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REVIEW

Reprogramming Metabolism and Immunity: Nanotechnology's Promise for Hepatocellular Carcinoma Precision Therapy

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Abstract: The treatment of hepatocellular carcinoma (HCC) faces multiple dilemmas, including limited applicability of local therapy, easy development of resistance to targeted drugs, and low response rate to immune checkpoint inhibitors (ICIs). The core crux lies in the "metabolic reprogramming-immune suppression" vicious cycle and tumor heterogeneity. This review aims to clarify the crosstalk between metabolic reprogramming and immune suppression in HCC, and summarize the design principles of nanoplatforms for synchronous intervention in metabolism and immunity. Nanotechnology, with core advantages of precise targeting, tumor microenvironment responsiveness, and multifunctional synergy, enables targeted regulation of glucose, fatty acid, and amino acid metabolic pathways. It synergizes with ICIs and local therapies to reshape the immunosuppressive microenvironment, and the "metabolic subtype-nanocarrier" matching strategy shows promising clinical potential. Current applications face challenges in carrier performance, personalized strategies, and clinical translation. Future development focusing on carrier optimization, multi-omics-based subtype matching, and standardized evaluation systems will promote nanotechnology to evolve from "broad-spectrum regulation" to "precise adaptation", providing a core tool for overcoming HCC treatment bottlenecks and advancing precision therapy.

Keywords: hepatocellular carcinoma, metabolic-immunomodulation, nanodelivery systems, combination therapy, tumor microenvironment, clinical translation

Introduction

The global disease burden of HCC (HCC) exhibits significant regional disparities. In areas with high incidence of hepatitis B virus (HBV)/hepatitis C virus (HCV) infection, such as East Asia and Africa, the incidence and mortality rates have remained persistently high, imposing a heavy burden on public health systems.[1] The current HCC treatment system has prominent shortcomings: local therapies such as surgical resection and transarterial chemoembolization (TACE) are only applicable to early-stage patients, and over 70% of patients are diagnosed at an advanced stage; targeted drugs like sorafenib are prone to developing resistance due to tumor metabolic adaptation;[2,3] single-agent therapy with immune checkpoint inhibitors (ICIs) is limited by the "immune suppressive" phenotype of the tumor immune microenvironment (TIME), resulting in a low overall response rate.[4,5]

The core to overcoming these dilemmas lies in clarifying the key driving mechanisms of HCC progression. Recent studies have confirmed that HCC cells acquire energy and raw materials for proliferation through metabolic reprogramming. Metabolites such as lactate and kynurenine, as well as nutritional deprivation of arginine and tryptophan, directly inhibit immune cell function. In turn, the immunosuppressive microenvironment further exacerbates tumor metabolic abnormalities, forming a "metabolic reprogramming-immune suppression" vicious cycle.[6,7] More importantly, this cycle

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is closely associated with angiogenesis: the hypoxic microenvironment induced by metabolic abnormalities leads to overexpression of vascular endothelial growth factor (VEGF), promoting tumor angiogenesis. Abnormal blood vessels, in turn, exacerbate insufficient immune cell infiltration, forming a triple vicious cycle of "metabolic reprogramming-immune suppression-angiogenesis", which further strengthens the malignant phenotype of tumors.[8,9] Therefore, synchronous intervention in metabolic abnormalities, immune disorders, and angiogenesis has become a scientific breakthrough to overcome the bottleneck of HCC treatment.

The TIME of HCC presents a typical "immune suppressive" phenotype: myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), and regulatory T cells (Tregs) are highly enriched, which inhibit immune responses by secreting IL-10, TGF-β, or consuming key nutrients. In contrast, cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells undergo functional exhaustion or insufficient infiltration due to the deteriorating metabolic microenvironment such as acidosis and hypoxia,[10,11] providing an "immune privilege" environment for HCC cells to evade immune surveillance. HCC cells primarily support proliferation through reprogramming of three core pathways (glucose, fatty acid, and amino acid metabolism), and abnormalities in each pathway are deeply involved in the regulation of TIME immunosuppression[12]—the Warburg effect in glucose metabolism leads to lactate accumulation; Arginase 1 (ARG1) and indoleamine 2,3-dioxygenase 1(IDO1) mediate nutrient consumption in amino acid metabolism; cholesterol accumulation and oxidative abnormalities in fatty acid metabolism induce T cell exhaustion, and high fatty acid synthase (FASN) expression promotes the polarization of TAMs toward an immunosuppressive phenotype. Moreover, HCC metabolic reprogramming exhibits significant subtype specificity: HBV/HCV-related HCC is characterized by enhanced glycolysis, while non-alcoholic fatty liver disease (NAFLD)-related HCC is manifested by lipid metabolism disorders and sensitivity to ferroptosis.[13] This heterogeneity provides a target basis for precise metabolic intervention.

Compared with traditional metabolic intervention drugs, nanocarriers exhibit irreplaceable core advantages: active enrichment in TIME can be achieved through modification with galactose, Glypican-3 antibody, CD11b antibody, etc, improving drug concentration at the tumor site and reducing toxicity to normal tissues; they can simultaneously load multiple drugs with different mechanisms or integrate diagnostic and therapeutic functions, breaking the limitations of traditional single-agent therapy;[14,15] pH-sensitive, reactive oxygen species (ROS)-sensitive, enzyme-sensitive, and other designs enable precise drug release in the acidic and high-ROS microenvironment of HCC, avoiding premature drug leakage.[16,17] In addition, the emergence of novel nanodelivery systems such as exosomes and bacteria provides more possibilities for metabolic-immunomodulation.[18]

To intuitively clarify the logical correlation between metabolic abnormalities, immune suppression, and nanotechnology-based solutions, and lay a foundation for the subsequent elaboration of core mechanisms and nano-strategies, we summarize the multi-dimensional matching relationship among the three as follows (Table 1).

Based on the above background, this review proposes a core scientific hypothesis: functionalized nanocarriers can reverse the immunosuppressive microenvironment, enhance the sensitivity of HCC to ICIs, and improve therapeutic efficacy by precisely targeting key metabolic hubs such as hexokinase 2 (HK2), glutaminase 1 (GLS1), and FASN in HCC-TIME. To verify this hypothesis, this review constructs a systematic research framework of "mechanism

Table 1 Correlation Table of Metabolism-Immunity-Nanotechnology

Dimension	Core Mechanisms	Nanotechnology Solutions
Metabolic abnormalities	Enhanced glycolysis (HK2/LDHA overexpression), hyperactive fatty acid synthesis (FASN/CD36 upregulation), glutamine dependence (GLS1/SLC1A5 activation)	Stimuli-responsive nanocarriers targeting metabolic enzymes; multi-pathway co-delivery systems
Immune suppression	Enrichment of MDSCs/TAMs, T cell exhaustion (PD-1/PD-L1 upregulation), DC maturation impairment	Immune checkpoint blockade nanoplatforms; immunosuppressive cell elimination nano-systems; innate immune activation nanoparticles
Clinical bottlenecks	Drug resistance (metabolic adaptation), poor targeting, low ICI response rate	Multi-target synergistic nanoplatforms (metabolism-immunity-angiogenesis); biomarker-guided personalized nano-strategies

analysis→strategy development→synergistic application→clinical translation", forming a complete logical chain from basic research to clinical application, and providing a systematic reference for precision therapy of HCC.

Pathological Mechanisms and Regulatory Targets of Key Metabolic Pathways in HCC-TIME

To ensure the comprehensiveness and rigor of this review, a systematic literature search was performed in PubMed, Web of Science, and Embase databases using a combination of keywords including "hepatocellular carcinoma", "metabolic reprogramming", "tumor immune microenvironment", "nanotechnology", and "immunotherapy" (publication years: 2018–2025). Studies were included if they focused on the crosstalk between HCC metabolic pathways and immune regulation, or the design and application of nano-based metabolic-immunomodulatory platforms, with clear mechanisms and reliable experimental data. Reviews without original research data, preclinical studies with ambiguous intervention targets, and studies unrelated to the core theme (eg, non-HCC tumors, non-metabolic/immune-focused nanotechnology) were excluded. A total of 133 eligible studies were ultimately selected to construct the theoretical framework and support the key conclusions of this review.

Metabolic reprogramming of HCC is not an abnormality of a single pathway but the result of multi-level regulation including signaling pathways, non-coding RNAs, and metabolic enzyme modifications. Moreover, each metabolic pathway has direct or indirect cross-links with TIME immunosuppression. This section systematically analyzes the reprogramming mechanisms of three core metabolic pathways (glucose, fatty acid, and amino acid metabolism) and their regulatory effects on the function of TIME immune cells, providing a target basis for the subsequent design of nano-strategies.

Glucose Metabolism Reprogramming

Glucose metabolism reprogramming of HCC cells is centered on enhanced aerobic glycolysis. Even in the presence of sufficient oxygen, they still preferentially obtain energy through glycolysis. This metabolic adaptation not only supports tumor proliferation but also directly shapes the immunosuppressive microenvironment through lactate accumulation, enzyme activity regulation, and other ways.

Multi-Level Regulatory Network of Glucose Metabolism Reprogramming

Glucose metabolism reprogramming of HCC is coordinately regulated by signaling pathways, non-coding RNAs, and metabolic enzyme modifications: At the signaling pathway level, the yes - associated protein 1 (YAP1)-hypoxia inducible Factor-1α (HIF-1α)-glucose transporter 1(GLUT1) axis enhances glycolytic flux by upregulating GLUT1; calcium/calmodulin-dependent protein kinase kinase 2, beta activates the PI3K/AKT pathway to promote lactate production; AR specifically upregulates HK2 transcription through the PKA/CREB pathway.[19–21] At the non-coding RNA level, lncRNAs (DGUOK-AS1, NBR2), miRNAs (miR-202, miR-124), etc, achieve self-regulation of glucose metabolism or cross-regulation with lipid metabolism by targeting key molecules; circRNA CDR1as reinforces the synergy between glycolysis and immune suppression by sponging miR-7.[22–25] At the metabolic enzyme modification level, O-glycosylation at the T980 site of FASN is a key node for glucose-lipid metabolism crosstalk; TRIM37 activates aerobic glycolysis by ubiquitin-mediated degradation of P53.[26,27] The multi-level regulation and pathway crosstalk characteristics of glucose metabolism reprogramming provide an important basis for the development of multi-target synergistic intervention strategies.

Regulation of TIME Immune Function by Glucose Metabolism Reprogramming

Abnormal glucose metabolism of HCC inhibits the function of TIME immune cells through three mechanisms: accumulation of metabolic products, direct molecular interactions, and cascading effects of the acidic microenvironment: Lactate secreted in large quantities by HCC cells is transported into macrophages via MCT1, inducing their polarization toward the M2 phenotype and inhibiting pyroptosis. Meanwhile, it inhibits glucose uptake and glycolysis in T cells through the SENP1-MondoA-TXNIP axis. Tregs can take up lactate to enhance their immunosuppressive activity, and this effect is synergistically reinforced with PD-1 blockade.[28–30] HK2 enhances the anti-apoptotic ability

of HCC by binding to mitochondrial VDAC, thereby reducing the sensitivity to NK cell cytotoxicity. Abnormal glycans on the surface of tumor cells and lactate accumulation induced by high LDHA expression both inhibit DC function and impair T cell activation.[31–33] CA12 is highly expressed in tumor-infiltrating macrophages, which promotes their survival in the acidic microenvironment by regulating pH homeostasis and induces CCL8 secretion to drive HCC metastasis. The acidic environment also impairs T cell function and upregulates the expression of immune checkpoint molecules.[34,35] The impact of HCC glucose metabolism reprogramming on TIME involves multiple aspects. The design of subsequent nano-strategies needs to balance "glucose metabolism inhibition" and "immune microenvironment remodeling", and more efficiently reverse immune suppression through multi-target synergistic intervention.

