lncRNA-mediated regulation of PI3K-AKT-mTOR signaling in hepatocellular carcinoma: Mechanisms, tumor heterogeneity and therapeutic targeting (Review)

BERJAS ABUMSIMIR[1], WALEED K. ABDULSAHIB[2], PARESHKUMAR N. PATEL[3], RENUKA JYOTHI S.[4], GUNJAN SINGH[5], LAXMIDHAR MAHARANA[6], VIMAL ARORA[7], JASUR RIZAEV[8] and DJAMILA POLATOVA[9]

[1]Faculty of Allied Medical Sciences, Hourani Center for Applied Scientific Research, Al-Ahliyya Amman University, Amman 19111, Jordan; [2]Department of Pharmacology and Toxicology, College of Pharmacy, Al Farahidi University, Baghdad 10071, Iraq; [3]Department of Pharmacy, Faculty of Pharmacy, Gokul Global University, Sidhpur, Gujarat 384151, India; [4]Department of Biotechnology and Genetics, School of Sciences, JAIN (Deemed-to-be University), Bangalore, Karnataka 560027, India; [5]Department of Pharmacy, Sharda School of Pharmacy, Sharda University, Greater Noida, Uttar Pradesh 201310, India; [6]Department of Pharmaceutical Sciences, Siksha 'O' Anusandhan (Deemed-to-be University), Bhubaneswar, Odisha 751030, India; [7]University Institute of Pharma Sciences, Chandigarh University, Mohali, Punjab 140413, India; [8]Department of Public Health and Healthcare Management, Rector, Samarkand State Medical University, Samarkand 100400, Uzbekistan; [9]Scientific-Practical Medical Center for Pediatric Oncology, Hematology and Immunology, Tashkent 100115, Uzbekistan

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Abstract. Hepatocellular carcinoma (HCC) remains a major cause of cancer mortality due to late diagnosis, profound molecular heterogeneity and limited durable responses to systemic therapies. Among the pathways driving HCC progression, the mechanistic target of rapamycin (mTOR) acts as a central metabolic and oncogenic hub regulating cell growth, proliferation, autophagy, angiogenesis, immune adaptation and survival. Accumulating, largely preclinical, evidence suggests that long non-coding RNAs (lncRNAs) can act as upstream regulators and downstream effectors of mTOR signaling, forming regulatory circuits that may influence tumor evolution and therapeutic response. The present review synthesized current insights into lncRNA-mediated modulation of mTOR pathway dynamics in HCC and described how oncogenic and tumor-suppressive lncRNAs have been reported to regulate phosphatidylinositol 3-kinase (PI3K)-protein kinase B (AKT)-mTOR signaling through epigenetic remodeling, competitive endogenous RNA activity, transcriptional control, RNA-protein interactions and metabolic and immune reprogramming. The present review highlighted context-dependent roles of lncRNAs in epithelial-mesenchymal transition, stemness, ferroptosis resistance, angiogenesis, hypoxia adaptation and immune evasion via mTOR-linked axes. Drawing on transcriptomic, single-cell and spatial profiling studies, the present review outlined a conceptual framework for the heterogeneity of lncRNA-mTOR networks across HCC ecosystems. Finally, the present review appraised the translational potential of targeting lncRNA-mTOR circuitry using antisense oligonucleotides, siRNA platforms, CRISPR-based strategies, nanoparticle delivery and rational combinations with mTOR inhibitors, immunotherapy and anti-angiogenic agents while distinguishing proof-of-concept, preclinical and clinically established evidence. Importantly, most direct lncRNA-mTOR links in HCC derive from cell-line and xenograft studies, biomarker associations remain exploratory and have not been validated for clinical utility, spatial and single-cell evidence is largely correlative and lncRNA-directed therapeutics have, to the best of the authors' knowledge, not yet been evaluated in clinical trials in HCC. HCC remains difficult to treat due

Correspondence to: Dr Waleed K. Abdulsahib, Department of Pharmacology and Toxicology, College of Pharmacy, Al Farahidi University, Qatar Al-Nada Street, Baghdad 10071, Iraq
E-mail: waleedkabdulsahib@atomicmail.io

