Editorial | Open Access

Hepatoma Research

Liu. *Hepatoma Res.* 2026;12:49 **DOI:**10.20517/2394-5079.2026.82

Advancing immunotherapy and tumor microenvironment research in hepatocellular carcinoma

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Citation: Liu L. Advancing immunotherapy and tumor microenvironment research in hepatocellular carcinoma. *Hepatoma Res.* 2026;12:49. https://dx.doi.org/10.20517/2394-5079.2026.82

Received: 26 Jun 2026
Revised: 24 Jul 2026
Accepted: 11 Aug 2026
Published: 19 Aug 2026

Academic Editor: Huiguo Ding
Copy Editor: Ting-Ting Hu
Production Editor: Ting-Ting Hu

INTRODUCTION

Hepatocellular carcinoma (HCC), as a great global health challenge, is characterized by its staggering incidence, profound biological heterogeneity, and dismal prognosis. Particularly in China, the burden of HCC is acute, often exacerbated by the late-stage presentation of the disease, which severely limits eligibility for curative interventions. For decades, the clinical management of HCC was largely reactive, focusing primarily on late-stage therapeutic interventions with modest survival benefits. However, we are currently witnessing a profound paradigm shift. This evolution, as highlighted in the latest clinical guidelines, integrates prevention, surveillance, and early diagnosis into a seamless continuum of care, aiming to intercept the disease long before it reaches its lethal advanced stages.

The most transformative catalyst in this new era has been the advent of immune checkpoint inhibitors (ICIs), which have fundamentally reshaped the treatment landscape for advanced HCC. For over a decade, systemic therapy was defined by the "Monotherapy 1.0" era, dominated by single-agent tyrosine kinase inhibitors. It is now widely recognized that the structural architecture and immune evasion of HCC are tightly intertwined with the metabolic reprogramming of both tumor cells and surrounding stroma.

This special issue focuses on the immune microenvironment and immunotherapy of HCC, with collected articles covering research areas including HCC metabolism and immunotherapeutic strategies for HCC.

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SYSTEMIC TREATMENT LANDSCAPE OF HCC

ICI combination therapies are established as the standard first-line treatment for advanced HCC. Dual immunotherapy combinations, such as nivolumab plus ipilimumab[1] or durvalumab plus tremelimumab[2], have demonstrated the capacity to extend overall survival (OS) in clinical trials. According to clinical trial data, the OS of patients receiving first-line monotherapy for HCC is significantly inferior to that of those receiving doublet combination therapies. In the IMbrave150 and CARES-310 studies, doublet combination therapies yielded median OS of 19.2 and 23.8 months, respectively[3,4]. The remarkable long-term survival benefit achieved by first-line dual immunotherapy regimens in HCC is highly encouraging. According to the HIMALAYA study, the STRIDE regimen demonstrated a 5-year OS rate of 19.4% and a 6-year OS rate of 17.1%. However, clinical data indicate that patients receiving these dual ICI regimens experience a higher incidence of early mortality. Furthermore, these combinations have failed to show a statistically significant difference in progression-free survival (PFS)[5].

The articles in this collection can be organized into two deeply interconnected thematic parts, Metabolic Reprogramming as a Modulator of the tumor microenvironment (TME), and Immunopathology Therapeutic Integration.

METABOLIC REPROGRAMMING AS A MODULATOR OF THE TME

Chen *et al.* meticulously dissect the molecular characteristics of fatty acid (FA) metabolic reprogramming in HCC[6]. Utilizing multi-omics public datasets, the authors identify 42 core FA metabolism mediators and construct an unsupervised FA_score algorithm to quantify individual metabolic patterns. By pairing this score with an immune risk model, they unveil a sophisticated "Mixed Index" (MI) classification system. Crucially, the authors demonstrate that patients in the MI-2 subgroup - characterized by a high FA score and high immune risk - exhibit significantly poorer OS and a TME heavily enriched with immunosuppressive entities, including myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs). This research underscores the utility of FA metabolic signatures as complementary biomarkers for immune stratification and personalized treatment selection.

Complementing this quantitative approach, the comprehensive review by Ruan and Sun maps out the broader landscape of metabolic reprogramming, focusing on the dynamic crosstalk among the Warburg effect, glutamine addiction, and altered lipid oxidation[7]. A unique highlight of their work is the systematic evaluation of the non-canonical regulatory roles of metabolic enzymes. Enzymes such as hexokinase 2 (HK2), Pyruvate Kinase M2 (PKM2), and Lactate Dehydrogenase A (LDHA) are shown to translocate or interact independently of their catalytic functions to drive chromatin remodeling, stabilize oncogenic transcription factors like hypoxia inducible factor 1 subunit alpha (HIF-1α), and directly suppress $CD8^+$ T-cell cytotoxicity through extracellular acidification and histone lactylation. The authors conceptualize these interactions within discrete, spatially segregated "immune-metabolic niches," providing a robust rationale for combining small-molecule metabolic inhibitors with standard ICIs to relieve global immunosuppression.

