Am J Cancer Res 2025;15(11):4845-4856
www.ajcr.us /ISSN:2156-6976/ajcr0168156

Review Article

Post-ablation recurrence in hepatocellular carcinoma: molecular pathogenesis and targeted therapeutic innovations

Jiamin Chen[1,2*], Jinshu Pang[1,2*], Dongyue Wen[1], Fen Huang[3], Yun He[1], Hong Yang[1,2,4], Xiumei Bai[1,5]

[1]Department of Medical Ultrasound, The First Affiliated Hospital of Guangxi Medical University, Nanning 530021, Guangxi Zhuang Autonomous Region, China; [2]Key Laboratory of Early Prevention and Treatment for Regional High Frequency Tumor (Guangxi Medical University), Ministry of Education/Guangxi Key Laboratory of Early Prevention and Treatment for Regional High Frequency Tumor, Nanning 530021, Guangxi Zhuang Autonomous Region, China; [3]Department of Medical Ultrasound, Guangxi Hospital Division of The First Affiliated Hospital, Sun Yat-Sen University, Nanning 530022, Guangxi Zhuang Autonomous Region, China; [4]Collaborative Innovation Centre of Regenerative Medicine and Medical Bioresource Development and Application Co-constructed by The Province and Ministry, The First Affiliated Hospital of Guangxi Medical University, Nanning 530021, Guangxi Zhuang Autonomous Region, China; [5]Guangxi Key Laboratory of Enhanced Recovery after Surgery for Gastrointestinal Cancer, The First Affiliated Hospital of Guangxi Medical University, Nanning 530021, Guangxi Zhuang Autonomous Region, China. [*]Co-first authors.

Received August 17, 2025; Accepted November 23, 2025; Epub November 25, 2025; Published November 30, 2025

Abstract: Hepatocellular carcinoma (HCC) is one of the most common types of cancer worldwide. It is characterized by an extremely poor prognosis. Radiofrequency ablation (RFA) and microwave ablation (MWA) have become the main local therapies for early HCC. Nevertheless, the high recurrence rate is a key factor that limits the efficacy of thermal ablation. Numerous studies have suggested that HCC recurrence after thermal ablation involves many mechanisms. These include remodeling of immunosuppressive microenvironment, evasion of programmed cell death, metabolic reprogramming, reprogramming of metabolic adaptation, activation of epigenetic aberrations, acquisition of stemness traits, enhancement of epithelial-mesenchymal transition (EMT), induction of angiogenesis, and regulation by non-coding RNAs. To tackle these underlying mechanisms, precision intervention strategies have been gradually developed. These included, but were not limited to, immune-targeted therapy, modulation of cell death pathways, regulation of metabolic pathways, epigenetic therapeutic strategies, stem cell inhibition interventions, EMT reversal therapy, anti-angiogenesis interventions, and multi-target combination strategies. Our review systematically summarizes the research progress from 2017 to 2025, classifying the multidimensional molecular mechanisms and precision intervention strategies for HCC recurrence following thermal ablation. This provides a theoretical foundation for individualized comprehensive treatment and future research directions.

Keywords: Hepatocellular carcinoma, thermal ablation, recurrence, intervention

Introduction

Hepatocellular carcinoma (HCC) ranks as the sixth most prevalent cancer globally and is the third leading cause of cancer-related mortality, posing a significant threat to public health [1]. Radiofrequency ablation (RFA) and microwave ablation (MWA) are crucial local treatment modalities for early-stage HCC. Due to their high complete ablation rates and minimally invasive nature, these techniques are widely utilized in clinical practice [2, 3]. In patients with small tumors, thermal ablation therapy can yield favorable therapeutic outcomes [4]. However, for lesions larger than 5 cm in diameter, the recurrence rate significantly increases, adversely affecting long-term survival [5]. Studies indicate that postoperative residual areas, particularly those near major blood vessels, are susceptible to the formation of viable residual cells due to uneven thermal effects and blood flow cooling, which creates a conducive environment for tumor recurrence and metastasis [6-8].

https://doi.org/10.62347/HFLG3477

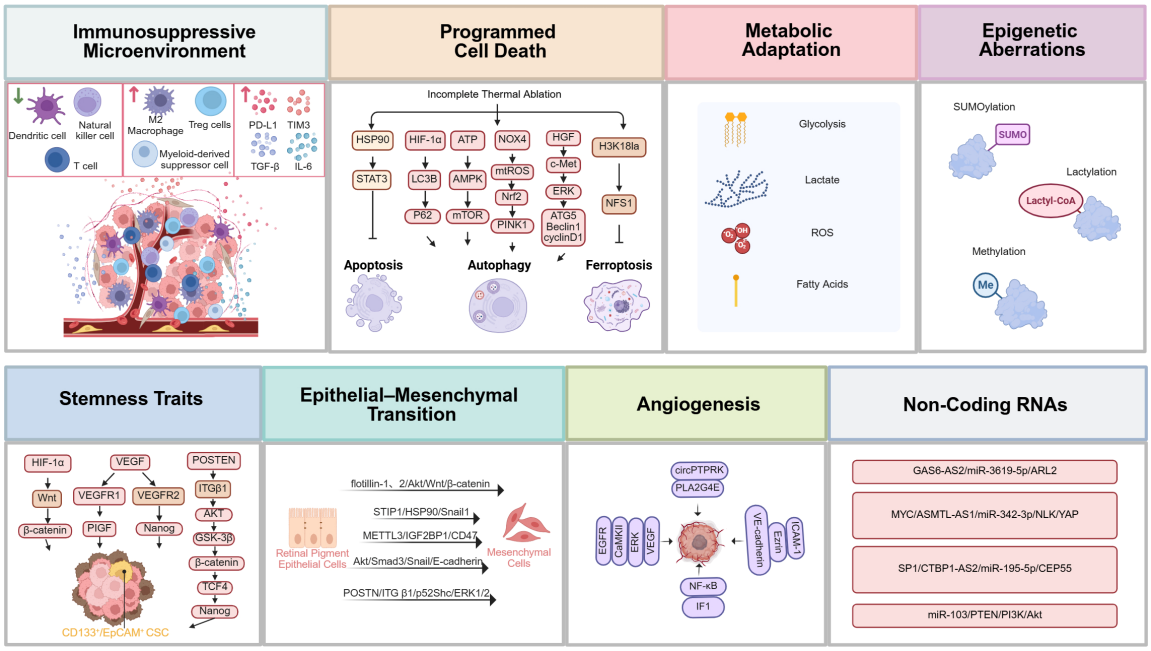

Figure 1. Multidimensional molecular mechanisms underlying HCC recurrence following thermal ablation. This image was created using the biorender.com website.

