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REVIEW

Advances in the Study of Bioactive Nanoparticles for the Treatment of HCC and Its Postoperative Residual Cancer

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Abstract: Primary hepatocellular carcinoma (HCC, hepatocellular carcinoma) is the third leading cause of tumor death in the world and the second leading cause in China. The high recurrence rate at 5 years after surgery also seriously affects the long-term survival of HCC patients. For reasons such as poor liver function, large tumors, or vascular invasion, only relatively limited palliative treatment is available. Therefore, effective diagnostic and therapeutic strategies are needed to improve the complex microenvironment and block the mechanism of tumor development in order to treat the tumor and prevent recurrence. A variety of bioactive nanoparticles have been shown to have therapeutic effects on hepatocellular carcinoma and have the advantages of improving drug solubility, reducing drug side effects, preventing degradation in the blood, increasing drug exposure time, and reducing drug resistance. The development of bioactive nanoparticles is expected to complete the current clinical therapeutic approach. In this review, we discuss the therapeutic advances of different nanoparticles for hepatocellular carcinoma and discuss their potential for postoperative applications with respect to possible mechanisms of hepatocellular carcinoma recurrence. We further discuss the limitations regarding the application of NPs and the safety of NPs.

Keywords: HCC, NPs, treatment

Introduction

Hepatocellular carcinoma (HCC) is the fifth most prevalent cancer in the world.[1] The incidence and mortality of HCC continue to rise in many countries, accounting for 90% of HCC in China with a recurrence rate of over 50% 5 years after resection in HCC patients.[1–3] Infection with hepatitis B or C virus,[4] exposure to carcinogens,[5] excessive alcohol consumption,[6] obesity,[7] and diabetes[8] are all important causes of HCC. The aforementioned etiology that leads to HCC encompasses multiple stages, including multiple processes of hepatocyte injury, regeneration, fibrosis, and heterogeneous proliferation.[9]

Most patients are already in the progressive stage upon diagnosis because they are asymptomatic, which has a greater impact on survival. HCC can currently be diagnosed by a variety of means, such as ultrasound, CT, MRI, and puncture biopsy, but the accuracy and potential for medically induced metastases make it even more difficult to diagnose. HCC can be treated with liver transplantation, surgical resection, and local ablation; however, only 30% of newly diagnosed liver cancer patients are eligible for treatment.[10] Despite recent advancements in the systemic treatment of HCC, long-term survival in patients with advanced disease is uncommon.[11] Currently, systemic chemotherapy, transhepatic arterial chemoembolization, and radiation therapy comprise the most prevalent adjuvant treatments for HCC. However, the side effects and toxic effects of systemic chemotherapy are substantial and have obvious killing effects on normal

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cells.[12,13] Transhepatic arterial chemoembolization is easily affected by the formation of cancer thrombi or distant metastases in the blood vessels, and radiation therapy is ineffective or discontinued because patients are unable to tolerate it.[14] Accordingly, HCC remains one of the most challenging cancers to till date.

With existing therapies, patient survival rates have not improved significantly, and continuous administration of drugs has exacerbated drug resistance in HCC cells. In addition, HCC, as a highly malignant tumor, is relatively less sensitive to chemotherapy. Therefore, there is a great need to utilize nanodrug delivery systems that can not only reduce HCC drug resistance but also increase chemotherapy sensitivity while promoting tumor cell apoptosis. This review will summarize the research progress on the therapeutic effects of different NPs in HCC and discuss the application prospects of this new form of HCC therapy. At the same time, we further summarized the relevant mechanism of HCC postoperative recurrence and further discussed whether NPs that can play a role in HCC treatment can also play a certain role in residual cancer after HCC.

Advantages of Nanoparticles in the Treatment of HCC

In recent years, the development of nanotechnology and biomaterials has led to applications in many areas of cancer treatment, as well as new ideas for the treatment of patients with recurrence of HCC following palliative resection. Nanoparticles (NPs) are solid particles with diameters between 10 and 1000 nm that can encapsulate or adsorb drugs for disease-specific diagnosis or treatment.[15] Biologically active NPs are able to carry a wide variety of drugs and protect them from degradation in harsh environments while achieving long-term controlled drug release function via biocompatibility and target recognition properties, thereby significantly reducing the side effects of drugs and demonstrating a very positive role in the treatment of tumors.[16–18] In addition, NPs can be modified by specific ligands, such as galactose, mannose, lactose and maltose, which can enhance specificity, lower toxicity, lower immunogenicity, and prolong circulation time. And can aid in the targeting and internalization of specific cell populations, including cancer cells.[19] Furthermore, endocytosis allows for intracellular drug staging, and drugs can be released with altered cellular microenvironment acidity and alkalinity, particularly in the acidic environment of cancer cells. In comparison to conventional radiotherapy and chemotherapy, the NPs-mediated hepatic-targeted drug delivery system (HTDDS) enhances the therapeutic efficacy of targeted therapy for HCC.[20] Correspondingly, the ability to achieve liver-targeted drug delivery, temporarily store drugs in the liver, and actively identify liver cancer cells is highly promising for the treatment of postoperative residual carcinoma patients.[21]

Nanoparticles have been widely used as carriers for loading bioactive agents, particularly those with low solubility in water, due to their unique properties.[22,23] The advantages of encapsulating drugs in NPs include increased drug solubility, decreased drug side effects, prevention of drug degradation in the blood, increased drug exposure time, and decreased drug resistance.[24] Additionally, NPs facilitate the development of protein-based therapeutics. Meanwhile, NPs have a number of benefits, including enhancing protein uptake and cellular responses, activating specific genes and intracellular signaling, and modulating cellular responses to soluble factors.[25,26] During their action, NPs can mimic the natural morphology and function of the extracellular matrix (ECM) and deliver and release bioactive substances, including proteins, peptides, and small molecules, to numerous tissues.[27–30] During the course of action, not only is drug target recognition achieved but also the zero-level drug release characteristics at the tumor site are controlled, decreasing the frequency of local drug delivery, and the ability to maintain the drug release rate (Figure 1).[31,32]

