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REVIEW

Progress in the Application of Nanobiotechnology in the Ablation Therapy of Hepatic Carcinoma

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Abstract: Hepatocellular carcinoma (HCC) remains one of the most prevalent and lethal primary liver malignancies worldwide. Despite significant advances in surgical resection and local ablation therapies, challenges such as low early detection rates, high postoperative recurrence, and limited local tumor control persist in clinical practice. In recent years, the rapid advancement of nanobiotechnology has opened new avenues for precise diagnosis and personalized therapy of HCC. Owing to their excellent biocompatibility and functional tunability, various nanocarriers have been extensively explored in ablation-based treatments to achieve targeted drug delivery, controlled release, enhanced image guidance, and immune modulation. These innovations have substantially improved both the efficacy and safety of ablation therapies. This review focuses on recent progress in the application of nanobiotechnology to HCC ablation, systematically summarizing its mechanisms, innovative strategies, and future prospects across radiofrequency ablation (RFA), microwave ablation (MWA), cryoablation (CRA), high-intensity ultrasound focused ablation (HIFU), irreversible electroporation (IRE) and photothermal therapy (PTT). This review aims to comprehensively summarize recent advances in the application of nanobiomaterials—biocompatible and functionally engineered nanomaterials—in ablation-based therapies for HCC, emphasizing their roles in enhancing therapeutic efficacy, imaging guidance, and immune modulation.

Keywords: hepatic carcinoma, nanobiotechnology, ablation

Introduction

Primary hepatic carcinoma primarily manifests as hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma, or a combination of both hepatocellular and cholangiocarcinoma, each characterized by various pathological types. The incidence of these cancers is increasing.[1] By 2025, it is projected that the volume of individuals identified with hepatic carcinoma will exceed one million annually.[2] HCC is the most frequently occurring malignant tumor originating in the liver[3] and it ranks among the most prevalent and fatal cancers worldwide.[4]

Viral infections and exposure to aflatoxins are the most common causes worldwide.[5] In East Asian countries and Africa, HBV is the main cause of hepatic carcinoma.[6] In Western countries, alcohol abuse is among the primary contributors of liver cirrhosis and HCC. In addition, alcohol intake, metabolic dysfunction related fatty liver disease (MASLD), and viral hepatitis have a synergistic carcinogenic effect.[5]

Orthotopic liver transplantation or radical resection are the best treatment options for HCC.[7] For patients with small HCC (<3cm) or those who are not suitable for surgical treatment, ablation therapy is one of the good treatment strategies.[8] Ablation has the advantages of minimal impact on liver function, minimally invasive, fewer complications, good reproducibility, and precise therapeutic effects. The main methods include radiofrequency ablation (RFA), microwave ablation (MWA), cryoablation (CRA), high-intensity ultrasound focused ablation (HIFU), irreversible electroporation

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Graphical Abstract

(IRE) and photothermal therapy (PTT). In Table 1, we provide a detailed overview of the applications, advantages, and disadvantages of various ablation techniques. At present, the most commonly utilized techniques are RFA and MWA.[9]

Traditional ablation modalities for hepatocellular carcinoma, face limitations such as incomplete ablation, uneven thermal distribution, and difficulty in monitoring therapeutic boundaries.[16,17] These challenges often lead to local recurrence and suboptimal tumor control. Nanobiotechnology has recently emerged as a promising approach for improving both diagnosis and treatment. Owing to their biocompatibility and tunable physicochemical properties, nanocarriers enable targeted delivery, controlled release, and enhanced imaging or immune modulation.[18,19] Recent

Table 1 Different Ablation Applications Through Various Methods

Ablation Technique	Application	Advantages	Disadvantages	Ref.
RFA	Oncology therapies, management of arrhythmias, pain relief strategies	Minimal risk, affordable, quick procedure, accurate with minimal scarring, fewer complications	Restricted penetration, can lead to nerve injury, might need several sessions, not suitable for larger tumors	[10]
MWA	Oncology therapies	Fast procedure, minimal scarring, wider indications, large killing range, capacity to withstand the effects of blood circulation	Restricted penetration can lead to nerve injury, might necessitate several treatment sessions, not suitable for every type of tumor	[11]
CA	Oncology therapies, pain management	Non-invasive, precise, low risk of complications, low anesthesia requirements	Restricted penetration, might necessitate several sessions, not suitable for every type of tumor, has the potential to cause nerve injury.	[12]
HIFU	Oncology therapies, uterine fibroid treatment	Non-invasive, precise, low risk of complications, large killing range	Restricted penetration, necessitates imaging assistance, not suitable for every type of tumor, costly	[13]
IRE	Oncology therapies	Fast procedure, precise, minimal invasive, no damage to adjacent structures	Required specific anesthesia, highly complex	[14]
PTA	Oncology therapies	Non-invasive, precise, fast procedure, needle catheter ablation for hemostasis	Restricted penetration, may necessitate several sessions, not suitable for every type of tumor, can lead to skin injury.	[15]

studies have shown that integrating nanotechnology with ablation therapy can substantially enhance local tumor control and systemic antitumor responses.[20] For instance, RRM2-targeted nanocarriers combined with radiofrequency ablation significantly improved ablation-induced necrosis and inhibited tumor growth in preclinical HCC models.[21] Although clinical translation remains in its infancy, several preclinical and early-phase studies have reported that nanomedicine-based systems can modulate the tumor microenvironment and augment ablation efficacy in HCC models.[22] The integration of nanomedicine with established ablation technologies represents a crucial step from mechanistic innovation toward clinical translation. To systematically illustrate the enhancing roles of nanotechnology across various ablation modalities for hepatocellular carcinoma, Table 2 summarizes the representative nanomaterials, core functions, and major applications associated with each ablation technique discussed in this review. This review focuses on nanobiomaterials and their applications in ablation therapy for hepatocellular carcinoma, highlighting their mechanisms, therapeutic advantages, and translational potential.

Nanomaterials Commonly Used in Hepatic Carcinoma Ablation Therapy

Nanoparticles (NPs), which have a size range of 10–1000 nanometers, are solid particles with a high surface to volume ratio and unique physicochemical properties, including high loading capacity, significant intracellular uptake, targeted delivery, and the ability to bind multiple drugs,[23] making them effective drug transporters. NPs have controllable shape, size, ability to encapsulate multiple components, and functional surface properties, which

Table 2 Key Functions and Applications of Nanomaterials in Different Ablation Techniques for Hepatocellular Carcinoma

Ablation Technique	Key Nanomaterials / Technologies	Core Functions	Main Applications
RFA	ThermoDox, SPIONs, nCP: Fe	Heat-triggered drug release, MRI enhancement, improved drug penetration	Enlarged effective ablation zone, better margin visualization, reduced local recurrence
MWA	NaCl liposomes, DOX/ICG liposomes, Mn-Ti MOF, SPIONs	Thermal sensitization, ROS amplification, multimodal imaging, immune activation	Enhanced MWA efficiency, less residual tumor, improved imaging guidance, modulated immune microenvironment
CRA	Graphene oxide, Fe_3O_4 nanoparticles, CS-TPP-trehalose carriers	Promoting ice nucleation, ice-ball shape control, cryoprotection / improved heat transfer	Stronger cryo-induced tumor killing, better ice-ball boundary imaging, reduced normal-tissue injury
HIFU	PFH/DOX@PLGA/Fe_3O_4, PFOB–MnO_2 nanoemulsion, nanobubble liposomes	Acoustic enhancement, cavitation amplification, multimodal imaging, HIFU-triggered drug release	Lower HIFU dose, larger and more uniform ablation, synergistic chemo-/immunotherapy
IRE	SPIONs, various nanoparticle-based drugs / nano-embolization	Increased membrane permeability, enhanced nanoparticle uptake	Improved complete ablation rate, higher intratumoral drug delivery
PTT	Fe3O4@PDA, CREKA-carbon nanotubes, Bio-MnO_2	High photothermal conversion, tumor-stroma targeting, MRI enhancement	Precise tumor heating, efficient photothermal tumor killing, imaging-guided PTT

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endow them with special benefits such as improved internalization and permeation, prolonged circulation time, altered drug release, improved pharmacokinetics and high contrast, and reduced adverse events.[24] Therefore, nanotechnology offers significant potential for the treatment of hepatic carcinoma.

At present, commonly used nanomaterials for hepatic carcinoma ablation therapy include inorganic nanoparticles, liposomes, etc. In managing hepatic carcinoma, they can be used to construct nanocarriers to assist in the diagnosis of hepatic carcinoma and improve the effectiveness of hepatic carcinoma treatment.

Inorganic Nanoparticles

Inorganic nanoparticles have been extensively investigated in the biomedical arena owing to their tunable size, elevated surface-to-volume ratio, various quantum effects, and multiple modes of accessibility.[25] The remarkable benefits of inorganic nanoparticles as drug nanocarriers include their superior stability, notable monodispersity, and favorable potential for functionalization.[26] Metal nanoparticles and magnetic nanoparticles (MNPs) have been utilized as carriers for therapeutic agents, including medications aimed at treating hepatic carcinoma.[27]

Among different types of metal nanoparticles, noble metal nanoparticles have received significant attention because of their chemical stability.[25] Gold nanoparticles are especially appealing due to their capabilities as therapeutic nanocarriers. They are chemically inert, readily available, allow for precise control over size and shape, and can be utilized for photothermal and photoacoustic conversion, enhancing their versatility.[28] Gold NPs, commonly known as colloidal gold, are one of the most extensively studied and well-known NPs.[29] Researchers used gold nanocages loaded with anti-miR-181b for gene photothermal combination therapy, significantly inhibiting tumor growth in SMMC-7721 tumor mice.[25] This suggests that gold nanoparticles could serve as multifunctional therapeutic nanocarriers for hepatic carcinoma treatment.