Over the past few years, the studies on the molecular mechanisms of HCC recurrence after ablation procedures have made progress. Research has revealed complex mechanisms, including immune escape, dysfunction of programmed cell death, metabolic and epigenetic reprogramming, maintenance of tumor stemness, and additional relevant mechanisms. Concurrently, precision intervention strategies have been increasingly explored, grounded in these molecular mechanisms. This review systematically summarizes research progress from 2017 to 2025, aiming to provide a theoretical foundation and guidance for understanding the mechanisms underlying HCC recurrence after thermal ablation and for developing innovative therapeutic strategies.

Multidimensional molecular mechanisms driving HCC recurrence following thermal ablation

Thermal ablation can effectively diminish the primary tumor burden. However, residual tumor cells in incompletely treated regions may survive. These cells can adapt to the post-ablation microenvironment and undergo malignant progression through diverse mechanisms. This process ultimately drives tumor recurrence and metastasis. Existing studies have identified several mechanisms involved in HCC recurrence after thermal ablation. These include remodeling of the immune microenvironment, evasion of cell death pathways, metabolic and epigenetic reprogramming, maintenance of cancer stem cells, epithelial-mesenchymal transition, and abnormal angiogenesis. This section systematically summarizes the key molecular mechanisms underlying HCC recurrence following thermal ablation. It thereby provides a theoretical foundation for developing precise intervention strategies (**Figure 1**).

Remodeling of immunosuppressive microenvironment

Residual HCC regions rapidly undergo significant changes in the immune microenvironment after thermal ablation, with the local microenvironment swiftly transitioning to an immunosuppressive state. This reprogramming is characterized by: (1) impaired function and reduced infiltration of effector immune cells, such as T cells, dendritic cells (DCs), and natural killer (NK) cells; (2) abnormal recruitment and activation of immunosuppressive cell, including myeloid-derived suppressor cells (MDSCs), M2-polarized tumor-associated macrophages (M2-TAMs), and regulatory T cells (Tregs); (3) upregulation of immune checkpoint molecules, such as PD-1 and Tim-3; and (4) increased

secretion of immunosuppressive cytokines, such as TGF-β and IL-6. Collectively, these alterations compromise anti-tumor immunity, promote immune evasion, and drive tumor recurrence [9-12].

Evasion of programmed cell death

Programmed cell death, including apoptosis, autophagy, and ferroptosis, is essential for regulating tissue homeostasis and removing aberrant cells. Although thermal ablation promotes anti-tumor effects by inducing tumor cell death, incomplete ablation may stimulate adaptive responses in residual tumor cells, allowing them to escape programmed cell death and consequently decrease the effectiveness of the treatment. It has been reported that incomplete radiofrequency ablation (iRFA) results in the upregulation of HSP90, the activation of STAT3 signaling pathways, which subsequently inhibits the induction of apoptosis [13, 14]. In addition, autophagy is triggered after iRFA, promoting cell survival through maintenance of mitochondrial structure and a reduction in oxidative stress. Important regulatory pathways are the HIF-1α/LC3B/P62, ATP/AMPK/mTOR and NOX4/mtROS/Nrf2/PINK1 axes [15-17]. Moreover, hepatocyte growth factor was found to accelerate the transition from autophagy to a proliferative phenotype via the c-Met/ERK pathway and its downstream targets, ATG5, Beclin1, and cyclin D1, which in turn expedite tumor relapse [18]. Regarding ferroptosis, incomplete microwave ablation (iMWA) was suggested to reduce the sensitivity of HCC cells to ferroptosis via the H3K18la/NFS1 pathway, thereby aiding the cells in evading ferroptosis [19]. In summary, tumor cells escape cell death after incomplete thermal ablation through various signaling pathways, suggesting that multitarget combination therapy could be an effective approach to enhance the efficiency of thermal ablation.

Reprogramming of metabolic adaptation

Residual HCC cells after incomplete thermal ablation exhibit marked metabolic reprogramming, mainly involving alterations in glucose metabolism, oxidative stress, and lipid metabolism. In glucose metabolism, iRFA-induced microcirculatory impairment results in tissue hypoxia [20], a key driver of glycolytic activation in tumor cells [21]. Residual HCC cells display enhanced glycolytic flux [22] and excessive lactate accumulation, which suppresses the proliferation and cytotoxicity of tumor-infiltrating cytotoxic T lymphocytes (CTLs) [23]. The resulting immunosuppressive microenvironment facilitates tumor immune escape [24, 25]. With respect to oxidative stress, intracellular reactive oxygen species (ROS) promote tumor growth and metastasis [26]. Following iRFA, residual HCC cells exhibit markedly elevated ROS levels, which enhance cellular invasiveness, induce M2 macrophage polarization, and ultimately drive metastatic dissemination [27]. Lipid metabolism is also profoundly affected. IMWA increased mitochondrial spare respiratory capacity and impaired glycolytic capacity. Moreover, the upregulation of the fatty acid transporter CD36 promotes excessive lipid uptake and overactive metabolism, thereby aggravating metabolic dysregulation and contributing to tumor progression through lipid-metabolism mediated distant effects [11].

Activation of epigenetic aberrations

After thermal ablation, residual HCC cells significantly promote tumor progression through epigenetic remodeling. SUMOylation, a key epigenetic modification, occurs through the covalent attachment of SUMO2/3 to lysine residues on target proteins. SUMOylated SETDB1 binds to the IFN-I promoter and suppresses its transcription, establishing an immunosuppressive tumor microenvironment [28, 29]. In residual HCC following iRFA, SUMO2 expression and overall SUMOylation levels are elevated, accompanied by suppressed IFN-I transcription. These findings suggest SUMOylation-mediated regulation, as previously reported, although the specific SUMOylation sites in residual HCC following iRFA have yet to be identified [30]. At the same time, iMWA upregulates lactate levels, induces lactylation modification of the histone H3K18 site, and promotes the transcriptional expression of NFS1, thereby reducing the sensitivity of HCC cells to ferroptosis and enhancing their resistance to platinum-based chemotherapy [19]. In addition, METTL3-mediated m^6A methylation modification can enhance the mRNA stability of the immune checkpoint molecule CD47 by binding to IGF2BP1, further promoting tumor immune escape [31].

Acquisition of stemness traits

In recurrent HCC, $CD133^+$ and $EpCAM^+$ cancer stem cells (CSCs) are significantly enriched, indicating that CSCs play a crucial role in tumor recurrence following thermal ablation [32]. Studies have shown that iRFA-induced hypoxia can enhance the stemness of CSCs through the HIF-1α/Wnt/β-catenin pathway [33]. Vascular endothelial growth factor (VEGF) promotes the expression of CSCs markers and maintains cell self-renewal through the VEGFR1/PIGF and VEGFR2/Nanog signaling pathways, respectively [34, 35]. In addition, activated hepatic stellate cells can activate the ITGβ1/AKT/GSK-3β/β-catenin/TCF4/Nanog pathway through POSTN, further inducing the stemness phenotype [36]. In summary, incomplete thermal ablation promotes the enrichment and functional maintenance of CSCs and increases the risk of tumor recurrence by activating endogenous stemness signals and remodeling the microenvironment, providing a potential intervention strategy for combined therapy targeting CSCs.