Application of NPs in the Treatment of HCC

NPs and Chemotherapy for HCC

Metal and non-metal NPs can be loaded with chemotherapeutic agents that inhibit tumor cell proliferation and angiogenesis during therapy, such as sorafenib (Sora),[33] thereby reducing the dose of chemotherapeutic drugs and achieving relatively satisfactory therapeutic effects. After modification, metal nanoparticles (metal NPs) such as iron, gold, and silver can significantly reduce their biotoxicity and be used to treat HCC. Among them, Fe NPs can be loaded with Sora and i RGD peptide with amino acid sequence CRGDK/RGPD/EC (MIL-101(Fe)@sor + i RGD), which decreases glutathione (GSH) and glutathione peroxidase 4 (GPX-4) levels while providing iron ions to effectively inhibit

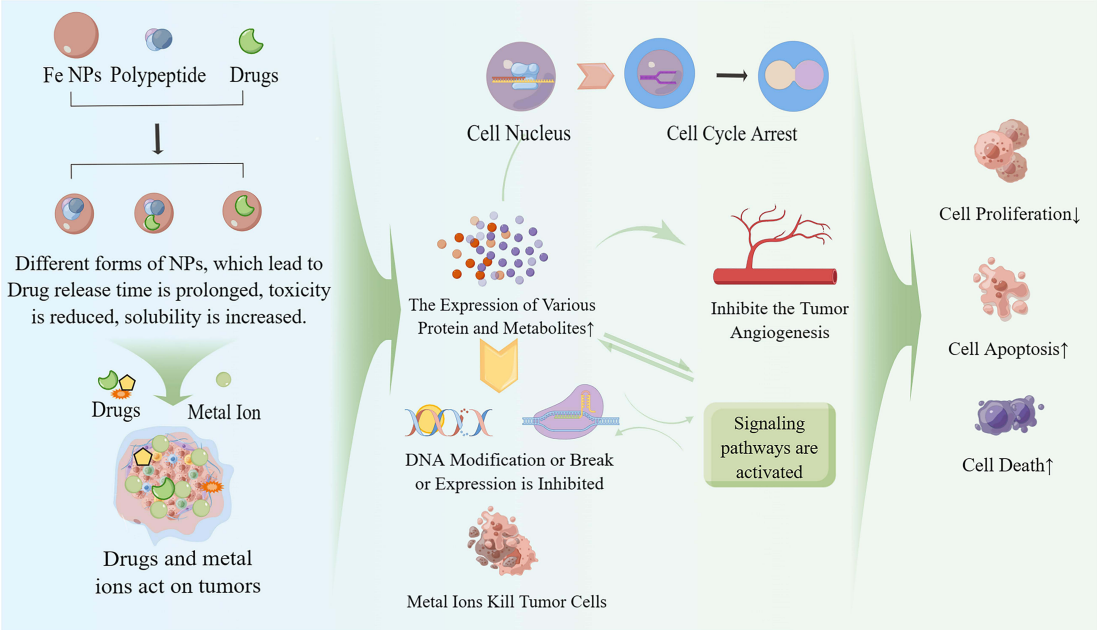

Figure 1 Schematic diagram of NPs acting on tumor cells. Reprinted with permission from Figdraw (www.figdraw.com).
Abbreviation: NPs, nanoparticles.

tumor growth, with good biosafety.[34] Fe_3O_4 has very low biotoxicity and can be doped with poly (ADP-ribose) polymerase 1 (PARP-1) inhibitor (ABT-888) and temozolomide (TMZ) in Fe_3O_4 / Fe nano-scaffolds, Compared with drug alone, ABT-888/TMZ/NPs can significantly cause DNA damage, cell cycle arrest, PARP-1 fragmentation, Caspase-3 gene activation, and reduce the expression of poor prognostic related genes, so as to achieve the objective of treating tumors.[35] Raptinal is a novel anticancer drug that can initiate the apoptotic pathway through the release of cytochrome C and caspase 3, encapsulate mitochondrial function, and significantly induce the expression of apoptotic genes. In addition, Raptinal loaded with Ag NPs significantly reduced bilirubin and AFP levels in the treated group compared with free Raptinal, which indicates a significant reduction in the aggressiveness of the tumor.[36] Additionally, platinum has some utility in the treatment of recurrent tumors. Due to the high glucose consumption of HCC cells and the excessive production of reactive oxygen species (ROS), Shoshan et al prepared titanium-coated, non-oxidized platinum nanoparticles. The titanium-coated, non-oxidized platinum nanoparticles not only enable tumor cells to take up Pt NPs more efficiently but also cause DNA damage when the internal Pt NPs are oxidized to oxidized platinum when they come into contact with reactive oxygen species. Thus, the therapeutic effect on HCC cells can be achieved.[37]

Arsenic trioxide (ATO) was initially discovered and utilized in the treatment of acute promyelocytic leukemia (APL), but the current formulation has applications in the treatment of other types of cancer.[38] Huang et al,[39] prepared ATO-loaded ZnAs@SiO2 nanoparticles (NPs) to test the efficacy of ATO in the treatment of HCC, and found that the SHP-1/JAK2/STAT3 signaling pathway was activated, which significantly inhibited the growth and metastasis of hepatocellular carcinoma cells and could be applied to the treatment of HCC. DNA methyltransferases 1 (Dnmt1) protein and PCNA were highly correlated with the prognosis of HCC, and ATO-filled m PEG-PLGA-PLL NPs were able to decrease the expression of Dnmt1 gene and DNA methylesterase gene, induce caspase 3 activation, release free N-terminal structural domain of gasdermin-E (GSDME), and ultimately induce apoptosis in HCC cells.[40] Chitosan is a nontoxic, cation-rich, biodegradable carrier that can protect DNA from nuclease degradation, and chitosan nanoparticles have shown high activity against hepatocellular carcinoma cells.[41,42] In this regard, triptolide (TP) is highly effective against a variety of cancers, including hepatocellular carcinoma; however, its high toxicity, low solubility in water, and unknown therapeutic targets limit its clinical application.[43,44] Nevertheless, galactosylated chitosan TP nanoparticles (GC-TP-NPs) with high drug-carrying capacity can overcome this problem, as they have a sustained release pattern, effective in vitro cellular uptake, and high hepatic tumor accumulation in vivo, in addition to exhibiting lower systemic toxicity and androgenic