Fatty Acid Metabolism Reprogramming

Fatty acid metabolism reprogramming of HCC exhibits significant subtype specificity. Abnormal fatty acid metabolism in both tumor cells and TIME immune cells contributes to the formation of the immunosuppressive microenvironment. In-depth analysis of the fatty acid metabolism characteristics of different HCC subtypes and their regulatory mechanisms on immune cell function is the key to achieving precise metabolic intervention.

Subtype Characteristics of Fatty Acid Metabolism Reprogramming in HCC Cells

Fatty acid metabolism reprogramming of HCC cells is mainly manifested by enhanced synthesis, abnormal oxidation, and altered lipid transport, with distinct characteristics among different subtypes: Sorafenib-induced cancer stem cells (CSCs) show increased lipid droplet accumulation, upregulation of ATP citrate lyase and FASN, downregulation of carnitine palmitoyltransferase 1A, etc, with inhibition of the AMP-activated protein kinase (AMPK) pathway as the core mechanism].[36] The E2F transcription factor 1, spindlin 1, and sterol regulatory element-binding protein 1c complex promotes fatty acid synthesis and tumor metastasis by regulating FASN expression.[37,38] Excretory-secretory products of Clonorchis sinensis induce high FASN expression in intrahepatic cholangiocarcinoma (iCCA), and elevated free fatty acids reduce the response rate to immune checkpoint blockade.[39] NAFLD-related HCC is characterized by lipid accumulation and enhanced fatty acid oxidation (FAO), with activation of the PPARα pathway and association with lipid peroxidation.[25] In addition, fatty acid metabolism cross-regulates with glucose metabolism through acetyl-CoA and the AMPK pathway. PHB1 and nuclear-localized PHGDH are also involved in maintaining metabolic homeostasis.[26,40–42] The subtype specificity and pathway crosstalk characteristics of fatty acid metabolism reprogramming provide a clear direction for precise targeted intervention.

Fatty Acid Metabolism Reprogramming and Functional Remodeling of Immune Cells

Immune cells such as TAMs and T cells in TIME alter their functional phenotypes through fatty acid metabolism reprogramming, promoting the formation of the immunosuppressive microenvironment: In p53-inactivated HCC, IL-34 secreted by CSCs induces high CD36 expression and FAO reprogramming in macrophages, leading to the M2 phenotype. APOE+ TAMs inhibit $CD8^+$ T cell activation through cholesterol transport. 5-LOX in CD163+ TAMs promotes tumor proliferation through leukotrienes.[43–45] Lipid accumulation in TIME induces $CD8^+$ T cells to highly express exhaustion markers such as PD1 and Lag3. The FASN inhibitor cerulenin can restore their cytotoxicity and synergize with anti-PD-1 therapy. 6-Gingerol can reprogram M2-type TAMs and reduce lipid deposition.[39,44,46] Immune-cold HCC is enriched in fatty acid metabolism pathways and has high ECM expression, resulting in insufficient immune cell infiltration. In contrast, immune-hot HCC has downregulated lipid metabolism regulatory genes (MLXIPL, FASN, SCD) and is more suitable for ICI therapy.[47] The fatty acid metabolite PUFAs can induce ferroptosis and immunogenic cell death (ICD) in tumor cells through lipid peroxidation, providing targets for metabolic-immune synergistic therapy. Immune cell function is determined by metabolic state; targeted regulation of fatty acid metabolism in TAMs/T cells reverses HCC immune suppression, and attention should be paid to the metabolic interactions between "tumor cells-immune cells" in different subtypes.

Amino Acid Metabolism Reprogramming

HCC cells and TIME immunosuppressive cells achieve the dual goals of "nutritional competitive advantage" and "immune escape" through amino acid metabolism reprogramming: tumor cells rely on "addiction" to specific amino acids (such as glutamine) to support proliferation, while immunosuppressive cells inhibit T cell activation by consuming key amino acids (such as arginine and tryptophan). Both together promote HCC progression.

Reprogramming Characteristics of Core Amino Acid Metabolic Pathways in HCC

Amino acid metabolism reprogramming of HCC is centered on abnormal metabolism of glutamine, tryptophan, and asparagine, and is closely associated with tumor proliferation and drug resistance: In HCC tissues, GLS2 is down-regulated, while GLS1 and GS are upregulated. HCC cells rely on GLS1-mediated glutaminolysis for energy and nitrogen supply. The GLS1 inhibitor CB-839 can inhibit tumor proliferation and reverse 5-FU resistance. High SLC1A5 expression promotes TACE resistance.[48–50] MYC-driven HCC enhances tryptophan uptake and preferentially produces I3P. High TDO2 expression catalyzes the conversion of tryptophan to kynurenine. IDO1 is highly expressed in immunosuppressive cells to consume tryptophan, all of which promote tumor progression.[51–53] HCC can be divided into high and low metabolic subtypes based on asparagine metabolism. The high metabolic subtype relies on asparagine and glutamine metabolism and exhibits more significant immune suppression, with GOT2 as the key regulatory gene.[54] The GMScore scoring system related to glutamine metabolism can predict patient prognosis and treatment resistance.[55] Abnormalities in various amino acid metabolic pathways not only support tumor survival but also are associated with treatment resistance and immune suppression, providing a clear direction for multi-target synergistic intervention.

TIME Immune Suppression Mediated by Amino Acid Metabolism Reprogramming

Abnormal amino acid metabolism constructs an immunosuppressive microenvironment through the dual mechanisms of "nutritional deprivation" and "metabolite toxicity": MDSCs highly express ARG1 and IDO to consume arginine and tryptophan. TGF-β induces DCs to form an "Arg1-polyamine-IDO1" immunosuppressive relay pathway. Tumor cells extensively uptake glutamine, leading to nutritional deficiency in T cells and NK cells.[56,57] Ammonia produced by glutamine metabolism, kynurenine (a tryptophan metabolite), and the synergistic effect of lactate and abnormal glutamine metabolism respectively inhibit T cell activation, induce Treg differentiation, and suppress DC maturation.[33,53,57] The cholesterol efflux effect of APOE+ TAMs synergizes with amino acid metabolism-induced nutritional deprivation. PTBP1, GDH1, SLC25A15, etc, mediate treatment resistance and strengthen immune suppression or reduce immunotherapy sensitivity by regulating glutamine metabolism.[44,58–60] Amino acid metabolism reprogramming of HCC inhibits immune responses through "nutritional competition + metabolic toxicity" and is associated with treatment resistance. In particular, the key role of abnormal glutamine metabolism provides a theoretical basis for combination therapy. In the future, it is necessary to clarify the synergy between various pathways and their association with other metabolic pathways, providing support for the design of multi-target nano-regulatory systems.

Correlation Between Metabolic Reprogramming and HCC Prognosis

The expression level of metabolic enzymes is an important biological marker for evaluating the prognosis of HCC patients. High expression of HK2, FASN, IDO1, GLS1, etc, all indicates rapid tumor progression, high recurrence risk, or short survival time. Moreover, GLS1 expression can predict the sensitivity to 5-FU chemotherapy.[31,39,49,61] These metabolic markers can not only be used for prognosis evaluation but also guide the selection of treatment regimens. For example, patients with high HK2 expression are suitable for glucose metabolism-targeted nano-drugs, and patients with high FASN expression can benefit from the combination of fatty acid metabolism inhibitors and ICIs. The development of a combined detection system for metabolic enzymes and immune molecules can provide tools for precise diagnosis and treatment. Serum metabolic markers such as PC 36:4 and phenylalanine also have prognostic evaluation and therapeutic effect monitoring value.[62] HCC metabolic markers have multiple values but require large-sample verification to promote clinical translation. The clinical value of metabolic enzymes as HCC prognostic markers has been confirmed, but their application in treatment guidance is still in the exploration stage. In the future, large-

sample, multi-center clinical studies are needed to verify their predictive value for nano-metabolic drugs or combination therapy, promoting the implementation of "marker-guided personalized therapy".

Core Regulatory Mechanisms of the Hepatocellular Carcinoma Metabolism-Immunity Axis

The regulation of the hepatocellular carcinoma metabolism-immunity axis is a complex network system, centered on the remodeling of the immune microenvironment by metabolic reprogramming and the reverse regulation of tumor metabolism by immune cells. The key mechanisms involve the crosstalk of glycolysis, glutamine metabolism, lipid metabolism, and related signaling pathways (Figure 1).

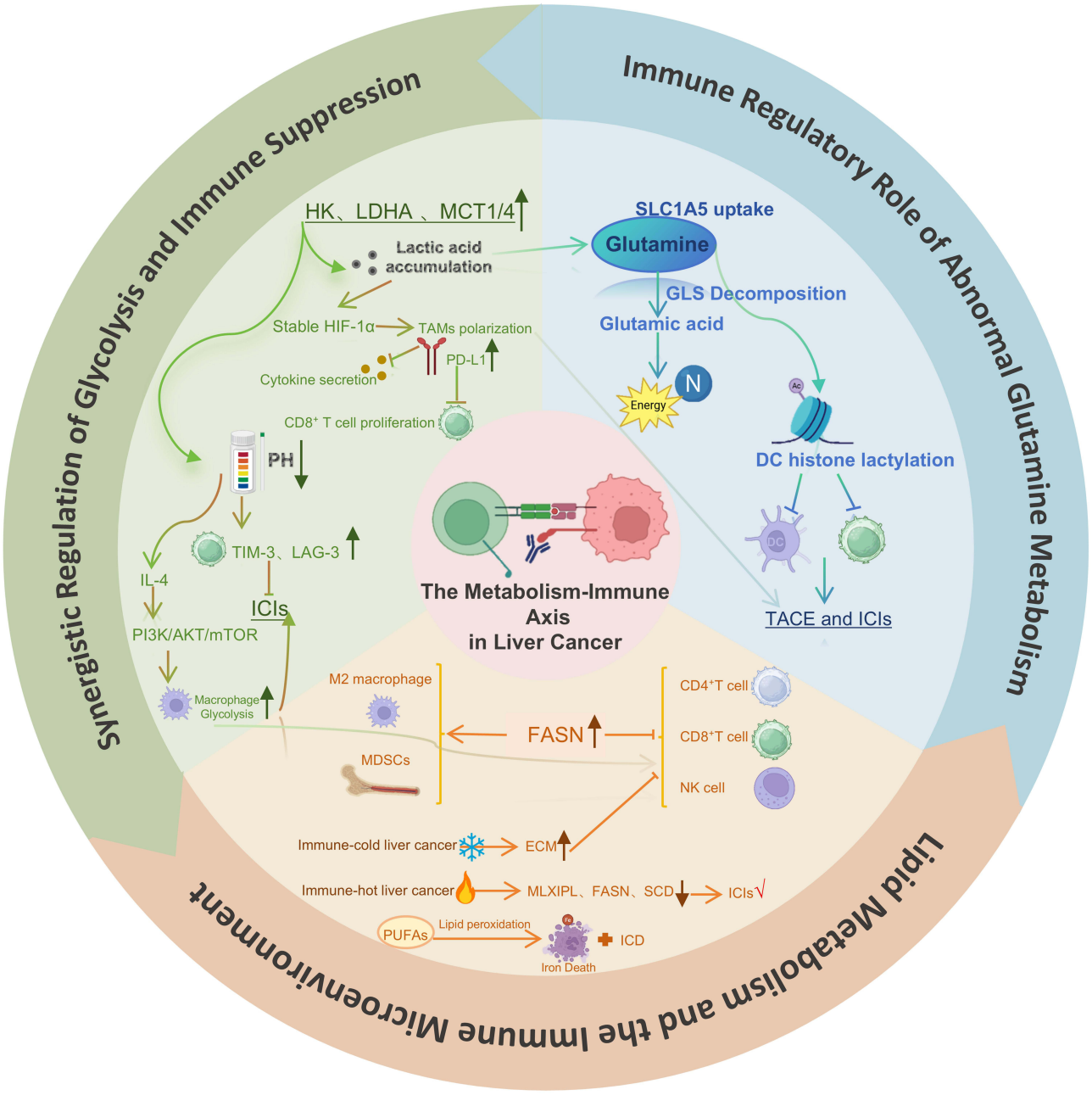

Figure 1 Core regulatory mechanism of liver cancer metabolism immune axis.

