Review Article

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Nanoparticles and the treatment of hepatocellular carcinoma

Abstract: Currently, liver cancer is the leading cause of cancer-related death worldwide, with a low 5-year survival rate, which will further decrease if advanced metastasis is present. Hepatocellular carcinoma (HCC) is the main type. However, due to the lack of specific symptoms in the early stages, it is more difficult to detect HCC, and many patients would have already been diagnosed with advanced liver cancer. At this point, many treatment methods available at early diagnosis would have become ineffective. Therefore, there is an urgent need for more effective treatment methods for HCC. In recent years, nanoparticles have been used in the treatment of HCC due to their good biocompatibility and other advantages. Different types of nanoparticles are modified to play a role in the treatment of HCC, such as regulating tumor microenvironment, enhancing the activity of drug targeting and killing cancer cells, and reducing systemic side effects. It can significantly improve the therapeutic effect of HCC and bring more hope for the treatment of HCC. In this review, several common nanoparticles are introduced, and their characteristics are described in detail. In addition, the construction of a highly efficient drug delivery system by nanoparticles and the combination of nanoparticle-targeted therapy, chemotherapy, and radiotherapy are reviewed.

Keywords: hepatocellular carcinoma, nanoparticles, therapy, tumor microenvironment, drug delivery system, combination with other therapies

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List of Abbreviations

HCC	hepatocellular carcinoma
ICC	intrahepatic cholangiocarcinoma
HBV	hepatitis B virus
HCV	hepatitis C virus
AFP	alpha fetoprotein
BCLC	Barcelona Clinic Liver Cancer
CNLC	Chinese Liver Cancer Staging
RFA	radiofrequency ablation
MWA	microwave ablation
LA	laser ablation
IRE	irreversible electroporation
CRA	cryoablation
HIFU	high-intensity focused ultrasound
TACE	transcatheter arterial chemoembolization
ICIs	immune checkpoint inhibitors
ICB	immune checkpoint blockade
PD-1	programmed cell death-protein 1
PD-L1	programmed cell death-ligand 1
CTLA-4	cytotoxic T lymphocyte antigen
TME	tumor microenvironment
TAMs	tumor-associated macrophages
CAFs	cancer-associated fibroblasts
Tregs	regulatory T cells
DDS	drug delivery system
EPR effect	enhanced permeability and retention effect

RES	reticuloendothelial system
LNPs	lipid nanoparticles
PNPs	polymer nanoparticles
SPR	surface plasmon resonance
OS NPs	organosilica NPs
MRI	magnetic resonance imaging
PAI	photoacoustic imaging
SLN	solid lipid nanoparticles
NLC	nanostructured lipid carriers
PEG	polyethylene glycol
LPHNPs	lipid–polymer hybrid nanoparticles
PAMAM	polyamidoamine
RGD	arginine-glycine-aspartic acid
MSNs	mesoporous silica nanoparticles
FDA	Food and Drug Administration
APCs	antigen-presenting cells
IONPs	iron oxide nanoparticles
MNPs	magnetic nanoparticles
MTC	magnetic targeting carriers
SPIONs	superparamagnetic iron oxide nanoparticles
QT	quercetin
QMNPs	quercetin-conjugated magnetite nanoparticles
CRISPR	clustered, regularly interspaced short palindromic repeats
Cas9	CRISPR-associated nuclease protein 9
RNP	ribonucleoprotein
siRNA	small interfering RNA
SNALPs	stable nucleic acid lipid particles
GA	glycyrrhetinic acid
LA	lactobionic acid
CA	cationized amylose
TPE	tetraphenylethylene
FA	folic acid

1 Introduction

Liver cancer is the sixth most frequently diagnosed cancer worldwide and is among the top three leading causes of cancer-related death worldwide [1,2]. Each year, up to 854,000 new cases of hepatocellular carcinoma (HCC) are diagnosed, and up to 810,000 deaths occur [3]. As the population ages, the number of HCCs is increasing globally and the mortality rate continues to rise annually [4], with a 5-year relative survival rate of only 21% [5]. Therefore, liver cancer treatment has garnered significant attention. The types of liver cancer include HCC, intrahepatic cholangiocarcinoma (ICC), and mixed HCC. HCC represents the predominant diagnosis and cause of death, accounting

for 75–85% of cases [1]. Hepatitis B virus (HBV) and hepatitis C virus (HCV) currently stand as the foremost global risk factors for HCC. Due to the implementation of the hepatitis B vaccination program, the incidence and mortality of HCC caused by hepatitis B have been relatively low in recent years. Other risk factors include alcohol, metabolic syndrome, diabetes, obesity, non-alcoholic fatty liver disease, and aflatoxin-contaminated food [4,6,7]. The main risk factors vary across different regions. For example, HBV and aflatoxin infection are considered the most prominent risk factors for HCC in most high-risk countries in Asia, with the exception of Japan and Egypt, where HCV is the leading cause of HCC, particularly in Japan, where more than 70% of HCC cases are thought to be HCV-related [8]. HCV is the leading cause of HCC in Western Europe, while in Central and Eastern Europe, nearly 50% of the HCC cases are associated with alcohol-related liver disease [9].

Early detection, diagnosis, and treatment are crucial for cancer prevention and treatment. HCC can be detected by serum biomarkers such as AFP (alpha fetoprotein) [10], PIVKA-II combined with AFP [11], abdominal ultrasound, multi-item computed tomography, and other imaging examinations [12]. However, due to its insidious onset without specific symptoms during early stages, most patients are diagnosed at advanced stages. Current treatments for liver cancer comprise surgical resection and liver transplantation, ablation therapy, transarterial chemoembolization, immunotherapy, and others [13]. Surgery serves as a radical treatment for liver cancer [14], but the diagnosis of HCC often presents at an advanced stage, involving peripheral blood vessels or metastasis, rendering surgical resection unsuitable [15]. As the first approved first-line therapy for advanced HCC, Sorafenib, and the emerging first-line therapy Lenvatinib may lead to drug resistance and adverse side effects with prolonged administration [16,17]. A high recurrence rate after surgical resection, limited eligibility for transplantation, drug resistance, and chemotherapy-induced side effects all contribute to poor clinical outcomes in HCC. Therefore, there is an urgent need for novel approaches to treat HCC more effectively.

Nanotechnology has emerged as a promising field. Nanomaterials have received extensive attention due to their low toxicity and biocompatibility, and significant progress in cancer diagnosis and treatment has been made in recent years. Different nanoparticles have specific characteristics, such as the high stability of magnetic nanoparticles (MNPs), high surface area of gold nanoparticles, and drug encapsulation of lipid particles [18], which enable nanoparticles to not only reduce the systemic toxicity caused by chemotherapy in tumor treatment but also effectively improve tumor reactivity [19]. Therefore, nanoparticles can

not only build an efficient DDS but also regulate the tumor microenvironment (TME) to improve the therapeutic effect on tumors. In this study, the characteristics of common nanoparticles and the role of nanoparticles in the current common treatment are introduced, and some clinical studies of nanoparticles are also described, hoping to provide a new method and approach for the treatment of HCC by nanoparticles (Figure 1).

2 Current liver cancer treatments and their limitations

2.1 Surgical resection and liver transplantation

Surgical resection is the main treatment for HCC [3] and also a radical treatment for early HCC. Indications for surgical excision vary by country and equipment. Surgical resection is generally recommended for patients with tumor diameter ≥3 cm and tumor number ≤3 [3]. Hepatectomy is considered for patients with nonmetastatic disease and normal underlying liver function or with compensated cirrhosis and no evidence of portal hypertension [20]. However, surgical removal is not always a cure. The 10-year recurrence-free survival rate after surgery is only about 22–25% [21]. Among them, the 5-year recurrence rate of small liver cancer (<2 cm) without microvascular invasion is 50–60%, of which about 74.6% of the recurrent lesions are located in the liver, and only 15% of the recurrent tumors can be resected [22,23]. In addition, complications such as liver failure may occur after surgery [3]. Studies have shown that the cost, time, and complication rate of ablation are lower than that of surgical resection [24]

In addition, liver transplantation is allowed if the tumor meets the Milan criteria [25], with a single tumor ≤5 cm or 2–3 tumors ≤3 cm, and no large vascular invasion or extrahepatic tumor dissemination on imaging. Liver transplantation is regarded as the first choice for liver cancer treatment because of its good survival rate and recurrence-free survival rate [20]. However, currently, the number of liver donors is outrunning supply [22].