toxicity, with the same pro-apoptotic and anti-proliferative effects on HCC cells in vitro and in vivo.[44] In addition, dextran-based nanocarriers are biocompatible, have low toxicity, and can be used to target and control the release of curcumin to hepatocellular carcinoma cells L929 and HepG2 with the potential to treat the HCC.[45] Accordingly, poly (lactic acid)-glycolic acid [PLGA], one of the linear polyesters in polymeric nanoparticles, has been used in the treatment of hepatic carcinoma, since it can be degraded in vivo to lactic acid (LA) and glycolic acid (GA), which is further degraded to carbon dioxide and water and is thus not toxic to the organism. Pan et al,[46] encapsulated artemisinin (Artesunate, ART) in GA-modified NPs, and in vitro cytotoxicity experiments demonstrated that the GA-modified NPs had a higher affinity for HCC cells, a higher cellular uptake capacity, a lower cancer cell survival rate, and significant targeting properties, which can be utilized for the targeted treatment of HCC. Bile acids are synthesized in the liver from cholesterol, and in the human enterohepatic circulation, bile acids circulate frequently and efficiently. The concentration of GSH in the cytoplasm of tumor cells is approximately 2–10 mM, which is significantly higher than its concentration in the extracellular matrix (approximately 2–20 μm).[47] T Fang et al,[48] fabricated redox-sensitive PLGA nano-NPs (TSP/FP) loaded with oridonin (ORI) and GSH, which can apply to the high affinity of the APDTKTQ (Ala-Pro-Asp-Thr-Lys-Thr-Gln) peptide for the receptor of advanced glycation end-products (RAGE) can help cells uptake TSP or FP to release ORI, thus maximizing the therapeutic effect on HCC.

In the chemotherapy of liver cancer, NPs mainly promote the apoptosis of tumor cells by activating Caspase 3, and they can also eliminate tumor cells by regulating gene expression and activating signaling pathways (Figure 2).

NPs and Photothermal Therapy for HCC

Photothermal therapy (PTT) is a specialized treatment modality in which bioactive materials with high photothermal conversion efficiency are injected into the body, and light energy is converted into heat energy to kill tumor cells using

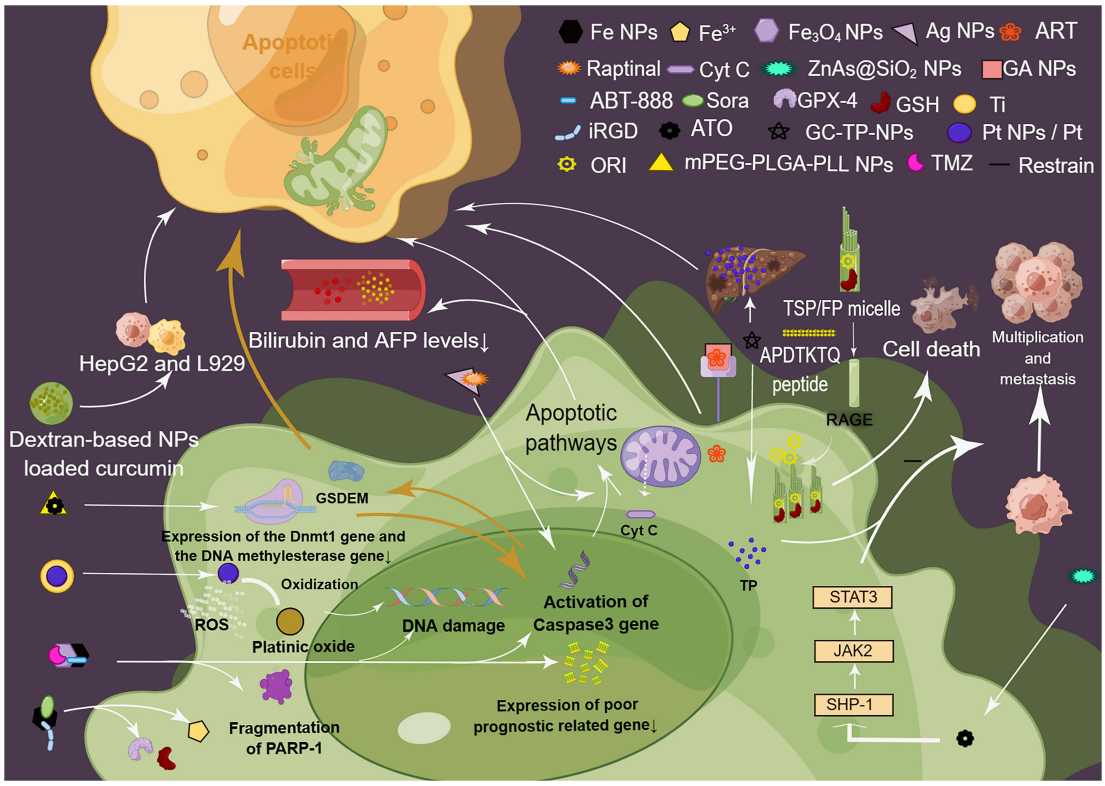

Figure 2 Schematic diagram of NPs and chemotherapy for HCC. NPs, nanoparticles. iRGD, Peptide chain of the amino acid sequence CRGDK/RGPD/EC. GSH, glutathione. PARP-1, poly (ADP-ribose) polymerase 1. ABT-888, PARP-1 inhibitor. Reprinted with permission from Figdraw (www.figdraw.com).

Abbreviations: TMZ, temozolomide; ROS, reactive oxygen species; ATO, arsenic trioxide; Dnmt, DNA methyltransferases; GSDEM, gasdermin-E; Cyt C, cytochrome C; ORI, oridonin; TP, triptolide; TAP/FP, redox-sensitive PLGA nano-NPs; APDTKTQ, a peptide Ala-Pro-Asp-Thr-Lys-Thr-Gln; RAGE, the receptor of advanced glycation end-products; ART, Artesunate.

target recognition technology and external light sources.[49] Currently, numerous NPs have been validated for use in the photothermal therapy of tumors.