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Synergistic Regulation of Glycolysis and Immune Suppression

HCC cells rely on the Warburg effect to preferentially supply energy through glycolysis, with high expression of key enzymes such as HK and LDHA, and transporters such as MCT1/4, leading to lactate accumulation and pH reduction in the tumor microenvironment.[30,63] Lactate can stabilize HIF-1α to promote M2-type TAM polarization and upregulate PD-L1, inhibit CD8+ T cell proliferation and cytokine secretion, and can be taken up by Tregs to enhance their immunosuppressive activity, synergizing with PD-1 blockade to reinforce the effect.[30,63] The acidic microenvironment directly impairs T cell function and upregulates the expression of TIM-3 and LAG-3, reducing ICI efficacy.[35] IL-4 induces enhanced glycolysis in macrophages by activating the PI3K/AKT/mTOR pathway, mediating immunotherapy resistance.[64] Targeting key glycolytic molecules or lactate transporters can simultaneously improve metabolism and immune suppression, helping to enhance ICI efficacy.

Immunomodulatory Role of Abnormal Glutamine Metabolism

As an "essential amino acid" for tumor cells, glutamine is extensively taken up via SLC1A5 and decomposed into glutamate by GLS for energy and nitrogen supply.[50,55] The GMScore scoring system related to glutamine metabolism can predict patient prognosis and resistance to TACE and ICIs. Patients with high GMScore have increased Treg infiltration and decreased M1-type macrophages.[55] High SLC1A5 expression is associated with tumor progression and poor prognosis, and can promote TACE resistance by regulating the hypoxic microenvironment and angiogenesis.[50] Tumor-derived lactate synergizes with abnormal glutamine metabolism to induce histone lactylation in DCs, inhibiting DC maturation and CD8+ T cell function.[33] Nano-strategies targeting SLC1A5 or GLS are key directions to break the metabolic-immune vicious cycle.

Interaction Between Lipid Metabolism and the Immune Microenvironment

As a key enzyme in lipid synthesis, FASN is highly expressed in HCC and is closely associated with poor prognosis and immune suppression. Its expression level is negatively correlated with the infiltration of CD4+ T cells, CD8+ T cells, and NK cells, and positively correlated with the infiltration of M2-type macrophages and MDSCs.[65] Immune-cold HCC is enriched in fatty acid metabolism and adipogenesis pathways and has high ECM expression, resulting in insufficient immune cell infiltration. In contrast, immune-hot HCC has downregulated lipid metabolism regulatory genes (MLXIPL, FASN, SCD) and is more suitable for ICI therapy.[47] The lipid metabolite PUFAs can induce ferroptosis and ICD in tumor cells through lipid peroxidation, providing targets for metabolic-immune synergistic therapy.[66] Differences in lipid metabolism subtypes affect immune phenotypes. Targeting FASN or inducing ferroptosis can provide new therapies for immune-cold HCC.

Crosstalk Regulation of Key Signaling Pathways

The synergy between metabolic reprogramming and immune suppression relies on the crosstalk of multiple signaling pathways: HIF-1α can simultaneously promote the expression of glycolysis-related genes and PD-L1, mediating the synergy between lactate accumulation and immune suppression.[63] The PI3K/AKT/mTOR pathway promotes M2 polarization by regulating macrophage metabolic reprogramming, affecting T cell activation.[64] The NF-κB signaling pathway, activated by M1-like TAMs, upregulates proliferation-related genes and enhances the anti-apoptotic ability of HCC cells, reducing TACE efficacy.[67] The AHR signaling pathway, activated by kynurenine, induces Treg differentiation, inhibits CTL function, and promotes tumor cell proliferation and metabolic reprogramming.[53] Multi-target intervention targeting core signaling pathways can efficiently break the regulatory loop of "metabolism-immunity-tumor proliferation".

Nanotechnology-Mediated TIME Metabolic Reprogramming Strategies and Mechanisms

Based on the pathological mechanisms of core metabolic pathways in HCC-TIME, nanotechnology can achieve targeted intervention in glucose, fatty acid, and amino acid metabolic pathways by precisely delivering small-molecule inhibitors,

nucleic acid drugs, natural active ingredients, etc, while synergistically remodeling the immune microenvironment. This section systematically elaborates on nano-regulatory strategies targeting the three metabolic pathways, analyzes their design principles, mechanisms of action, and synergistic effects, providing technical solutions for HCC metabolic-immunomodulation.

Design Principles and Core Technologies of Nanocarriers

The performance of nanocarriers directly determines the effect of metabolic regulation. Their design needs to follow the four principles of "material adaptability, targeting precision, response sensitivity, and function integration". Through material selection, targeting modification, and stimulus-responsive design, efficient drug delivery, controlled release, and multi-functional synergy are achieved.

Material Selection and Performance Optimization

The material selection of nanocarriers needs to be combined with drug types and therapeutic requirements, and differentially adapted according to physicochemical properties and biocompatibility: Liposomes have good biocompatibility and modifiability, can encapsulate hydrophilic or hydrophobic drugs, and can target HCC cells with high expression of folate receptors through folate modification, improving drug enrichment efficiency at the tumor site.[57] Polymer nanoparticles (such as PLGA) can precisely control drug release rates (such as sustained release and pulsed release) by adjusting composition and molecular weight, have high biosafety and degradability, and are suitable for long-term treatment. The glycolytic inhibitors loaded by them can be continuously released in TIME to avoid drug concentration fluctuations.[68] Inorganic nanoparticles (such as MnO_2 and gold nanoparticles) have unique functions: MnO_2 can respond to H_2O_2 in TIME to generate oxygen, improving hypoxia and promoting drug release; gold nanoparticles can be used for photothermal therapy and imaging-guided therapy by virtue of their good optical properties, achieving "diagnosis and treatment integration".[69] Different material nanocarriers have their own advantages and disadvantages in HCC metabolic-immunomodulation. For example, although liposomes have good biocompatibility, their in vivo circulation time is short and they are easily cleared; PLGA nanoparticles have a controllable degradation cycle, but targeting modification is difficult; inorganic nanoparticles have diverse functions, but some materials (such as quantum dots) have potential toxicity risks. In the future, appropriate materials should be selected according to specific therapeutic needs (such as short-term efficient intervention vs. long-term safe regulation), or the advantages should be integrated through material composites (such as lipid-polymer hybrid carriers).

Targeting Modification Strategies

Targeting modification of nanocarriers is the key to improving tumor enrichment efficiency, mainly divided into two types of strategies: liver/tumor targeting and immune cell targeting: In liver/tumor targeting, galactose modification can achieve liver targeting by recognizing asialoglycoprotein receptors on the surface of hepatocytes; Glypican-3 antibody modification can specifically bind to Glypican-3 antigen on the surface of HCC cells, achieving precise targeting of tumor cells.[70] In immune cell targeting, CD11b antibody modification can target MDSCs or TAMs; CD44 antibody modification can target activated T cells; CSF-1R antibody modification can specifically bind to CSF-1R on the surface of TAMs, achieving precise regulation of immune cells.[71] Current single-target modification is difficult to meet the intervention needs of complex TIME. Dual-ligand or multi-ligand modification has become a new trend. For example, galactose + GPC3 antibody dual-modified carriers can simultaneously achieve liver targeting and HCC cell-specific recognition, improving tumor enrichment efficiency while reducing uptake by normal hepatocytes;[72] CD11b + PD-L1 antibody dual-modified carriers can not only target MDSCs to inhibit their immunosuppressive function but also block the PD-L1 pathway to activate T cells, achieving "immune cell targeting + immunomodulation" dual effects.[73] In the future, it is necessary to further optimize ligand combinations and modification ratios to balance targeting specificity and carrier stability.

Stimulus-Responsive Design

The stimulus-responsive design of nanocarriers can achieve "on-demand drug release" in TIME, avoiding premature drug leakage in normal tissues, mainly including three types of designs: pH-sensitive carriers use the acidic microenvironment

of TIME (pH 6.5–6.8) to achieve drug release through the cleavage of pH-sensitive chemical bonds such as hydrazone bonds and ester bonds;[74] ROS-sensitive carriers trigger carrier disintegration and drug release through the oxidation of disulfide bonds, selenide bonds, etc, by relying on high concentrations of ROS in TIME;[75] enzyme-sensitive carriers complete drug release through the degradation of enzyme-sensitive peptide bonds or polysaccharide chains targeting matrix metalloproteinases and cathepsins highly expressed in TIME.[74] Single stimulus response is easily affected by TIME heterogeneity (such as insignificant acidity in some tumor regions). Multi-stimulus synergistic response design can improve the precision of drug release. For example, pH/ROS dual-responsive carriers first undergo structural pre-change in the acidic environment of TIME, and then further trigger rapid drug release through high ROS, ensuring efficient drug enrichment in the core region of tumors;[76] in addition, the design combining exogenous stimulation (such as near-infrared light) and endogenous stimulation (such as pH) (such as pH/light dual response) can further optimize the drug release sequence through external precise regulation.[77] In the future, it is necessary to conduct in-depth research on the dynamic change rules of the TIME microenvironment and design more suitable response mechanisms.

Design and Application of Nano-Platforms for Regulating the Hepatocellular Carcinoma Metabolism-Immunity Axis

By virtue of their unique physicochemical properties, nano-platforms can achieve targeted delivery, responsive release, and multi-functional synergy of metabolic inhibitors, immunomodulators, and anti-angiogenic drugs, becoming a core tool for regulating the hepatocellular carcinoma metabolism-immunity axis. According to functional positioning, nano-platforms are mainly divided into three categories: metabolic intervention type, immunomodulation type, and metabolic-immune-angiogenesis synergistic regulation type.