2.2 Ablation therapy

For patients with early liver cancer, there are generally three strategies: surgical resection, ablation therapy, and liver transplantation. Ablation therapy includes radiofrequency ablation (RFA), microwave ablation (MWA), and laser ablation (LA).
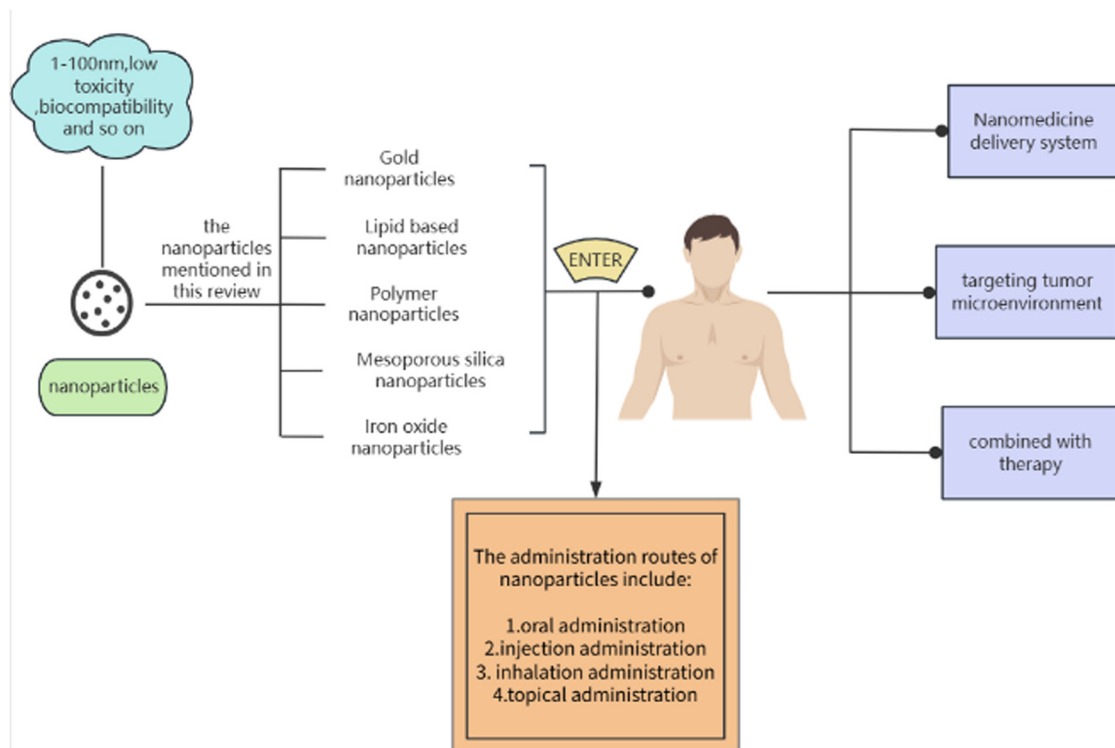

Figure 1: Mind map of the review.

2.2.1 RFA

For single HCC ≤ 2 cm without vascular invasion or extra-hepatic dissemination, ablation is the preferred initial treatment option, and RFA is the most widely used technique [26]. The primary goal of ablation therapy is complete necrosis of liver cancer cells and establishment of a safety margin > 10 mm at the outer edge of the lesion [27]. Therefore, tumor size can influence the efficacy of ablation. When the tumor exceeds 3 cm, the therapeutic effectiveness of RFA is significantly reduced, characterized by incomplete ablation and high local recurrence rates [27]. Emerging evidence suggests that ablation therapy not only acts as a localized treatment but also exerts immunomodulatory effects. RFA can promote the expression of PD-1/PD-L1, and sunitinib can activate the immune response to inhibit the effect of PD-1/PD-L1 [28], thus supporting the combination of ablation and immunotherapy for liver cancer management [29].

2.2.2 MWA

The first generation of MWA for clinical use was reported in the 1990s [30]. Tumor tissues can be directly destroyed by the thermal damage generated by electromagnetic waves in the MWA [31]. MWA has a high frequency, so it can increase the temperature to enlarge the cauterization range of tumors and shorten the cauterization time [29]. Compared to hepatectomy, MWA is easier to treat lesions located in the center of the liver and can reduce liver damage while maximizing the preservation of normal liver tissue [32]. Compared to RFA, MWA has the advantages of larger heating volume, insensitivity to carbonization, and less susceptibility to the heat sink effect of blood flow [31]. T cells and macrophages are seen to increase in HCC lesions after MWA treatment and tumor-specific immune responses appear or increase [33]. However, clinical data on RFA are limited [34].

2.2.3 Other ablation therapy

At present, when ablation is mentioned clinically, most of them refer to the above two ablation methods. However, in addition to the above two methods, there are other ways of ablation, such as LA, irreversible electroporation (IRE), cryoablation (CRA), and high-intensity focused ultrasound (HIFU). However, other forms of ablation have their limitations. For example, CRA is recommended when HCC is located near other organs or under the diaphragm because RFA is not effective. CRA uses low temperatures to form ice inside the cell and crystals outside the cell, which destroys the cell and causes the cell contents to be released outside

the cell, triggering an immune response that kills the tumor cells [35]. However, there are little data about RFA, and RFA can easily lead to complications such as shock. Compared to RFA, LA is more effective for lesions with a diameter of 20 mm or less and has a lower complication rate [36]. Adwan *et al.* conducted a study comparing the safety and efficacy of MWA and LA, and the results showed that the MWA group had a higher survival rate, indicating that MWA was superior to LA [37]. It was found that the local efficacy of LA was affected by the tumor size and volume [38]. IRE is a non-thermal ablation technology that forms pores on the phospholipid bilayer of the cell membrane through high pulses, leading to cell apoptosis. However, the operation of IRE requires the placement of electrodes close to the critical anatomical structure, which is challenging and carries the risk of primary incomplete ablation [39]. In addition, the IRE may be affected by the presence of pacemakers or surgical clips that ablate the edges, resulting in inaccurate ablation edges [40]. As a non-invasive therapy, HIFU has attracted widespread attention in recent years for its excellent performance in the treatment of small HCC. Compared with RFA, HIFU can not only avoid tumor-targeted puncture but also avoid tumor spreading along the needle path that often occurs in RFA therapy [36]. However, it should not be ignored that HIFU may cause skin burn or pain after treatment and even lead to serious complications such as ablation of the surrounding small intestine, with a high recurrence rate [41,42]. These problems limit the application of these ablation methods.

2.3 Transcatheter arterial chemoembolization (TACE)

According to the widely used Barcelona staging system (BCLC), TACE is recommended as the first-line treatment for advanced HCC [43]. TACE inhibits the growth of tumors by injecting chemotherapy drugs into the hepatic artery [44]. However, due to the heterogeneity of tumors, the clinical response to TACE therapy varies with different individuals [43]. Adverse reactions of post-embolization syndrome, such as abdominal pain, fever, and intestinal obstruction, are common after TACE [45]. Tumor recurrence is common since TACE needs to be repeated many times to control the tumor well [44]. Due to the adverse effects of chemotherapeutic drugs, repeated TACE can lead to deterioration of liver function and miss the opportunity for other treatments [45,46]. Therefore, TACE is often used in combination with other therapies, such as thermal ablation, RFA, sorafenib, and camrelizumab [44,47–50], or used as downstaging therapy to make the patient eligible for liver transplantation [48].