With good biocompatibility and relatively good therapeutic effects, graphene derivatives and their hybrids have garnered a great deal of attention from researchers in recent years and are widely used in cancer nanomedicine; they also have a certain amount of potential in the PTT tumor species. Graphene quantum dots (QDS)-mediated chitosan magnetic nanodelivery system (DOX-Fe3O4@CGA), with conjugated bonds, can adsorb photons and convert them into heat, promote the heating of the surrounding environment and the production of reactive oxygen species (ROS), and realize the targeted photothermal synergistic chemotherapy of HCC.[50]

Metal NPs play a relatively broad role in PTT treatment, and superparamagnetic iron oxide (SPION) NPs can induce lysosomal membrane permeabilization (LMP) in tumor cells, protect small interfering RNA (siRNA) from degradation by biological systemic nucleotides, improve the heating efficiency of π -π conjugation enhanced magnetic saturation, and induce apoptosis in hepatocellular carcinoma (HCC) cells in a controlled manner, which can be applied for the treatment of HCC.[51–53] Adipose-derived mesenchymal cells (AD-MSCs) have the ability to homing and damage the liver. After encapsulation of AD-MSCs with SPIO-coated gold nanoparticles (SPIO @ AuNPs), they can be successfully transfected into AD-MSCs. SPIO @ AuNP-loaded AD-MSCs can thermally ablate surrounding liver cancer tumor cells.[54]

PTT achieves targeted therapy for HCC patients, thereby improving patient comfort and therapeutic outcomes (Table 1).

Altered Gene Expression Levels of HCC

Inhibiting the cell cycle, modifying gene expression levels, and regulating signaling pathways can be used to treat HCC. To achieve tumor cell-specific apoptosis and death, Fe_3O_4 can be combined with FITC-binding cyclic the exposed arginine-glycine-aspartic (RGD) tripeptide to create nanoprobes that target and identify genes regulating integrin αvβ3 and vascular endothelial growth factor receptors (VEGFRs), which are highly expressed in many tumor tissues.[55–57] In targeted gene therapy for HCC Fe_3O_4 NPs are anticipated to be applied to postoperative residual carcinoma in HCC. HCC cell lines and tissues can negatively regulate the expression of miR326 through the PI3K/AKT/c-myc axis, and its down-regulation is positively correlated with the prognosis of HCC. AuNPs carrying miR326 can inhibit the expression of cell cycle factors in vitro and in vivo, leading to tumor cell cycle transition disorders and inhibiting the PI3K/AKT/c-myc axis through a negative feedback loop, further inhibiting the proliferation of HepG2, Hep3B, Huh-7, and other cell lines.[58] Enterococci-mediated AuNPs inhibit the proliferation of HepG2 cells via intracellular ROS-mediated apoptosis, decrease the expression of the proliferating cell nuclear antigen (PCNA) gene, and have therapeutic potential for HCC.[59]

MSN carries ursolic acid (UA) (USMNs-CL) with good anticancer activity and hepatoprotective effects, which exhibited strong proliferation and cell cycle inhibition and apoptosis in HepG2 cells at the G2/M phase, inhibition and cell cycle arrest, blocking tumor cell DNA replication, and significantly causing early and late apoptosis in HepG2 cells, thereby providing a means to improve the bioavailability and prolong the release of anticancer drugs.[60] Xue et al,[61] discovered that MSNs containing Adriamycin hydrochloride (DOX) and miR-375 significantly increased DOX uptake,

Table 1 Photothermal Therapy

NPs	Mechanism	References
DOX-Fe3O4@CGA	Adsorb photons and convert them into heat. Producing reactive oxygen species (ROS).	[50]
SPION	Induce lysosomal membrane permeabilization (LMP) in tumor cells. Protect small interfering RNA (siRNA), Improve the heating efficiency of π -π conjugation. Induce apoptosis.	[51–53]
SPIO @ AuNP- AD-MSCs	Transfection of AD-MSCs. Thermally ablate surrounding liver cancer tumor cells.	[54]

and miR-375 reduced p-glycoprotein (P-gp) overexpression, which leads to multidrug resistance (MDR) in tumor cells, by inhibiting the expression of astrocyte elevated gene 1 (AEG-1) and targeting AEG-1-induced apoptosis.

Chitosan has numerous benefits, including biodegradability and low toxicity, and can be used in gene therapy. Accordingly, folic acid-chitosan nanoparticles (FA-CS) loaded with mouse interferon-inducible protein-10 (IP-10) plasmid DNA may achieve antitumor effects by inhibiting HCC cell proliferation and inducing HCC cell apoptosis by modulating immune responses and inhibiting tumor neovascularization, which is a novel HCC therapy.[62] In addition, Xue et al,[63] discovered that the preparation of galactosylated carboxymethyl chitosan-magnetic iron oxide nanoparticles (Gal-CMCS- Fe_3O_4 -NPs) enhanced the transfection efficiency of the Ras-related region family 1A (RASSF1A) gene, which is capable of inhibiting hepatocellular carcinoma cells, inhibiting tumor growth, and increasing the sensitivity of hepatocellular. Chitosan NPs can also encapsulate anionic albumin, which can alter redox homeostasis and inhibit NF-κB expression and ALDH1A1 in cancer cells, causing high apoptosis-mediated toxicity with great potential for inhibiting CSCs and treating HCC (Figure 3).[64]

Combination Therapy for HCC

Combination therapy refers to the rational combination of drugs or other cellular metabolites with comparable but distinct effects for the treatment of disease. In addition to reducing the toxic side effects of drugs, combination therapy also inhibits the development of drug resistance in tumor cells.