Metabolic Intervention Nano-Platforms

Metabolic intervention nano-platforms focus on regulating tumor metabolic reprogramming, blocking abnormal pathways such as glycolysis, glutamine metabolism, and lipid metabolism by targeting the delivery of metabolic inhibitors (Table 2), improving the immunosuppressive microenvironment from the source, and designing differentiated strategies for different metabolic subtypes.

Glycolysis Inhibition Nano-Platforms

Targeting the Warburg effect and different glucose metabolism subtypes, researchers have developed a variety of glycolysis inhibition nano-platforms: Core enzyme-targeted platforms, such as the photothermally controllable nano-platform (B/T-HM) based on hollow mesoporous Prussian blue (HPB), load the HK2 inhibitor 3-bromopyruvate and are modified with tumor cell membranes. Near-infrared light irradiation can trigger drug release, reduce lactate production, and downregulate PD-L1 (Figure 2A), which is suitable for HBV/HCV-related HCC with high HK2 expression.[78] pH-responsive polymer nanoparticles load the LDHA inhibitor oxamate, which can rapidly release drugs in the acidic tumor environment, and combination with anti-PD-1 therapy can increase CD8+ T cell infiltration.[79] In lactate metabolism-targeted platforms, the pH-sensitive nano-carrier (AZD-UPS NPs) targets the delivery of the MCT1 inhibitor AZD3965, which can block lactate uptake and improve treatment safety.[80] PVP-modified calcium peroxide nanoparticles (CaO_2 NPs) can improve the hypoxic and acidic tumor microenvironment, and combination with PD-1 inhibitors achieves the conversion of “cold tumors” to “hot tumors”[84] Multi-target synergistic platforms, such as lipid-polymer hybrid

Table 2 Matching Table of Core Metabolic Targets and Nanocarriers

Metabolic Pathway	Key Targets	Nanocarrier Types	Ref.
Glucose metabolism	HK2, LDHA, MCT1	Hollow mesoporous Prussian blue, pH-responsive polymers, pH-sensitive nanocarriers	[78–80]
Fatty acid metabolism	FASN, CD36, GPX4	Liposomes, ROS-responsive nanoparticles, pH/ROS dual-responsive nanoparticles	[38,81]
Amino acid metabolism	GLS1, SLC1A5, IDO1	Magnetic nanoparticles, PLGA nanoparticles, TREM2 antibody-modified liposomes	[50,82,83]

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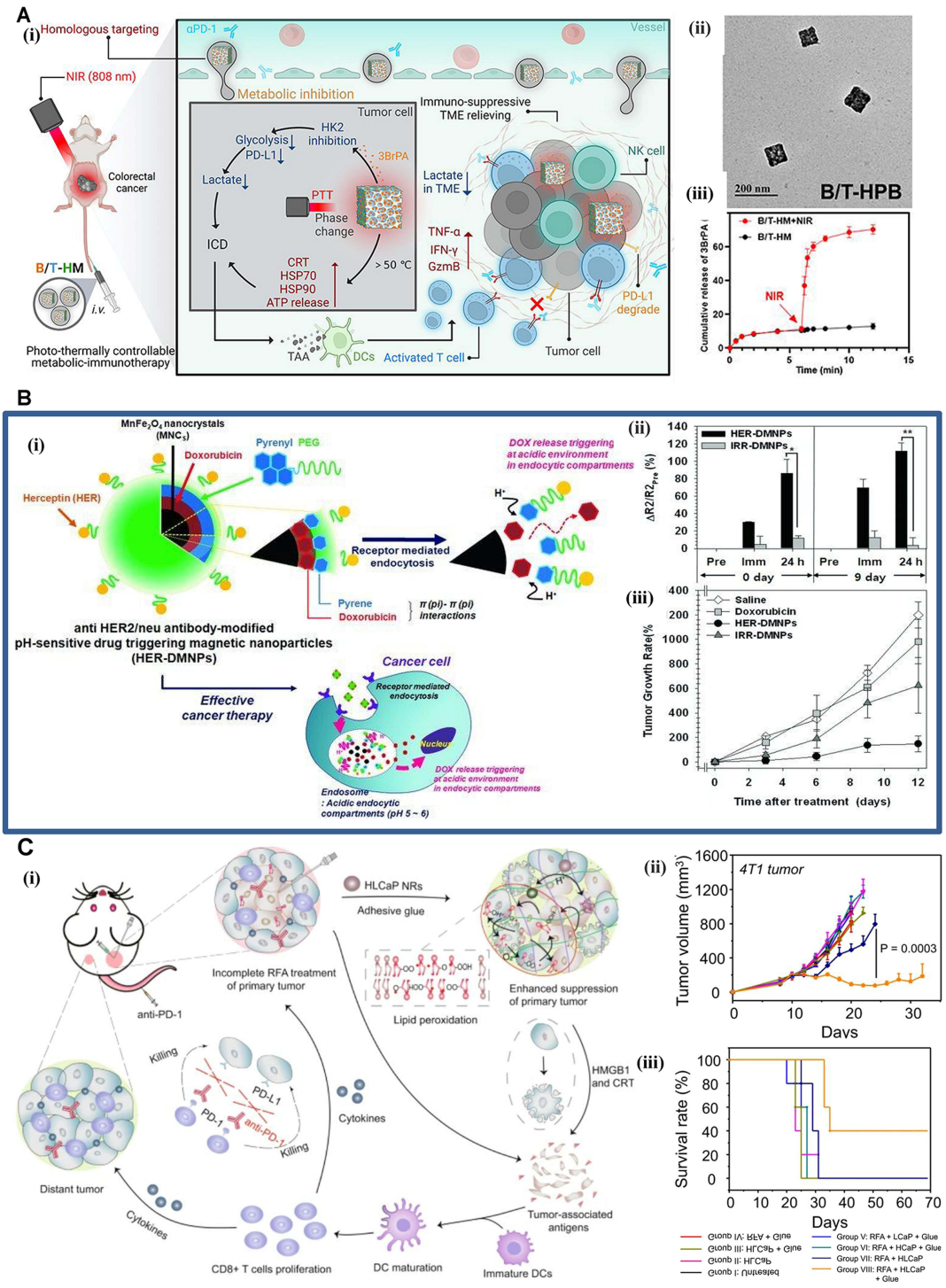

Figure 2 Metabolic intervention nanoplatform. (**A**) Mechanism diagram, electron microscopy image, and photothermal controlled release characteristic diagram of the synergistic regulation of tumor metabolism and T cell activation.[78] (i) Schematic of photothermally controlled tumor metabolic modulation for enhanced T cell immunotherapy; (ii) TEM image of B/T-HPB; (iii) 3BrPA release curves from B/T-HM with/without 808 nm NIR irradiation (0.5 W/cm^2, 5 min). Data: mean ± s.d., n=3. Reprinted from Ma J, Hua L, Zhu Y, et al Photo-thermally controllable tumor metabolic modulation to assist t cell activation for boosting immunotherapy. Int J Nanomedicine. 2024;19:11181–94. (**B**) HER2/neu antibody modified pH sensitive magnetic nanoparticles, targeted enrichment monitoring, and anti-tumor efficacy.[82] (i) Schematic of HER-DMNPs for targeted cancer therapy and MRI; (ii) Tumor ΔR2/R2Pre in mice after HER-DMNPs/IRR-DMNPs injection (days 0.9); * P, ** P <0.001; (iii) In vivo antitumor efficacy (HER-DMNPs, IRR-DMNPs, DOX, saline). Reprinted from Lim E, Huh Y, Yang J, et al Ph-triggered drug-releasing magnetic nanoparticles for cancer therapy guided by molecular imaging by mri. Advanced materials (Deerfield Beach, Fla). 2011;23(21):2436–42. Copyright © 2011 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. (**C**) Schematic diagram of HLCaP nanoreactor combined with radiofrequency ablation and the effect of tumor inhibition.[66] (i) Schematic of HLCaP NRs enhancing RFA and antitumor immunity via tumor debris; (ii) Tumor growth curves; c: Mobility-free survival rate of 4T1 tumor-bearing mice (tumor volume >1000 mm^3 = death). Reprinted from Yang Z, Zhu Y, Dong Z, et al Tumor-killing nanoreactors fueled by tumor debris can enhance radiofrequency ablation therapy and boost antitumor immune responses. Nat Commun. 2021;12(1):4299.

nanoparticles co-loading HK2 inhibitors and CA12 inhibitors, modified with galactose + GPC3 dual ligands, can simultaneously block glycolysis and the mechanism of maintaining the acidic microenvironment.[85] The design of glycolysis inhibition nano-platforms needs to fit the characteristics of different glucose metabolism subtypes. Multi-target synergy and microenvironment-responsive design can improve the precision and efficacy of intervention.

Glutamine Metabolism Inhibition Nano-Platforms

Targeting abnormal glutamine metabolism and GLS1-high expression subtypes, nano-platforms mainly function by targeting the delivery of GLS inhibitors or SLC1A5 antagonists: In targeted delivery platforms, HER2/neu antibody-modified pH-sensitive magnetic nanoparticles (HER-DMNPs) can load glutaminase inhibitors, target HCC cells through HER2/neu receptor-mediated endocytosis, and the $MnFe_2O_4$ core supports MRI imaging monitoring (Figure 2B), adapting to the acidic tumor microenvironment to achieve precise drug release.[82] SLC1A5 antibody-modified PLGA nanoparticles load SLC1A5 antagonists, which can specifically block glutamine uptake, simultaneously reducing tumor cell nutrient supply and improving the nutritional deficiency state of immune cells.[50] In combination therapy platforms, the Fe_3O_4@PMO-Cy5.5-Dox nano-platform can co-load doxorubicin and glutaminase inhibitors, achieving local precise co-delivery through TACE and monitoring effects with imaging technology.[86] The liposome nano-platform co-loading GLS1 inhibitors and asparaginase avoids compensatory metabolic activation after single-target intervention through dual-target intervention.[54] The design of glutamine metabolism-targeted nano-platforms needs to balance targeting precision and synergistic effects. Dual-target or combination therapy strategies can improve intervention effects.

Lipid Metabolism Inhibition Nano-Platforms

Lipid metabolism inhibition nano-platforms mainly target key molecules such as FASN and CD36, and design differentiated strategies for different lipid metabolism subtypes: In fatty acid synthesis inhibition platforms, poly (L-aspartic acid)-polyethylene glycol-modified combretastatin A4 nanoparticles (CA4-NPs) can destroy tumor neovascularization, reduce lipid supply, and induce a hypoxic microenvironment. Combination with PD-L1 inhibitors can enhance the killing effect of $CD8^+$T cells, which is suitable for iCCA with rich blood vessels and high FASN expression.[87] FASN antibody-modified liposomes load the FASN inhibitor cerulenin, which can specifically target FASN-high expression tumor cells, inhibit fatty acid synthesis, and reduce the polarization of TAMs toward the M2 type, suitable for NAFLD-related HCC and iCCA.[39] In ferroptosis-inducing platforms, tumor debris-driven HLCaP nanoreactors can catalyze PUFAs to generate lipid peroxides and induce ferroptosis, suitable for NAFLD-related HCC sensitive to ferroptosis (Figure 2C).[66] pH/ROS dual-responsive nanoparticles load the GPX4 inhibitor RSL3 and CD36 inhibitors, which can block fatty acid uptake and induce lipid peroxidation, synergistically triggering ferroptosis, suitable for lipid-accumulating HCC with high CD36 expression.[81] Lipid metabolism inhibition nano-platforms need to fit subtype characteristics. Targeting key molecules or inducing ferroptosis can efficiently improve abnormal lipid metabolism and immune suppression.