Metal oxide NPs, such as iron oxide NPs, have been widely used in various applications such as sensing and catalysis, but they are rarely used as pure materials for drug delivery.[30] However, they still have potential in this field as they can be used as therapeutic drugs themselves, ligands to carry another treatment method, and magnetic resonance imaging (MRI) agents.[31] Due to the fact that both common oxidation states of iron (+2/+3) can exhibit ferromagnetism, their magnetism is ideal for imaging or magnet mediated drug delivery.[32] In addition to the magnetic properties of iron oxide NPs, this property can also be used to induce hyperthermia and treat hepatic carcinoma with heat. The application of magnetic and iron oxide NPs based on their more typical carrier capacity makes them attractive materials for internal treatment of hepatic carcinoma.[31]

MNPs (such as Fe3O4) are renowned for their intriguing characteristics in biomedical uses, which include enhancing contrast in MRI, inducing heat, and facilitating delivery guided by magnetic fields.[33] Due to the high uptake of superparamagnetic iron oxide NPs (SPIONs) by the liver, SPIONs mediated contrast-enhanced MRI provides an accurate means for the diagnosis of hepatic carcinoma.[25] Researchers have created various high-performance contrast agents utilizing SPION for the detection of hepatic carcinoma via MRI, one of which is more effective than the commonly used Feraheme® in clinical practice about 10 times, which helps to accurately and sensitively detect liver lesions through MRI.[25]

The biocompatibility, especially biodegradability, of inorganic nanomaterials is the main issue in their clinical applications.[34] To tackle this challenge, comprehensive studies are required to gain a complete understanding of their interactions within biological systems.

Liposomes

Liposomes are spherical entities made up of self-assembled lipid membranes enclosing an internal aqueous phase, designed for the encapsulation of therapeutic agents, and are inspired by the structure of natural cell membranes.[35] They exhibit excellent biocompatibility and biodegradability, possess a high capacity for encapsulating therapeutic agents, and have the potential to enhance bioavailability while minimizing adverse effects.[35] By merely modifying the surface characteristics of liposomes, such as their charge and functional groups, the efficiency of drug delivery can be enhanced, paving the way for further advancements in liposome-based drug delivery systems.[25] Polyethylene glycol (PEG) has good biocompatibility between different functionalizations, therefore, PEGylated liposomes are regarded as excellent nanocarriers with high biosafety and have been extensively researched for hepatic carcinoma treatment.[25] PEGylated

liposomes offer several advantages, including the ability to inhibit plasma protein activation, evade quick eradication by the mononuclear phagocytic system (MPS) for prolonged circulation, and enhance drug delivery to tumor tissues by enhanced permeability and retention (EPR) effects.[36]

Although liposomes have a long history in biomedical applications,[36] they still face some challenges compared to other drug delivery systems. Liposomes have limited stability, shorten blood circulation time after intravenous injection, and greatly reduce drug delivery effectiveness.[37] The manufacturing of liposomal nanomedicine is more intricate compared to conventional therapies, and their relatively low stability presents considerable challenges for large-scale production and analysis.[25] Given the complexities of clinical trials for liposomal nanomedicine in contrast to conventional therapies, additional control groups are required to thoroughly assess the anti-cancer efficacy and side effects of liposomal nanomedicine, significantly raising both the cost and duration of these trials.[25] However, due to the success of liposomes in nanomedicine, many efforts have been devoted to this exciting field.

Functionalization and Targeting Strategies of Nanomaterials

Functionalization of nanomaterials plays a critical role in optimizing physicochemical stability, biocompatibility, and therapeutic precision in HCC ablation.[38] *Surface PEGylation* or polymer shielding enhances colloidal stability and circulation time by reducing opsonization and macrophage uptake.[39] Ligand conjugation—such as folic acid, galactose/asialoglycoprotein receptor (ASGPR) ligands, and glypican-3 (GPC3) antibodies or peptides—enables active recognition of HCC cells that overexpress corresponding receptors.[38] In addition, stimuli-responsive coatings (pH-, temperature-, or enzyme-sensitive linkages) allow on-demand activation and controlled drug release within the ablation zone, aligning drug exposure with local energy delivery.[40] Furthermore, size-transformable or charge-adaptive shells can enhance intratumoral penetration and distribution, particularly in perivascular or hypoxic tumor regions.[41]

The dense extracellular matrix, hypoxia, acidosis, and abnormal vasculature of the targeting strategies and the tumor microenvironment (TME) restrict nanoparticle diffusion and uniform thermal distribution.[42] TME-oriented nanodesigns —such as MnO_2-based oxygen-generating nanoplatforms—can relieve tumor hypoxia, improve ablation-induced immune responses, and enhance therapeutic uniformity.[43] Moreover, integrating immune-modulating components (eg, cytokines or checkpoint inhibitors) into nanocarriers can reprogram the immunosuppressive microenvironment and potentiate systemic antitumor immunity.[44]

Collectively, these functionalization and targeting strategies improve delivery efficiency, ablation precision, and immune synergism, paving the way for clinical translation of multifunctional nanobiomaterials in HCC therapy.

Nanobiotechnology and Radiofrequency Ablation

Radiofrequency Ablation

RFA is a primary interventional oncology approach for HCC that offers benefits such as being minimally invasive, safe, highly effective and associated with fewer complications. It can effectively manage regional tumors, boost regional immune response, enhance the tumor ecosystem and increase the effectiveness of chemotherapy agents.[45] The fundamental principle behind RFA is thermal destruction, where a percutaneous electrode is implanted into the tumor body and then an oscillating current (450–500kHz) is transmitted to generate ion stirring and frictional heat.[46] The ability to control local tumors is influenced by the heat absorption effect.[47] The heat absorption effect significantly contributes to the reappearance of HCC following RFA. Conducting intraoperative radiofrequency after occluding hepatic blood flow can help minimize heat dissipation.[45]

For HCC small tumor patients with a size of $\leq$ 3cm, RFA should be considered as first-line treatment.[48] However, RFA is not applicable to lesions larger than 3cm.[49] To tackle this clinical challenge, recent initiatives have emphasized a multimodal approach to managing HCC by integrating RFA with various technologies. For example, the combination of nanomedicine and RFA has better anti-cancer effects than using drugs alone or RFA alone.[45] RFA-induced hyperthermia can increase the responsiveness of hepatoma cells to chemotherapeutic agents, meanwhile, the use of nanomedicine can eliminate remaining neoplastic tissue and micrometastases located in the sublethal area of RFA.[45] As RFA equipment and technology advance, along with the growing clinical experience, numerous early-stage HCC patients can experience

substantial therapeutic benefits following RFA.[47] Looking ahead, nanotechnology and medical nanotechnology are sure to play a significant role in enhancing the efficacy of RFA therapy for HCC.

Nanobiotechnology-Enhanced Radiofrequency Ablation

Numerous studies have shown that integrating nanomedicine with RFA is more effective in eradicating hepatic carcinoma compared to the use of either drugs alone or RFA alone.[47] The potential mechanism behind heat-based therapy or the modification of the microenvironment caused by RFA can boost the passive administration of nanomedicine, enhancing its penetration capacity and retention properties.[50,51]

Limitations of Radiofrequency Ablation

RFA is the predominant tactic for addressing various types of small liver tumors, particularly in the case of primary hepatic cancer.[52] RFA is incorporated into the treatment protocols for the majority of HCC cases and is presently the most widely utilized ablation tactic for early-stage HCC.[53]

In some cases, RFA is favored over surgical excision due to its decreased financial outlay, lower incidence of complications, and minimal toxic impact to adjacent tissues.[10] The success rate of RFA technology is comparatively low for tumors with a large diameter and lesions situated close to critical anatomical features.[52]

In general, partial ablation and regional disease recurrence continue to be the primary challenges hindering favorable outcomes for patients following ablation.[54] Further improvements in ablation techniques and an improved comprehension of the physiological effects of RFA on target tissues can enhance the therapeutic efficacy of ablation. Many reports indicate that achieving uniform diffusion of transdermal injection drugs such as ethanol and amphotericin on larger tumor volumes is difficult.[55] Direct catheter injection of high concentration chemotherapy has also been attempted, but its clinical application is limited due to the invasiveness of surgery or vascular imaging device implantation.[55] We can seek to improve the efficacy of RFA by using nanoparticle liposomes to penetrate tumor tissue and more effectively release local chemotherapy.[52,56]

Liposomal Nanoparticle-Assisted Radiofrequency Ablation

Liposomal particles have complete biocompatibility, cause minimal toxicity or antigen reactions, and exhibit biological inertness. Combining with liposomes can protect drugs from environmental damage in the body. The function of ThermoDox is grounded in the structural modifications of liposomes when heated above 39°C, which can quickly deliver doxorubicin (DOX) to the specific tumor site.[45]

Extending liposome circulation represents an effective approach to enhance drug accumulation within tumors, such as using PEGylated liposomes carrying DOX.[57] A longer circulation time can improve the interaction among pharmaceuticals and malignant cells, which is a significant contributor in enhancing the effectiveness of chemotherapy drugs.[57]

Doxil combined with RFA can enhance cellular demise within the outer and transition zones of tumors, and attain enhanced tumor eradication and extended survival time.[58] Researchers reported that in primary and metastatic hamster osteosarcoma, the combination therapy of thermosensitive liposome encapsulated DOX (TL DOX) and conventional hyperthermia was more effective in reducing tumor growth than single or combined non TL DOX therapy.[59]

Recent investigations have reported the design of multifunctional thermoresponsive liposomes incorporating fullerene/magnetic iron oxide (C60-Fe3O4).[60] Through PEG2000 modification and the co-loading of DOX together with folate ligands, these nanosystems enable prolonged drug release, tumor-targeted delivery, and heat-triggered therapeutic responses. Comprehensive characterization using high-resolution transmission electron microscopy (HR-TEM) and dynamic light scattering confirmed their physicochemical stability, while in vitro and in vivo studies demonstrated effective controlled release and tumor selectivity (as shown in Figure 1).[60] Collectively, such hybrid liposomal formulations hold considerable promise as advanced nanocarriers in the field of cancer nanomedicine.