Abbreviations: AKT, protein kinase B; ASO, antisense oligonucleotide; ceRNA, competing endogenous RNA; CRISPR, clustered regularly interspaced short palindromic repeats; GAS5, growth arrest-specific transcript 5; HCC, hepatocellular carcinoma; HIF, hypoxia-inducible factor; HULC, highly upregulated in liver cancer; ICI, immune checkpoint inhibitor; LINC00958, long intergenic non-protein coding RNA 958; LNA, locked nucleic acid; lncRNA, long non-coding RNA; LNP, lipid nanoparticle; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; mTOR, mechanistic target of rapamycin; mTORC1, mechanistic target of rapamycin complex 1; mTORC2, mechanistic target of rapamycin complex 2; NEAT1, nuclear paraspeckle assembly transcript 1; PD-L1, programmed death-ligand 1; PI3K, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homolog; siRNA, small interfering RNA; SREBP, sterol regulatory element-binding protein; TSC, tuberous sclerosis complex

Key words: hepatocellular carcinoma, long non-coding RNA, mechanistic target of rapamycin signaling, phosphatidylinositol 3-kinase-protein kinase B pathway, tumor microenvironment, RNA therapeutics, precision therapy, biomarkers

to molecular heterogeneity and limited durable responses to therapy. The present review clarified how lncRNAs regulate PI3K-AKT-mTOR signaling in liver cancer, offering insight into tumor evolution while critically appraising the evidence for emerging, largely preclinical RNA-based strategies in precision oncology.

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1. Introduction

Hepatocellular carcinoma (HCC) is the predominant primary liver malignancy and a leading cause of cancer mortality worldwide. Despite advances in surveillance, surgery, locoregional therapies, targeted agents and immunotherapy, outcomes for advanced HCC remain poor because most patients present with molecularly heterogeneous, inflammation-associated and cirrhosis-compromised disease (1-3). Diverse etiologies, hepatitis b virus (HBV), hepatitis c virus (HCV), alcohol, aflatoxin and metabolic dysfunction-associated steatotic liver disease (MASLD), converge on shared oncogenic programs including genomic instability, metabolic rewiring, immune dysregulation and aberrant growth signaling (4-6).

The phosphatidylinositol 3-kinase (PI3K)-protein kinase B (AKT)-mechanistic target of rapamycin (mTOR) axis is a central integrator of growth, nutrient sensing, autophagy, angiogenesis and survival in HCC. mTOR functions in two distinct complexes, mTORC1 (Raptor-containing; protein and lipid synthesis, suppression of autophagy) and mechanistic target of rapamycin complex 3 (mTORC2; Rictor-containing; AKT Ser473 phosphorylation, cytoskeletal organization and survival signaling), to coordinate anabolic and catabolic processes; persistent mTOR activation is associated with aggressive phenotypes, epithelial-mesenchymal transition, stemness, immune escape and therapy resistance (7-12). Long noncoding RNAs (lncRNAs), transcripts >200 nt with regulatory roles, have emerged as versatile modulators of cancer biology, acting as scaffolds, decoys, guides and competing endogenous RNAs (13-15). In HCC, dysregulated lncRNAs influence proliferation, invasion, metabolism, angiogenesis, immune suppression and therapeutic response.

Prior reviews have examined lncRNAs in HCC, PI3K-AKT-mTOR signaling in HCC, or non-coding RNA regulation of the PI3K-AKT pathway, largely as catalogues of individual transcripts (Table I). To the best of the authors' knowledge, a synthesis that grades the evidence for individual lncRNA-mTOR links and then places them in the context of metabolic rewiring, immune remodeling, hypoxia adaptation and spatial single-cell states has not been undertaken. This gap limits translational progress because lncRNA-driven modulation of mTOR is thought to operate across tumor, stromal and immune compartments and may underlie context-dependent resistance mechanisms. Compared with earlier reviews, the present review offered three specific advances: i) An evidence-graded appraisal of five exemplar lncRNA-mTOR axes that separates direct from inferred interactions and states the experimental model supporting each (Table II); ii) a critical analysis of how metabolic, immune and spatial single-cell contexts may modify these axes, explicitly separating demonstrated findings from conceptual inference; and iii) a translational roadmap that distinguishes proof-of-concept, preclinical and clinically established evidence for RNA-directed approaches and for mTOR inhibition in HCC.