Immunomodulatory Nano-Platforms

Immunomodulatory nano-platforms focus on activating anti-tumor immunity or blocking immunosuppressive pathways, improving the immune microenvironment and enhancing the killing activity of immune cells by delivering immune checkpoint inhibitors, immune activators, etc, while forming synergy with metabolic intervention.

Immune Checkpoint Blockade Nano-Platforms

Immune checkpoint blockade is a core strategy for immunomodulation. Nano-platforms can improve drug targeting and reduce immune-related adverse events (irAEs): In targeted delivery platforms, PD-L1 aptamer-modified PET/NIRF dual-modal imaging probes [^{68}Ga]Ga-NOTA-Cy5-R1 can non-invasively detect tumor PD-L1 expression and guide the timing of combination use, achieving integration of targeted delivery and efficacy monitoring.[88] pH-sensitive PEG-modified αCD47, αCTLA-4, and αPD-1 antibodies shield their activity in normal tissues and restore activity in the acidic tumor microenvironment, significantly reducing irAEs (Figure 3A).[89] In antibody engineering platforms, pH 6.0-sensitive anti-CTLA-4 antibody variants (such as Ipi25) constructed by Tyr→His mutation in the CDR region can avoid CTLA-4

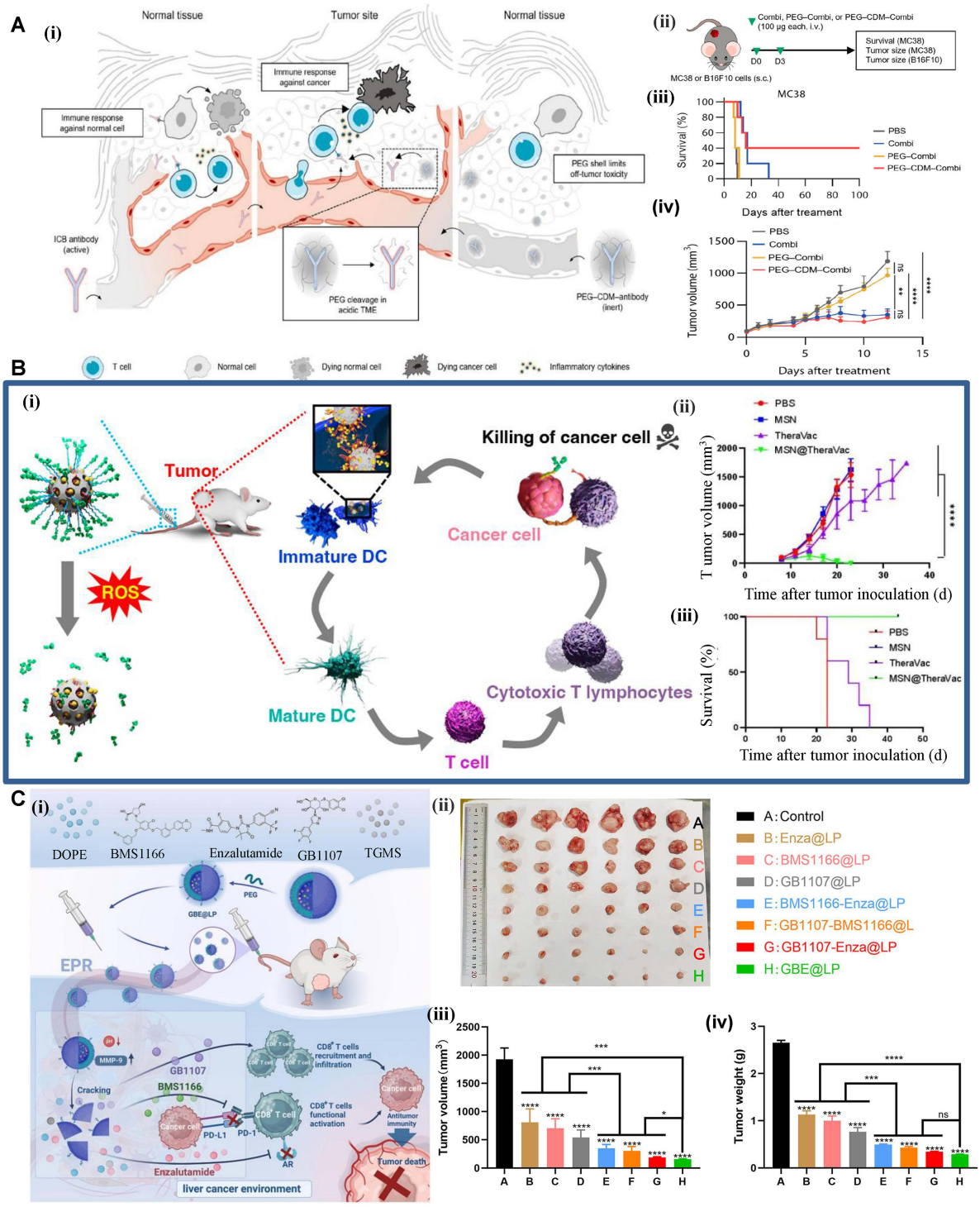

Figure 3 Immune checkpoint blockade nanoplatform. (**A**) The core mechanism of "shielding activation" of pH sensitive PEG modified antibodies and their anti-tumor effects.[89] (i) Masked antibody with PEG−CDM; (ii) Therapeutic regimen; (iii) Survival curve of each group (n = 5, biologically independent mice). Statistical significance was calculated by log-rank (Mantel-Cox) test (*P < 0.0332, **P < 0.0021). (iv) MC38 tumor growth after treatment. Data are mean ± standard error of mean (SEM) of n = 8 biologically independent mice (**P < 0.0021 and ****P < 0.0001). Reprinted from Song SH, Ghosh T, You DG, et al Functionally masked antibody to uncouple immune-related toxicities in checkpoint blockade cancer therapy. ACS Nano. 2023;17(11):10065–77. Copyright © 2023, American Chemical Society. (**B**) MSN@TheraVac Schematic diagram of structure and mechanism of action and its tumor inhibiting effect.[92] (i) Proposed concept of MSN@TheraVac used for tumor treatment; (ii) Individual and average CT26 tumor growth curves after treatment; (iii) Survival curves of treated mice. **** P < 0.0001, n.s. nonsignificant. Reprinted from Huang Y, Nahar S, Alam MM, et al Reactive oxygen species-sensitive biodegradable mesoporous silica nanoparticles harboring theravac elicit tumor-specific immunity for colon tumor treatment. ACS Nano. 2023;17(20):19740–52.Copyright © 2023, American Chemical Society. (**C**) GBE@LP Schematic diagram of structure and mechanism of action.[93] (i) Graphical illustration of the immunization strategy of GBE@LP for liver cancer treatment; (ii) Tumor final volume of tumor-bearing mice; (iii) Tumor final weight of tumor-bearing mice; (iv)Tumor growth curves of individual mice in different groups of the tumor-bearing mice. (n = 6, * P < 0.05, *** P < 0.001, **** P < 0.0001).Reprinted from Lu S, Zhang C, Wu H, et al A ph/mmp-9 smart dual-responsive liposome gbe@lp co-delivers and controls the release of gb1107/bms1166/enzalutamide for liver cancer immunotherapy. Materials today. Bio. 2025;32:101801.Copyright © 2026 Elsevier B.V.

lysosomal degradation and reduce irAEs. The engineered mipi series of CTLA-4 antibodies can bind both human and mouse CTLA-4, ensuring the stability of immune activation activity.[90,91] Targeting modification of nano-platforms and antibody engineering transformation provide key technical support for safe and efficient immune checkpoint blockade.

Immune Activation and Microenvironment Remodeling Nano-Platforms

Such platforms reshape the anti-TIME by activating immune cells such as DCs and NK cells or eliminating immunosuppressive cells: In innate immune activation platforms, ROS-responsive mesoporous silica nanoparticles (MSN@TheraVac) load HMGN1 and R848 and are conjugated with αPD-L1, which can synergistically activate DCs and block the PD-L1/PD-1 axis (Figure 3B).[92] CpG ODN-loaded PLGA nanoparticles (PCNs) target DCs through CD40 antibody modification, and combination with metabolic inhibitors improves T cell activation efficiency.[94] In immunosuppressive cell elimination platforms, PLGA nanoparticles coated with PD-L1-high expression macrophage membranes (PRM NDs) can clear pro-inflammatory cytokines and reconstruct the PD-1/PD-L1 inhibitory axis.[95] TREM2 antibody-modified liposomes target TREM2+ TAMs, and CD11b antibody-modified nanoparticles load IDO1 inhibitors to target MDSCs, reversing immunosuppression after TACE and restoring T cell activity, respectively.[83] In metabolic regulation synergy platforms, cancer cell membrane-coated pH-responsive NO-releasing nano-systems (MP@AL) generate NO by consuming lactate, forming a metabolic-immune synergy loop.[96] Such nano-platforms reshape the immune microenvironment through multi-mechanism synergy, providing an efficient solution for improving HCC treatment effects.

Metabolic-Immune-Angiogenesis Synergistic Regulation Nano-Platforms

Such platforms integrate metabolic intervention, immunomodulation, and anti-angiogenic functions, and synchronously break the triple vicious cycle of "metabolic reprogramming-immune suppression-angiogenesis" by co-delivering related drugs, which is a current research hotspot.

Multifunctional Liposome Platforms

Multifunctional liposome platforms achieve synchronous intervention in metabolism, immunity, and angiogenesis through multi-responsive design and multi-drug co-loading: pH/MMP-9 dual-responsive liposomes (GBE@LP) co-load Gal-3 inhibitors, PD-1 inhibitors, and enzalutamide, which precisely release drugs in the HCC microenvironment, achieving synergy of converting "cold tumors" to "hot tumors", reversing T cell exhaustion, and inhibiting angiogenesis (Figure 3C).[93] VEGF antibody and GLS1 antibody dual-modified liposomes co-load GLS1 inhibitors and PD-L1 inhibitors, simultaneously targeting tumor blood vessels, metabolic targets, and immune checkpoints, and synchronously blocking the triple vicious cycle.[97] Multi-target synergy and microenvironment-responsive design improve the treatment efficiency of complex subtype HCC.

Nanoreactors and Local Therapy Combination Platforms

The combination of nanoreactors and local therapy achieves multi-dimensional synergistic enhancement: Calcium phosphate (CaP) nanoparticle-stabilized lipiodol Pickering emulsions (CCaP-LPE) load CA4P, neutralize the acidic tumor microenvironment, destroy blood vessels, and increase CD8+ T cell infiltration.[98] TILA-TACE combined with VEGF inhibitor nanoparticles neutralizes lactic acidosis and inhibits angiogenesis, significantly improving the 3-year survival rate.[99] RFA combined with HLCaP nanoreactors induces ferroptosis and ICD, and synergizes with anti-PD-1 antibodies and anti-angiogenic drugs to inhibit distant metastasis.[66] The combination of local therapy and nano-platforms makes up for the defect of immune suppression and strengthens the efficacy of advanced HCC.