Enhancement of epithelial-mesenchymal transition (EMT)

EMT plays a crucial role in HCC recurrence after incomplete thermal ablation, enabling tumor cells to exhibit stronger migration and invasion. Studies have shown that iRFA can activate the Akt/Wnt/β-catenin pathway by upregulating flotillin-1/2 [37], promote Snail1 nuclear translocation through the STIP1-HSP90 complex [38], and induce EMT through multiple mechanisms such as the METTL3/IGF2BP1/CD47 axis [31]. Additionally, platelet lysate can downregulate E-cadherin expression through the Akt/Smad3/Snail pathway, thereby accelerating the EMT process [39], while POSTN signaling further enhances the EMT phenotype by activating the ITGβ1/p52Shc/ERK1/2 pathway [40]. In summary, EMT is regulated by multiple signaling pathways and plays an important role in tumor recurrence and treatment resistance.

Induction of angiogenesis

Angiogenesis plays a key role in the recurrence and metastasis of HCC after thermal ablation. Heat stimulation induces upregulation of exosomal circPTPRK and activates PLA2G4E, thereby promoting the formation of new blood vessels [41]. At the same time, iRFA can enhance the expression of ICAM-1 in tumor-associated endothelial cells, activate the ICAM-1/Ezrin/VE-cadherin axis, destroy the endothelial barrier and increase permeability, and promote the metastasis of tumor cells [42]. Metabolic-related factors are also involved in the regulation of angiogenesis: IF1 upregulation promotes angiogenesis through the NF-κB pathway [43], while the EGFR/Ca^{2+}/CaMKII/ERK/VEGF pathway can drive angiogenesis [44]. In summary, the proangiogenic environment that forms after thermal ablation is an important driving factor for tumor progression.

Regulation by non-coding RNAs

Non-coding RNAs play a key regulatory role in HCC recurrence after ablation. After iRFA, GAS6-AS2 acts as a competing endogenous RNA by sponging miR-3619-5p, thereby relieving miR-3619-5p-mediated suppression of ARL2 [45]. Similarly, exosomal ASMTL-AS1 is activated by MYC and exacerbates the malignant progression of residual HCC after iRFA through the miR-342-3p/NLK/YAP signaling pathway [46]. CTBP1-AS2 is induced by SP1 and enhances the invasion and drug resistance of HCC after iMVA through the miR-195-5p/CEP55 axis [47]. In addition, miR-103 targets PTEN and activates the PI3K/Akt pathway, promoting the proliferation and migration of RFA-mimicking transition zone liver cancer cells [48]. These studies highlight the significance of RNA regulatory networks in HCC recurrence and provide potential targets for RNA interference therapy.

Precision therapeutic strategies for HCC recurrence following ablation

As our understanding of the mechanisms driving HCC recurrence after thermal ablation deepens, a range of precision intervention strategies have emerged. Researchers have proposed multi-faceted therapeutic approaches aimed at immune evasion, activation of cell survival pathways, metabolic reprogramming, and epigenetic alterations. These strategies encompass immunotherapy, promotion of cell death, metabolic reprogramming, stem cell-targeted therapies, and combinatorial interventions. This section will provide a comprehensive review of the current advancements in precision intervention research based on the mech-

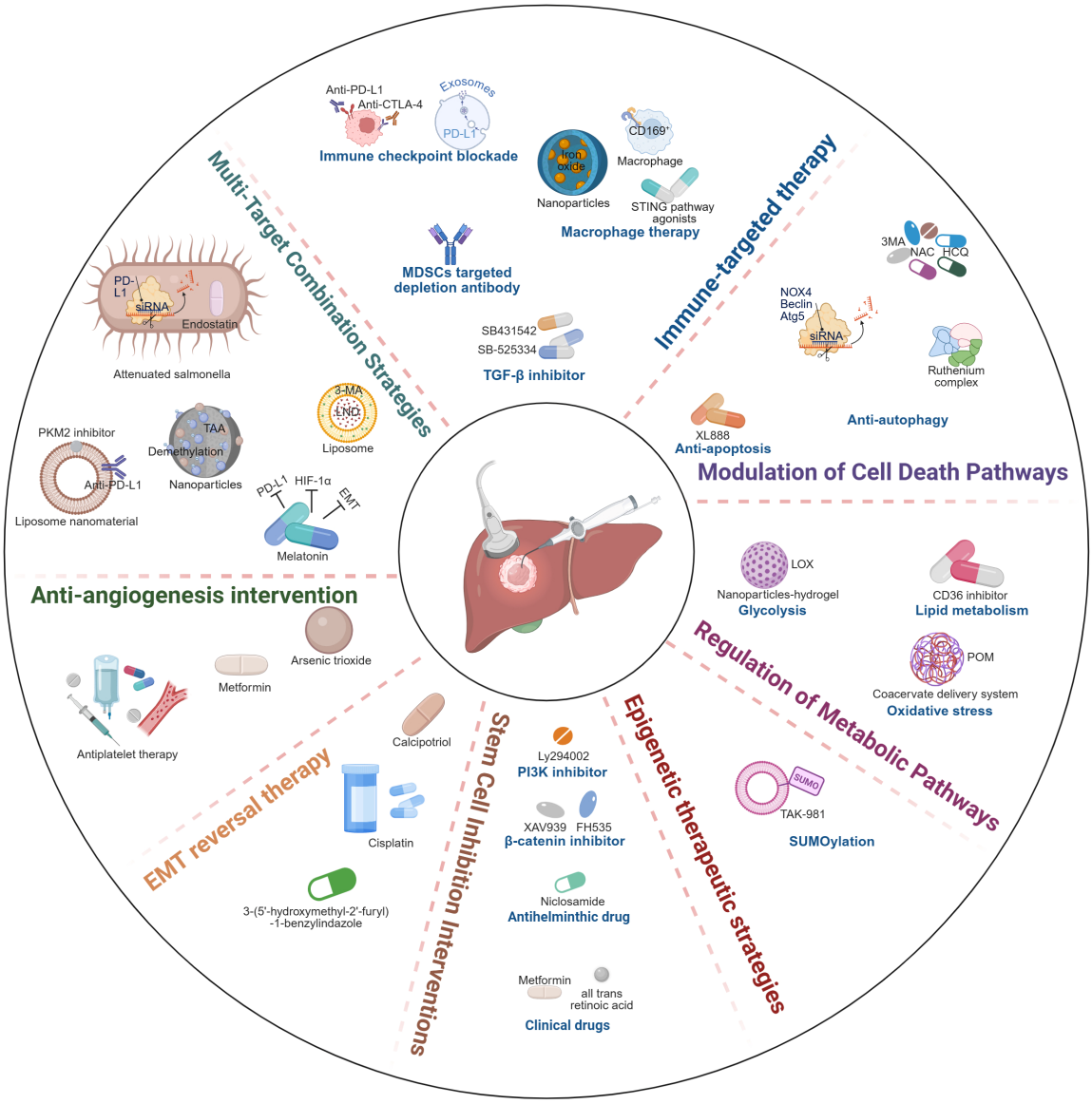

Figure 2. Precision therapeutic strategies targeting post-ablation recurrence of HCC.

anisms of HCC recurrence following thermal ablation (**Figure 2**).