Metal Nanoparticle-Enhanced Magnetic Resonance Imaging for Radiofrequency Ablation Guidance

In the treatment of HCC with RFA, although RFA is less invasive than liver resection,[61] in some randomized controlled trials, the incidence of local recurrence after RFA is higher than that after liver resection.[62] To avoid local recurrence, researchers have proposed an MRI evaluation method using pre applied superparamagnetic iron oxide (SPIO), which can

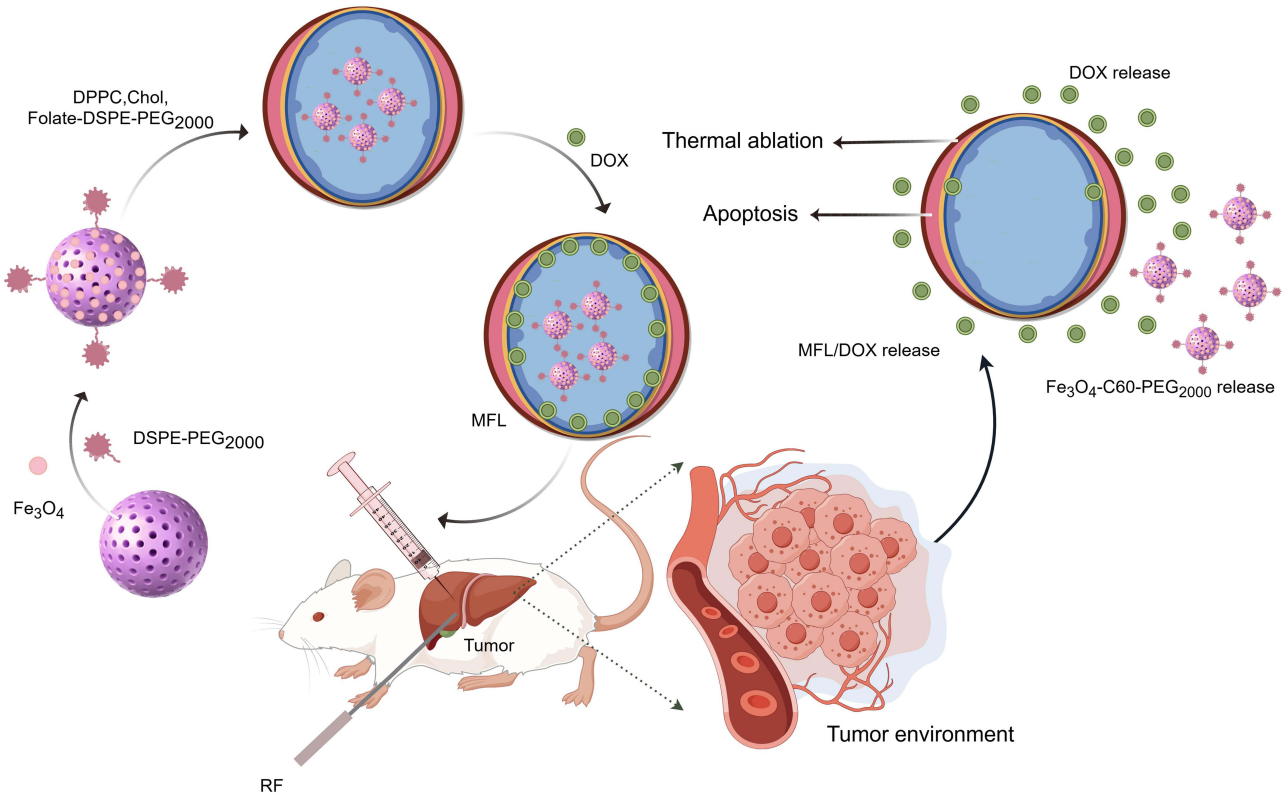

Figure 1 Schematic illustration of the mechanism of MFL loaded with Fe_3O_4–C_{60}–PEG_{2000} and DOX for enhanced RF ablation of hepatocellular carcinoma (By Figdraw). Fe_3O_4 nanoparticles were coated with DSPE-PEG_{2000} and incorporated with C_{60}, then encapsulated within multifunctional liposomes composed of DPPC, Chol, and folate-modified DSPE-PEG_{2000}. After injection into the tumor site, MFL accumulates within the tumor microenvironment. Upon RF irradiation, the liposomes disintegrate and release DOX and Fe_3O_4–C_{60}–PEG_{2000} nanocomposites, inducing localized thermal ablation and apoptosis, thereby enhancing antitumor efficacy.

distinctly differentiate the minimal ablation margin (AM) from 50adjacent hepatic parenchyma as well as ablated tumors.[63]

SPIO is a visualization agent absorbed by Kupffer cells that can attenuate MR signals relative to the hepatic parenchyma, but neoplastic liver lesions are absent of Kupffer cells and therefore exhibit high intensity.[64] Researchers have studied the effectiveness of MRI and pre administered SPIO in AM measurement and compared it with enhanced CT. The minimum thickness of the AM deemed appropriate for therapeutic ablation of HCC has been established.[64] The use of SPION enhanced MRI can image tissue inflammation, especially macrophage accumulation.[65] After intravenous injection, SPIONs are engulfed by macrophages, which result in a measurable loss of MRI signal intensity (SI) due to their capacity to reduce T1, T2, and T2*.[66] The experimental study of SPION enhanced MRI evaluation of macrophage build-up has been effectively performed across different disease models, including inflammatory conditions and cancer.[67,68] Researchers have found that SPION enhanced MRI can non invasively quantify the accumulation of perioperative macrophages in rabbits with VX2 tumors following localized RFA.[66] Considering the crucial function of macrophages in the tumorigenic effect triggered by ablation, researchers have suggested that blocking the undesired oncogenic effects caused by thermal ablation can be accomplished by minimizing the accumulation of cells surrounding the lesion, a non-invasive imaging tool for RFA induced in vivo macrophage accumulation around the lesion may be valuable for quantifying and ultimately regulating the oncogenic effects induced by ablation.[66]

While SPIONs have received approval for T2-weighted MRI, their use is restricted because of their extended clearance time in the body (over 30-day period)[69] and the generation of reactive oxygen species (ROS) linked to iron overload.[70] Researchers have created an innovative therapeutic biomineralized nanoparticle composed of iron-doped calcium phosphate (nCP: Fe), which offers bimodal (T1-T2) MRI contrast enhancement and thermal responsiveness within clinically approved radiofrequency ranges and powers, making it suitable for the ablation of solid tumors.[71]

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Magnetic characterization indicates that the doping of Fe3+ increases the paramagnetism of the material. Calcium phosphate, being the primary mineral constituent of the human body, exhibits superior conversion potential compared to other engineered nanoparticles.[71]

In recent years, magnetite iron oxide nanostructures are extensively utilized in the pharmaceutical industry owing to their remarkable biological affinity and negligible toxigenicity.[60] The inherent magnetism of MNPs used for drug delivery has attracted great attention in the exploration of a large number of nanomaterials for biomedical applications.[60]

Nanobiotechnology and Microwave Ablation

Microwave Ablation

Following RFA, MWA has gained attention as a next-generation thermal ablation technique capable of overcoming some of the inherent limitations of RFA. MWA is a minimally invasive treatment method that primarily relies on imaging guidance to eradicate all malignant cells by minimally invasive techniques, while preserving a sufficient safe range (at least 5mm) of healthy tissue around the ablated lesion.[72] MWA provides a new treatment method for HCC,[73–76] which plays a vital role in the treatment of early HCC. In comparison to surgical procedures, MWA provides advantages such as a lower incidence and mortality rate, along with a broader range of indications.[11] When compared to RFA, MWA therapy for hepatic carcinoma can have a larger target and shorter surgical time.[48] Due to the heat dissipation effect of the adjacent vascular system, the morphological changes in the treatment area are not easily affected.[48]

In recent times, many different high-energy devices and generators are designed to created expand the extent of ablative areas, attain broader ablative peripheries, and mitigate regional neoplastic escalation.[77] MWA operates on the principle of dielectric heating, which takes place when non-ideal dielectric materials are subjected to alternating electromagnetic fields(EM).[78,79] The microwave (MW) field oscillates rapidly (2450 megahertz per second), causing polar molecules to rotate out of synchronization, resulting in some electromagnetic energy which is absorbed and then converted into heat.

During the processing, MWA generates electromagnetic waves encircling the insulated and standalone antenna.[80] The predominant portion of the heat is generated by the excitation of dipolar water molecules, while the effect of ion polarization on heat generation is much smaller.[80,81] MWA devices use frequencies≥900MHz, with the two main frequencies being 915 and 2450 MHz. 2450 MHz is the most commonly used type, while 915 MHz can generate deeper penetration, which may result in larger ablation areas.[82] The MWA system creates a large heat-emitting zone (within 2 centimeters of the antenna), allowing for homogeneously distributed necrosis of the intended lesion. MWA is reduced impact by the vaporization and carbonization defense of adjacent biological matrices, so the heat dispersion effect has a smaller impact on the treatment effect. Due to the EM properties of MW, MWA is not limited by biological matrices conductivity, since the transmission of energy is independent of the tissue's electrical characteristics.[83]

MWA still faces some technical challenges, including limited ablation areas, metastasis near ablation areas, and the likelihood of thermal injury to nearby visceral tissues.[84] Therefore, improving MWA therapy technology and developing safer and completely ablative new therapies for HCC are crucial for eliminating recurrence and residual tumors.