To place this synthesis in the context of existing literature, Table I compared the scope of the present review with representative recent reviews addressing related but narrower aspects of lncRNA biology and PI3K-AKT signaling in liver and other cancers, illustrating the specific integrative gap this article addresses.

The present review first summarized mTOR biology and lncRNA mechanisms in liver cancer, then reviewed exemplar lncRNAs that mechanistically link to mTOR. It also synthesized cross-mechanistic themes, examine tumor microenvironment and spatial single-cell evidence and evaluate translational strategies for targeting lncRNA-mTOR circuitry with RNA therapeutics, clustered regularly interspaced short palindromic repeats (CRISPR) approaches, nanoparticle delivery and rational drug combinations. Fig. 1 provided an overview of the multilayered regulatory architecture.

2. mTOR primer in hepatocellular carcinoma

Canonical PI3K-AKT-mTOR pathway. The PI3K-AKT-mTOR axis integrates extracellular growth cues with intracellular metabolic status to regulate hepatocyte proliferation, survival and biosynthesis (7). In HCC, ligand binding to receptor tyrosine kinases, most prominently insulin-like growth factor 1 receptor (IGF1R), epidermal growth factor receptor (EGFR), fibroblast growth factor receptor (FGFR) and mesenchymal-epithelial transition factor receptor (MET), activates class I PI3Ks, generating phosphatidylinositol (3,4,5)-trisphosphate (PIP3) and recruiting AKT to the plasma membrane (12). Full AKT activation requires phosphorylation at Thr308 3-phosphoinositide-dependent protein kinase 1 and Ser473 (mTORC2), enabling AKT to inhibit the tuberous sclerosis complex (TSC)1-TSC2 complex, the principal negative regulator of mTORC1. Loss of TSC2 function, whether through phosphorylation, mutation, or lncRNA-mediated repression, releases ras homolog enriched in brain (Rheb)-GTP to activate mTORC1. This canonical cascade is frequently hyperactivated in HCC due to upstream oncogenic signaling, metabolic stress and microenvironmental cues, positioning mTOR as a central oncogenic hub (16,17).

mTORC1 and mTORC2 functions. mTOR exists in two structurally and functionally distinct complexes. mTORC1, defined by Raptor, senses amino acids, growth factors and energy status to promote protein synthesis via ribosomal protein s6 kinase β-1 (S6K1) and eukaryotic translation initiation factor

Table I. Scope of the present review relative to representative recent reviews cited.

Authors, year	Primary focus	mTOR pathway integration	Immune/TME coverage	Spatial/ single-cell data	Translational RNA-therapeutics roadmap	(Refs.)
Wu *et al*, 2020	PI3K-AKT-mTOR-related lncRNAs in HCC	Yes (pathway-centric catalogue)	Limited	Not addressed	Limited	(102)
Sallam *et al*, 2026	Noncoding RNAs across liver cancer biology and precision oncology	Partial (general ncRNA scope, not mTOR-focused)	Partial	Not addressed	Partial	(138)
Roy *et al*, 2025	lncRNAs in the oncogenic tumor microenvironment (pan-cancer)	Not liver- or mTOR-specific	Yes (TME-focused)	Not addressed	Partial	(122)
Khan and Zhang, 2022	Classification, molecular mechanisms and therapeutic potential of lncRNAs in HCC	Not mTOR-focused	Limited	Not addressed	Partial	(15)
Goyal and Kaur, 2025	lncRNAs and autophagy as drivers of HCC progression	Partial (autophagy-centered)	Limited	Not addressed	Limited	(34)
Hussain *et al*, 2024	ncRNA regulation of PI3K-AKT signaling in HCC; therapeutic perspectives	Yes (pathway-centric, all ncRNA classes)	Limited	Not addressed	Partial	(39)
Shi *et al*, 2021	lncRNA and microRNA networks in HCC and its tumor microenvironment	Not mTOR-specific	Yes (TME-focused)	Not addressed	Limited	(59)
Present review (2026)	lncRNA-mTOR circuitry in HCC	Yes (mechanistic + systems-level)	Yes	Yes, as a conceptual synthesis	Yes (dedicated roadmap)	-

Comparison is based on the stated focus and structure of each cited publication; see References for full citations. mTOR, mechanistic target of rapamycin; TME, tumor microenvironment; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; lncRNA, long non-coding RNA; HCC, hepatocellular carcinoma; ncRNA, non-coding RNA.