Novel Carrier Synergy Platforms

Novel carriers such as exosomes and bacteria achieve targeted delivery and multi-functional synergy by virtue of their natural advantages: Exosomes load GLS1 siRNA, PD-L1 siRNA, and apatinib, targeting and silencing metabolic enzyme and immune checkpoint genes, while inhibiting angiogenesis, with excellent biocompatibility and targeting.[100] Attenuated Salmonella, modified by metabolic engineering, colonizes the hypoxic region of tumors, releases GLS1 inhibitors and IL-12 in situ, synchronously inhibiting glutamine metabolism, activating immune responses, and

destroying abnormal blood vessels.[101] The natural characteristics of novel carriers provide safer and more efficient treatment options for advanced HCC.

Nano-Metabolic Regulation and Multi-Therapy Synergistic Treatment Strategies

It is difficult to break the triple vicious cycle of "metabolism-immunity-angiogenesis" in HCC by relying solely on metabolic intervention or single therapy. By virtue of the advantages of multi-target synergy and multi-modal integration, nanotechnology can achieve precise synergy between metabolic regulation and multiple therapies such as ICIs, local therapy, and anti-angiogenic therapy, significantly improving treatment effects. This section systematically elaborates on the core mechanisms, strategies, and key technical platforms of the synergy between nano-metabolic regulation and multiple therapies.

Core Mechanisms of Synergistic Therapy

The core of the "metabolism-immunity" vicious cycle in HCC lies in the mutual reinforcement of metabolic reprogramming and immune suppression: Abnormal glucose/lipid/amino acid metabolism inhibits immune cell function through nutritional deprivation (such as tryptophan and arginine consumption), accumulation of toxic metabolic products (such as ammonia and lactate), and signaling pathway crosstalk (such as AHR and mTOR activation). In turn, immunosuppressive cells (such as MDSCs and Tregs) further drive metabolic reprogramming by secreting cytokines (such as TGF-β and IL-6). Synergistic therapy breaks this cycle through two pathways: on the one hand, targeting key metabolic targets (such as GLS1, FASN, and IDO1) to block metabolic abnormalities and reduce the inducement of immune suppression; on the other hand, regulating the immune microenvironment (such as reversing M2-TAM polarization and blocking PD-L1) to restore the killing function of immune cells. The two form a positive feedback of "metabolic improvement-immune activation". For example, the combination of glucose metabolism inhibitors and PD-1 antibodies can reduce lactate production and enhance CD8+ T cell infiltration; the combination of fatty acid metabolism intervention and CSF-1R inhibitors can inhibit fatty acid oxidation in TAMs and weaken their immunosuppressive effect. Breaking the "metabolism-immunity" vicious cycle is the core logic of HCC synergistic therapy. In the future, personalized combination regimens should be formulated based on the patient's metabolic subtype and immune characteristics to maximize treatment benefits.

Core Synergistic Treatment Strategies

Based on nano-platforms, metabolic-immune synergistic treatment strategies mainly maximize treatment effects through combination methods such as "metabolic intervention + immune checkpoint blockade", "metabolic intervention + immune activation", "local therapy + metabolic-immune regulation", and "biomarker-based personalized synergistic strategies". Specific strategies need to be precisely selected according to HCC subtype, microenvironment characteristics, and treatment stage (Table 3).

Table 3 Nanotechnology and Combined Therapy Strategies

Combination Mode	Representative Regimens	Core Mechanisms	Ref.
Metabolic intervention + ICIs	GLS1 inhibitor + PD-1 antibody, LDHA inhibitor + PD-1 antibody	Reverse immunosuppressive microenvironment, enhance T cell infiltration	[49,79,97]
Local therapy + nano-modulation	TACE + CaP nanoparticles, RFA + HLCaP nanoreactors	Improve acidosis, induce ferroptosis, enhance chemotherapy/radiotherapy efficacy	[66,98,99]
Multi-target synergy (metabolism-immunity-angiogenesis)	Metabolic inhibitor + anti-angiogenic drug + PD-1 inhibitor, Gal-3 inhibitor + PD-1 inhibitor	Break the triple vicious cycle of "metabolic reprogramming-immune suppression-angiogenesis"	[93,101]

Metabolic Intervention + Immune Checkpoint Blockade

"Metabolic intervention + immune checkpoint blockade" is a classic synergistic model. Metabolic inhibitors improve the immunosuppressive microenvironment to enhance ICI sensitivity, and precise design needs to be combined with metabolic subtypes: For glycolysis-active subtypes, 3-BrPA, LDHA inhibitor nano-platforms combined with PD-1/PD-L1 inhibitors, or MCT1 inhibitor nanoparticles combined with CTLA-4 inhibitors are used;[78–80,90] for glutamine metabolism-abnormal subtypes, GLS inhibitors, SLC1A5 antagonist nano-platforms combined with CTLA-4 inhibitors, or IDO1 inhibitor nanoparticles combined with PD-L1 inhibitors are selected;[49–51] for lipid metabolism-abnormal subtypes, FASN inhibitor nano-platforms combined with PD-L1 inhibitors and ECM degrading enzymes, or CD36 inhibitor nanoparticles combined with PD-1 inhibitors are used;[39,43,47,74] for example, the targeted delivery of the LDHA inhibitor oxamate and the SLC16A3 inhibitor lonidamine via nano-carriers, combined with anti-PD-1 antibodies, have shown better therapeutic effects than single agents (Figure 4A).[79,102] The core of this synergistic model lies in precise subtype matching. The targeted delivery of nano-carriers further improves the safety and efficacy of combination therapy.

Metabolic Intervention + Immune Activation

The "metabolic intervention + immune activation" strategy reshapes the metabolic microenvironment through metabolic inhibitors, and simultaneously activates innate immunity and adaptive immunity to form a synergistic killing effect. Simultaneous delivery or sequential delivery strategies can be adopted: In the simultaneous delivery strategy, the Nano-IFNγ/Zole nano-platform loads zoledronic acid and IFNγ, synergistically promoting the conversion of TAMs to the M1 type. The MSN@TheraVac nano-platform loads TLR agonists and is conjugated with αPD-L1, which responds to ROS to release drugs, activate DCs, and block the PD-L1/PD-1 axis;[92,103] in the sequential delivery strategy, HA/PTX chemotherapy nanocomposites are first used to induce tumor cell apoptosis and release antigens, then PCNs and PINs are used to activate DCs and combined with lactate scavengers to regulate metabolism (Figure 4B), or GLS1 inhibitor nanoparticles are first used to block glutamine metabolism, then CAR-T cells are infused to reduce their exhaustion.[94] Reasonable selection of delivery methods and drug combinations can maximize the synergistic effect of metabolic regulation and immune activation, improving treatment effects.

Local Therapy + Metabolic-Immune Regulation

Local therapies (TACE, RFA, etc.) are the main treatment methods for HCC, but they are prone to inducing metabolic reprogramming and immune suppression. Combining nano-regulation of the metabolic-immune axis can significantly improve efficacy and reduce recurrence risk. Precise regulation strategies need to be adopted according to the microenvironment changes after local therapy: TACE combined with CaP-EPI nanoparticles can enhance chemotherapy effects and regulate tumor metabolism; combination with glutaminase inhibitors can enhance tumor cell death;[104] nano-carriers can also be used to co-deliver metabolic inhibitors and TREM2 antagonists, combined with anti-PD-L1 antibodies to reverse immunosuppression after TACE (Figure 4C);[83] TILA-TACE combined with GLS1 inhibitor nanoparticles can neutralize lactic acidosis and block glutamine metabolism;[99] RFA combined with HLCaP nanoreactors can induce ferroptosis and ICD, and synergize with anti-PD-1 antibodies to inhibit distant metastasis;[66] nano-carriers can also be used to co-deliver lactate dehydrogenase inhibitors and CSF-1R inhibitors to block the recruitment of M2-type TAMs;[105] RFA combined with FASN inhibitor nanoparticles can inhibit lipid metabolism reprogramming and restore T cell function.[106] The precise combination of local therapy and nano-metabolic-immune regulation can specifically improve the abnormal microenvironment after treatment, significantly improving efficacy and reducing recurrence risk.

Biomarker-Based Personalized Synergistic Strategies

Biomarker-guided personalized therapy is the key to improving HCC efficacy, which can achieve precise matching of "metabolic subtype-nano-carrier-synergistic therapy": Among metabolic-related biomarkers, GMScore can predict patient resistance to TACE and ICIs. Patients with high GMScore are suitable for glutamine metabolism inhibitor nano-platforms combined with ICIs; patients with high FASN expression are suitable for FASN inhibitor nanoparticles combined with PD-L1 inhibitors and ECM degrading enzymes; patients with high HK2 expression are suitable for glucose metabolism inhibitor nano-platforms combined with PD-1 antibodies;[31,39,47,55,78] among immune-related biomarkers, PD-L1-positive patients can select PD-L1 antibody-modified dual-target nano-carriers; immune-cold patients