2.4 Systemic anti-tumor therapy

2.4.1 Targeted therapies

Systemic anti-tumor therapy includes molecular targeted therapy, immunotherapy, and chemotherapy [13]. HCC has a poor response to chemotherapy, and the average patient cannot tolerate chemotherapy due to poor liver functions. Some molecules play an important role in the development of cancer, and these can be potential targets for cancer-targeted therapies. Common targeted therapeutic drugs and their targets are shown in Table 1. For HCC, the most important target is the vascular endothelial growth factor and its receptor [58]. Bevacizumab, a humanized mono-clonal antibody that binds VEGF-A, has been investigated as a potential treatment for advanced HCC [59]. Molecularly targeted drugs have significantly improved the current survival rate of liver cancer. IMbrave150 is a global open Phase III clinical trial investigating atezolizumab in combination with Bevacizumab for advanced HCC [60]. Compared with first-line drugs, the survival rate in the experimental group was significantly improved, but there was no significant difference in toxicity [60]. However, drug resistance caused by tumor heterogeneity is still the main reason for the failure of current targeted therapy, and the economic cost of treatment is also an unavoidable problem in the current treatment process [61].

2.4.2 Immune checkpoint inhibitors (ICIs)

In recent years, immunotherapy has been widely studied. ICIs, peptide vaccines, dendritic vaccines, *etc.*, are currently available for HCC immunotherapy [62]. Immune checkpoint blockade (ICB) therapy is a recently developed treatment [63]. ICIs are monoclonal antibodies that can prevent the interaction of immune checkpoint proteins with their ligands, avoiding T cell inactivation thereby restoring and enhancing their immune effects [64,65]. Currently, the main targets of ICIs are programmed cell death protein 1 (PD-1) along with its ligand (PD-L1) and cytotoxic T lymphocyte antigen (CTLA-4) [66]. After the use of PD-1 and PD-L1 inhibitors, PD-L1 on tumor cells can be effectively inhibited from binding to PD-1 on T cells so as to restore the immune function of suppressed T cells, thereby killing tumors. Immunotherapy of PD-1 and PD-L1 is promising, especially for patients with advanced HCC [67]. However, due to the heterogeneity of tumors, ICI monotherapy has limited efficacy and some immune-related adverse reactions [64,68]. Therefore, combining ICIs with anti-angiogenic targeted drug therapy, such as carrelizumab and apatinib, has received wide attention [69,70].

Table 1: Common targeted drugs and their corresponding targets, mechanisms of action, and routes of administration

Targeted drug	Targets	Mechanism	Route of administration	Ref.
Sorafenib	VEGFR, PDGFR, Raf, c-kit, FLT-3	Inhibits tumor peripheral angiogenesis, tumor cell hypoxic necrosis, and interferes with the signal pathway	Oral administration	[51,52]
Lenvatinib	VEGFR, PDGFR, FGFR	Inhibits tumor angiogenesis and hepatoma cell proliferation and interferes with the signal pathway	Oral administration	[52]
Apatinib	VEGFR-2, PDGFR c-kit	Inhibits tumor angiogenesis and hepatoma cell proliferation	Oral administration	[52]
Bevacizumab	VEGF-A	Inhibits tumor angiogenesis and hepatoma cell proliferation, increased sensitivity to chemotherapy, and improves TME	Intravenous injection	[53]
Imatinib	Bcr-Abl fusion protein, kinasec-Met, PDGFR, VEGFR	Inhibits tumor angiogenesis and hepatoma cell proliferation	Oral administration	[54,55]
Pembrolizumab	PD-1 receptors	ICIs, restores T cell activity and enhances immune response	Intravenous injection	[53]
Rapamycin	mTOR	Inhibitory mTOR activity and regulates cell metabolism and immunity	Oral administration and intravenous injection	[56,57]

3 Nanoparticles

Nanoparticles refer to particles with diameters in the range of 1–100 nm [71]. The administration routes of nanoparticles include oral, injection, inhalation, and topical administration (Figure 2). Different kinds of nanoparticles have different synthesis methods. Metal nanoparticles can be synthesized by LA, pyrolysis, chemical reduction, radiation-induced synthesis, microwave-assisted synthesis, and other methods. The polymer nanoparticles (PNPs) can be synthesized by Ouzo polymerization, multi-solvent nanoprecipitation, and emulsion polymerization. Methods for the synthesis of lipid-based nanoparticles include emulsion solvent evaporation and the use of magnetic substances [72]. The effect of NPs is not only related to the phase size, charge, and surface area but also to surface hydrophobicity and ligand density shape. Some studies have shown that particles with a diameter of about 50 nm can maintain good intracellular transport and cellular uptake [73]. Larger NPs appear to be safer than smaller nanoparticles due to their small surface area relative to their total mass, as this reduces the chances of the nanoparticles interacting with surrounding biomolecules, thereby reducing possible adverse reactions in the body [74]. Under the enhanced permeability and retention effect (EPR effect), large NPs are well preserved in blood vessels but easily cleared by tumor tissues. Small NPs can penetrate deep into tumor tissue. Therefore, it is necessary to consider the size of the NP design in advance when designing the target NPs [75].

Nanoparticles for DDS include organic and inorganic nanoparticles. The organic nanoparticles include lipid nanoparticles (LNPs) and PNPs, while the inorganic nanoparticles include metal and inorganic nonmetal nanoparticles. Nanoparticles can deliver therapeutic drugs to specific sites, improve the uptake rate of drugs, and enhance the therapeutic effect [76–79]. Several common nanoparticles are introduced in this review.

3.1 Gold nanoparticles

Gold nanoparticles are effective and safe, with tunable size, low osmotic pressure, good biocompatibility, chemical stability, high X-ray absorption coefficient, unique photoelectric properties, and tunable surface plasmon resonance (SPR) [80,81]. Owing to these properties, gold nanoparticles are widely used in medicine [82]. Gold nanoparticles can be used to deliver a variety of substances. Because of its biocompatibility, it can be designed into spherical, oval, rod-shaped, triangular, or flower-shaped shapes according to the requirements [83,84], with safety achieved by changing the size or composition of the gold nanocarrier [85]. Nanoparticles of limited size can easily pass through the body efficiently, and the smallest nanoparticles have lower toxicity
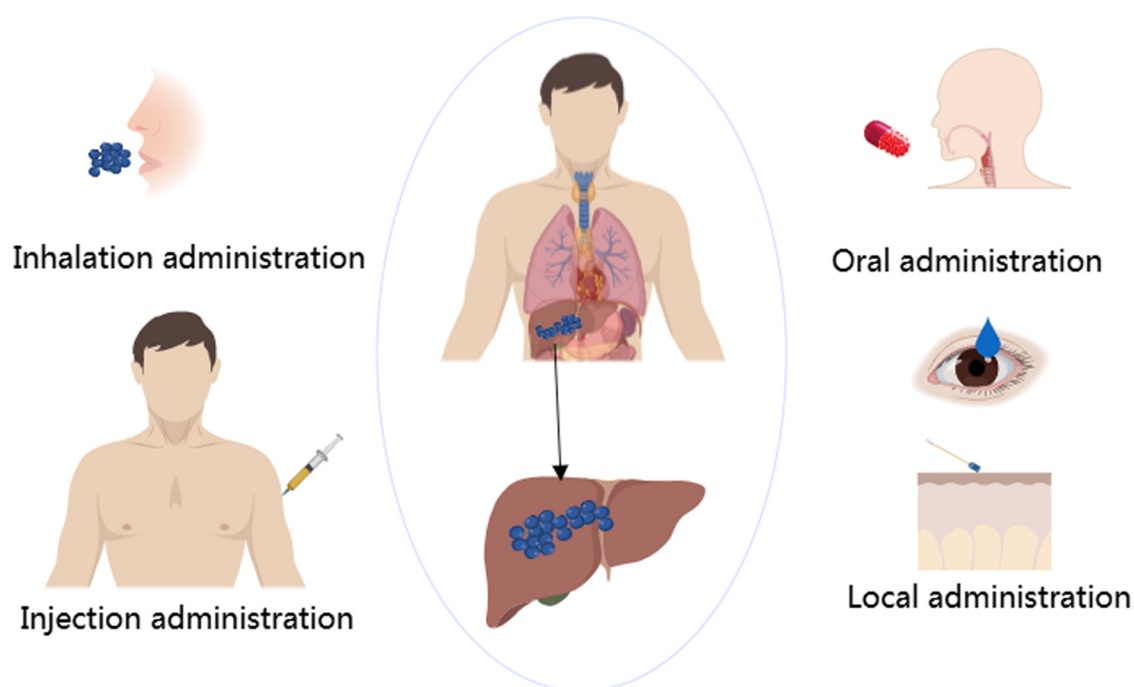

Figure 2: Drug delivery pathway of nanoparticles.

and uptake [80]. The uptake of gold nanoparticles is influenced by their size, with smaller nanoparticles exhibiting reduced toxicity and enhanced absorption efficiency [86]. Among them, ultra-small gold nanoparticles can be completely removed by the kidney or liver [87].