Immune-targeted therapy

Considering the immunosuppressive microenvironment induced by thermal ablation, multidimensional immunotherapy approaches have been proposed. It has been reported that the combination of RFA with anti-PD-L1 or CTLA-4 therapy can potentiate the function of $CD8^+$ and $CD4^+$ T cells and modulate the immune microenvironment [49, 50]. Meanwhile, MWA combined with dual PD-1/CTLA-4 blockade also significantly elevates the levels of Th1-type immune responses and enhances overall survival in animal models [51]. Additionally, leveraging the multifunctional properties of polydopamine-based nanoregulators, researchers have constructed a precise delivery platform for the targeted administration of GW4869 and amlodipine, which inhibits exosome generation and secretion, and triggers autophagic degradation of PD-L1, offering a novel approach to immune activation [49]. Increasing attention has been paid to the TGF-β signaling pathway. Inhibitors such as SB431542 and SB-525334 have been shown to alleviate immunosuppres-

sion and synergize with anti-PD-1 therapy or MWA to exert an antitumor effect [52, 53]. With respect to activation of effector cells, $CD169^+$ macrophage transplantation or D-mannose-ferrosoferric oxide nanoparticles trigger M1 polarization, leading to enhanced systemic effects and antitumor immunity [54, 55].

Furthermore, STING pathway agonists promote M1 polarization, antigen presentation, and T cell activation. Researchers have utilized Ca^{2+}-responsive sodium alginate as a carrier to form an injectable hydrogel, which achieves in situ gelation triggered by Ca^{2+}, provides sustained drug release, and significantly improves the local delivery efficiency and therapeutic effects of STING agonists [56]. Targeted depletion of MDSCs using antibodies can also alleviate immune suppression after RFA, thereby increasing the levels of Th1 cytokines and $CD8^+$ T cells [12]. In conclusion, multi-targeted immune intervention protocols could significantly enhance the systemic immune response to thermal ablation for the prevention of HCC recurrence.

Modulation of cell death pathways

Heat stress induced by incomplete thermal ablation weakens the therapeutic effect and promotes recurrence by activating multiple survival mechanisms in HCC cells, including the inhibition of apoptosis, enhancement of autophagy, and escasion of ferroptosis. Therefore, targeting these escape pathways is expected to significantly improve therapeutic efficacy. In terms of apoptosis regulation, the HSP90 inhibitor XL888 blocks the binding of HSP90 to STAT3, inhibits the STAT3-Mcl-1 pathway, and promotes the apoptosis of HCC cells after thermal ablation [13]. The main strategies for inhibiting autophagy include (1) drug inhibition of autophagy, such as 3-methyladenine (3-MA), hydroxychloroquine, and N-acetylcysteine, combined with c-Met inhibitors to inhibit tumor survival [14, 17, 18, 57]. (2) genetic intervention, such as NOX4 inhibitors or siNOX4 and silencing Beclin-1/Atg5 [16, 17], and (3) signaling pathway regulation, intervening in the HIF-1α/LC3B/P62 pathway through Ruthenium Complex, reversing autophagy dependence and improving the immune environment [15]. In conclusion, interventions targeting these key pathways are expected to become an important strategy for improving the efficacy of thermal ablation therapy and reducing tumor recurrence.

Regulation of metabolic pathways

Metabolic reprogramming after thermal ablation provides an adaptive survival advantage to the residual HCC cells, characterized by enhanced glycolysis, increased oxidative stress, and reprogrammed lipid metabolism associated with tumor progression. To overcome these metabolic changes, various targeted approaches have been developed to reverse metabolic adaptations and enhance therapeutic efficacy. In glycolysis, lactate accumulation fosters an immunosuppressive environment. An injectable nanoparticle-hydrogel conjugate capable of sustained lactate oxidase release has demonstrated efficacy in reducing lactate levels and restoring immune activity [23]. Strategies for regulating oxidative stress include (1) the radiofrequency dynamic therapy to increase ROS levels, facilitate M1 macrophages polarization, reduce immunosuppressive cell populations and enhance T-cell responses [58]; (2) an injectable delivery system based on a coacervate, loaded with polyoxometalates that release ROS scavengers to prevent M2 macrophages polarization and alleviate immune suppression [27]. In enhanced lipid metabolism, the overexpression of CD36 in distant tumors after iMWA is closely associated with immune evasion. Pharmacologic inhibition of CD36 restores T-cell-mediated antitumor immunity in non-ablated lesions, which abrogates the immune-suppressive impact of iMWA [11]. In summary, multitargeted metabolic interventions not only disrupt tumor metabolic plasticity but also synergistically reprogram the immune microenvironment, offering promising therapeutic avenues for integrating thermal ablation with immunotherapy.

Epigenetic therapeutic strategies

Residual HCC following incomplete thermal ablation undergoes epigenetic reprogramming that drives disease progression. As previously described, SUMOylation in residual HCC post-iRFA modulates IFN-I transcription, thereby reinforcing immune suppression and tumor progression. Focusing on the role of SUMOylation in chromatin regulation, researchers employed the SUMO inhibitor TAK-981 to block

SUMOylation. This intervention markedly increased IFN-I transcription and restored the immune microenvironment. Consequently, TAK-981 effectively restrained tumor progression, highlighting its promising potential for clinical translation [30].

Stem cell inhibition interventions

Incomplete thermal ablation can promote the enrichment and maintenance of CSCs, becoming an important cause of HCC recurrence. A variety of drugs have been shown to effectively inhibit the stemness and self-renewal of CSCs, including a β-catenin inhibitor (FH535 or XAV939), a PI3 kinase inhibitor (Ly294002), or niclosamide, an antihelminthic drug [59]. In addition, metformin can intervene in the maintenance process of CSCs by inhibiting the secretion of POSTN by hepatic stellate cells and downregulating CSCs markers, providing a new therapeutic strategy for anti-recurrence after thermal ablation [36]. All-trans retinoic acid effectively eliminates residual tumor stem cells by inhibiting the PI3K/AKT pathway and significantly inhibits tumor growth after iRFA [32]. In summary, multi-target intervention on CSCs provides a significant theoretical basis and promising prospects for enhancing the long-term efficacy of thermal ablation therapy.

EMT reversal therapy

EMT plays a key role in HCC recurrence and progression after thermal ablation. Studies have shown that YC-1 can regulate the expression of E-cadherin, N-cadherin, and vimentin, and further inhibit EMT by activating the β-catenin signaling pathway, thereby effectively preventing the progression and metastasis of HCC [60]. In addition, Calcipotriol plus cisplatin treatment blocked the progression of residual HCC cells by downregulating POSTN expression and attenuating EMT [40].