Liposomal Nanoparticle-Mediated Microwave Ablation

Liposomes are commonly used drug carriers with high encapsulation capacity and good biocompatibility. When combined with liposomes, they can protect drugs from damage in the internal environment.[85] Some liposomes can deliver their drug load within cells or even in different cellular compartments.[55] The benefits of using liposome carriers include reduced systemic phagocytosis and prolonged circulation time, selective drug delivery through leaky tumor endothelium (enhanced permeability and retention), and reduced toxicity.[86] Liposome Doxil is the first nanodrug approved by the US Food and Drug Administration for use in animal experiments for cancer treatment. Liposomes have been extensively advanced since drug delivery systems to augment the effectiveness of HIFU and RFA.[87]

Researchers have reported the synergistic therapeutic effect of liposomes coencapsulating NaCl and DOX in the combination therapy of MW hyperthermia and cancer chemotherapy.[88] The small cavity volume within liposomes enhances spatial enclosure efficiency, and liposomes are ideal thermal seeds. Researchers have synthesized sodium

chloride liposomes (NaCl-LPs) serves as an effective nanocarrier to improve MWA of HCC, and systematically evaluated that NaCl-LPs as nanoparticles can potently improve the sensitivity of MWA, and demonstrates superior therapeutic effects compared to MWA both in laboratory experiments and within a living organism. MWA and NaCl LPs have significant tumor suppressive effects as well as reduced neoplasm relapse rates. In sublethal MWA conditions, NaCl-LPs exhibit significant temperature elevation and tumor necrosis.[85] Meanwhile, NaCl-LPs have good biocompatibility and non-toxic properties, and have broad clinical application prospects. In addition, researchers have developed doxorubicin-loaded liposomes (DNPs) as an effective nanoplatform, demonstrating that mild MWA combined with DNPs can improve the ablation efficiency of HCC and have a significant inhibitory effect on liver tumors.[89] This may be a promising nanoparticle based approach for treating HCC and demonstrates potential for future clinical applications.

DOX can be used as a therapeutic agent for HCC, and indocyanine green (ICG) can be used as an imaging agent for multispectral photoacoustic tomography (MSOT) tumor identification.[90] Researchers developed DOX/ICG-loaded liposomes (DILPs) and integrated them with MWA for managing HCC. The results showed the effectiveness of DILPs in the diagnosis of HCC by MSOT, as well as the improved accuracy and efficiency of DILPs combined with MWA in the treatment of HCC.[91]

In clinical practice, the survival rate for HCC with the occurrence of metastatic disease is low, and while various treatment options such as liver resection, transplantation, and thermal ablation can be effective locally, they are limited in their applicability for patients with distant metastasis.[92] Researchers have encapsulated DOX and MW sensitizer (1-butyl-3-methylimidazolium-L-lactate, BML) within fucoidan-linked liposome nanoparticles (TBP@DOX). When exposed to adjuvant MW treatment, this formulation can achieve targeted accumulation and significant localized delivery of DOX in HCC as well as metastatic pulmonary carcinoma.[92] It can effectively treat in situ and metastatic HCC in mice with neoplasm growth, achieving effective suppression of intrahepatic HCC growth and extrahepatic pulmonary metastasis and notable reduction in extensive dissemination.[92]

Liposome nanoparticles can enhance the thermosensitive effect of MWA, strengthen the anti-cancer effect against hepatic carcinoma, enhance the ablation effectiveness for hepatic carcinoma, and achieve better therapeutic effects. Liposome nanobiotechnology has significant potential in clinical MWA treatment of HCC.

Metal–Organic Frameworks-Based Nanoplatforms for Microwave Ablation

The heat generation space of MWA is limited, and the tumor area is not fully covered, which could result in elevated rates of recurrence and metastasis.[93,94] Meanwhile, non-selective MWA inevitably damages the healthy tissue surrounding the lesion.[95] Because of the tumor's intricate internal environment, a single heat treatment is frequently constrained and may struggle to yield the sought-after results.[96,97]

Metal-organic frameworks (MOFs) are innovative nanomaterials formed from metal ions and organic ligands, offering benefits like a extensive surface expanse, elevated porosity, excellent carrying capacity, and a uniform structure.[98] Furthermore, MOF materials exhibit excellent biocompatibility and biodegradability, thus having great potential for application in the evaluation and management of hepatic carcinoma.[98–100]

Ti MOFs can yield ROS below MW excitation, and the porous framework of titanium-based MOFs can improve the elastic interactions of ions within tissues, generating increased heat for MW hyperthermia.[101] Thus, titanium-based MOFs could serve as optimal MW sensitizers since they generate heat and ROS simultaneously when exposed to MW radiation. The MOF nanosheets possess a greater lateral size-to-thickness ratio as well as a higher variety of accessible reactive sites, facilitating the swift diffusion of ROS and enhancing treatment efficacy.[102]

Researchers have synthesized Mn-doped Ti MOFs (Mn-Ti MOFs) with good biocompatibility and biodegradability as a novel MW sensitizer, possessing high specific surface area, high porosity and good dispersibility.[103] Mn-Ti MOFs also exhibit enhanced MW-induced ROS generation, which generates heat under MW irradiation and can be used for MRI localization of liver tumor sites and guidance of MW therapy.[103]

Researchers have created a nanomedicine based on an iron-containing metal-organic framework (PFP Apa MFO) by integrating perfluoropentane (PFP) and apatinib (Apa).[104] Following absorption by hepatocellular carcinoma, iron can induce cell iron death. PFP can be activated to form bubbles, serving as an ultrasound agent to visualize ablation margins. Apa is a potent anti-angiogenic medication that can hinder the growth of residual tumors following MWA. The study

showed that the integration of MWA with PFP Apa MOF markedly enhanced ablation efficiency and exhibited a pronounced inhibitory effect on hepatic carcinoma.[104]

Although significant progress has been made in the application of MOFs in the biomedical field, there are still many obstacles, such as the toxicity, biodegradability and degradation process of MOFs,[105] which require further exploration.

Other Nanoparticle-Based Strategies for Microwave Ablation

When MWA is used for larger tumors or when tumor location is difficult, residual tumor progression and recurrence may still occur after ablation,[106] thereby affecting treatment outcomes and long-term quality of life. MWA eliminates neoplasms by causing coagulative necrosis in neoplasm cytological entity. If MWA is inadequate, residual tumor tissue may remain.[106] Nano particle biotechnology can improve ablation efficiency, reduce hepatic carcinoma recurrence, and has broad prospects.

Metal Nanoparticle-Mediated Microwave Ablation

Percutaneous MWA (pMWA) is an expeditiously developing strategy for the treatment of hepatic carcinoma and other indications, which involves placing a probe under image guidance with an antenna at its distal end that can heat and kill adjacent abnormal tissue.[107] One of its main limitations is the lack of control over the heating area around the ablation needle, which cannot be well controlled or shaped to conform to the desired tumor shape or avoid adjacent critical structures.[107] This limitation may lead to incomplete treatment and/or serious complications.[108]

Localized delivery of SPIONs can achieve more targeted ablation, as these particles undergo rapid oscillations in response to alternating magnetic fields when exposed to MW energy, yielding a rise in heat output.[107] Superparamagnetic iron oxide Feraheme nanoparticles (FHNPs) are particularly promising for clinical translation, as they have been approved by the FDA for the therapeutic strategies of iron deficiency anemia and are also used as MRI enhancing agents.[109,110] Due to their nanoscale dimensions (approximately tens of nanometers), administration through the skin to target anatomical structures is achievable via ultra-fine needles (22G or thinner).

Researchers have shown that the local administration of FHNPs can greatly improve the heating of liver tissue during pMWA and manipulate the configuration of the ablation area surrounding the pMWA needle by injecting FHNPs into the tissue.[107] In essence, this strategy can boost the security and potency of pMWA intervention for solid malignancies and multiple other disorders. Additionally, researchers have injected MNPs into tumors to investigate the impact of varying input power levels, demonstrating that MNPs, as effective external heat sources, can significantly lower the required input power for ablative MW.[111]

Mannose-Modified Nanoparticles Promoting Immune Response Post-Microwave Ablation

The recapitulation and metastasis of HCC following MWA pose significant clinical challenges.[112] Studies indicate that the recurrence rate after three years can reach up to 25.8%, with the five-year recurrence rate being even greater.[113,114] Therefore, there is an immediate necessity to investigate effective treatment strategies aimed at decreasing the recurrence of HCC following MWA. Cancer immunotherapy, which focuses on modulating the immune response system to target tumorigenic cells, has demonstrated significant promise in addressing the recurrence and metastasis of hepatic carcinoma following MWA treatment,[115,116] since MWA can break down tumorigenic cellular structures as well as liberate cellular structures fragments containing neoplasm-specific antigens, these can be utilized for cancer vaccination.[117,118]

Due to inadequate intracellular absorption and exhibition of antigens in antigen-presenting cells (APCs), including dendritic cells (DCs), the immune response induced by MWA therapy is insufficient to effectively suppress the growth and spread of hepatic cancer.[112] Therefore, there is an urgent need for strategies that enhance APC antigen presentation to obtain a strong immune response and suppress HCC recurrence after MWA therapy.[92,119]

Carbon dots (CDs) have advantages such as simple fabrication, chemical stability, biocompatibility and luminescence, and the surface of CDs may incorporate multiple active sites, such as carboxyl, hydroxyl and amine groups.[112] The reactive groups present on the surface of CDs create structural domains that can efficiently interact with various biomolecules, including RNA and proteins.[120]

Studies have revealed that CDs can selectively interact with large neutral amino acid transporter 1, leading to significant cancer suppression within a living organism.[121] Researchers have found that mannose-derived carbon dots (Man CDs) can induce effective DC maturation and demonstrate that Man CDs can successfully capture various "danger signals" (DS).[112] The enhancement of DS uptake can effectively activate DC cell maturation, induce antigen processing and presentation enhancement, leading to a strong anti-tumor immune reaction (as shown in Figure 2). These results indicate that intratumoral administration of Man CDs after MWA treatment inhibits the growth of native neoplasms and suppresses the growth of dispersed neoplasms, providing a protective effect against tumor recurrence.

