MSN in tumor cells can be improved by modulating its particle size, shape and surficial chemical characteristics, and promoting drug accumulation in HCC tumor cells.[78] Magnetic mesoporous silica nanoparticles (M-MSNs) exhibit magnetic mediated targeting capabilities by applying foreign magnetic field, while maintaining the advantages of MSN.[80]

MSN can be synthesized by four methods:[81] template guidance method, sol gel method,[148] microwave assisted technology and chemical etching technology. The synthesized MSN can improve drug solubility, prolong drug action time in vivo, enhance liver targeting and pH responsive release ability by delivering targeted drugs.[82]

Compared with other nanoparticles, MSN has better drug loading advantages, summarized as follows:[78,146,149] The pore size is uniform, adjustable, and has a narrow distribution, which can load different drugs. The internal mesoporous structure is arranged in an orderly manner, allowing for high loading of different drugs. The silanol groups on the surface have high appetency with phosphatide on the cell membrane and can actively enter the cell. The size of the inlet hole can be controlled by attaching diverse types of functional groups to the exterior of MSN. Surface charges can chemically couple with various molecules in the inner and outer pores, loading different types of drugs. It has good biocompatibility, biodegradability, chemical and thermal stability.

Application of Silica Nanoparticles in Targeted Therapy for Liver Cancer

Ma et al prepared samples of different sizes. Ru@MSN is the conjugation of mesoporous silica (MSN) carrying antitumor ruthenium compound (RuPOP) with folate (FA).[150] This functional vector can elevate the selectivity of MSN between tumor cells and normal cells by specifically recognizing and binding to HepG2 cells overexpressing FR.[150] In addition, Ru@MSNs can induce HepG2 cells to produce excessive ROS, and mediate oxidative damage of biomolecules to induce cancer cell death.[151] Ru@MSNs, as the generated ROS, can also cause the accumulation of phosphorylated p53, and promote apoptosis of tumor cells.[152] Among them, p53 is considered a negative regulator of cell proliferation.[153] The size of nanoparticles has a crucial influence on medicine delivery, cellular uptake, and anti-cancer effects.[154] Ma et al concluded that the drug loading efficiency of 20, 40, and 80 nm Ru@MSNs was about 23.7, 21.1, and 17.6%, respectively.[150] Among them, smaller sized (20 nm) nanomedicines exhibit higher anti-cancer activity against HepG2 cells, while larger sized (80 nm) nanomedicines have a higher inhibition on DOX resistant R-HepG2 cells.[150]

Consequently, we hold the opinion that nanoparticles Ru@MSN can not only be used for the treatment of HCC, but also can replace the anti-cancer ruthenium complex with targeted drugs for curing HCC.

Metal Nanoparticles and Their Application in Targeted Therapy for Hepatoma

There are various types of metal nanoparticles, including gold nanoparticles, silver nanoparticles, and iron nanoparticles. The controllable physicochemical properties of gold nanoparticles have attracted widespread attention.[155]

Physicochemical Properties and Advantages of Metal Nanoparticles

Compared to other nanostructures, the use of metal nanoparticles is more primitive.[156] Metal nanoparticles have problems such as excessive generation of active oxygen, protein damage, inflammation leading to poisoning, and high local body temperature.[75]

The characteristics of gold nanoparticles are linked with their form, diameter, and spatial arrangement.[76] Gold nanoparticles have the following advantages in cancer treatment:[77,157,158] structural stability, size variability, strong chemical stability, controllable release, low toxicity, easy identification of tumor targets accumulated in vitro and in vivo, biocompatibility, simple preparation, and easy surface modification. Gold nanoparticles can boost the curative effect of drugs at lower doses and reduce their adverse reaction by carrying targeted drugs to the site of action.[159] Gold nanoparticles also have a curse side. Li et al proposed that AuNP can hinder cell proliferation, affect genome stability, and DNA repair by dysregulating cell cycle genes.[75] Therefore, when using metal nanoparticles as delivery carriers, special attention should be paid to their toxicity to avoid causing damage to the body. In addition, gold nanoparticles also is of great importance in nanobiosensors.[156]

The characteristics and advantages of silver nanoparticles and gold nanoparticles are similar. Silver nanoparticles (Ag-NPs) can pass into cells through endocytosis and localize in the perinuclear space of lysosomal compartment cells in the cytoplasm.[160,161] Ag-NPs can cause oxidative stress, cell apoptosis, and mitochondrial damage in cancer cells.[162] Ag-NPs can also inhibit tumor angiogenesis by affecting the activity of vascular endothelial growth factor.[163]

Based on the above characteristics, we believed that gold and silver nanoparticles can be used alone for the therapy of HCC, as well as for the preparation of targeted drug delivery systems for the therapy of HCC.