Anti-angiogenesis intervention

Tumor angiogenesis following thermal ablation is an important factor influencing treatment efficacy and promoting tumor recurrence. Studies have shown that antiplatelet therapy and ICAM-1-targeted therapy can improve vascular permeability and effectively block the progression of HCC after iRFA [42]. In addition, metformin promotes the normalization of abnormal blood vessels in HCC after iRFA by regulating the miR-302b-3p/TXNIP axis [61]. Arsenic trioxide can significantly inhibit angiogenesis by inhibiting the p-Akt/HIF-1α/Ang-1/Ang-2/Tie2 pathway [62]. The above studies offer diversified intervention strategies for tumor vascular remodeling following thermal ablation, paving the way for new directions in enhancing treatment effects and preventing recurrence.

Multi-target combination strategies

In recent years, the treatment strategy for HCC after thermal ablation has been gradually expanding from single-target intervention to multi-target combined therapy. Researchers have developed a combined strategy targeting immunosuppression and abnormal angiogenesis. RFA combined with attenuated Salmonella-delivered siRNA-PD-L1-endostatin treatment can synergistically enhance immune cell infiltration and anti-angiogenic ability [63]. Liposomal nanoparticles co-loaded with a modified PKM2 inhibitor and an immune checkpoint inhibitor, such as anti-PD-L1, can effectively modulate the immunosuppressive microenvironment by interfering with glycolysis and the immune checkpoint pathway [64]. Moreover, drugs such as melatonin and sunitinib have demonstrated promising anti-relapse potential in multi-mechanism combined interventions by acting simultaneously on immune regulation, hypoxia adaptation, and EMT pathways [65, 66].

Combined treatment strategies related to epigenetics, metabolism, autophagy and ferroptosis are also constantly expanding the boundaries of comprehensive intervention after thermal ablation. For example, nanomedicines containing antigen capture systems and m6A demethylase inhibitors can enhance the antigen-presenting ability of DCs [67]. Liposomes co-loaded with 3-MA and lonidamine LND improve the sensitivity of RFA treatment by jointly blocking glycolysis and autophagy [14]. NFS1 deficiency combined with oxaliplatin treatment established a link between ferroptosis and chemotherapy, effectively overcoming heat-resistant metastasis [19]. Additionally, a nano-epigenetic therapeutic platform that integrates MAT2A inhibitors, manganese dioxide nanoparticles and anti-PD-L1 antibodies synergistically activates immune responses by mediating DNA

and RNA demethylation modifications and restoring the activity of the STING pathway, significantly inhibiting recurrence and metastasis [68].

In summary, synergistic multi-target combination therapy had shown significant advantages and has provided a new direction and opportunities for the comprehensive treatment of HCC after thermal ablation.

Conclusion and perspectives

With the continuous advances in elucidating the mechanisms of HCC recurrence following thermal ablation, substantial progress has been made in basic research. At the mechanistic level, systematic findings have been achieved, including immune microenvironment reprogramming, resistance to programmed cell death through autophagy, EMT, angiogenesis, and non-coding RNA regulation. However, studies on new types of cell death, such as ferroptosis and disulfidoptosis, are still limited, and many of their mechanisms remain unclear. Research on epigenetic changes and metabolic reprogramming is also in its early stages and needs deeper investigation.

In the context of HCC recurrence after ablation, immunotherapy strategies have been widely explored, including the activation of effector immune cells, the depletion of immunosuppressive cells, and the inhibition of immune checkpoints. A systemic intervention framework has been initially established. In contrast, therapeutic approaches targeting emerging forms of programmed cell death, such as ferroptosis and disulfidptosis, are still in the developmental stage and lack effective implementation. Although epigenetic regulation strategies have shown therapeutic promise, other intervention modalities require further development and rigorous validation.

Small molecule inhibitors, such as SI-1, NIO-1, and AZD5582, have significantly altered the treatment landscape of HCC, serving as effective tools for translating mechanistic insights into therapy and showing great promise in the treatment of post-ablation HCC. Recently, several clinical drugs, including melatonin, metformin, all-trans retinoic acid, and arsenic trioxide, have been reported to have promising therapeutic effects in preventing HCC recurrence after thermal ablation, thus providing a valuable supplement to the repurposing strategy of existing drugs. The combination of nanoparticle carriers, hydrogel sustained-release systems, and attenuated Salmonella delivery systems has the potential to enable localized, efficient, and multimodal therapeutic delivery, which was not previously unavailable and could expand the depth and specificity of therapeutic approaches.

Several key research directions are emerging regarding the mechanisms and management of HCC recurrence after thermal ablation: (1) Advancing mechanistic insights and uncovering heterogeneity: Enhance the depth of mechanistic investigations by integrating multi-omics approaches to elucidate the biological heterogeneity of residual HCC following thermal ablation. (2) Discovery of novel targets and repositioning of existing drugs: The goal is to speed up the development of new inhibitors and explore new uses for existing drugs. This is based on key molecules discovered through mechanistic research. It is also important to systematically evaluate the therapeutic potential of these drugs against newly identified targets. These efforts aim to help translate basic research findings into clinical practice. (3) Combination intervention strategies: Develop integrated multi-target therapies that combine immune modulation, metabolic reprogramming, epigenetic regulation, and cell death pathways to overcome the limitations of monotherapies and promote precision interventions of synergistic mechanisms. (4) Optimization of drug delivery system safety and functionality: Investigate the biocompatibility, tissue targeting, and intelligent release of newly developed delivery platforms, including nanomaterials and hydrogels, and improvement of their effectiveness in cellular and animal models for the basis of the clinical application. (5) Integrated diagnosis and treatment development: Develop therapeutic delivery systems that are also endowed with real-time imaging capability, for example, nanoparticles containing drugs and ultrasound contrast agents. This strategy enables accurate intervention in tumor relapse and early diagnosis of postoperative relapse through imaging methods, allowing for dynamic regulation of treatment plans and significantly improving the accuracy and timeliness of personalized treatment.

Building on deeper mechanistic insights and technological innovations, effective control of HCC recurrence after thermal ablation is on the horizon. These advances will prolong patient survival and elevate the precision of minimally invasive therapy to a new level.

Acknowledgements

BioRender was used to create Graphics. This work was funded by the National Natural Science Foundation of China (No. 82460352), the Joint Project on Regional High-Incidence Diseases Research of Guangxi Natural Science Foundation (No. 2024GXNSFBA999019), the National Natural Science Foundation of China (No. 82160350, 81960329), and Innovation Project of Guangxi Graduate Education (No. YCSW2024259).

Disclosure of conflict of interest

None.

Address correspondence to: Xiumei Bai and Hong Yang, Department of Medical Ultrasound, The First Affiliated Hospital of Guangxi Medical University, No. 6 Shuangyong Road, Nanning 530021, Guangxi Zhuang Autonomous Region, China. E-mail: bxm1223@pku.org.cn (XMB); yanghong@gxmu.edu.cn (HY)

References

[1] Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I and Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2024; 74: 229-263.