MSNs can target tumors via surface modification and accumulate sufficiently within tumor cells for tumor combination therapy, as well as capture/insert metals for PTT.[65,66] Yang et al,[67] utilized MSNs loaded with Sora and PTT near-infrared PTT reagent indocyanine green (ICG), which was found to increase the secretion of IFN-G from CD8+ T cells and enhance the number of immune cells in the tumor and spleen, as well as reduce angiogenesis, with potent immune response and recurrence-preventing activity, having a wide application for the treatment of HCC. Meanwhile, Zheng

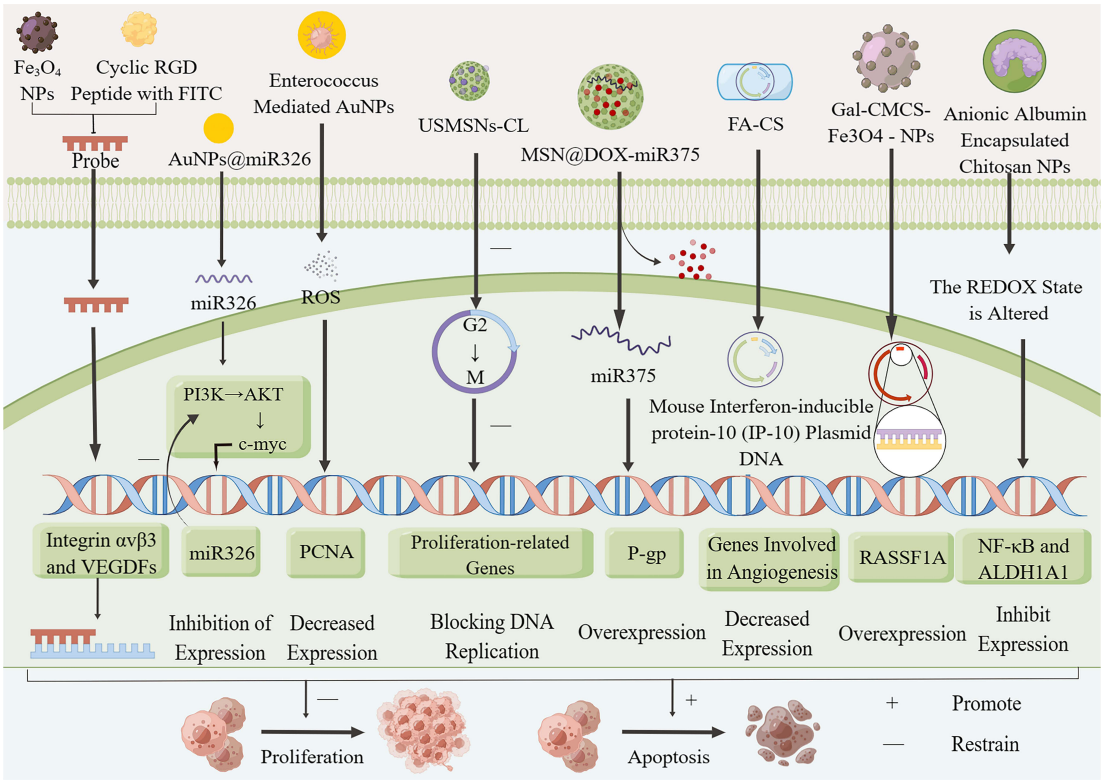

Figure 3 Schematic diagram of Altered Gene Expression Levels of HCC. Reprinted with permission from Figdraw (www.figdraw.com).
Abbreviations: NPs, nanoparticles; ROS, reactive oxygen species; VEGDF, vascular endothelial growth factor receptors; RGD, the exposed arginine-glycine-aspartic tripeptide; P-gp, p-glycoprotein; FA-CS, folic acid-chitosan nanoparticles; Gal-CMCS- Fe_3O_4 -NPs, galactosylated carboxymethyl chitosan-magnetic iron oxide nanoparticles; RASSF1A, Ras-related region family 1A.

et al,[68] prepared MSNs co-loaded with Sora and vascular endothelial growth factor-targeting siRNA (siVEGF) NPs (Sora/ siVEGF@MSNs-LA), which could target the induction of S-cell cycle arrest, enhanced the anti-cancer effect of Sora and siVEGF, and had great potential in the treatment of HCC. In addition, MSN modified by polyamidoamine ligand (PAMAM-APT) co-loaded Sora and pEGFR (SEHPA), which effectively promoted the uptake of Sora by HCC cells while synergistically inhibiting the expression of EGFR and downstream PI3K-Akt pathway, jointly inhibiting angiogenesis and achieving efficient EGFR gene therapy, is a promising dual gene-chemotherapy drug delivery system,[69] which has promising applications in the treatment of HCC. Among the shape-controlled magnetic mesoporous silica nanoparticles (M-MSNs), rod-shaped MSNs have stable drug release function and low cytotoxicity, which can assist clinicians in monitoring treatment outcomes by MRI, which might used to suicide gene therapy of HCC.[70]

The use of N-galactosylated chitosan-5-fluorouracil (GC-FU) for electrostatic condensation with miRNA-122 and the co-delivery of miRNA-122 and the anticancer drug 5-Fu, which improved blood salt stability, effectively induced apoptosis and inhibited the proliferation of HCC cells,[71] may have great potential for the future synergistic treatment of HCC.

Multiple NPs contribute to the reduction of tumor cell resistance. Sora inhibits multiple receptor tyrosine kinases and downstream Raf signaling molecules (Raf-1 and B-Raf), but within 6 months, the vast majority of patients develop resistance to sorafenib.[72] Using CXCR4-targeted PLGA-PEG NPs to encapsulate sorafenib and mestinon and modifying the surface of PLGA-PEG NPs with the CXCR4 antagonist LFC131 peptide enhanced the delivery and accumulation of anticancer drugs at the tumor site, thereby enhancing the antitumor effect.[73] Polyethylene glycol (PEG) and polyethyleneimine (PEI) conjugated ultrasmall nano-graphene oxide (NGO-PEG-PEI) loaded with C6 - ceramide in combination with Sora (NGO-PEG-PEI/Cer) exhibited a synergistic effect, significantly inhibiting tumor growth and improving survival time in vivo, and may also play a role in the destruction of HCC by inactivating MDR and Akt signaling in HCC cells role as a promising potential therapeutic strategy for the treatment of drug-resistant HCC.[74]