Gold nanoparticles are highly efficient due to their inertness, chemical stability, and ability to protect molecules such as cytokines from degradation [85]. They are considered to be suitable drug carriers for tumor therapy due to their small size, strong biocompatibility, and precise targeting ability [88]. Compared with lipid particles, gold nanoparticles have the advantage of absorbing and generating heat by photons [89], which can greatly enhance the effectiveness of photothermal therapy [90]. Small-sized gold nanoparticles can achieve surface functionalization of organosilica nanoparticles (OS NPs), which is conducive to improving the stability and radiation-sensitizing ability of nanoparticles, as well as improving the targeting ability of silica nanoparticles [91]. In addition, gold nanoparticles can produce immune responses with microenvironmental stimuli [92]. The surface particles of gold nanoparticles are rough and have a high surface-to-volume ratio, which is favorable for synthesizing nanomaterials with low toxicity [93]. Therefore, based on the above characteristics, gold nanoparticles are widely used in MRI (magnetic resonance imaging), PAI (photoacoustic imaging), and other tumor diagnostic methods and are widely used as drug carriers in chemotherapy and radiotherapy [94].

3.2 Lipid-based nanoparticles

Lipid-based nanoparticles include liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and other forms. LNPs are one of the most common carriers for delivery systems [95], and most of the nanoparticles currently used for targeted delivery are composed of polymers or lipids [96]. Ideally, the drug carrier should be cleared quickly after drug release [97]. LNPs are mainly composed of physiological lipids and have low toxicity, so lipid carriers are also referred to as "nanosafe" carriers [98]. Lipid-based nanoparticles have good biocompatibility and biodegradability [99]. LNPs are mainly composed of lipid or lipoid materials plus auxiliary cholesterol, lipid, and polyethylene glycol (PEG)-lipid [100], in which the key component, cationic ionizable lipid, can achieve efficient nucleic acid encapsulation, cell delivery, and endosomal release [101]. Liposomes are easily degraded by lipase in the digestive system and recognized by the reticuloendothelial system (RES), resulting in reduced bioavailability [102,103].

Liposome complexes were developed to address this issue, in which polymers such as alginate, chitosan, cyclodextrin, and collagen are used to modify the structure of liposomes [104]. Liposome complexes improve the physicochemical properties of liposomes, have better stability, and protect the activity of delivery molecules [104]. SLN formulations can be integrated as solids or liquids, capable of loading a large amount of drugs, and can adhere to the intestinal wall to increase the bioavailability and solubility of drugs, thereby protecting drugs from degradation in the acidic environment of the stomach [105]. LNPs have now been widely utilized for systemic delivery of RNA therapeutics [100]. LNPs loaded with siRNA enter the cell membrane by forming endosomes and then release siRNA inside the cell to achieve therapeutic effect (Figure 3). Lipid-based nanoparticles are commonly employed in liver cancer treatment due to their many inherent advantages as drug carriers and their preferential accumulation in the liver after systemic administration [106].

3.3 Polymer nanoparticles

Polymer nanoparticles have a variety of structural forms, such as nanocapsules, nanospheres, and micelles [107]. They have high physical and chemical stability, strong modification ability with multiple targeting groups, and a high transfection success rate [108]. Polymer nanoparticles have diverse functions, which can not only target and image cancer cells but also encapsulate drugs in their core, improving the solubility and delivery efficiency of drugs. In addition, appropriate shapes and sizes can be designed to control the release dose of drugs as requested [109,110]. Additionally, control of drug release in the polymer nano-drug delivery system (nano-DDS) can also be achieved by changing the pH, magnetic thermal environment, and other conditions [111,112]. Various forms of polymers, such as poly L-lysine (PLL) [109], cyclodextrin [113], and poly L-arginine (PLA) [114], can be utilized. Lipid–polymer hybrid nanoparticles (LPHNPs) consist of liposomes and polymeric nanoparticles, with a lipid layer enveloping a polymer-formed core. Therefore, LPHNPs possess the advantages of both polymer and LNPs, including high encapsulation efficiency and good stability of the polymer core. The lipid shell enhances stability, facilitates cellular uptake, and promotes better interaction with biomolecules [115,116]. Anbazhagan *et al.* prepared FA and PTX-supported polyamylamine (PAMAM) dendrimer and conjugated arginine-glycine-asparagine (RGD) to overcome multidrug resistance in oral cancer cells. Moreover, RGD-PAMAM-FP can deliver more PTX in KBCH-R8-5 cells than PAMAM-FP [117].
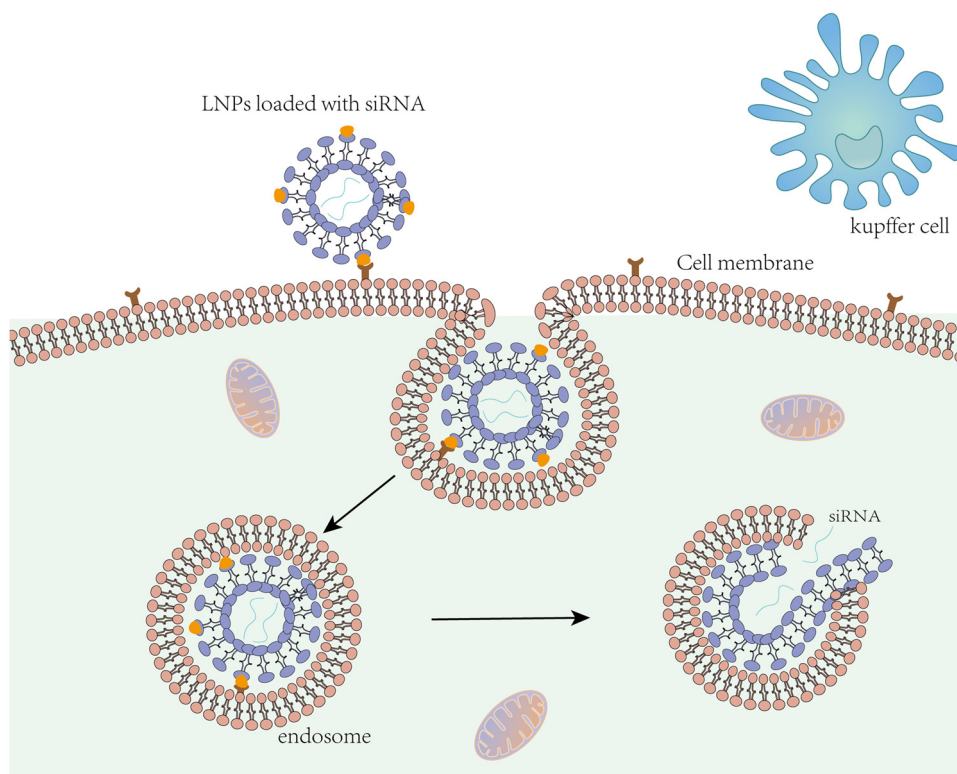
Figure 3: Lipid nanoparticles loaded with siRNA enter liver cells.