Upregulation of gene expression related to neovascularization in the ablation surrounding area can trigger inflammatory responses, including synthesis of mitogenic factors or chemokines and enlistment of pro-inflammatory M2 macrophages.[106] The aforementioned reactions necessitate repair processes as well as enhance the immunosuppressive neoplasm microenvironment. Especially, M2 macrophages facilitate wound healing through extracellular matrix remodeling, angiogenesis and immunosuppression.[122] Therefore, the rise in M2 macrophages within the neoplasm immune cellular environment facilitates the proliferation and spread of residual neoplasm, resulting in unfavorable outcomes for patients with HCC.[123] Scientists have developed d-mannose-chelated iron oxide nanoparticles (man IONPs) to reprogram M2-like macrophages into an anti-tumor M1 phenotype (as shown in Figure 3).[106]

These studies have authenticated the macrophage polarization effect of man IONPs and shown their efficacy in hindering regional neoplasm advancement by using a murine model of hepatic carcinoma. Man IONPs were found to slow the progression of residual tumors following MWA intervention, reduce the percentage of M2 macrophages as well as mitigate immune suppression in the vicinity of the ablated area.[106] Therefore, the combination of man IONPs with MWA could offer an original strategy for hepatic carcinoma therapy.

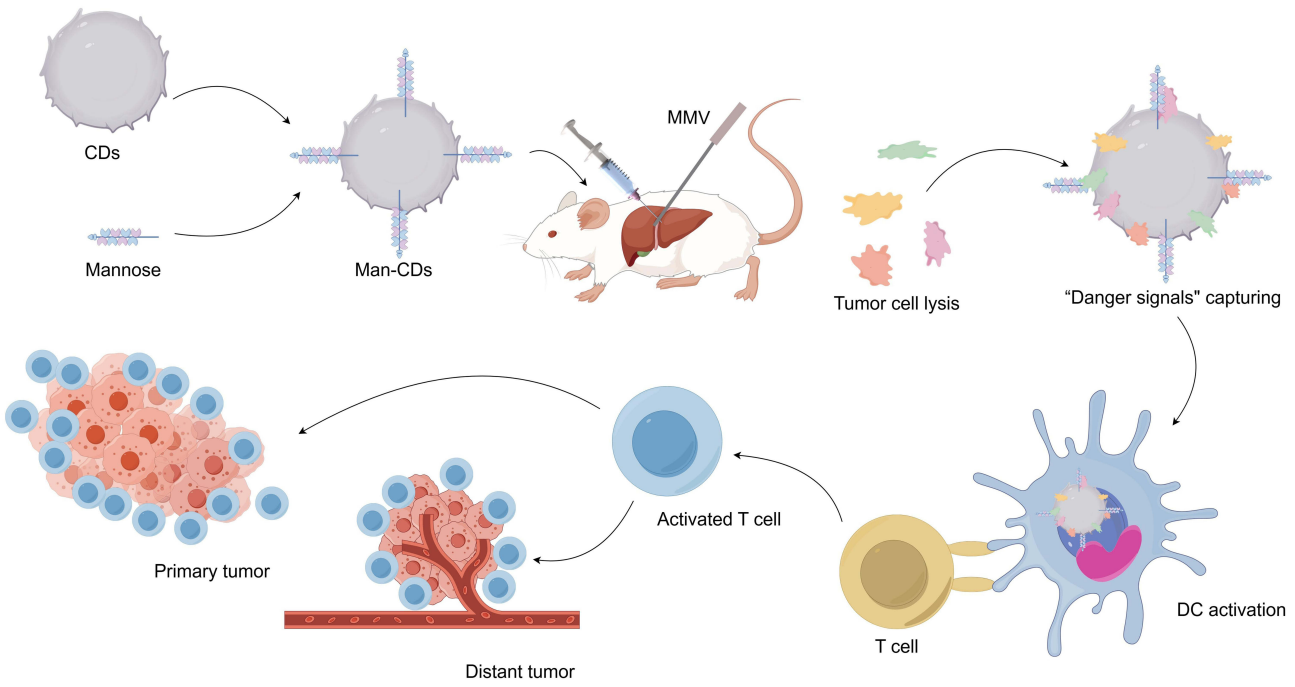

Figure 2 Schematic illustration of Man-CDs enhancing microwave ablation–induced antitumor immunity in hepatocellular carcinoma (By Figdraw). CDs were modified with mannose to form Man-CDs, which were injected intratumorally following MWA. Tumor cell lysis during MWA releases "danger signals" that are efficiently captured by Man-CDs. These Man-CDs promote DC activation and antigen presentation, leading to T-cell activation and systemic antitumor immune responses. Activated T cells subsequently inhibit the growth of both primary and distant tumors, achieving synergistic immunotherapeutic effects.

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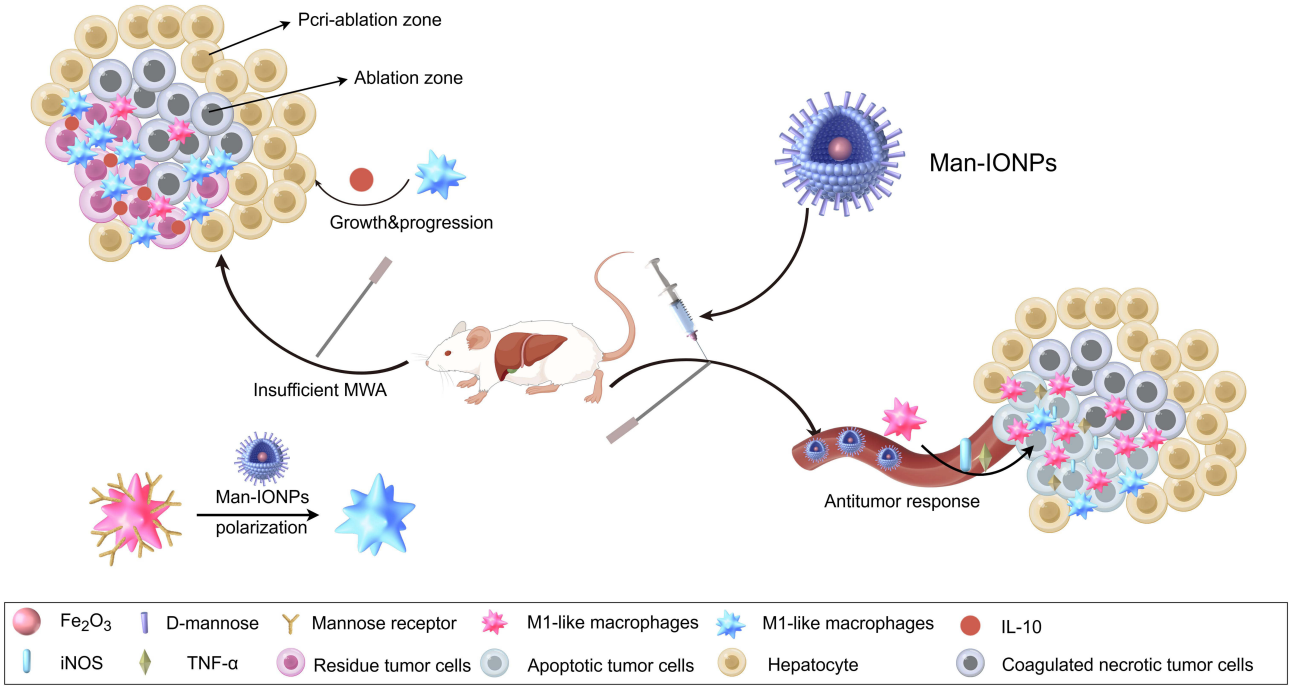

Figure 3 Schematic illustration of Man-IONPs enhancing antitumor immunity after insufficient MWA of hepatocellular carcinoma (By Figdraw). Insufficient MWA leads to incomplete tumor necrosis and promotes local tumor regrowth through inflammatory responses in the peri-ablation zone. Intratumoral injection of Man-IONPs induces macrophage polarization from the pro-tumoral M2 phenotype to the antitumoral M1 phenotype, characterized by upregulation of iNOS and TNF-α. This reprogramming enhances antitumor immune responses, reduces residual tumor cell survival, and inhibits recurrence and progression following MWA.