Other Treatment Modalities

In addition to their therapeutic effects in the aforementioned therapeutic modalities, NPs can also be altered to exert therapeutic effects. Mesoporous hollow alumina nanoparticles (MHA) prepared using alumina and grafted with hyaluronic acid (HA) exhibited significantly enhanced targeting effects and significant pro-apoptotic and tumor suppressive effects.[75] Moreover, Zhang et al,[76] synthesized an amphiphilic polymer containing bile acid (CA) and adsorbed it onto the surface of PLGA NPs. According, they demonstrated that the binding of CA to the bile acid transporter on the cell membrane increased the adhesion of NPs to cells, accelerated the intracellularization of NPs, and inhibited the proliferation of HCC cells. Comparative in vitro cytotoxicity studies of silver-containing reduced graphene oxide (rGO-Ag) nanoparticles revealed that compared with normal liver cells, hepatocellular carcinoma cells (HepG2) cells were more susceptible to the effects of oxidases such as lipid peroxidase, superoxide dismutase, and catalase, and the GSH level decreased and DNA damage was more obvious (Table 2).[77]

Table 2 Combination Therapy and Other Treatment Modalities

NPs	Mechanism	References
MSN@Sora-ICG	Increase the secretion of IFN-G from CD8+ T cells. Enhance the number of immune cells. Reduce angiogenesis.	[67]
Sora/ siVEGF@MSNs-LA	Target the induction of S-cell cycle arrest. Enhance the anti-cancer effect of Sora and siVEGF.	[68]
SEHPA	Promote the uptake of Sora. Inhibit the expression of EGFR. Downstream PI3K-Akt pathway. Inhibit angiogenesis. Achieve efficient EGFR gene therapy.	[69]

(*Continued*)

Table 2 (Continued).

NPs	Mechanism	References
GC-FU@miRNA-122	Improve blood salt stability.	
	Induce apoptosis.	
	Inhibited the proliferation of HCC cells.	[71]
PLGA-PEG@Sora/ mestinon	Enhanced the delivery and accumulation of anticancer drugs at the tumor site.	[73]
NGO-PEG-PEI/Cer	Inhibiting tumor growth.	
	Improving survival time.	
	Inactivating MDR and Akt signaling.	[74]
MHA	Enhanced targeting effects and pro-apoptotic and tumor suppressive effects.	[75]
PLGA-CA	Increase the adhesion of NPs to cells.	
	Accelerate the intracellularization of NPs,	
	Inhibit the proliferation of HCC cells.	[76]
rGO-Ag	Susceptible to the influence of lipid peroxidase, superoxide dismutase, and catalase.	
	Decreased the GSH level.	
	Damage DNA.	[77]

Discussion

For HCC patients, the advent of NPs has opened up more possibilities for their treatment. However, surgery is still the effective means of patient treatment, and postoperative recurrence represents a major challenge for clinicians. Surgery is challenging, and treatment modalities such as chemotherapy are still used to prevent postoperative HCC recurrence. In the study of postoperative tumor recurrence, it was found that it was mainly related to surgical stimulation and postoperative changes in the tumor microenvironment, and these factors have very positive implications for the prevention and treatment of surgical residual cancer and future HCC recurrence.

Mechanism of Residual Carcinoma After HCC Surgery

Effect of Surgical Stimulation in the Recurrence of HCC Residual Carcinoma

Although surgery offers patients with cancer the opportunity to be cured, it is also a significant factor in the recurrence of residual carcinoma following HCC surgery. Researchers have demonstrated that anesthetic drugs administered during surgical anesthesia may also promote cancer recurrence and metastasis, with intravenous anesthetic isoproterenol and inhaled volatile anesthetics having more profound effects on inflammation, immune cell phenol types, and cancer progression.[78] Additionally, local recurrence can rapidly exceed the initial tumor's volume, despite the fact that surgery can remove solid tumors.[79,80] Moreover, studies have demonstrated an increased risk of metastatic growth following the resection of primary tumors.[81] The primary reason for this is that surgery causes cancer cells to be shed and enter the circulatory system and upregulates the expression of adhesion molecules in organs.[82] In addition, it induces changes in the target tissue as well as changes in the cancer cells themselves, thereby increasing the ability of the cells to migrate and invade. In light of the preceding, the effect of wide and narrow margins on macroscopic HCC has been studied in liver surgery, with 5-year survival rates of 74.9 and 49.1% in the wide margin and narrow margin groups, respectively; since the recurrence of HCC was observed in the narrow margin group, the wide margin procedure was, therefore, deemed advantageous for patient survival.[83]

Surgery also causes alterations in the physiological functions of the patient, primarily manifesting as a state of stress.[84] Herein, the role of natural killer cells (NK cells) in recognizing and killing tumor cells is inhibited and postoperative immune function is impaired, with residual tumor cells gaining the potential to metastasize. In addition, it may also permit the continued growth of cancer cells remaining at the tumor cut edge. Surgical procedures may also induce hypoxia in the liver, thereby activating NF-B and hypoxia-inducing factors (HIFs) and accelerating tumor cell growth in regions where hypoxia and inflammation are prevalent.[85] Moreover, when hepatectomy is performed, repeated

liver damage occurs, and hepatic stellate cells (HSC) are activated to dedifferentiate into myofibroblast-like cells, which leads to the development of hepatic fibrosis and the occurrence of HCC.[86]

Effect of Tumor Microenvironment on Residual Carcinoma Development After HCC Surgery

Numerous pro-angiogenic factors, including TGF-1, have been identified in studies involving angiogenic factors that may stimulate the growth of HCSCs and accelerate the proliferation and metastasis of residual carcinoma after HCC surgery.[87,88] Accordingly, increased postoperative levels of the inflammatory mediator prostaglandin E2 (PGE2) have been found to mediate the transfer of anti-tumor T helper (TH1) cytokines to TH2 cytokines in tumor cells, thereby promoting the proliferation of regulatory T (Treg) cells, a decrease in the number of activated CD8+ T cells, and the promotion of an immunosuppressive tumor microenvironment.[89–91] Surgery not only activates -adrenergic nerve fibers and receptors, thereby accelerating tumor progression, but also reshapes the tumor microenvironment, increases venous and tumor pressures, causes interstitial edema, and promotes tumor-associated neovascularization and neoplastic capillary lymphatics.[92–94] This explains why tumors are considered "unhealable wounds".[95]