3.4 Mesoporous silica nanoparticles (MSNs)

MSNs are commonly used in biomedicine. Silica is considered safe by the US Food and Drug Administration (FDA) [118]. When using nanoparticles for disease treatment, it is necessary to consider cellular uptake and intracellular transport, which are closely related to the properties of nanomaterials. Due to their unique properties, MSNs are one of the ideal carriers for loading and delivering various drugs and biomolecules due to their stability, large surface area, pore volume, storage space for loaded drugs, high thermal stability, and good biocompatibility [119,120]. The amount of therapeutic molecules loaded can be varied by changing the size of the MSN pores and channels [121]. At the same time, MSNs have great advantages in biological degradation and excretion [122]. Functionalization or modification of the MSN surface can improve cargo loading and cell uptake [123]. Porous and nonporous silica NPs can be hydrolytically degraded to water-soluble acids and excreted in urine [124]. Compared with traditional drugs, MSNs may immunomodulate HCC TME after being taken up by immune cells [125], allowing antigen-presenting cells (APCs) to recognize tumor vaccines carried by MSNs. Furthermore, miRNAs and growth factors released from MSNs can enrich regulatory T cells (Tregs) through the PI3K/Akt pathway [126,127].

3.5 Iron oxide nanoparticles (IONPs)

MNPs have gained widespread use in recent years. Compared to other inorganic nanoparticles, MNPs have more potential for targeted delivery due to their unique properties. Among these, IONPs are particularly noteworthy due to their good biocompatibility, unique magnetic properties, stable biochemical properties, easy surface functionalization, and shape change. Excessive iron will lead to an increase in active oxygen and cause poisoning [128]. IONPs are typically coated with protective materials such as PEG, polyvinyl alcohol, or chitosan coated with γ-Fe_3O_2 or Fe_3O_4 [129]. As Fe_3O_4 has broad near-infrared absorption and high photothermal conversion efficiency, IONPs are often used for drug delivery by binding specific proteins or utilizing external magnetic fields known as magnetic targeting carriers (MTCs) [130]. IONPs can also increase tumor temperature, thereby enhancing the therapeutic effect of radiotherapy and chemotherapy [131]. Studies have shown that IONPs can inhibit tumor cell growth by transforming macrophages to an M1-like phenotype and increasing reactive oxygen species production (Figure 4) [132]. IONPs can be functionalized with other bioactive substances and then bound to the composite to enter cells [133]. Superparamagnetic iron oxide nanoparticles (SPIONs), formed after surface modification with a silicon dioxide layer, exhibit
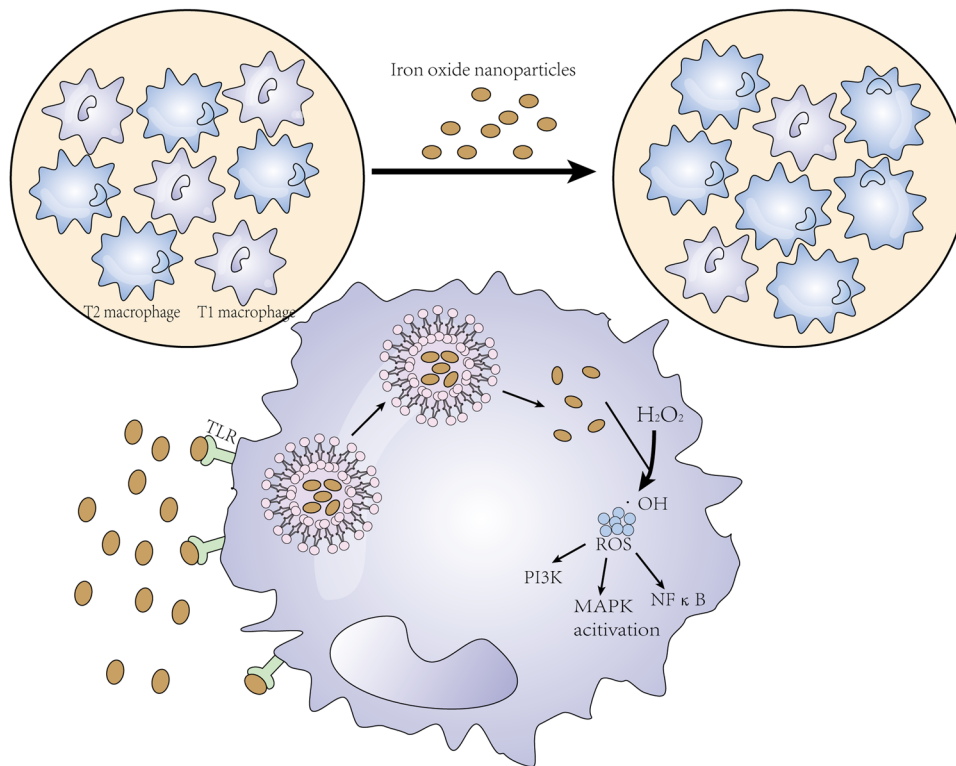
Figure 4: IONPs increase the production of ROS in macrophages and promote the polarization of M1 tumor-associated macrophages (TAMs) in M2 TAMs.

greater stability, and better biocompatibility while increasing the volume-surface-area ratio and reducing the release of iron.

4 Nanoparticles and liver

4.1 Nanoparticles enter the liver cells

Nanoparticles can be administered orally or intravenously. Studies have shown that after administration, nanoparticles can be distributed in multiple organs, including the heart, lungs, brain, liver, and kidney [134]. Nanoparticles smaller than 6 nm can be excreted into the urine through the kidneys [135]. As a biological filtration system, the liver has the highest accumulation of nanoparticles, especially those larger than 6 nm [134]. After enrichment and accumulation in the liver, nanoparticles are metabolized and excreted from the body, resulting in less therapeutic effect of drugs than expected or even producing hepatotoxicity [136]. Further, the clearance of nanoparticles by the liver is related to the size and surface charge of the nanoparticles. Nanoparticles have to pass through many barriers before reaching the target sites. The first one is the RES, composed of the liver and spleen, which can quickly remove foreign bodies in circulation. Others are crossing the vascular endothelium into the target tissue, passing through the extracellular matrix, cytoplasmic membrane, and intracellular localization [137]. RES is mainly composed of Kupffer cells, which can phagocytize nanoparticles, remove foreign bodies, and block the entry of nanoparticles into liver cells. Therefore, nanoparticles need to avoid Kupffer cells, penetrate the endothelium, and finally, enter the liver cells after passing through the Disse gap [138].

4.2 Interaction between nanoparticles and liver cells

The liver is composed of 60–70% parenchymal cells and non-parenchymal cells; parenchymal cells are hepatocytes, and non-parenchymal cells include hepatic sinusoidal endothelial cells, Kupffer cells, and hepatic stellate cells. Most nanoparticles are removed *via* the hepatobiliary pathway after absorption by non-parenchymal cells. Monocytes in the blood adhere to the liver tissue and are polarized in Kupffer cells.

When the nanoparticles have high cationic and anionic surface charges, they adsorb a large amount of serum proteins to form a "protein crown" and increase the interaction with macrophages [138]. In addition, the larger surface area of the nanoparticles increases their affinity for interacting with neighboring receptors [138]. After being ingested into liver cells, nanoparticles can interact with a variety of enzymes. For example, large SiO_2 nanoparticles (160–180 nm) significantly inhibited the catalytic activity of human liver microsomes [134]. When nanoparticles are present in the liver tissue, they stimulate oxidative stress and inflammation. Gaiser *et al.* found that Ag nanoparticles induced upregulation of mRNA expression of different inflammatory cytokines in liver tissue, especially IL-8, TNF-α, and receptor IL-1RI, suggesting that repeated exposure to Ag nanoparticles induced an increase in serum proinflammatory cytokines [139].