4E-binding protein 1 (4EBP1), stimulate lipid biosynthesis through sterol regulatory element-binding proteins (SREBP) activation and suppress autophagy by phosphorylating unc-51-like autophagy activating kinase 1 (ULK1). These outputs collectively support biomass accumulation and rapid proliferation, hallmarks of aggressive HCC (18-20). mTORC2, defined by Rictor, regulates cytoskeletal organization, cell survival and metabolic adaptation. By phosphorylating AKT at Ser473, mTORC2 reinforces upstream PI3K signaling, creating a feed-forward loop that amplifies oncogenic signaling. In HCC, mTORC2 also modulates glycolytic flux, redox balance and invasive behavior, making it a key driver of tumor progression and metastasis (21). In summary, mTORC1 is the principal driver of anabolic growth, lipid synthesis and autophagy suppression, whereas mTORC2 acts largely through AKT Ser473 phosphorylation and cytoskeletal and survival signaling; this distinction matters because rapalogs inhibit mTORC1 acutely but leave mTORC2 largely intact.

Upstream regulators in HCC. Multiple oncogenic, metabolic and microenvironmental cues converge to regulate mTOR activity in hepatocellular carcinoma. Growth factor signaling represents a major upstream driver, with aberrant activation of receptor tyrosine kinases such as EGFR, IGF1R, MET and FGFR stimulating the PI3K/AKT cascade. Activated AKT phosphorylates and inhibits the TSC1-TSC2 complex, thereby relieving suppression of the small GTPase Rheb and promoting mTORC1 activation (22,23).

Nutrient availability constitutes a second critical regulatory layer. Amino acids, particularly leucine and arginine, activate Rag GTPases that recruit mTORC1 to the lysosomal surface, where interaction with Rheb enables kinase activation. HCC cells frequently reprogram nutrient acquisition and metabolic pathways to sustain mTOR signaling despite fluctuating environmental conditions (24,25).

Microenvironmental stress signals further influence mTOR activity. Hypoxia induces stabilization of hypoxia-inducible

Table II. Exemplar lncRNAs modulating mTOR in HCC.

lncRNA	Subcellular location	Mechanistic class	Key mTOR node(s) affected	Link type and experimental model	Evidence level (Grade A-D)	Key references
HULC	Cytoplasm	ceRNA (miRNA sponge)	Rheb; S6K1; IGF1R (proposed, not directly shown)	Indirect/proposed for mTORC1 nodes. Direct for the miR-200a-3p/ZEB1 axis in HCC cells and xenografts; plasma detection in patient samples	C for the mTOR link (proposed); B for the miR-200a-3p/ZEB1 axis	(40,124,125)
MALAT1	Nucleus	RNA-protein scaffold; transcriptional regulator	S6K1 alternative splicing via SRSF1 → mTOR activation; AKT/TSC2 (proposed)	Direct for SRSF1-S6K1 splicing-mTOR in liver progenitor cells, HCC cell lines and xenografts; AKT/TSC2 links proposed only	B	(43,126,127)
NEAT1	Nuclear paraspeckle	Hypoxia-responsive ceRNA/enhancer	mTOR → NEAT1 (glycolysis); Raptor, HIF-mTOR feed-forward loop and PD-L1 (proposed)	Indirect. HIF-2α → NEAT1 and mTOR → NEAT1 shown in HCC cells; NEAT1 → mTOR and PD-L1 links proposed; ICI data from melanoma and glioblastoma only	C (D for ICI and PD-L1 claims)	(46,48,49,70, 128,129)
LINC00958	Cytoplasm	ceRNA → metabolic regulator (SREBP1 coupling)	HDGF/SREBP1 lipogenesis; mTORC1/p70S6K	Direct for the miR-3619-5p/ HDGF/SREBP1 lipogenic axis (HCC cells, xenograft); mTORC1/p70S6K link reported in HCC cells	B	(50,51,130,131)
GAS5	Nuclear/cytoplasmic	miRNA decoy; receptor decoy (GR)	PTEN; TSC2 (proposed)	Direct for PTEN in HCC cells; TSC2, glucocorticoid-receptor decoy and rapalog sensitization not shown in HCC (extrapolated)	B (PTEN); D (TSC2)	(57,132,133)