Application of Sorafenib United With Gold Nanoparticles in Curing Hepatoma

Huang et al prepared sorafenib derivative capped gold nano-particles (AuNPs New Sor).[157] AuNPs New Sor is a relatively stable solid sphere whose size remains relatively stable within 24 hours.[157] The preparation method of AuNPs New Sor is as follows:[157] at first, melt the stored sorafenib ramifications (complex 10b, 10m, and 10q) in dimethyl sulfoxide (DMSO), and then add gelatin AuNPs to these solutions. Among them, gelatin AuNPs can be synthesized by Turkevich method using sodium citrate chemical reduction of HAuCl4.[164] AuNPs have many advantages such as protecting drugs from degradation in physiological environments, adjustable size and shape, surface modifiability, and good biocompatibility.[165] AuNPs New Sor has the following effects:[157] AuNPs New Sor can deliver novel sorafenib ramifications into neoplasm location to normalize the tumor microenvironment. AuNPs New Sor can also produce superior tumor angiogenesis inhibition by down-regulating EGFR and VEGFR-2. Based on the above introduction, it is believed that AuNPs New Sor can exhibit more competitive anti-tumor activity than free sorafenib.

Cai et al investigated the synergistic anti-tumor effects of SOR and gold NPs-loaded anti-miR221. It is believed that the miR221 inhibitor loaded with gold nanoparticles (AuNPs anti-miR221) can boost the action result of sorafenib by downregulating p27 and upregulating DNMT1, thereby heightening the susceptibility of sorafenib to HCC cells.[166] Furthermore, AuNPs anti-miR221 has small size, it can generate a strong osmotic retention effect, which helps sorafenib enter tumor cells and exert anti HCC effects.[166]

Conclusion and Prospect

Advances in nanotechnology offer new hope in the targeted therapy for HCC. Based on the advantages of low toxicity, biodegradability, and good biocompatibility of nanomaterials, they can solve the problems of targeted drug resistance, low drug bioavailability, and non-specific delivery. Compared with single targeted drug therapy, nanocarrier delivery of drugs targeting tumor cells is mainly achieved through two strategies:[62] passive and active. The passive targeting strategy increases the cumulation of local drugs in the liver through the accumulation of nanoparticles.[62] The active targeting strategy enhances the targeting specificity of drugs by using cell-specific ligands to decorate the surface of nanoparticles.[62] In contrast, active targeting strategies have higher selectivity and specificity.[62] Nanoparticle mediated targeted drug delivery systems (NTDDS) can assist in specific drug into tumor cells by enhancing the permeability retention effect.[167] NTDDS has the function of delivering targeted therapeutic drugs at high concentrations to tumor cells, avoiding drug dissolution and fragmentation before reaching the target site, prolonging the circulation time of targeted drugs in the body, and improving drug bioavailability.[8,168] NTDDS can also enhance the targeting specificity of the delivery system by mediating the internalization of the delivery carrier into the surface ligand of liver cancer cells.[167]

However, there are still some limitations in the research of nanotechnology united with targeted drugs in HCC: Most of the nano-drug research is still in the clinical trial stage, and the fitment of nano-drugs with the human body has not been studied. The research evaluation standards are non-uniform, making it challenging to compare the drug loading efficiency and toxicity of different nanoparticles. Therefore, most of the problems in the research and development of nanodrugs for liver cancer focus on the drug-loading synthesis process; however, the release of drugs from nanocarriers is also important. In order to further improve the application of nanomedicine in the treatment of HCC, we should determine the standard evaluation system, strengthen the research on the reversible binding of nanoparticles and drugs, and pay more attention to the application of nanomedicine in solid HCC. It is believed that, with the efforts of many scientists, nanomedicine will occupy an important position in the future targeted therapy of HCC.

Abbreviations

HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; EPR, enhancing permeability retention; TDDS, targeted drug delivery system; SOR, Sorafenib; VEGFR, vascular endothelial growth factor receptor; PDGFR, platelet-derived growth factor receptor; TRIM54, tripartite motif 54; FSP1, ferroptosis suppressor protein 1; ERK, extracellular signal-regulated kinase; FGFR, fibroblast growth factor receptor; RET, rearranged during transfection; KIT, receptor tyrosine kinase; OS, overall survival; ORR, objective response rate; PFS, progression-free survival; FDA, Food and Drug Administration; PI3K/AKT, Phosphatidylinositol 3-Kinase/Protein Kinase B; ICIs, immune checkpoint inhibitors; CTLA-4, the cytotoxic T lymphocyte-associated protein 4; PD-1, Programmed Cell Death Protein 1; ADRs, adverse drug reactions; AE, adverse event; PEG, polyethylene glycol; HepG2, human hepatocellular carcinoma cell line; SLNs, Solid lipid nanoparticles; SLN, Solid lipid nanoparticle; NPs, nanoparticles; DEN, diethylnitrosamine; SPOONs, superparamagnetic iron oxide nanoparticles; Sor Mag-SLNs, Sorafenib-loaded magnetic solid lipid nanoparticles; us-LNPs, Ultra small lipid nanoparticles; MK-siRNA, siRNA against the midkine gene; YTHDF 1, YTH N6-methyladenosine RNA binding protein 1; CSC, liver cancer stem cells; NP-SOR-Ab, polymer nanoparticle loaded with sorafenib; PVA, polyvinyl alcohol; PAE-PEG-NH2, poly (β-amino ester)-polyethylene glycol-amine; CCM, cancer cell membrane; TMC, trimethyl chitosan; SiNPs, Silicon dioxide nanoparticles; SSN, solid silica nano-particles; MSN, mesoporous silica nanoparticles; M-MSNs, Magnetic mesoporous silica nanoparticles; Ag-NPs, Silver nanoparticles; AuNPs New Sor, sorafenib derivative capped gold nano-particles; NTDDS, Nanoparticle mediated targeted drug delivery systems.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest.

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