5 Nanoparticles and tumor

5.1 TME

TME is composed of immune cells, non-immune components, and extracellular matrix [140–142], including T cells, B cells, TAMs, extracellular matrix, and cytokines [143]. The common characteristics of TME are hypoxia and acidic pH, which can reduce the sensitivity of tumor cells to anticancer drugs [144,145]. TME has gained extensive attention because immune cells in the TME play an important role in the process of tumorigenesis [146]. Nanoparticles accumulate in the liver because of isolation by macrophages or Kupffer, which is a great challenge to transport nanoparticles to the tumor site for treatment. Studies have shown that Kupffer cells with high expression of M2 marker (CD163) can absorb more nanoparticles than Kupffer cells with low expression of surface CD163 [147]. TME is heterogeneous, and early TME even tends to play an anti-tumor role [148]. Among them, macrophages infiltrating the TME become TAMs [149], which can be divided into M1 and M2 macrophages. Type M1 has pro-inflammatory and anti-tumor properties, whereas type M2 has pro-tumor effects [150]. Hypoxia is a typical feature of TME, which promotes the M2 phenotype by hypoxia [151], interferes with the function of immune cells [146], and supports the growth of tumors. Cancer-associated fibroblasts (CAFs) participate in tumor growth and metastasis, prevent immune cells from entering TME, and play an important role in the occurrence and development of TME [152]. Tregs support tumor cells indirectly and directly by interacting with stromal cells and secreting growth factors [151]. The composition of TME and the regulation of nanoparticles on the components of TME are shown in Figure 5.
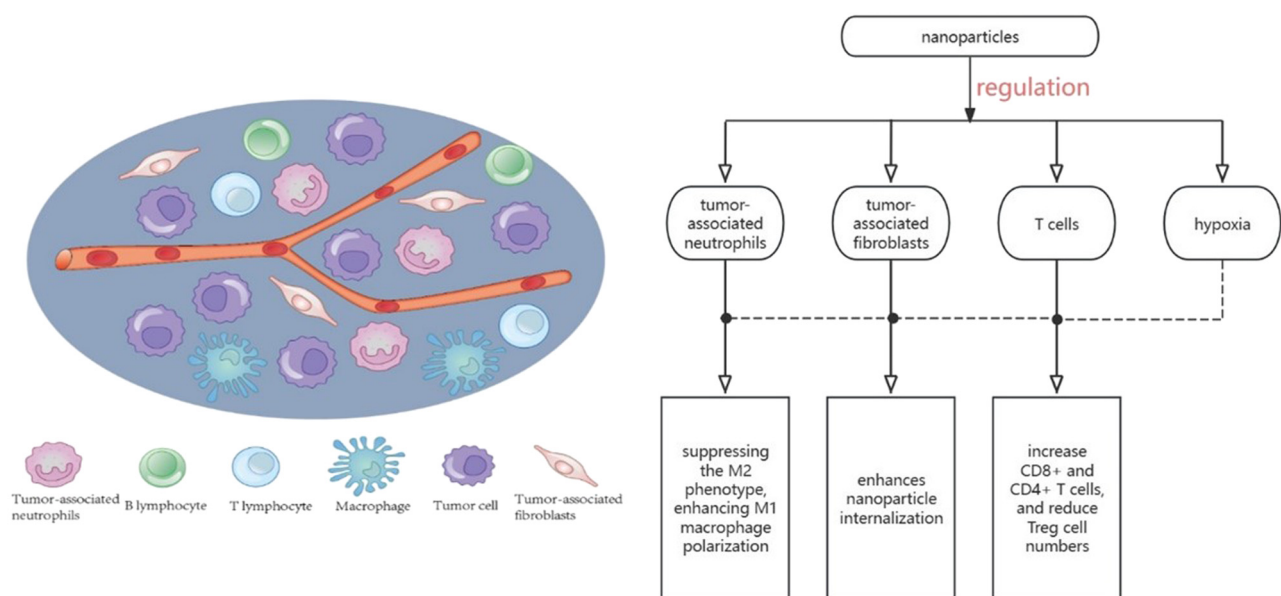

Figure 5: TME is composed of immune cells, non-immune components, and extracellular matrix, including T cells, B cells, TAMs, extracellular matrix, and cytokines. Nanoparticles can play an important role in tumor development by regulating the composition of TME.

5.2 Nanomedicine delivery system

DDS refers to successful targeting and accumulation of therapeutic substances at the desired site to improve drug efficacy and reduce side effects [153]. DDS can be selected to actively or passively target malignant cells or tissues according to the characteristics of nanoparticles [154]. Nanocarriers have EPR effects dependent on passive targeting, which can better promote accumulation in tumor cells [155]. However, during passive targeting, DDS efficiency may be greatly reduced due to the non-specific uptake of nanoparticles by mucosal barriers or particles. Active targeting is the selective recognition of targeted cells by carrying ligands that bind to receptors or carriers on the surface of nanoparticles [96]. When used as DDS, nanoparticles can improve the half-life of drugs and have better solubility and bioavailability, thus better controlling distribution, reducing toxicity of drugs, and improving their efficacy [156,157]. Therefore, the nanocarrier can deliver drugs to targets without damaging the surrounding normal cells [158]. Nanoparticle delivery includes anti-tumor drugs, compounds, and siRNAs [159]. Common nanocarriers and their loaded drugs are shown in Table 2.

5.3 Nanoparticles targeting TME

As mentioned above, various composition structures of the tumor site are of great significance for the occurrence and development of tumors and also have an impact on the targeted therapy of tumors. For example, the abnormal vascular structures at the tumor site can sometimes render targeted therapy ineffective, the extracellular matrix can sometimes inhibit the penetration of drugs into the deep tissue of the tumor, and the hypoxic environment of the tumor sometimes leads to decreased responsiveness to anticancer therapy [182]. The regulation of TME can not only reduce the obstacles of nanoparticle delivery but also improve the sensitivity of the tumor to treatment and improve the therapeutic effect of the tumor. Therefore, the role of nanoparticles targeting various components of TME to regulate TME has been widely studied.

Nanoparticles can regulate the polarization of TAMs, inhibit the survival and function of TAMs, and target TAMs localized to TME. The problems of short cycle time, non-specific delivery, and poor drug solubility in traditional TAM-targeted therapy have been overcome [183]. Jiang *et al.* also designed biomimetic MNPs. Fe_3O_4-SAS@PLT can induce apoptosis, promote macrophage polarization M1, and disrupt immunosuppression of TME [184]. TAMs

Table 2: Common nanocarriers and their loaded drugs

Nanocarriers	Drug	Target	Mechanism	Ref.
PLA and PLGA NPs	Sorafenib, PTX, 5-FU, genes	HepG2, HCC1, Hep3B	Delivery of drugs and genes	[160–162]
PEG NPs	Sorafenib and SAL	HepG2	Increase the cellular uptake and reduce general cytotoxicity and delivery of drugs	[162–164]
Lipid NPs	Sorafenib and doxorubicin	HepG2, Hep3B	Improve efficiency and delivery of drugs	[162,165,166]
Silica NPs	Sorafenib, doxorubicin, and genes	HepG2, SMMC-7721	Delivery of drugs and genes and photothermal therapy	[162,167]
Carbon NPs	Sorafenib and doxorubicin	HepG2, SMMC-7721	Delivery of drugs, enhance drug release, and photothermal therapy	[162,168]
Calcium NPs	Sorafenib, doxorubicin, and genes	HepG2, SMMC-7721	Delivery of drugs, immune adjuvant properties, and reduce the general cytotoxicity	[169–171]
Gold NPs	Sorafenib, doxorubicin, 5-FU, and genes	HepG2, Huh-7	Delivery of drugs, immunotherapy, photothermal therapy, and radiotherapy	[85,89,172,173]
Liposomes	Sorafenib, doxorubicin, 5-FU, and genes	HepG2, H22	Delivery of drugs and genes	[99,174,175]
Zinc oxide NPs	Sorafenib, doxorubicin, and genes	HepG2	Delivery of drugs and genes	[176–178]
Albumin NPs	Doxorubicin	HepG2	Delivery of drugs	[179,180]
Chitosan-based NPs	Gemcitabine, 5-FU, doxorubicin, and curcumin	HepG2	Delivery of drugs	[179,181]