Evidence grades in Table II refer to the strength of support for the lncRNA-mTOR link specifically and are a qualitative framework devised for the present review: Grade A, direct interaction or regulatory relationship demonstrated in HCC models by binding, reporter, rescue, or perturbation experiments and validated *in vivo*; Grade B, functional evidence in HCC models with pathway read-outs but with a partly indirect or inferred mechanism (for example, no binding or rescue assay, or *in vivo* support limited to xenografts); Grade C, correlative or prognostic association in HCC samples, or a mechanistic link demonstrated only for an adjacent node or pathway; Grade D, extrapolated from non-HCC models or hypothetical. In the assessment of the present authors, no link currently satisfies Grade A. 'Direct' denotes a relationship supported by perturbation or interaction experiments in HCC systems; 'indirect/proposed' denotes inference from expression correlation, pathway signatures, or non-HCC studies. lncRNAs mTOR HCC, hepatocellular carcinoma.

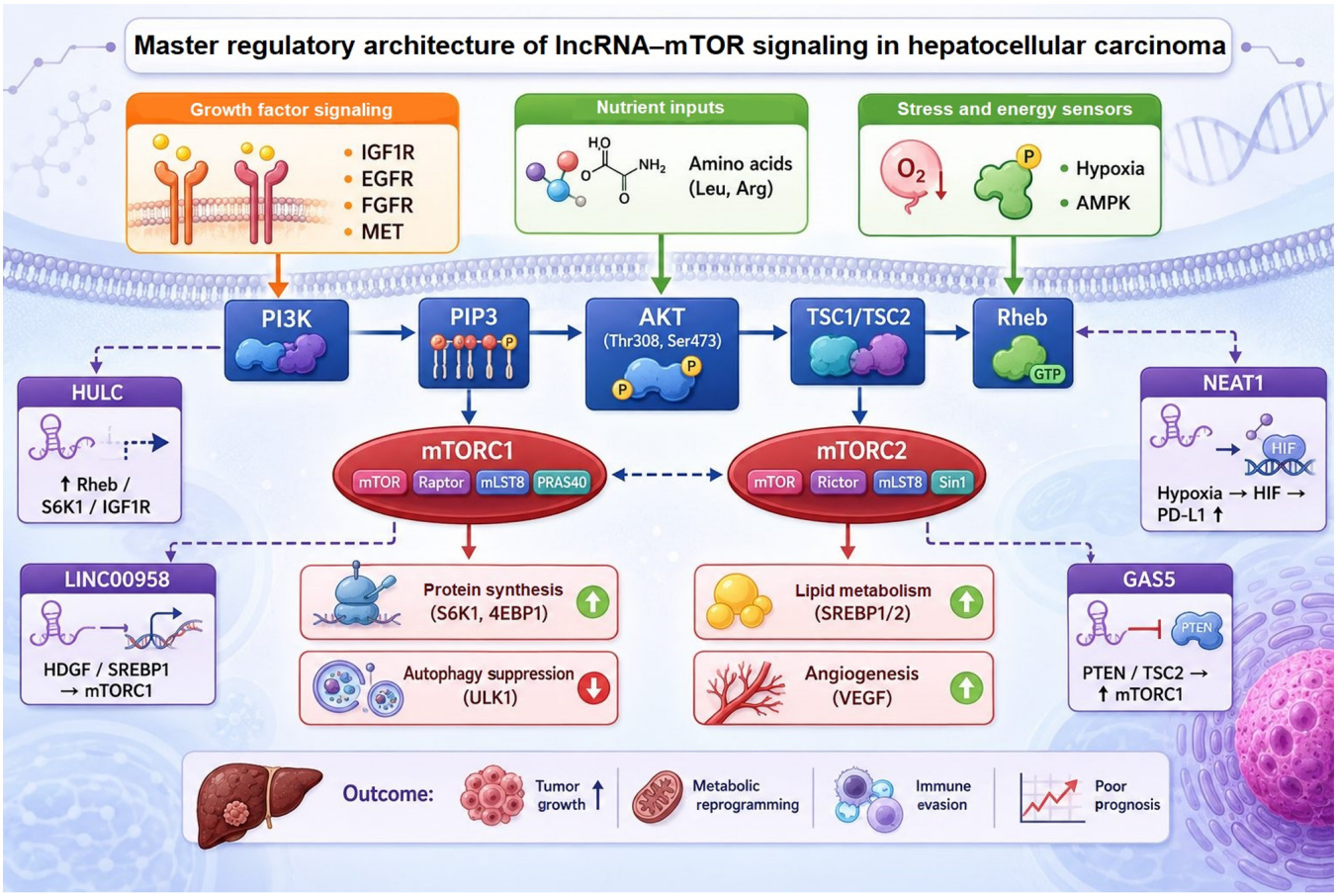


Figure 1. Master regulatory architecture of lncRNA-mTOR signaling in hepatocellular carcinoma. This schematic integrates the major upstream cues, intracellular signaling nodes and downstream effector programs that collectively shape mTOR pathway activity in HCC. Growth factor receptors (IGF1R, EGFR, FGFR, MET), nutrient availability (leucine, arginine) and stress-energy sensors (hypoxia, AMPK) converge on the PI3K-PIP3-AKT axis, which regulates the TSC1/TSC2-Rheb checkpoint controlling mTORC1 activation. mTORC1 promotes protein synthesis (S6K1, 4EBP1) and suppresses autophagy (ULK1), while mTORC2 phosphorylates AKT at Ser473 and regulates cytoskeletal organization and cell survival; lipid biosynthesis (SREBP1/2) and HIF-1α-dependent VEGF induction are downstream outputs of mTORC1. Key oncogenic lncRNAs, including HULC, LINC00958 and NEAT1, enhance mTOR signaling through ceRNA activity, metabolic rewiring and hypoxia-responsive feedback loops, whereas the tumor-suppressive lncRNA GAS5 restores PTEN/TSC2-mediated inhibition of mTORC1. Together, these multilayered regulatory interactions illustrate how lncRNAs function as critical modulators of