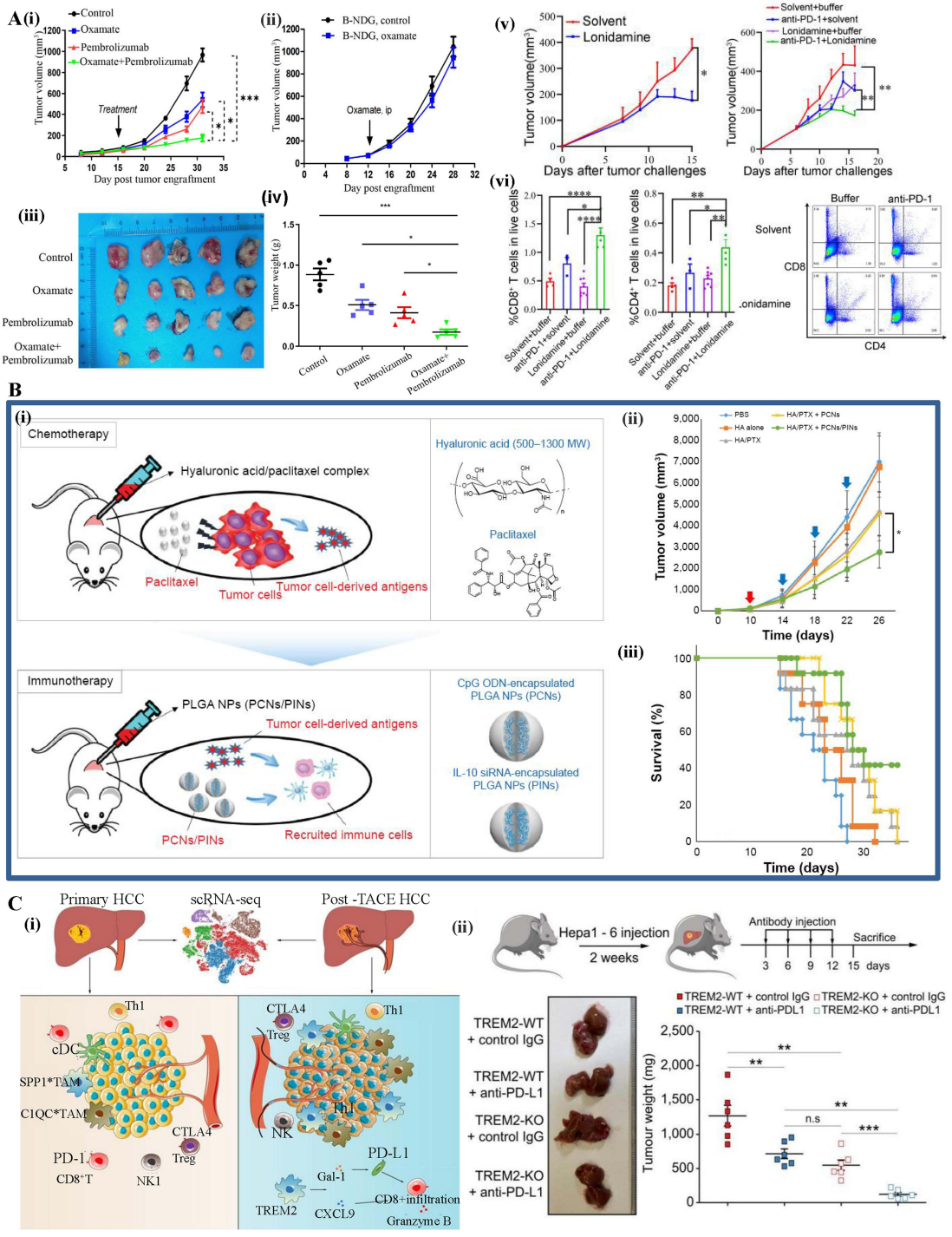

Figure 4 Nanometabolism regulation and multi therapy core collaborative therapy strategy. (**A**) The synergistic anti-tumor effect of "different metabolic inhibitors+anti-PD-1".[79,102] (i) Tumor growth curves (control, Oxamate monotherapy, Pembrolizumab monotherapy, combination); CDX volume, mean ± SD (n=5); *P<0.05, ***P<0.001. (ii) Tumor growth in NSCLC-bearing B-NDG mice (Oxamate vs. PBS); no significant difference (n=5). (iii), (iv) Tumor photos and weights of each group at treatment end (n=5); *P<0.05, ***P<0.001. Reprinted from Qiao T, Xiong Y, Feng Y, et al Inhibition of Idh-a by oxamate enhances the efficacy of anti-pd-1 treatment in an nsclc humanized mouse model. Front Oncol. 2021;11:632364. (v) Tumor growth of E0771/MC-38 cells in C57BL/6 mice (lonidamine ± anti-PD-1); *P<0.05, **P<0.01. (vi) $CD8^+/CD4^+$ T cell percentage in MC-38 TME (mean ± SEM); *P<0.05, **P<0.01, ****P<0.0001. Reprinted from Yu T, Liu Z, Tao Q, et al Targeting tumor-intrinsic slc16a3 to enhance anti-pd-1 efficacy via tumor immune microenvironment reprogramming. Cancer Lett. 2024;589:216824. (**B**) The complete process and actual therapeutic effect of the "sequential delivery strategy"[94] (i) Schematic of sequential delivery: HA/PTX (chemo) followed by PLGA NPs (PCNs/PINs, immunomodulatory) for chemoimmunotherapy. (ii) Tumor growth curve (n=12); treatments: PBS, HA alone, HA/PTX ± PLGA NPs (*P<0.05 vs PCNs group); filled arrow: HA/PTX, unfilled arrow: PLGA NPs. (iii) Kaplan–Meier survival plot; red arrow: anticancer drug, blue arrow: immune modulators. Reprinted from Heo MB, Kim S, Yun WS, et al Sequential delivery of an anticancer drug and combined immunomodulatory nanoparticles for efficient chemoimmunotherapy. Int J Nanomedicine. 2015;10:5981–92. (**C**) Mechanism and therapeutic effect of TREM2 deficiency combined with anti-PD-L1 antibody.[83] (i) Mechanism diagram; (ii) Anti-PD-L1 treatment procedure, representative HCC tumor photos (orthotopic model) and tumor weight (n=6); ** P<0.01, *** P<0.001. Reprinted from Tan J, Fan W, Liu T, Zhu B, et al Trem2(+) macrophages suppress cd8(+) t-cell infiltration after transarterial chemoembolisation in hepatocellular carcinoma. J Hepatol. 2023;79(1):126–40.© 2023 European Association for the Study of the Liver. Published by Elsevier B.V. All rights reserved.

with insufficient CD8+ T cell infiltration are suitable for triple nano-platforms of "metabolic inhibitors + immune activators + anti-angiogenic drugs";[88,93,98] in terms of composite biomarkers, combined detection of exosomal MUC-1 and PD-L1 can be used for patient stratification; the G6PD target identified by SHRPI is suitable for targeted nano-carriers combined with hypoxia-responsive drug delivery systems; the "high GLS1 expression + PD-L1 positive" subtype recommends synergistic therapy with glutamine metabolism inhibitors and PD-1 antibodies;[49,107,108] serum metabolic biomarkers such as PC 36:4 and phenylalanine can be used for efficacy monitoring and real-time adjustment of treatment regimens.[62] The precise application of multiple types of biomarkers provides a clear direction for personalized nano-therapy of HCC, helping to maximize treatment benefits.

Key Supporting Technologies for Clinical Translation

The clinical translation of nano-synergistic therapy relies on three major supporting technologies: efficacy monitoring, patient stratification, and safety optimization. These technologies directly determine the feasibility and effectiveness of clinical applications and need to be continuously improved in combination with clinical needs.

Efficacy Monitoring Technologies

In HCC treatment, efficacy monitoring technologies provide key basis for the adjustment of "metabolism-immune" synergistic therapy regimens by accurately capturing treatment-related biological signals: The core principle is to use imaging technology or molecular detection to real-time track tumor metabolic changes and immune microenvironment dynamics. For example, gadolinium-based MRI mo62nitors tumor blood supply and metabolically abnormal regions;[109] fluorescent probes targeting CD8+ T cells realize non-invasive visualization of immune cell infiltration;[110] liquid biopsy detects serum metabolic markers such as lactate and kynurenine, and immune markers such as PD-L1+ exosomes to comprehensively evaluate treatment response.[62,108] The monitoring dimensions cover both metabolic and immune aspects. The metabolic dimension focuses on the activity of metabolic enzymes such as GLS1 and FASN and the concentration of products such as lactate and kynurenine; the immune dimension tracks indicators such as the proportion of effector T cells and the polarization state of TAMs.[109] The supporting role for treatment adjustment is reflected in judging whether the drug effectively blocks metabolic pathways and activates anti-tumor immunity through dynamic monitoring, and timely optimizing drug dosage or combination strategies to avoid ineffective treatment. Current efficacy monitoring faces problems such as difficulty in simultaneous monitoring of "metabolism-immune" indicators and the need for invasive sampling in some cases. In the future, it is necessary to develop non-invasive multi-modal combined monitoring or liquid biopsy technologies to accurately guide the adjustment of personalized therapy.

Patient Stratification Technologies

In HCC "metabolism-immune" synergistic therapy, patient stratification technologies provide core support for the formulation of personalized treatment regimens by accurately dividing patient subtypes: The stratification basis focuses on two major dimensions: metabolic characteristics and immune status. The metabolic dimension identifies different metabolic reprogramming subtypes by detecting the expression levels of metabolic enzymes such as GLS1 and FASN and the concentrations of glucose/lipid/amino acid metabolites;[110,111] for example, through metabolomic analysis, patients with high HK2 expression and lactate accumulation are classified as glycolytic subtypes, while those with high FASN and CD36 expression are classified as lipid metabolic subtypes;[12,39] through immunohistochemical detection of PD-L1 expression and CD8+ T cell infiltration density, patients are divided into immune-hot and immune-cold subtypes;[47,53] the key role of this technology in optimizing treatment regimens is to match suitable regimens for different stratification results—for example, for the "high FASN expression + M2-TAM enrichment" subtype, the combination of fatty acid metabolism inhibitors and TAM reprogramming drugs is preferred; for the "high GLS1 expression + PD-L1 positive" subtype, synergistic therapy with glutamine metabolism inhibitors and PD-1 antibodies is recommended, avoiding the efficacy differences caused by "one-size-fits-all" treatment.[38] Current patient stratification technologies have problems such as inconsistent standards, high detection costs, and difficulty in dynamically tracking subtype changes. In the future, it is necessary to establish a multi-center "metabolism-immune" composite standard, develop low-

cost and rapid detection technologies, and improve the accuracy of regimen matching in combination with dynamic monitoring.

Safety Optimization Technologies

In HCC "metabolism-immune" synergistic therapy, safety optimization technologies reduce treatment-related risks by accurately regulating the scope and dosage of drug action: The targets focus on normal cell protection and toxic side effect blocking. For example, galactose-modified liposomes specifically recognize asialoglycoprotein receptors on hepatocytes, reducing the uptake of metabolic inhibitors by normal liver tissue;[70] pH-sensitive PLGA nanoparticles only release drugs in the acidic tumor microenvironment (pH 6.5–6.8), avoiding off-target toxicity in normal tissues.[16] The latter controls the slow release of drugs through nano-carriers to reduce toxic side effects caused by peak concentrations.[112,113] The implementation methods include "targeted attenuation" and "dosage regulation". The former avoids drug release in normal tissues by means of tumor microenvironment-responsive carriers (such as pH-sensitive carriers); the latter controls the slow release of drugs through nano-carriers to reduce toxic side effects caused by peak concentrations.[114,115] The safety of HCC "metabolism-immune" synergistic therapy can be improved through "toxicity antagonism" design: modifying hepatoprotective agents such as glycyrrhetinic acid on carriers loaded with cytotoxic metabolic inhibitors,[116] or co-loading low-dose glucocorticoids in nano-systems to alleviate immune-related adverse events such as rash and diarrhea,[117] ensuring synergistic efficacy while reducing problems such as liver injury. In the future, it is necessary to optimize regimens in combination with individual patient differences and establish an individualized evaluation system balancing "efficacy-safety".

Clinical Translation Challenges and Future Development Directions

Although nanotechnology shows great potential in HCC metabolic-immunomodulation, it still faces multi-dimensional challenges from the laboratory to clinical practice, including carrier performance, personalized strategies, and regulatory industrialization. This section systematically analyzes these challenges and proposes targeted optimization solutions, providing a path reference for the clinical translation of nanotechnology.

Core Challenges

Performance Bottlenecks and Biosafety Risks of Nanocarriers

Current nanocarriers face three major performance and safety issues in clinical translation: Most nanocarriers rely on the EPR effect for passive targeting, and the enrichment rate in solid tumors is usually less than 5%. For example, unmodified PLGA nanoparticles only achieve 2–3% tumor accumulation in HCC models.[118] Active targeting modification still has problems such as off-target binding or failure to internalize after targeting; some inorganic nanomaterials (such as quantum dots) degrade slowly and are prone to long-term accumulation in the liver and kidneys, causing oxidative stress and organ damage;[119] the degradation products of polylysine-based polymer nanoparticles may induce inflammatory responses in normal tissues.[120] As exogenous substances, nanocarriers are easily recognized and cleared by the MPS, and their surface characteristics may activate the complement system or induce antibody production, triggering immune reactions.[119] Targeting efficiency, accumulation toxicity, and immunogenicity are core obstacles to the clinical translation of nanocarriers, which need to be specifically addressed through material optimization and design innovation.