[2] Seror O, N'Kontchou G, Ibraheem M, Ajavon Y, Barrucand C, Ganne N, Coderc E, Trinchet JC, Beaugrand M and Sellier N. Large (>or=5.0-cm) HCCs: multipolar RF ablation with three internally cooled bipolar electrodes--initial experience in 26 patients. Radiology 2008; 248: 288-296.

[3] Liao R, Song P, Duan Y, Ye W, Yin K, Kang M, Yu Y, Yang J and Tang W. A well-matched marriage of immunotherapy and radiofrequency ablation to reduce the relapse and progression of hepatocellular carcinoma. Biosci Trends 2022; 16: 377-380.

[4] Livraghi T, Meloni F, Di Stasi M, Rolle E, Solbiati L, Tinelli C and Rossi S. Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: is resection still the treatment of choice? Hepatology 2008; 47: 82-89.

[5] Leung U, Kuk D, D'Angelica MI, Kingham TP, Allen PJ, DeMatteo RP, Jarnagin WR and Fong Y. Long-term outcomes following microwave ablation for liver malignancies. Br J Surg 2015; 102: 85-91.

[6] Ahmed M, Brace CL, Lee FT Jr and Goldberg SN. Principles of and advances in percutaneous ablation. Radiology 2011; 258: 351-369.

[7] Poch FG, Rieder C, Ballhausen H, Knappe V, Ritz JP, Gemeinhardt O, Kreis ME and Lehmann KS. The vascular cooling effect in hepatic multipolar radiofrequency ablation leads to incomplete ablation ex vivo. Int J Hyperthermia 2016; 32: 749-756.

[8] Jiang C, Liu B, Chen S, Peng Z, Xie X and Kuang M. Safety margin after radiofrequency ablation of hepatocellular carcinoma: precise assessment with a three-dimensional reconstruction technique using CT imaging. Int J Hyperthermia 2018; 34: 1135-1141.

[9] Shi ZR, Duan YX, Cui F, Wu ZJ, Li MP, Song PP, Peng QL, Ye WT, Yin KL, Kang MQ, Yu YX, Yang J, Tang W and Liao R. Integrated proteogenomic characterization reveals an imbalanced hepatocellular carcinoma microenvironment after incomplete radiofrequency ablation. J Exp Clin Cancer Res 2023; 42: 133.

[10] Zang C, Zhao Y, Liu G, Li K, Qin L, Zhang Y, Sun J, Wang Q, Ma L, Zhao P, Sun Y, Guo D, Yuan C, Dong T and Zhang Y. Variations in dynamic tumor-associated antigen-specific T cell responses correlate with HCC recurrence after thermal ablation. Front Immunol 2022; 13: 982578.

[11] Liu QQ, Li HZ, Li SX, Bao Y, Wang TC, Hu C and Xiao YD. CD36-mediated accumulation of MDSCs exerts abscopal immunosuppressive responses in hepatocellular carcinoma after insufficient microwave ablation. Biochim Biophys Acta Mol Basis Dis 2024; 1870: 167493.

[12] Wu H, Li SS, Zhou M, Jiang AN, He Y, Wang S, Yang W and Liu H. Palliative radiofrequency ablation accelerates the residual tumor progression through increasing tumor-infiltrating MDSCs and reducing T-cell-mediated anti-tumor immune responses in animal model. Front Oncol 2020; 10: 1308.

[13] Sun C, Bai M, Ke W, Wang X, Zhao X and Lu Z. The HSP90 inhibitor, XL888, enhanced cell apoptosis via downregulating STAT3 after insufficient radiofrequency ablation in hepatocellular carcinoma. Life Sci 2021; 282: 119762.

[14] Zhao J, Lei L, Dai W, Jiang A, Jin Q and Tang Z. Simultaneous inhibition of heat shock proteins and autophagy enhances radiofrequency abla-