not only play a role in polarization but also regulate antigen processing. ZnCDA, for example, is made up of nanopolymer coating cyclic dimeric adenosine monophosphate formation. ZnCDA priority targets TAMs in order to regulate the antigen processing and rendering, thereby generating anti-tumor T cell responses, to a certain extent, solves the problem of lack of targeted delivery of STING pathway [185]. In addition, nanoparticles can be combined with other therapies to relieve the hypoxic environment of TME by producing oxygen *in situ* or delivering oxygen to TME, thus inhibiting tumor cells [183]. The structure of nanostructured manganese dioxide under acidic pH can be converted into oxygen and Mn^{2+}, and glutathione oxidation for oxidized glutathione, which regulates the TME hypoxia environment to increase the anticancer curative effect [186]. Core–shell nanoparticles are nanoparticles with gold as the core and silver as the shell, which can target CAFs in TME and effectively inhibit the expression of osteopontin in CAFs without affecting the expression of CAF biomarkers, thus impeding the progression of cancer [187]. Abnormal blood vessels in TME limit T cell infiltration, impede drug delivery, block tumors, and hinder therapeutic response. Nanoparticles can simultaneously deliver anti-angiogenic drugs and other anti-tumor drugs, significantly amplifying the effects of both nanoparticles and chemotherapy. Antiangiogenic drugs are able to normalize blood vessels temporarily, and the purpose of promoting vascular normalization is to improve the efficacy of other antitumor treatments [183].

6 Nanoparticles in combination with therapies

6.1 Nanoparticles combined with chemotherapy

Although chemotherapy is widely used for cancer treatment, it is easy to develop drug resistance along with non-specificity, leading to adverse reactions. To address these issues, nanoparticles have been used for drug delivery [188]. Encapsulating chemotherapeutic drugs in nanoparticles not only reduces their toxicity associated with cosolvents but also reduces precipitation and improves drug stability [71]. As an effective DDS, nanoparticles can reshape TME, penetrate barriers of tumor tissue, and target drugs to tumor tissue. They can achieve active and passive targeting while improving the properties of drugs and increasing the concentration of drugs in tumor sites, thereby improving

efficacy and reducing side effects [189]. Li *et al.* established an active target for mesoporous silica DDS nanoparticles by folic acid (FA)-modified pegylated lipid bilayer (FA-LB-MSNs). Bioadhesion between FA and its receptor significantly increased the uptake of FA-LB-MSNs by NB4 cells. Compared with MSN alone, FA-LB-MSNs exhibited sustained drug release, enabling the simultaneous release of PTX and TanIIA from the carrier [190].

6.2 Nanoparticles combined with targeted therapy

Most anticancer drugs exhibit limited accumulation at cancer sites, resulting in systemic toxicity. The nanoparticles have no heterogeneity in the tumor, along with superior encapsulation capabilities and EPR effect, which enables better aggregation within tumor regions. Therefore, utilizing nanoparticles for targeted therapy offers improved therapeutic outcomes while minimizing off-target effects.

6.2.1 Passive targeting

The EPR effect was first proposed by Matsumura and Maeda [191] more than 30 years ago when they found that some macromolecules accumulated preferentially in tumor tissues. Passive targeting of nanoparticles refers to the passive accumulation of nanoparticles in tumor sites [192], which can be achieved by the EPR effect in tumor cells [155]. Passive targeting mainly depends on the physical and chemical properties of the drug and carrier, such as size and surface charge [193]. Small nanoparticles can penetrate tumor tissues more effectively than large nanoparticles through the EPR effect. Although large nanoparticles have better retention in blood vessels, they are quickly eliminated from the tumor tissue after extravasation [194]. Passive targeting enhances the EPR effect by exploiting the incomplete basement membrane of vasculature in the TME, while drug release targeting specific sites can be achieved by utilizing the specific pH and enzyme environment of tumors [193].

6.2.2 Active targeting

However, passive targeting methods suffer from the heterogeneity of the EPR effect, and the EPR effect alone is not sufficient to achieve nanoparticle accumulation. Active targeting can enhance the EPR effect and improve drug

delivery efficiency beyond passive targeting. Active targeting can serve as an improved strategy for passive targeting to enhance the stagnation of nanoparticle accumulation at tumor sites [195]. To achieve accurate tumor targeting, active targeting requires affinity recognition, retention, and promotion of target cell uptake by functionalizing the surface of the nanoparticle carrier [193,196]. Active targeting is based on specific intermolecular recognition [162], and the binding of ligands to receptors on the surface of target cells can increase the uptake of nanoparticles by cells and improve therapeutic efficacy [197]. Strategies for active targeting include receptor–antibody, aptamer–ligand, and polysaccharide. Ligands are a variety of biomolecules, such as antibodies, proteins, vitamins, and other small organic molecules, while receptors are surface molecules of tumor cells, molecules secreted by tumor cells, or proteins in organs. The density of ligands on nanoparticles determines their affinity for substrates, with higher densities leading to increased cellular uptake capacity [198]. Active targeting enables more particles to enter tumor tissues by specifically identifying targeted cancer cells while reducing free nanoparticle concentration, thereby enhancing the EPR effect [192].

6.3 Nanoparticles combined with radiotherapy

Radiotherapy relies on high radiation to destroy DNA in tumor cells directly or indirectly. With the development of nanotechnology, heavy metal nanoparticles such as gold and silver nanoparticles have shown good radiosensitization effect and are easy to metabolize and eliminate while effectively absorbing and emitting radiation energy [199,200]. Gold nanoparticles are capable of accelerating DNA fragmentation when exposed to radiation [201]. Additionally, liposomes and polymers have also been used as carriers to deliver radiosensitizers [202]. Tumor recurrence after radiotherapy is common due to radiation resistance of tumor cells caused by tumor hypoxia [203,204]. Due to limited angiogenesis of the tumor, extensive hypoxia occurs in tumor cells, thereby promoting their proliferation [205]. It has been demonstrated that combining gold nanoparticles with radiotherapy can enhance the efficacy of anti-tumor therapy, especially in hypoxic regions [206]. Quercetin (QT) also has radiosensitizing properties and can be conjugated with the radiosensitizer agent iron oxide to form quercetin-conjugated magnetite nanoparticles (QMNPs). It can also be combined with MSNs, which, when used in conjunction with radiotherapy, exhibit potent anti-cancer effects by inducing apoptosis of tumor cells

[207,208]. Yang $et\ al.$ designed a nanoparticle called AU-Pt NPS, composed of the metallic elements Au and Pt. Au-Pt NPs can enhance the killing effect of radiation and inhibit the growth of tumors without obvious damage to non-tumor tissue. Because Au-Pt NPs mimic enzyme activity, they can enhance co-radiosensitivity and catalyze the conversion of H_2O_2 into O_2 [209]. Guan $et\ al.$ designed a radio-immunostimulant nanomedical drug (IPI549@HMP), which was composed of monodisperse solid silica reacting with potassium permanganate ($KMnO_4$) solution and coated with a uniform layer of MnO_2. Then, the resulting $sSiO_2@MnO_2$ is etched with Na_2CO_3 solution to obtain H MnO_2. The final IPI549@HMP nanosystem can be obtained by modifying and loading drugs in turn. The results show that IPI549@HMP can be an effective radiosensitizer under anaerobic TME [210]. However, because liver cancer is not sensitive to radiotherapy, radiotherapy is typically used in breast cancer, bone metastasis, $etc.$