Extracellular matrix (ECM) and carcinoma nodal stratification protein-5 regulate many essential cellular processes in postoperative residual carcinoma of HCC that are closely linked to HCC proliferation and metastasis in tumor tissues.[96,97] In addition, it has been discovered that tumor stem cells (HCSCs) persist in cancer cell screenings and may reside in a particular microenvironment that maintains the balance between self-renewal and differentiation of HCSCs by providing the necessary substances.[98,99] Accordingly, those present in interstitial microdeposits and micro-metastases (mesenchymal or hematogenous), a type of occult tumor that remains in situ following therapeutic resection, are referred to as microresidual disease (MRD).[100] Following primary tumor resection, the level of inhibitory factors secreted by cancer cells decreases, and dormant metastases or tumors in the primary lesion begins to rejuvenate, leading to a decrease in systemic anti-angiogenic factors, an increase in angiogenesis, and continued cancer cell growth (Figure 4).[101]

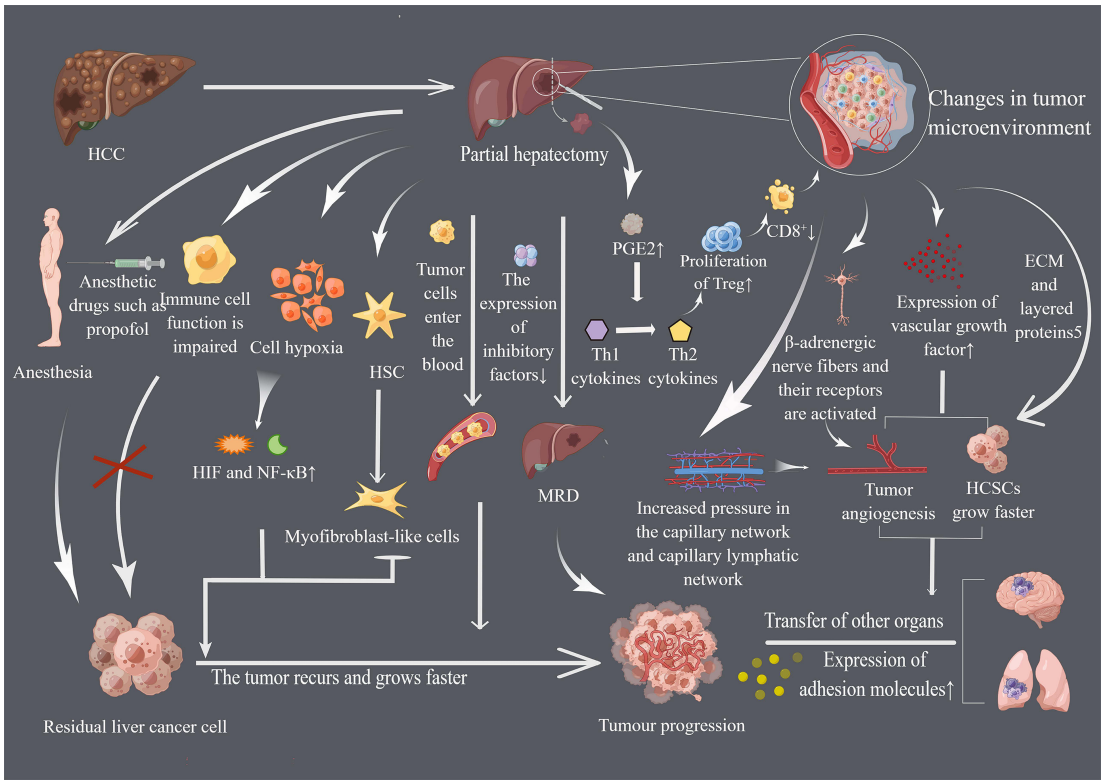

Figure 4 Mechanisms of the development of postoperative residual carcinoma in HCC. Factors such as surgical anesthesia, altered immune status, surgical stimulation, tumor cell entry, inadequate resection, and altered tumor microenvironment provide survival opportunities for postoperative participating tumors and are important mechanisms for the development of postoperative residual carcinoma in HCC. Reprinted with permission from Figdraw (www.figdraw.com).

The Potential Application of NPs in the Recurrence of Residual Cancer After HCC Surgery

Recurrent HCC after surgery can be of monoclonal (single-center) origin due to intrahepatic metastasis or of polyclonal (multicenter) origin with ab initio carcinoma, but the determination of the mode of origin of recurrent HCC is not easy.[102] Moreover, based on the existing studies, we have little understanding of the mechanisms of HCC recurrence, which is a major obstacle for us to determine its origin and type. In addition, due to the complexity of postoperative recurrence of HCC, we are not able to identify the molecular types of recurrent tumor cells or find the exact targets to target for treatment, which is one of the directions of our future research.

Above, we mentioned that multiple NPs play an important role in the treatment of HCC. In PTT treatment, MSN@Sora-ICG, however, showed strong anti-recurrence activity and has potential in the prevention of recurrence after HCC treatment.[67] However, no studies have confirmed that NPs can play a role in the treatment of residual cancer after HCC surgery or in the prevention of recurrence.

In the process of tumor recurrence, the tumor microenvironment plays an important role. It is not difficult to find that many nanoactive carriers can alter the tumor microenvironment, among which IL-6, TNF-α, etc. are prone to increase the secretion of solid tumors and the tumor microenvironment and promote the recurrence of HCC after surgery.[103] The cells and molecules in the tumor microenvironment are in a dynamic process of change, reflecting the nature of tumor microenvironment evolution, which culminates in the massive accumulation of inflammatory-related factors such as IL-6, TNF-α, MMP, etc., which accumulate in large quantities in the tumor microenvironment and together promote tumor immune escape, tumor growth, and metastasis.[104,105] Therefore, can we use bioactive nanocarriers to improve the tumor microenvironment so as to achieve prevention of tumor recurrence or therapeutic effects after tumor resection?