Nanobiotechnology and Cryoablation

Cryoablation

In contrast to heat-based ablation, cryoablation provides a cold-induced mechanism for tumor destruction, making it an important complementary approach. CRA is a method that involves freezing tissue to a destructive temperature, followed by a thawing process. This approach is commonly applied in the treatment of both benign and malignant primary tumors.[124] CRA offers benefits in hepatic carcinoma treatment through its precise image-guided procedures, which have been shown to lower complications, reduce costs, and shorten recovery time.[125] Compared to alternative thermal ablation modalities like MWA and RFA, it provides a secure and productive strategy for targeted therapeutic intervention.[12,126] CRA serves as an effective palliative approach for liver metastasis, offering not only promising therapeutic outcomes but also pain relief for patients suffering from liver metastasis. This method serves a vital function in palliative care, significantly boosting the life satisfaction for individuals with metastatic tumors.[12]

The most common method of CRA cooling is to circulate nitrogen or argon gas through the probe for cooling.[127] It then quickly expands into a gaseous state, generating temperatures that can drop to −190°C, a phenomenon referred to as the Joule-Thomson effect.[128] One obvious disadvantage of CRA is that not only is the cost of the probe relatively high, but the cost of helium and argon is also relatively high.[129] In addition, CRA can cause inflammatory reactions, leading to systemic cytokine mediated hypothermia syndrome in some cases (mainly in large liver tumor ablation), accompanied by hypotension, dyspnea, and disseminated intravascular coagulation.[129] Ongoing research suggests that nanocarriers hold great promise as catalysts in CRA therapy, imaging assistance, and for the simultaneous delivery of therapeutic agents, enabling less invasive, precise, and comprehensive hepatic carcinoma treatment with immune regulation.[126] Additionally, newly developed multifunctional nanocarriers are crucial in advancing CRA therapy for hepatic carcinoma. The integration of nanoparticles with cryotherapy can address the limitations of established chemotherapy or CRA alone, including pharmacological resistance induced by chemotherapy, generalized toxicity as well as uneven neoplastic cell elimination.[126]

Nanoparticle-Assisted Cryoablation

The disadvantage of traditional ablation is incomplete destruction of hepatic carcinoma tumor tissue and limited size of treatable tumors.[126] Although CRA is convenient and effective, challenges like inadequate ice formation persist, the possibility of ice balls extending excessively to surrounding normal tissues as well as decreased neoplastic cell mortality in the vicinity of the ablation area.[126] Owing to these elements, residual tumors treated with CRA may recur. Therefore, it is necessary to use image-guided local CRA as an adjuvant therapy to accurately target tumors. Preferably, drug distribution should be preserved within the tumor site that has been ablated. Nanoparticles enable image-guided cancer therapy by inducing tumor-selective ice formation, protecting healthy tissue, and supporting localized, sustained drug release. Tailoring nanoparticle composition allows integration of cryoablation with other treatments, highlighting a promising strategy in image-guided nanomedicine (as shown in Figure 4).[126]

Application of Nanoparticles in Cryoablation

During the freezing process, ice nucleation is considered a crucial step in the process. It is widely accepted that the formation of a critical ice nucleus is essential for initiating ice nucleation.[126] Studies have revealed that graphene oxide nanosheets measuring less than the critical ice nucleus size (approximately 8 nm) impede the formation of ice, whereas nanosheets that exceed this size (greater than 11 nm) encourage ice growth.[130] When the diameter

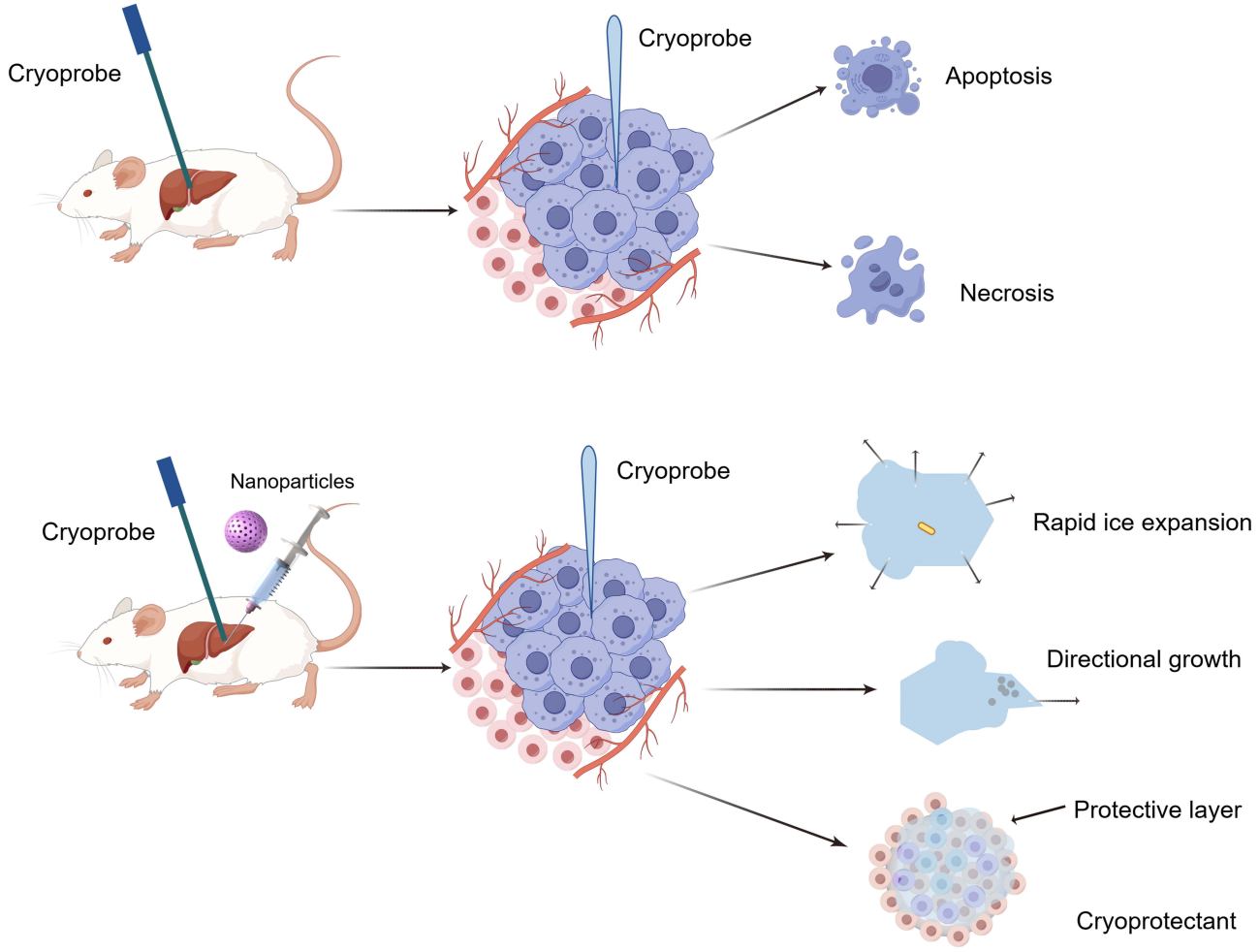

Figure 4 Schematic illustration of nanoparticle-assisted cryoablation enhancing tumor cell destruction (By Figdraw). (Upper panel) Conventional cryoablation induces tumor cell apoptosis and necrosis through freezing–thawing cycles but often results in incomplete ablation. (Lower panel) The introduction of nanoparticles into the tumor before cryoablation promotes rapid ice nucleation and directional ice crystal growth, facilitating more uniform and deeper freezing within the tumor tissue. Additionally, nanoparticles can form a protective cryoprotectant layer that minimizes collateral damage to surrounding normal tissues, achieving enhanced precision and therapeutic efficacy in cryoablation.

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surpasses 11 nanometers, the temperature for ice formation initiation of aqueous droplets encompassing graphene oxide nanoparticles experiences a slight increase, though the change is not substantial. Therefore, the size of nanomaterials seems to have a lower limit, which is of great significance for the growth rate of ice. The surface area is closely related to size. When increasing the formation of ice, the surface area of nanoparticles is an important factor to take into account, as it directly influences the heat exchange between the nanoparticles and their environment.[130]

Metal Nanoparticle-Mediated Thermal Conduction in Cryoablation

Metallic nanoparticles typically exhibit superior thermal conductivity compared to nanoparticles made from polymers or lipids, allowing for more efficient heat exchange.[126] They can penetrate the entire tumor, facilitating a more consistent temperature gradient throughout the CRA process. In addition, when nanoparticles aggregate around cancerous tissue and enter cells due to the EPR effect, they can promote the formation of intracellular ice.

Biodegradable magnesium oxide nanoparticles increase the pace of internal cellular processes freezing and can serve as adjuncts for CRA while minimizing the risk of toxicity.[131] Researchers have shown that Fe3O4 nanoparticles increase the likelihood of intracellular freezing and dehydration of cells after freeze-thaw cycles, and the generation of intracellular ice rises alongside the concentration of nanoparticles within the tumor.[132]

Considering the capacity of nanoparticles to enhance ice formation, controlled adjustment of the shape of ice balls can be achieved.

The accumulation of nanoparticles within tumors, particularly their aggregation on cell membranes, can facilitate the formation of an ice ball that conforms to the tumor's irregular contours. It is feasible to achieve controlled freezing or ice growth when injecting low-temperature enhanced aluminum nanoparticle water suspension and low-temperature protected dimethyl sulfoxide (DMSO) at different locations.[133] Graded nanostructures, such as branched nanostructures or nanofibers, have a elevated outer area relative to volume. Branched gold nanostructures as well as flower shaped bimetallic nanoparticles composed of gold and silver can increase heat in PTT.[134] These well-organized thermal nanostructures can quickly lower the temperature of cancerous tissues.