tion of hepatocellular carcinoma. Biomater Sci 2024; 12: 6082-6098.
[15] Yu ZJ, Guo SW, Wang BS, Ouyang S, Zhang XH, Zhao ZZ and Wang JQ. Ruthenium complex suppresses proliferation of residual hepatocellular carcinoma after incomplete radiofrequency ablation therapy. Recent Pat Anticancer Drug Discov 2024; [Epub ahead of print].
[16] Jiang J, Chen S, Li K, Zhang C, Tan Y, Deng Q, Chai Y, Wang X, Chen G, Feng K, Zhang L, Xie CM and Ma K. Targeting autophagy enhances heat stress-induced apoptosis via the ATP-AMPK-mTOR axis for hepatocellular carcinoma. Int J Hyperthermia 2019; 36: 499-510.
[17] Peng C, Li X, Ao F, Li T, Guo J, Liu J, Zhang X, Gu J, Mao J and Zhou B. Mitochondrial ROS driven by NOX4 upregulation promotes hepatocellular carcinoma cell survival after incomplete radiofrequency ablation by inducing of mitophagy via Nrf2/PINK1. J Transl Med 2023; 21: 218.
[18] Zhang R, Lin XH, Liu HH, Ma M, Chen J, Chen J, Gao DM, Cui JF and Chen RX. Activated hepatic stellate cells promote progression of post-heat residual hepatocellular carcinoma from autophagic survival to proliferation. Int J Hyperthermia 2019; 36: 253-263.
[19] Huang J, Xie H, Li J, Huang X, Cai Y, Yang R, Yang D, Bao W, Zhou Y, Li T and Lu Q. Histone lactylation drives liver cancer metastasis by facilitating NSF1-mediated ferroptosis resistance after microwave ablation. Redox Biol 2025; 81: 103553.
[20] Lee DH, Lee JM, Yoon JH, Kim YJ and Han JK. Thermal injury-induced hepatic parenchymal hypoperfusion: risk of hepatocellular carcinoma recurrence after radiofrequency ablation. Radiology 2017; 282: 880-891.
[21] Luo Z, Tian M, Yang G, Tan Q, Chen Y, Li G, Zhang Q, Li Y, Wan P and Wu J. Hypoxia signaling in human health and diseases: implications and prospects for therapeutics. Signal Transduct Target Ther 2022; 7: 218.
[22] Chen Y, Bei J, Liu M, Huang J, Xie L, Huang W, Cai M, Guo Y, Lin L and Zhu K. Sublethal heat stress-induced O-GlcNAcylation coordinates the Warburg effect to promote hepatocellular carcinoma recurrence and metastasis after thermal ablation. Cancer Lett 2021; 518: 23-34.
[23] Chen Y, Bei J, Chen M, Cai W, Zhou Z, Cai M, Huang W, Lin L, Guo Y, Liu M, Huang X, Xiao Z, Xu Z and Zhu K. Intratumoral lactate depletion based on injectable nanoparticles-hydrogel composite system synergizes with immunotherapy against postablative hepatocellular carcinoma recurrence. Adv Healthc Mater 2024; 13: e2303031.
[24] Shi L, Wang J, Ding N, Zhang Y, Zhu Y, Dong S, Wang X, Peng C, Zhou C, Zhou L, Li X, Shi H, Wu W, Long X, Wu C and Liao W. Inflammation induced by incomplete radiofrequency ablation accelerates tumor progression and hinders PD-1 immunotherapy. Nat Commun 2019; 10: 5421.
[25] Zeng X, Liao G, Li S, Liu H, Zhao X, Li S, Lei K, Zhu S, Chen Z, Zhao Y, Ren X, Su T, Cheng AS, Peng S, Lin S, Wang J, Chen S and Kuang M. Eliminating METTL1-mediated accumulation of PMN-MDSCs prevents hepatocellular carcinoma recurrence after radiofrequency ablation. Hepatology 2023; 77: 1122-1138.
[26] Costa A, Scholer-Dahirel A and Mechta-Grigoriou F. The role of reactive oxygen species and metabolism on cancer cells and their microenvironment. Semin Cancer Biol 2014; 25: 23-32.
[27] Yang M, Liu D, Tan Y, Chen J, Yang F, Mei C, Zeng Q, Lin Y and Li D. Polyoxometalate-based injectable coacervate inhibits HCC metastasis after incomplete radiofrequency ablation via scavenging ROS. J Nanobiotechnology 2025; 23: 47.
[28] Du L, Liu W, Rosen ST and Chen Y. Mechanism of SUMOylation-mediated regulation of type I IFN expression. J Mol Biol 2023; 435: 167968.
[29] Decque A, Joffre O, Magalhaes JG, Cossec JC, Blecher-Gonen R, Lapaquette P, Silvin A, Manel N, Joubert PE, Seeler JS, Albert ML, Amit I, Amigorena S and Dejean A. Sumoylation coordinates the repression of inflammatory and anti-viral gene-expression programs during innate sensing. Nat Immunol 2016; 17: 140-149.
[30] Liu J, Li X, Chen J, Guo J, Guo H, Zhang X, Fan J, Zhang K, Mao J and Zhou B. Targeting SUMOylation with an injectable nanocomposite hydrogel to optimize radiofrequency ablation therapy for hepatocellular carcinoma. J Nanobiotechnology 2024; 22: 338.
[31] Fan Z, Gao Y, Zhang W, Yang G, Liu P, Xu L, Wang J, Yan Z, Han H, Liu R and Shu M. METTL3/IGF2BP1/CD47 contributes to the sublethal heat treatment induced mesenchymal transition in HCC. Biochem Biophys Res Commun 2021; 546: 169-177.
[32] Wang S, Liu J, Wu H, Jiang A, Zhao K, Yan K, Wu W, Han H, Zhang Y and Yang W. All-trans retinoic acid (ATRA) inhibits insufficient radiofrequency ablation (IRFA)-induced enrichment of tumor-initiating cells in hepatocellular carcinoma. Chin J Cancer Res 2021; 33: 694-707.
[33] Zhang N, Chen R, Cao X and Wang L. Aberrantly expressed HIF-1α enhances HCC stem cell-like traits via Wnt/β-catenin signaling activation after insufficient radiofrequency ablation. J Cancer Res Ther 2023; 19: 1517-1524.
[34] Tan L, Chen S, Wei G, Li Y, Liao J, Jin H, Zou Y, Huang M, Peng Z, Guo Y, Peng S, Xu L and Kuang M. Sublethal heat treatment of hepato-

cellular carcinoma promotes intrahepatic metastasis and stemness in a VEGFR1-dependent manner. Cancer Lett 2019; 460: 29-40.
[35] Liu K, Hao M, Ouyang Y, Zheng J and Chen D. CD133(+) cancer stem cells promoted by VEGF accelerate the recurrence of hepatocellular carcinoma. Sci Rep 2017; 7: 41499.
[36] Zhang R, Yao RR, Li JH, Dong G, Ma M, Zheng QD, Gao DM, Cui JF, Ren ZG and Chen RX. Activated hepatic stellate cells secrete periostin to induce stem cell-like phenotype of residual hepatocellular carcinoma cells after heat treatment. Sci Rep 2017; 7: 2164.
[37] Jain S, Rustagi A, Kumar D, Yusuf MA, Shekhar S and Sarin NB. Meeting the challenge of developing food crops with improved nutritional quality and food safety: leveraging proteomics and related omics techniques. Biotechnol Lett 2019; 41: 471-481.
[38] Su T, Liao J, Dai Z, Xu L, Chen S, Wang Y, Peng Z, Zhang Q, Peng S and Kuang M. Stress-induced phosphoprotein 1 mediates hepatocellular carcinoma metastasis after insufficient radiofrequency ablation. Oncogene 2018; 37: 3514-3527.
[39] Jia G, Kong J, Yao C, Wu S and Sun W. Platelet lysates in Hepatocellular Carcinoma patients after radiofrequency ablation facilitate tumor proliferation, invasion and vasculogenic mimicry. Int J Med Sci 2020; 17: 2104-2112.
[40] Zhang R, Lin XH, Ma M, Chen J, Chen J, Gao DM, Cui JF and Chen RX. Periostin involved in the activated hepatic stellate cells-induced progression of residual hepatocellular carcinoma after sublethal heat treatment: its role and potential for therapeutic inhibition. J Transl Med 2018; 16: 302.
[41] Zhu Y, He Q and Qi M. Exosomal circPTPRK promotes angiogenesis after radiofrequency ablation in hepatocellular carcinoma. Exp Biol Med (Maywood) 2024; 249: 10084.
[42] Kong J, Yao C, Dong S, Wu S, Xu Y, Li K, Ji L, Shen Q, Zhang Q, Zhan R, Cui H, Zhou C, Niu H, Li G, Sun W and Zheng L. ICAM-1 activates platelets and promotes endothelial permeability through VE-cadherin after insufficient radiofrequency ablation. Adv Sci (Weinh) 2021; 8: 2002228.
[43] Kong J, Yao C, Ding X, Dong S, Wu S, Sun W and Zheng L. ATPase inhibitory factor 1 promotes hepatocellular carcinoma progression after insufficient radiofrequency ablation, and attenuates cell sensitivity to sorafenib therapy. Front Oncol 2020; 10: 1080.
[44] Dai H, Jia G, Wang H, Yang J, Jiang H and Chu M. Epidermal growth factor receptor transactivation is involved in the induction of human hepatoma SMMC7721 cell proliferation by insufficient radiofrequency ablation. Oncol Lett 2017; 14: 2463-2467.
[45] Li Z, Jiang M, Zhang T and Liu S. GAS6-AS2 promotes hepatocellular carcinoma via miR-3619-5p/ARL2 axis under insufficient radiofrequency ablation condition. Cancer Biother Radiopharm 2021; 36: 879-887.
[46] Ma D, Gao X, Liu Z, Lu X, Ju H and Zhang N. Exosome-transferred long non-coding RNA ASMTL-AS1 contributes to malignant phenotypes in residual hepatocellular carcinoma after insufficient radiofrequency ablation. Cell Prolif 2020; 53: e12795.
[47] Liu LX, Liu B, Yu J, Zhang DY, Shi JH and Liang P. SP1-induced upregulation of lncRNA CTBP1-AS2 accelerates the hepatocellular carcinoma tumorigenesis through targeting CEP55 via sponging miR-195-5p. Biochem Biophys Res Commun 2020; 533: 779-785.
[48] Tan Y and Zhao L. miR-103 promotes hepatocellular carcinoma cell proliferation and migration in the simulation transition zone of RFA through PI3K/Akt signaling pathway by targeting PTEN. Int J Clin Exp Pathol 2020; 13: 473-479.
[49] Liang J, Ma M, Feng W, Xu Q, Chen D, Lai J and Chen J. Anti-PD-L1 blockade facilitates antitumor effects of radiofrequency ablation by improving tumor immune microenvironment in hepatocellular carcinoma. Apoptosis 2025; 30: 55-68.
[50] Zhang L, Wang J, Jiang J, Zhang M and Shen J. CTLA-4 Blockade suppresses progression of residual tumors and improves survival after insufficient radiofrequency ablation in a subcutaneous murine hepatoma model. Cardiovasc Intervent Radiol 2020; 43: 1353-1361.
[51] Duan X, Wang M, Han X, Ren J, Huang G, Ju S and Zhang Q. Combined use of microwave ablation and cell immunotherapy induces nonspecific immunity of hepatocellular carcinoma model mice. Cell Cycle 2020; 19: 3595-3607.
[52] Ju S, Duan X, Wang Y, Zhang M, Bai Y, He X, Wang C, Liu J, Yao W, Zhou C, Xiong B and Zheng C. Blocking TGFβR synergistically enhances anti-tumor effects of anti-PD-1 antibody in a mouse model of incomplete thermal ablation. Int Immunopharmacol 2024; 138: 112585.
[53] Xiang S, Li J and Zhang M. TGF-β1 inhibitor enhances the therapeutic effect of microwave ablation on hepatocellular carcinoma. Int J Hyperthermia 2024; 41: 2359496.
[54] Song X, Li N, Liu Y, Wang Z, Wang T, Tan S, Li C, Qiu C, Gao L, Asano K, Tanaka M, Liang X, Liu X and Ma C. CD169-positive macrophages enhance abscopal effect of radiofrequency ablation therapy in liver cancer. Transl Oncol 2022; 15: 101306.