Traditional herbal medicine (THM) has shown a role in tumor recurrence, and it has been demonstrated that some THMs can play a role in the prevention of recurrence after HCC surgery. For example, cinobufacini (Huachansu), an aqueous extract from Bufo gargari-zans Cantor, the root of Salvia chinensis Benth [Shi-jian-chuan], the gizzard membrane of Gallus gallus domesticus Brisson [Ji-nei-jin], the root of Actinidia valvata Dunn [Mao-ren-shen], and the tuber of Pseudobulbus cremastrae seu Pleiones [Shan-ci-gu], which is anticipated to inhibit tumor growth and prolong the survival of patients.[106] Then, can we carry the drug into the nanocarrier to achieve controlled release of the drug to achieve long-term therapeutic effects? In addition, GC-TP-NPs also show a certain tumor inhibitory effect in vitro, and have a certain application potential in the treatment of residual cancer and prevention of recurrence of HCC after surgery.[44]

At present, electrostatic spinning technology is also widely used in the medical industry, so we can prepare a nanofiber membrane by dispersing bioactive nanoparticles in solvent through electrostatic spinning technology and implant it after surgery, which not only achieves sustainable release of chemotherapy drugs after surgery but also has the effect of treating residual cancer and preventing tumor recurrence after surgery. Our group has successfully prepared nanofiber membranes with such functions. Moreover, the research on NPs for the treatment of HCC is becoming more and more extensive, and some scholars have also found that their NPs themselves can promote apoptosis of HCC cells. For example, TiO2 NPs and ZnO NPs can effectively inhibit hepatocellular carcinoma HepG2 cells through the production of ROS, but the cancer-inhibiting effect is reduced after the combination of the two due to the relative reduction of pores, which also provides a new idea for future research on the treatment of HCC.[107]

In conclusion, bioactive nanoparticles have great potential in the treatment and prevention of recurrence of residual cancer after HCC surgery.

Limitations of NPs in the Treatment of HCC

Although NPs are becoming more prevalent in clinical research, they still have certain limitations. First, the reproducibility of NPs production is highly variable, and even minute variations in the preparation process can result in new NPs that are distinct from the original NPs. Because new particles in any ensemble have different surface location distributions (eg, small surfaces, vertices, defects, etc.) and the size and shape of new particles can vary widely, it is reasonable to anticipate that the characterization of individual new particles may deviate

significantly from that of the original new particles; therefore, to ensure their accuracy, comprehensive characterization of the nanoparticles at each stage and in each batch is required prior to application.[108,109] Second, in the construction of HCC models, 3D models are superior to the original 2D models for simulating the key roles of the tumor microenvironment and for understanding the interactions between HCC and NPs; therefore, whenever possible, 3D models are chosen to maximize the restoration of the normal life state of the model.[110,111] Moreover, since the target recognition receptors of target organs may mutate, this may result in off-targeting of targeted NPs and produce off-target side effects.[112] In addition, NPs are foreign to the patient's body, have a small diameter, and are likely to be captured by macrophages during vascular infiltration.[113] However, if NPs are modified, the clearance of NPs in vivo may pose a new and significant challenge. Lastly, NPs should be used sparingly, rather than in pursuit of therapeutic effects that would lead to the accumulation of NPs in vivo, causing toxic effects and putting the cart before the horse.

Warm therapy is contraindicated in the treatment of mesoendometriosis, which can lead to worsening of the disease.[114] In the treatment of patients who are not on anticoagulants and do not have cardiovascular or diabetic morbidity, systemic and topical a-type TXA appears to significantly reduce postoperative bleeding and the need for RBC transfusion after TKA.[115] When treating NPs, we should also be concerned about the effects of NPs on other organs; for example, Ni NPs can be toxic to testes.[116] Therefore, we cannot ignore the safety of drug administration, and we have to test NPs for the treatment of HCC to ensure that there are no or few adverse effects other than therapeutic effects to maximize the safety of patients' lives.

Summary and Outlook

HCC is one of the most malignant tumors known, and after diagnosis, most patients with advanced hepatocellular carcinoma have limited clinical options and a poor prognosis.[117] The development of a tumor is dependent not only on the tumor cells themselves but also on the "soil" in which they reside, ie, the tumor microenvironment. Therapeutic tools mediated by NPs can modify the tumor microenvironment by targeting one or more cytokines in the tumor microenvironment, thereby significantly inhibiting the biological behavior of HCC cells, such as their proliferation, metastasis, and apoptosis. In addition, NPs can effectively target HCC cells and CSCs, as well as capture CTCs, which are extremely rare in vivo, to facilitate early monitoring of residual carcinoma recurrence after HCC surgery and buy more treatment time for recurrence patients. It is also observed that drug-loaded nanoparticles exert their toxic killing effects on HCC cells by affecting signaling pathways, regulating the cell cycle, and inducing apoptosis, which can be used for the treatment of HCC.

HCC recurrence and postoperative residual cancer are also a major difficulty in the treatment of HCC, which is caused by the recurrence and metastasis of HCC is a multistage, multigene process characterized by dynamic alterations. NPs play a role in the treatment of HCC by regulating gene expression, inhibiting signaling pathways, and the production of pro-apoptotic substances to achieve the effect of cancer suppression, therefore, whether NPs can be placed on the surgical wound by other means to achieve prolonged release of chemotherapeutic drugs and further achieve postoperative treatment of residual cancer and prevent the effect of NPs on the surgical wound can be achieved by other means. This is also one of the directions of our group's subsequent research.

We also should be noted that the drug-release effect of various NPs may not achieve the desired targeting effect and that there is no assurance that there is no toxic effect on normal tissues or organs. Therefore, more in-depth research on NPs is required to develop a multifunctional and multifaceted cancer treatment modality, which would be a boon for patients with HCC. And simultaneously, With the advancement of technology and extensive research by scholars, it is believed that NPs will play an irreplaceable role in the treatment of residual carcinoma following HCC surgery.

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Disclosure

The authors report no conflicts of interest in this work.

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