Application of Liposomal Nanoparticles in Cryoablation

Certain polymer or lipid-based nanoparticles can safeguard healthy tissues from cold-induced injury, owing to their limited heat transfer efficiency.[126] Chitosan tripolyphosphate (CS-TPP) nanoparticles that are infused with the cryoprotectant trehalose exhibit the potential to safeguard NK cells from cryogenic trauma, eliminating the necessity for supplementary cytotoxic cryoprotectants like DMSO.[135] The rate of recovery for NK cells treated with CS-TPP is better than that of traditional cryoprotectant DMSO. CS-TPP nanoparticles facilitate cellular infiltration as well as boost the effectiveness of trehalose. Protecting essential immunocytes in proximity to healthy tissues may be beneficial for the immune response after hepatic carcinoma CRA. By utilizing mature nanomedicine and therapeutic nanoparticles, innovative treatment options can be achieved for hepatic carcinoma ablation technology by increasing tumor selectivity and triggering anti-tumor immune responses.

Nanoparticle-Enhanced Imaging for Cryoablation Guidance

The incorporation of nanoparticles into targeted tissues has been shown to enhance image contrast, thereby offering improved imaging guidance for cryosurgery.[136] Enhanced imaging of tumor boundaries and the edges of the ice ball could lead to increased treatment efficacy in cryosurgery. The delineation of tumor margins during CRA is crucial to guarantee that the ice ball remains confined within the tumor and does not encroach upon surrounding healthy tissue. Therefore, CRA is applicable solely for tumors that are identifiable via imaging techniques. For neoplasms without clear edges in the image, utilizing targeted nanoparticles to gather around the tumor periphery could be advantageous.[126]

Gold nanoparticles are extensively employed as contrast agents for CT imaging in both preclinical and clinical applications.[137] Silver nanoparticles are similarly utilized as contrast agents in CT imaging,[138] and MNPs are the most frequently employed nanoparticles in imaging applications, like Fe_3O_4 nanoparticles that have a diameter ranging from 20 to 30 nm. Research has demonstrated that they enhance the resolution and contrast of traditional imaging methods,

including magnetomotive optical coherence tomography (MMOCT) and MRI.[136] MMOCT experiments have shown that the contrast generated by MNPs in the dynamic response to external fields can lead to local variations in optical scattering.[136] SPIONs have been widely used in molecular and cellular imaging of MRI. The toxicity and uptake of iron oxide NPs by stem cells were studied in vitro, and the results showed that iron oxide absorption at approximately 20 picograms per cell did not significantly reduce cell proliferation.[136]

In summary, cryoablation offers a nonthermal approach for HCC by inducing tumor injury through rapid freeze–thaw cycles. Nanobiotechnology has enhanced its precision via improved ice formation and image guidance, though incomplete freezing and uneven tissue responses remain challenges. Consequently, research has extended to other modalities—HIFU, IRE, and PTT—which, when integrated with nanobiomaterials, provide complementary mechanisms for precise and immune-modulating ablation of HCC.

Nanobiotechnology and Other Ablation Techniques

Nanobiotechnology and High-Intensity Focused Ultrasound

High Intensity Focused Ultrasound

The clinical application of HIFU can be traced back to the 1950s, when it was recognized as a substitute therapy for conditions affecting the central nervous system.[139] HIFU is an exceptionally promising and notable non-invasive therapy for hepatic carcinoma, demonstrating high effectiveness. This technique causes tumor cell necrosis by elevating local temperatures and creating mechanical pressure.[13]

HIFU combines numerous ultrasound signals generated by electromechanical or piezoelectric ceramic transducers, which directly enter a spatial focal region, customarily a minimal quantity with a diameter of 5 millimeters as well as a measurement of 10 millimeters. The purpose is to augment and preserve a temperature of 60 °C or above in the target tissue for exceeding one second or longer, to trigger coagulative necrosis and the destruction of cells. Under the synergistic impact, the mechanical effect mainly generated by cavitation (the expansion and contraction of intracellular water under sound pressure to form microbubbles, which swiftly rupture to generate pressure waves) and the destructive impact on neoplastic vasculature also aid in tissue degradation. Throughout the ablation procedure, the HIFU beam must be located and observed with the assistance of magnetic resonance or ultrasound imaging.[140]

However, because of HIFU's limited infiltration depth and the potential for unintended side effects, its clinical application is limited.[141] Nanodrugs have good structural tunability and targeting properties, and have been used to improve the ablation effect of HIFU therapy for hepatic carcinoma.[141] Studies have shown that the incorporation of nanoparticles can significantly modify the acoustic properties of tumor tissue (tissue architecture, concentration, vascular supply, ultrasound transmission, and energy deposition during HIFU treatment), making it more sensitive to HIFU and achieving greater ablation effects at an equivalent or reduced HIFU exposure level.[142]

In addition, since the initial documentation of integrating HIFU with nanotechnology in 2000,[143] it is recognized that HIFU facilitates the discharge of therapeutic agents from carriers like nanoparticles and liposomes, thereby amplifying the ablation effects of HIFU while also improving safety. Following this discovery, studies have focused on developing nanomedicines aimed at boosting the effectiveness of HIFU.[144,145]

Application of Nanobiotechnology in High Intensity Focused Ultrasound

Researchers have developed a temperature-sensitive nanoplatform known as [PFH/DOX@PLGA/Fe_3O_4-folate (FA)], once the Fe_3O_4 encapsulated particles accumulate actively in hepatic carcinoma tissue through EPR effect and attachment of FA, T2 weighted imaging of the tumor can be performed.[146] The incorporation of PFH enables enhanced contrast ultrasound imaging of tumor tissues, thereby achieving multimodal imaging. Moreover, the inclusion of PFH and DOX greatly enhances the effectiveness of HIFU ablation, enhances chemotherapy efficacy, and reduces tumor volume, respectively. Therefore, this nano platform can not only achieve multi-mode imaging of hepatic carcinoma, but also realize multi-mode treatment.[146]

Researchers have also designed a perfluoroalkyl bromide (PFOB) nanoemulsion containing MnO_2 NPs, which can be combined with CT and MRI for multimodal imaging as well as utilized alongside HIFU ablation and immunotherapy for a multimodal therapeutic approach.[147] Utilizing PFOB can perform CT imaging on tumor tissue and transform it into

microbubbles when exposed to HIFU irradiation, enhance cavitation effect, and improve HIFU ablation effect.[147] Aside from enhanced HIFU ablation effects (allowing for reduced HIFU exposure levels and dosage intervals, thereby reducing collateral damage to normal tissues), it has been reported that these NPs also consume GSH due to the disruption of the tumor tissue antioxidant defense system mediated by MnO_2, and facilitate robust immunogenic cell death by stimulating dendritic cell maturation and boosting the activation of $CD4^+$ and $CD8^+$ T cells,[147] which markedly hinders the proliferation of the primary neoplasm and the occurrence of pulmonary metastasis through a combined therapeutic approach.[148]

Researchers have also developed liposomes based on nanobubbles, which can accumulate and release drugs 4–5 times more in tumor tissues compared to nanomedicine or HIFU.[149,150] In addition, these nanovesicle based liposomes not only effectively improve the efficacy of HIFU ablation, thereby shortening the irradiation time, but also encapsulate anti-tumor genes, short interfering RNA, and chemotherapy drugs to stimulate synergistic effects, further enhancing their anti-tumor efficacy.[149,150]

In addition, some researchers have used magnetic nanomaterials (SPIONs; 0.047% w/v) to halve the HIFU irradiation dose required for tumor destruction volume, significantly reducing the side effects caused by high HIFU doses.[151] They further found that the thermal enhancement provided by ferromagnetic nanomaterials surpasses that of gold nanoparticles, another potential material for HIFU hyperthermia, thus rendering MNPs more advantageous for clinical applications.[152]

Although most nanomedicines suitable for HIFU have minimal in vivo toxicity, a certain degree of liver toxicity can still be observed.[141] In addition, given that the majority of the previously mentioned studies on nano-enhanced HIFU treatment for hepatic carcinoma have been performed on small animal models, it remains to be determined whether using the identical dosage of HIFU in small rodents to activate these nanoparticle therapies is also applicable to humans. Future research should aim to address these challenges to increase the efficacy of nanomedicine in HIFU applications and facilitate its advancement into clinical practice.

Nanobiotechnology and Irreversible Electroporation

Irreversible Electroporation

IRE is a non-thermal ablation method that applies brief, high-voltage electric pulses between electrodes placed within the affected tissue, leading to cell apoptosis.[153,154]

IRE offers benefits such as reduced treatment duration and precise ablation targeting. It also presents distinct benefits for tumor treatment around liver blood vessels, subcapsules, gastrointestinal tract, and gallbladder.[155] IRE is unaffected by thermal dissipation effects, does not damage adjacent structures, and has advantages such as minimally invasive, brief treatment duration, and security and dependability.[14] When surgical options and conventional local ablation methods are impractical, IRE is primarily used to treat liver tumors. IRE is also very useful for liver tumor patients who are not appropriate for thermal ablation. IRE fails to damage the extracellular scaffold, thus safeguarding adjacent tissues. When the diameter of the liver tumor is less than 3cm, IRE can achieve complete ablation. Meanwhile, the nearby blood vessels, biliary vessels, and gastrointestinal system can also be protected. If residual tumors remain adjacent to the blood vessels, biliary vessels, or gastrointestinal system following thermal ablation, IRE can serve as a valuable adjunct to the thermal treatment.[155] After hepatic IRE ablation, a fibrous capsule does not develop around the area of ablation. In contrast to RFA, IRE promotes liver regrowth, preserves the integrity of extracellular structures, and promotes liver regeneration.[156]

At present, IRE has been proven to be a successful liver tumor ablation technique, but it still requires a specific anesthesia treatment and precise and parallel placement of multiple needles, which means a high degree of complexity and requires the experience of a large intervention team.[157]

Nanoparticle-Facilitated Irreversible Electroporation

Scientists assessed the internal absorption of nanoparticles within tumors when used alongside IRE or RFA in a rabbit VX2 model.[158] The researchers discovered that the concentration of nanoparticles within the tumor was highest one hour

post-RFA. In contrast, the IRE group showed an increase in nanoparticle uptake at the 18-hour mark, surpassing the levels observed in the RFA group, which exhibited a decline in uptake over time. This study indicates that IRE could enhance the process of molecular cellular assimilation. They also found that the combination therapy of nanoembolization and IRE ablation led to the accumulation of nanoparticles both within the cells and in the vicinity of tumors, as well as in un ablated liver cells, increasing the possibility of achieving ablation zones without tumor residue under the naked eye or microscope.[158] The application of nanobiotechnology in IRE is still an emerging field that requires creative exploration and research.