[55] Cui R, Wang L, Zhang D, Zhang K, Dou J, Dong L, Zhang Y, Wu J, Tan L, Yu J and Liang P. Combination therapy using microwave ablation and d-mannose-chelated iron oxide nanoparticles inhibits hepatocellular carcinoma progression. Acta Pharm Sin B 2022; 12: 3475-3485.
[56] Ge Y, Ge Z, Tian F, Tai X, Chen D, Sun S, Shi Z, Yin J, Wei G, Li D, Wang L, Xu W, Tong M, Liu F, Zhao L, Qian X and Ge X. Sulforaphane potentiates the efficacy of chemoradiotherapy in glioblastoma by selectively targeting thioredoxin reductase 1. Cancer Lett 2024; 611: 217429.
[57] Zhao Z, Wu J, Liu X, Liang M, Zhou X, Ouyang S, Yao J, Wang J and Luo B. Insufficient radiofrequency ablation promotes proliferation of residual hepatocellular carcinoma via autophagy. Cancer Lett 2018; 421: 73-81.
[58] Fang Y, Hu F, Ren W, Xiang L, Wang T, Zhu C, He R, Dong X, Liu C, Ding H and Zhang K. Nanomedicine-unlocked radiofrequency dynamic therapy dampens incomplete radiofrequency ablation-arised immunosuppression to suppress cancer relapse. Biomaterials 2025; 317: 123087.
[59] Huo Y, Chen WS, Lee J, Feng GS and Newton IG. Stress conditions induced by locoregional therapies stimulate enrichment and proliferation of liver cancer stem cells. J Vasc Interv Radiol 2019; 30: 2016-2025, e2015.
[60] Zhao W, Li X and Li Z. Combination therapy with local radiofrequency ablation and YC-1 inhibits the proliferation and metastasis of hepatocellular carcinoma through activating β-catenin signaling. Pharmazie 2016; 71: 524-529.
[61] Niu H, Dong S, Li G, Wu S and Sun W. Metformin promotes the normalization of abnormal blood vessels after radiofrequency ablation deficiency in hepatocellular carcinoma by microRNA-302b-3p targeting thioredoxin-interacting protein. Acta Biochim Pol 2023; 70: 1005-1014.
[62] Dong S, Li Z, Kong J, Wu S, Gao J and Sun W. Arsenic trioxide inhibits angiogenesis of hepatocellular carcinoma after insufficient radiofrequency ablation via blocking paracrine angiopoietin-1 and angiopoietin-2. Int J Hyperthermia 2022; 39: 888-896.
[63] Chen P, Li K, Chen J, Hei H, Geng J, Huang N, Lei M, Jia H, Ren J and Jin C. Enhanced effect of radiofrequency ablation on HCC by siRNA-PD-L1-endostatin co-expression plasmid delivered. Transl Oncol 2025; 53: 102319.
[64] Wang D, Nie T, Fang Y, Zhang L, Yu C, Yang M, Du R, Liu J, Zhang L, Feng L and Zhu H. Tailored liposomal nanomedicine suppresses incomplete radiofrequency ablation-induced tumor relapse by reprogramming antitumor immunity. Adv Healthc Mater 2025; 14: e2403979.
[65] Ren Y, Zhu L, Guo Y, Ma J, Yang L, Zheng C and Dong X. Melatonin enhances the efficacy of anti-PD-L1 by improving hypoxia in residual tumors after insufficient radiofrequency ablation. J Pharm Anal 2024; 14: 100942.
[66] Qi X, Yang M, Ma L, Sauer M, Avella D, Kaifi JT, Bryan J, Cheng K, Staveley-O'Carroll KF, Kimchi ET and Li G. Synergizing sunitinib and radiofrequency ablation to treat hepatocellular cancer by triggering the antitumor immune response. J Immunother Cancer 2020; 8: e001038.
[67] Xiao Z, Li T, Zheng X, Lin L, Wang X, Li B, Huang J, Wang Y, Shuai X and Zhu K. Nanodrug enhances post-ablation immunotherapy of hepatocellular carcinoma via promoting dendritic cell maturation and antigen presentation. Bioact Mater 2023; 21: 57-68.
[68] Li X, Liu Y, Ke J, Wang Z, Han M, Wang N, Miao Q, Shao B, Zhou D, Yan F and Ji B. Enhancing radiofrequency ablation for hepatocellular carcinoma: nano-epidrug effects on immune modulation and antigenicity restoration. Adv Mater 2024; 36: e2414365.