Lack of Personalized Metabolic-Immune Regulation Strategies

The high heterogeneity of HCC makes "one-size-fits-all" nano-therapy regimens difficult to meet clinical needs, mainly reflected in three aspects: Patients with different etiologies and stages have significant differences in metabolic reprogramming characteristics and immune phenotypes—for example, HBV-related HCC is dominated by glycolysis activation, while NAFLD-related HCC is characterized by lipid accumulation,[13,25] and a single nano-drug cannot be adapted to all patients;[121] the screening and efficacy prediction of nano-drugs mostly rely on cell lines or immunodeficient mouse models, which are difficult to accurately simulate the metabolic-immune micro-environment in patients. For instance, a glucose metabolism-targeted nano-drug that showed significant efficacy in HepG2 cell lines failed to achieve expected results in clinical trials due to the lack of consideration of patient

immune suppression.[122] Although metabolic markers such as HK2 and FASN have been discovered, most lack sufficient clinical verification and standardized detection and interpretation standards, and cannot effectively guide the selection and dosage adjustment of nano-drugs.[123] It is necessary to specifically address the problems related to heterogeneity, models, and markers to promote the landing of nano-therapy toward precision.

Key Bottlenecks in Regulation and Industrialization

The regulation and industrialization of nano-drugs face problems such as lack of standardization and high costs, restricting their clinical accessibility: Currently, there is a lack of exclusive PK/PD evaluation standards and unified toxicity assessment specifications for nano-metabolic drugs. For example, traditional pharmacokinetic models cannot accurately calculate the in vivo distribution and clearance rate of mesoporous silica nanoparticles, leading to difficulty in comparing data from different institutions.[124] Laboratories mostly use batch processes to prepare nanocarriers, with poor particle size uniformity and batch stability. For example, the particle size variation coefficient of liposomes prepared by conventional thin-film hydration method exceeds 20%, while large-scale production relying on microfluidic technology can reduce the variation coefficient to less than 10%.[125] However, the popularization of microfluidic equipment is limited by high costs; some nano-drugs have the phenomenon of "excessive nanonization". Although complex designs (such as multi-layer responsive carriers) improve laboratory efficacy, they significantly increase preparation difficulty and costs without bringing substantial clinical benefits. It is necessary to establish an exclusive evaluation system, popularize large-scale production technology, and avoid "excessive nanonization" to promote the efficient translation and clinical accessibility of nano-drugs.

Optimization Solutions

To address the above challenges, optimization solutions need to be proposed from three aspects: carrier design, strategy innovation, and system guarantee to promote the clinical translation of nanotechnology.

Optimization of Nanocarrier Performance and Improvement of Biosafety

The targeting efficiency and biosafety of nanocarriers can be optimized through a series of strategies: In terms of improving targeting efficiency, "dual-target modification" combining liver targeting with tumor cell targeting or tumor cell targeting with immune cell targeting is adopted to achieve multi-level targeting and improve enrichment efficiency. At the same time, penetration peptide modifications such as TAT and iRGD are introduced to enhance the penetration ability of carriers in the tumor stroma;[124] in terms of optimizing biosafety, biocompatible and degradable materials such as PEG-PLA, chitosan, and albumin are preferred. Surface "stealth" modification is performed with PEG, PEG-PE, etc, and the degradation rate is precisely controlled by adjusting material parameters to reduce long-term accumulation risks and immunogenicity.[120] These optimization strategies can effectively balance the targeting and safety of nanocarriers, laying a foundation for their clinical translation.

Construction of Personalized Metabolic-Immune Regulation Strategies

The construction of personalized metabolic-immune regulation strategies requires multi-dimensional collaborative advancement: Combining HCC metabolic typing (such as glycolytic type, fatty acid oxidation type, and glutamine-dependent type) with immune phenotypes, patients are stratified through multi-omics technologies such as transcriptomics and metabolomics, and personalized nano-therapy regimens are customized for different subtypes;[126] PDX models and organoid models are used to screen nano-drugs, retaining the patient's tumor metabolic-immune characteristics to accurately predict efficacy; a combined detection system for metabolic enzymes such as HK2, FASN, and GLS1 and immune molecules such as PD-L1 and CD8+ T cell infiltration is developed, and a "marker-efficacy" correlation database is established through convenient detection methods such as immunohistochemistry and liquid biopsy, providing a basis for patient stratification and efficacy monitoring.[125] The integrated application of multi-dimensional technologies is the core support for realizing precise and personalized nano-therapy of HCC.

Solutions to Key Issues in Regulation and Industrialization

To promote the clinical translation of nano-drugs, efforts need to be made in three aspects: establishment of a standardized system, improvement of industrialization feasibility, and avoidance of "excessive nanonization": Joint multi-disciplinary experts to establish exclusive PK/PD evaluation standards for nano-metabolic drugs, clarify methods for separating and detecting particulate and free drugs and pharmacokinetic parameters related to nano-characteristics, and improve the full-chain toxicity assessment specifications covering indicators such as long-term accumulation toxicity and immunogenicity;[127] popularize large-scale production technologies such as microfluidics to achieve uniform preparation and batch stability control of nanocarriers. Prioritize the translation of nano-drugs with simple structures and significant efficacy through cost-benefit analysis, and reduce costs through domestic production of raw materials and process optimization; establish clinical value-oriented design principles, evaluate the necessity of nanotechnology through peer review and clinical expert demonstration, and avoid over-pursuing complex designs. The clinical translation of nanotechnology in HCC metabolic-immunomodulation is core to the matching of "technical feasibility" and "clinical needs". It needs to be based on carrier performance optimization, centered on personalized strategies, and guaranteed by standardized systems and industrialization technologies. Through cross-field linkage, acceleration of translation will benefit more patients.

Future Outlook

Based on current research progress and clinical needs, the future development of nanotechnology for HCC metabolic-immunomodulation will focus on technological innovation, clinical translation breakthroughs, and interdisciplinary collaboration, promoting the leapfrog development of this field from basic research to clinical application.

Technological Innovation Directions

Future nanotechnology innovation will focus on more intelligent and precise regulation directions: Intelligent responsive nanocarriers will be upgraded to "metabolite concentration response" and "cell-specific response", developing metabolite-sensitive carriers such as lactate and glucose to achieve "on-demand drug release", and combining single-cell sequencing to develop precise drug release systems targeting specific cell subsets in TIME;[74,75] in-depth integration of interdisciplinary technologies, AI optimizes carrier structures through machine learning algorithms and realizes "personalized carrier design", and CRISPR collaborates with nanocarriers to achieve precise regulation of metabolic genes and "gene editing-immunotherapy" combination;[128] precise regulation at the single-cell level becomes a new breakthrough, realizing single-cell metabolic visualization guidance with technologies such as Raman imaging and SIMS, and developing nano-systems that can regulate the metabolic fate of immune cells, achieving dual regulation of "effector cell activation-inhibitory cell inactivation"[128] Multi-dimensional technological innovation will greatly improve the precision and effectiveness of HCC metabolic-immunomodulation, providing more powerful technical support for personalized therapy.

Key Directions for Clinical Translation

In clinical translation, the design of early clinical trials will focus on "narrow population, high benefit", prioritizing the verification of the safety and effectiveness of the combination of nano-metabolic regulation and ICIs. The best benefit population such as those with high GLS1 expression and PD-L1 positive is selected through biomarkers, and enrollment criteria are precisely set to reduce the exposure risk of non-benefit populations. At the same time, efficacy evaluation indicators are expanded. In addition to traditional indicators such as objective response rate and progression-free survival, immune-related and metabolic markers such as CD8+ T cell infiltration rate and serum GLS1 activity are included; combination therapy regimens will break the "simultaneous administration" model, and realize "temporal synergy" by virtue of the responsive characteristics of nano-carriers. For example, hypoxia-responsive nano-metabolic inhibitors are administered 1–2 weeks after TACE treatment. The optimal combination ratio and administration interval of metabolic inhibitors and ICIs are clarified through preclinical research to avoid increased toxicity caused by drug interactions.[129,130] The optimization of clinical trial design and the temporal synergy of combination regimens are the keys to improving the efficiency and safety of the clinical translation of nano-metabolic-immune therapy.

Needs for Interdisciplinary Collaboration

The interdisciplinary collaboration of nanotechnology for HCC metabolic-immunomodulation needs to focus on the in-depth integration of basic research and clinical applications, and the collaborative advancement of industrial ecosystem construction by multiple parties:[131] On the one hand, establish a closed-loop system of "material research and development-mechanism analysis-clinical verification", reverse-drive basic research with clinical pain points such as ICI resistance and nanocarrier accumulation toxicity, and build a "nano-drug clinical translation center" in large hospitals to integrate multiple platforms and shorten the translation cycle; on the other hand, promote collaborative cooperation between scientific research institutions, pharmaceutical enterprises, and regulatory authorities. Scientific research institutions focus on basic mechanisms and prototype carrier development, enterprises lead the optimization of large-scale production processes and clinical trial applications, and regulatory authorities set up a "breakthrough therapy" approval channel for nano-drugs and provide technical guidance. The future of this technology will focus on "solving clinical pain points", addressing existing challenges through technological innovation, clinical translation, and interdisciplinary collaboration. With technological iteration and ecological improvement, nanotechnology is expected to become a key means to break the HCC "metabolism-immune" vicious cycle, bringing new therapeutic hope to patients.

Conclusions

Nanotechnology offers an innovative solution to break the "metabolic reprogramming-immune suppression-angiogenesis" vicious cycle in HCC, with core advantages of precise targeted delivery, tumor microenvironment-responsive release, and multifunctional synergy. It synchronously intervenes in glucose, fatty acid, and amino acid metabolic abnormalities and reshapes the immunosuppressive microenvironment, significantly enhancing the efficacy of ICIs and local therapies.

Current applications face three key challenges: insufficient targeting efficiency and biosafety risks of nanocarriers, difficulty in adapting "one-size-fits-all" strategies to HCC metabolic-immune heterogeneity, and lack of exclusive evaluation standards and mature industrialization processes. Promising actionable strategies to address these challenges include: (i) dual-targeted nanocarriers (eg, galactose+GPC3 modified liposomes, CD11b+PD-L1 antibody functionalized nanoparticles) that co-target HCC cells and immunosuppressive cells (TAMs/MDSCs); (ii) prioritization of key metabolic targets such as GLS1 (glutamine metabolism) and FASN (fatty acid synthesis) for subtype-specific personalized intervention; (iii) rational combination of nano-metabolic regulation with TACE/ICIs to enhance clinical response in intermediate-advanced HCC.

Future development should focus on three core directions: optimizing nanocarrier design via dual-target modification and biocompatible materials, constructing personalized systems through multi-omics-based subtype matching and responsive nano-platforms, and establishing standardized evaluation specifications while promoting large-scale production. With technological iteration, nanotechnology will advance from "broad-spectrum regulation" to "precise adaptation", becoming a core tool for HCC precision therapy and addressing clinical treatment bottlenecks.

Data Sharing Statement

All data generated and/or analyzed in this study are included in this published article.

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Disclosure

The authors declare that they have no competing interests.

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