Furthermore, interventional modalities driven by novel biomarkers are continually expanding. Novel immunotherapies like chimeric antigen receptor T cell (CAR-T) therapy have shown good efficacy by targeting specific HCC antigens, including glypican 3 (GPC-3) and mesothelin[8]. Novel targeted therapies include fibroblast growth factor receptor 4 (FGFR-4) inhibitors. Researchers found that targeting FGFR-4 inhibitors could downregulate programmed death ligand 1 (PD-L1) and C-C motif chemokine ligand 2 (CCL2) to facilitate ICI therapy. Anti-PD-L1 combined with FGFR4 inhibitor BLU-554 or MAPK inhibitor trametinib markedly inhibited fibroblast growth factor 19 (FGF19)-ETS variant transcription factor 4 (ETV4) signalling-mediated HCC metastasis[9]. Serial tumor biopsies from patients with immune checkpoint blocker

(ICB)-resistant HCC demonstrate heightened tumor cell fatty acid uptake (FAU) with concomitant up-regulation of triggering receptor expressed on myeloid cells 2 ($TREM2^+$) lipid-associated macrophages (LAMs) in lipid-laden TME. Myeloid-specific Trem2 deficiency and anti-TREM2 antibody abolish FA-dependent energy production in ICB-resistant tumor cells, resensitizing them to ICB via epigenetic TME remodeling[10]. Thus, identification of common metabolic vulnerabilities for combinatorial immune checkpoint targeting can further improve the therapeutic efficacy of immunotherapy.

IMMUNOPATHOLOGY THERAPEUTIC INTEGRATION

Focusing on the rapidly rising global driver of non-viral liver cancer, Han *et al.* deliver a timely review on the distinct immune microenvironment of metabolic-associated fatty liver disease-related HCC (MAFLD-HCC)[11]. Driven by lipotoxicity, cholesterol accumulation, and gut-liver axis dysbiosis, MAFLD-HCC establishes a paradoxical "false-hot" but immune-resistant phenotype. The authors elucidate how specific pathogenic immune subsets - such as auto-aggressive $CXCR6^+PD\text{-}1^+$ $CD8^+$ T cells, $TREM2^+$ metabolic dysfunction-associated steatohepatitis (MASH)-associated macrophages (NAMs), and neutrophil extracellular traps (NETs) - collaboratively orchestrate a highly immunosuppressive niche. Crucially, this unique immunopathology explains why MAFLD-HCC often responds poorly to standard PD-1 blockades, which may paradoxically overactivate pathogenic T cells and worsen tissue fibrosis. The paper reviews emerging sensitization strategies, including metabolic interventions, microbiota transplantations, and small-molecule inhibitors targeting TREM2 pathways.

Li *et al*. synthesize late-phase clinical trial data to link dominant TME phenotypes (inflamed, immune-excluded, and immune-desert) to first-line systemic combinations and locoregional therapies (LRTs)[12]. The authors outline a mechanistic framework highlighting how vascular endothelial growth factor A (VEGF)-immunity normalization and radiation-induced cyclic guanosine monophosphate-adenosine monophosphate synthase-stimulator of interferon genes (cGAS-STING) type I interferon signaling can successfully reshape an immunologically "cold" tumor into a "hot" one. This biological synergy underpins the validation of the emerging "Transcatheter arterial chemoembolization (TACE)-plus" standard (combining TACE, ICIs, and anti-VEGF therapy), supported by landmark data from trials like EMERALD-1 and LEAP-012. Furthermore, the article provides actionable conversion and neoadjuvant algorithms designed to push the boundary from palliative care to curative surgical resection.

Notably, the aberrant activation of the Wnt/β-catenin signaling pathway is established as a core mechanism mediating intratumoral immune exclusion and primary resistance to ICIs. Developing antagonistic agents that target critical molecular nodes within this pathway, such as BCL9, can alter the physicochemical and cellular distribution profiles of the TME, thereby promoting the local infiltration of effector T cells. This interventional strategy provides a definitive approach to reverse current states of immune resistance by targeting such molecules[13].

CONCLUSION AND FUTURE PERSPECTIVES

Immunotherapy has fundamentally restructured the therapeutic landscape of HCC, driving a paradigm shift from traditional surgery to systematic treatment. While current ICI-based regimens have elevated the baseline of OS, realizing the full potential of these therapies requires resolving persistent clinical obstacles, including primary resistance, overlapping toxicities in combination regimens, and the lack of precise predictive biomarkers.

The continuous evolution of this field necessitates the deep integration of basic mechanistic research with the clinical development of novel antineoplastic agents. Moreover, regimens for perioperative care, LRTs and

systemic combination therapies are becoming increasingly complex, which calls for rigorous and sustained collaboration within multidisciplinary teams (MDT). Integrating molecular biomarker research with innovative clinical trial designs enables individualized precision management of HCC patients for more clinical benefits.

In conclusion, the articles assembled in this Special Issue demonstrate that the future of HCC therapy lies at the intersection of metabolic rewiring and immune modulation. By embracing this complexity, the scientific and clinical communities are well-positioned to turn metabolic vulnerabilities into definitive therapeutic victories, ultimately expanding curative opportunities and transforming the prognosis for patients worldwide.

DECLARATIONS

Authors' contributions

The author contributed solely to the article.

Availability of data and materials

Not applicable.

AI and AI-assisted tools statement

Not applicable.

Financial support and sponsorship

This study was supported by National Natural Science Foundation of China (Grant No. 92578203/Liu L, No. U25C2035/Liu L, No. 82373232/Liu L).

Conflicts of interest

Liu L is an Associate Chief Editor of *Hepatoma Research*. Liu L is also the Guest Editor of the special issue entitled "Advancing Immunotherapy and Tumor Microenvironment Research in Hepatocellular Carcinoma" in *Hepatoma Research*. Liu L was not involved in any steps of editorial processing, notably including reviewers' selection, manuscript handling, and decision-making.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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