Nanobiotechnology and Photothermal Ablation

Photothermal Ablation

PTT is a local treatment used to treat solid cancers or tumors in different parts of the body.[159] PTT is a hepatic carcinoma treatment strategy that uses light radiation to generate local heat in cancer cells.[160] This technique employs near-infrared light to target tumor tissue due to its excellent ability to penetrate tissues. The photothermal conversion raises the temperature within the tumor, resulting in damage to tumor cells via protein denaturation and disruption of cellular membranes.[159]

PTT is highly valuable for research purposes because of its ease of use, brief treatment duration, and rapid recovery process.[15] Most notably, PTT is an exceptionally efficient non-invasive therapy capable of eradicating different forms of cancer. Studies have shown that PTT can use less energy and longer wavelengths of light, with less harmful effects on other cells and tissues.[161]

PTT has gained significant attention as a novel focus of research in the treatment of hepatic carcinoma. While various approaches have been investigated to enhance the efficacy of thermal ablation therapy for hepatic carcinoma, PTT can lead to substantial harm to healthy tissues. This is primarily owing to the extensive presence of photothermal agents (PTA) throughout the organism as well as the potential for imprecise laser irradiation during treatment.[162] To enhance the rate of survival among patients with HCC while minimizing potential adverse effects on surrounding tissues, it is essential to investigate PTA that offer high selectivity and precision in treatment.[162]

Application of Nanobiotechnology in Photothermal Ablation

Polydopamine (PDA), which mimics adhesion proteins present in bivalve mollusks, exhibits superior biological compatibility as well as degradability. In recent years, it has found extensive application as a PTA in the research of PTT.[162] The Fe_3O_4 magnetic composite particles coated with PDA effectively minimize interference from the endothelial network system.[163] Fe_3O_4@PDA particles were administered into the neoplasms present in murine models, followed by laser irradiation, resulting in a rapid surface temperature rise of the tumor to 59.7 °C, demonstrating superior photothermal conversion ability. Researchers used multi walled carbon nanotubes (MWNTs) as carriers and modified CREKA (Cys Arg Glu Lys Ala) peptides with special attraction for fibrinogen as target fragments (CMWNTs PEG) to design a tumor PTT self amplifying drug delivery system.[164] The system amplifies tumor targeting through the positive feedback mechanism of coagulation reaction and demonstrates a remarkable ability to target tumors, leading to effective and selective tumor destruction.

Besides passive and active targeting, the application of external magnetic fields can further improve the targeted destruction of tumors by photothermal agents. In response to an external magnetic field, MNPs loaded with PTA in the bloodstream, such as superparamagnetic Fe_3O_4, can be guided to concentrate in tumor tissues. This targeted approach enables the selective elimination of tumor cells while sparing healthy tissue, thereby enhancing the specificity and efficacy of PTT.[164] Magnetic field-assisted PTT has shown successful results in preclinical studies, highlighting its potential for future clinical applications.[165] The extraordinary photothermal conversion efficiency of enzyme synthesized MnO_2 NPs (Bio-MnO_2 NPs) is 44%. Bio-MnO_2 NPs exhibit high thermal cycling durability and dissolvability, as well as dual pH and reduction reaction MRI enhancement for tumor diagnosis.[166] Bio-MnO_2 NPs have a high photothermal ablation effect, which can completely eradicate tumors and have high therapeutic biocompatibility without significant recurrence. Additionally, MR enhancement of stimulus response may achieve precise imaging guided PTT.[166]

Due to the easily adjustable nature of PTT, altering the variability of nanoparticle and optical properties enables us to activate the mechanism of PTT involving apoptosis rather than necrosis, which is a major asset in malignant cellular eradication.[167] Nanoparticle applications has achieved greater development globally. Scientists are utilizing the true potential of nanoparticles on a large scale to effectively eradicate hepatic carcinoma.

Summary and Expectation

In the past few decades, due to advances in nanotechnology, nanotechnology for hepatic carcinoma treatment has rapidly developed. Nanotechnology is also widely used in hepatic carcinoma ablation therapy. Minimally invasive tumor ablation is increasingly employed in hepatic carcinoma treatment. This approach serves as a primary option for patients who have not responded to chemotherapy or radiotherapy, or who are not candidates for surgical intervention. It holds promise as a primary treatment option for patients across different stages of the illness.

Applying nanotechnology to hepatic carcinoma ablation therapy can enormously enhance the treatment efficiency of hepatic carcinoma and significantly reduce the side effects during treatment. Unlike traditional targeted drugs or chemical transporters, the advancement of nanotechnology has consistently aimed at integrating its distinctive properties with pharmaceuticals for the treatment and imaging of HCC, with the goal of enhancing the precision of hepatic carcinoma therapies.[168]

Among the various types of nanocarriers, inorganic NPs stand out due to their remarkable stability, high monodispersity, and ease of functionalization. These properties make inorganic NPs suitable for use as carriers for therapeutic agents, including medications aimed at treating hepatic carcinoma. However, the biocompatibility, especially biodegradability, of inorganic nanomaterials is the main issue in their clinical applications.[25]

Due to the good biocompatibility and biodegradability of liposomes, as well as the advantages of high bioavailability and fewer adverse reactions, better therapeutic indicators can be obtained. While liposomes offer several benefits, they also face challenges, including reduced encapsulation efficiency and poor stability during storage. And due to the more complex production of liposome nanomedicine compared to traditional therapies, clinical trials of liposome nanomedicine are also more complicated, which greatly increases the cost and time of clinical trials.[25] Therefore, to improve patients' outcomes following drug administration, there is a need for more sophisticated multifunctional designs that closely mimic the biological environment, effectively navigate biological barriers, and ensure successful treatment.[169]

While the use of nanotechnology in hepatic carcinoma ablation has yielded promising results in both preclinical and early clinical studies, the effective translation of nanomedicine into clinical practice still faces multiple challenges.[170,171] The in vivo behavior of nanomaterials—including biodistribution, immune interaction, and metabolic clearance—remains incompletely understood, hindering the rational design and optimization of nanomedicines.[39] Further research on pharmacokinetics, biocompatibility, and long-term biosafety is essential to enhance their bioavailability and therapeutic efficacy. Another key issue is the limited drug-loading efficiency of current nanocarriers, which restricts dosage control and therapeutic outcomes. This can be addressed by developing novel nanocarriers with improved encapsulation capacity, stimuli-responsive release, and biodegradability.[172]

Additionally, large-scale and reproducible manufacturing of nanomedicines remains a major bottleneck. Regulatory standardization, cost-effective synthesis, and quality-control frameworks are urgently needed.[173] Collaborative efforts among materials scientists, clinicians, and industrial partners will be critical to overcome these translational barriers. Despite these challenges, the convergence of nanobiotechnology and image-guided ablation offers a promising pathway toward more precise, safe, and effective treatment of hepatocellular carcinoma.

Abbreviations

HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; MWA, microwave ablation; CRA, cryoablation; HIFU, high-intensity ultrasound focused ablation; IRE, irreversible electroporation; PTT, photothermal therapy; MASLD, metabolic dysfunction related fatty liver disease; NPs, nanoparticles; MNPs, magnetic nanoparticles; MRI, magnetic resonance imaging; SPIONs, superparamagnetic iron oxide NPs; PEG, polyethylene glycol; MPS, mononuclear phagocytic system; EPR, enhanced permeability and retention; ASGPR, asialoglycoprotein receptor; GPC3, glypican-3; TME,

tumor microenvironment; DOX, doxorubicin; TL DOX, thermosensitive liposome encapsulated DOX; HR-TEM, high-resolution transmission electron microscopy; SPIO, superparamagnetic iron oxide; AM, ablation margin; SI, signal intensity; ROS, reactive oxygen species; EM, electromagnetic fields; MW, microwave; DNPs, doxorubicin-loaded liposomes; ICG, indocyanine green; MSOT, multispectral photoacoustic tomography; DILPs, DOX/ICG-loaded liposomes; MOFs, metal-organic frameworks; Mn-Ti MOFs, Mn doped Ti MOFs; PFP, perfluoropentane; Apa, apatinib; pMWA, percutaneous MWA; FHNPs, Feraheme nanoparticles; APCs, antigen-presenting cells; DCs, dendritic cells; CDs, carbon dots; Man CDs, mannose-derived carbon dots; DS, danger signals; man IONPs, d-mannose-chelated iron oxide nanoparticles; DMSO, dimethyl sulfoxide; CS-TPP, chitosan tripolyphosphate; MMOCT, magnetomotive optical coherence tomography; FA, folate; PFOB, perfluoroalkyl bromide; PTA, photothermal agents; PDA, polydopamine; MWNTs, multi walled carbon nanotubes.

Author Contributions

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

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Disclosure

The authors declare no conflicts of interest.

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