6.4 Nanotherapy combined with gene therapy

6.4.1 CRISPR-Cas9 therapy

Many liver-related diseases are highly correlated with gene mutations, so gene editing is a reasonable approach to treat liver diseases by changing genome sequences. Among these, clustered, regularly interspaced short palindromic repeats (CRISPR) and CRISPR-associated nuclease protein 9 (Cas9) have been shown to be a powerful genome editing tool [211]. CRISPR-Cas9 is delivered by viral vectors, non-viral vectors, or physical methods to overcome tissue and cell membrane barriers to be transported to the nucleus [212]. One of the most commonly used is viral vector-mediated gene delivery, which has a very small loading capacity [213] and may cause mutations and immune responses if the viral vector integrates into host cells [214]. A number of nanodelivery systems have been developed to deliver CRISPR-Cas9, such as liposomes, LNPs, polymers, and gold nanoparticles [215]. The delivery complex can select Cas9 ribonucleoprotein (RNP), which avoids the trouble of DNA and RNA during transcription and translation, but the delivery of RNPs is limited by the loading capacity of viral and non-viral vectors [212]. The delivery of RNP $in\ vivo$ is currently focused on polymeric nanoparticles and liposomes [216]. Tang $et\ al.$ prepared a hybrid lipid NP (named Gal-LGCP) with a particle size of 106 nm, which has cell targeting, cell membrane penetration, and subcellular targeting, and can be used to deliver CRISPR-Cas9. In $in\ vitro$

experiments, Gal-LGCP induced about 60% PCSK9 knockouts in Hepa1-6 cells; *in vivo*, Gal-LGCP effectively targets liver cells. In addition, Gal-LGCP can also knock down PCSK9 in hepatocytes and downregulate LDLC levels [217].

6.4.2 siRNA therapy

Small interfering RNA (siRNA), mRNA, and plasmid RNA have the potential to treat many diseases through gene editing, silencing pathological genes, or expressing therapeutic proteins [218,219]. SiRNA can inhibit oncogene expression by stimulating enzymatic cleavage of target mRNA [220]. Due to the rapid degradation of naked DNA or RNA in body fluids, siRNA is easily degraded during application and has poor cellular uptake. SiRNA is difficult to accumulate in target tissues and penetrate target cells [218,221]. Previous studies have demonstrated that stable nucleic acid-lipid particles (SNALPs) formulated siRNAs of HBV exhibit higher efficacy in the liver [222]. The US FDA has approved the delivery of siRNAs by LNPs to target liver cells for treating transthyretin-induced amyloidosis [223]. Additionally, there are ongoing studies on synthesizing GCGA NPs, a new targeting carrier chitosan nanoparticles modified with glycyrrhetinic acid (GA) and lactobionic acid (LA), which protect siRNA from degradation and target hepatoma cells [224]. Furthermore, by loading siRNA into SP94 peptide-modified nanospheres assembled using cationized amylose (CA), SPIONs, and tetraphenylethylene (TPE), the formation of CSP/TPE@siRNA-SP94 NPs can significantly inhibit Huh-7 cell proliferation [225].

7 Partial clinical studies of nanoparticles

At present, many nanoparticles have entered clinical research. For example, Su prepared NP-SFB nanoparticles loaded with sorafenib in acetone water using the nanoprecipitation method and then modified them with the Traut reagent to obtain thiol-modified antibody (AB-SH). Then, the Ab-SFB-NP nano-DDS was prepared by mixing NP-SFB and AB-SH at room temperature for 2 h [226]. In controlled experiments, sorafenib delivery using the Ab-SFB-NP nanodelivery system has a significantly higher control rate than direct oral administration. The AB-SFB-NP nanodelivery system has high safety, although, in the experiments, diarrhea and other toxic reactions occurred, but after symptomatic treatment, the symptoms were controlled, and no death was

observed [226]. He *et al.* [227] prepared carrier-free indocyanine green nanoparticles (nanoICG) using a green and safe technique without altering the molecular structure of ICG. It has excellent photobleaching resistance, imaging sensitivity, and deposition of iodol in tumors. Therefore, nano-ICG is dispersed into iodide by ultra-stable homogeneous mixed preparation technology (SHIFT and nanoICG) for hepatic artery embolization combined with fluorescence laparoscopic hepatectomy, which is still in the first stage of research.

Zheng *et al.* added chitosan-SeNPs and lipiodol into the self-made Gel-SOR solution, stirred, and dialyzed for 24 h to obtain Gel-SOR-LUF-SeNPs. It was found that Gel-SOR-LUF-SeNPs not only have high anti-tumor efficacy but also low toxicity towards nude mice. Gel-SOR-LUF-SeNPs reduced the expressions of Ki67 and CD34, thereby inhibiting the proliferation of tumor cells, the formation of tumor blood vessels, and promoting the apoptosis of tumor cells, thereby significantly increasing the concentration of selenium in tumors and significantly inhibiting the growth of HepG2 tumors in nude mouse models [228]. Yang *et al.* prepared (ICG + S)@mSiO2 by adding ICG and sorafenib to the MSN aqueous solution and used it to simulate mice. Experiments have shown that SiO_2 is an ideal drug carrier with good biocompatibility and a high drug loading rate. (ICG + S)@mSiO$_2$ is a multifunctional diagnostic and therapeutic nanosystem with a highly efficient photothermal therapeutic effect, which can enhance immunity and release sorafenib to enhance tumor therapeutic effect [229].

However, not all clinical studies are in good progress. miR-34a is a naturally occurring tumor suppressor that is lost or expressed at reduced levels in a wide range of tumor types. MRX34, developed by Hong *et al.* [230], is a liposomal formulation of miR-34a with a length of 23-nt encapsulated in liposomal nanoparticles. In the Phase 1 study, one patient with HCC died due to severe immune-mediated toxicity. Therefore, because the overall response rate of 4% did not exceed the risk of serious immune-related adverse reactions, clinical development of MRX34 was discontinued [74].

8 Summary and outlook

As an emerging discipline, nanotechnology has made remarkable advancements in various fields due to its distinctive advantages. Especially in the medical domain, nanoparticles exhibit exceptional biocompatibility, superior body surface area ratio, and stable biochemical properties that offer a wide range of new approaches for more effective

HCC treatment. Nanoparticles can construct efficient DDS and synergize with conventional therapies to enhance drug targeting and improve therapeutic outcomes across diverse modalities. Nanoparticles have demonstrated their ability to modulate TME and facilitate increased production of reactive oxygen species to inhibit tumor cell growth.

At present, most nanoparticles used for targeted delivery in clinics are nanoparticles composed of lipids or polymers. LNPs possess low toxicity levels and are considered nano-safe carriers; hence, they represent the most commonly utilized carriers for siRNA delivery while exhibiting liver-targeting capabilities upon systemic administration. Polymer nanoparticles exhibit diverse morphological structures along with a variety of target groups. Furthermore, research on synthesizing LPHNPs has been conducted. These LPHNPs are composed of polymer encapsulated by lipid layers, thereby combining the advantages of both materials, such as high encapsulation efficiency and enhanced cellular uptake capability. Additionally, other types of nanoparticles, such as gold nanoparticles, MSNs, and IONPs, possess their unique advantages. By functionalizing the surfaces of these various nanoparticle types, they can better serve HCC treatment by enhancing the efficacy of conventional therapies, such as photothermal and targeted therapy, while also increasing the load of therapeutic drugs.

Although nanoparticles possess numerous advantages, there are still unsolved issues, such as the drug release kinetics and safety concerns associated with their use. In particular, the safety of heavy metal nanoparticles has hindered their wide clinical application. Consequently, it is imperative to allocate more attention to addressing these challenges and providing viable methodologies and approaches for the treatment of HCC utilizing nanoparticles.

This review first summarizes the limitations of common HCC treatments. Then, the common nanoparticles and their characteristics, as well as the regulation of TME by nanoparticles, are described. Next, we summarize the role of nanoparticles in some common treatments. Finally, we describe several clinical studies that included both success and failure. Our review aims to provide ideas for the use of nanoparticles in the treatment of HCC and bring better therapeutic effects to HCC patients.

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