mTOR-driven tumor growth, metabolic plasticity and immune evasion in HCC. In the schematic, arrows denote activation and blunt-ended lines denote inhibition; AKT inhibits (rather than activates) the TSC1/TSC2 complex, thereby relieving suppression of Rheb and mTORC1. Created with BioRender.com. lncRNA, long non-coding RNA; mTOR, mechanistic target of rapamycin; HCC, hepatocellular carcinoma; IGF1R, insulin-like growth factor 1 receptor; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; MET, mesenchymal-epithelial transition factor receptor; AMPK, AMP-activated protein kinase; PI3K, phosphatidylinositol 3-kinase; PIP3, phosphatidylinositol (3,4,5)-trisphosphate; AKT, protein kinase B; TSC, tuberous sclerosis complex; Rheb, ras homolog enriched in brain; mTORC1, mechanistic target of rapamycin complex 1; HULC, highly upregulated in liver cancer; LINC00958, long intergenic non-protein coding RNA 958; NEAT1, nuclear paraspeckle assembly transcript 1; ceRNA, competing endogenous RNA; GAS5, growth arrest-specific transcript 5; PTEN, phosphatase and tensin homolog; ULK1, unc-51-like autophagy activating kinase 1; SREBP, sterol regulatory element-binding protein; S6K1, ribosomal protein s6 kinase β-1.

factor (HIF)-1α, which cooperates with mTOR signaling to promote angiogenesis, glycolytic metabolism and tumor adaptation. However, severe hypoxic stress may also suppress mTORC1 through REDD1-mediated activation of the TSC1-TSC2 complex. In addition, endoplasmic reticulum stress and unfolded protein response pathways dynamically interact with mTOR signaling to coordinate cellular survival programs (26,27).

Energy homeostasis is primarily governed by AMP-activated protein kinase (AMPK), a key metabolic checkpoint that antagonizes mTORC1 through phosphorylation of TSC2 and Raptor. Suppression of AMPK signaling, frequently observed in HCC, permits sustained mTOR activation even under conditions of nutrient limitation and energetic stress (28-30).

Emerging evidence indicates that a number of these upstream regulatory pathways are extensively modulated by long non-coding RNAs. Through mechanisms including competitive endogenous RNA activity, epigenetic remodeling, transcriptional regulation and RNA-protein interactions, lncRNAs fine-tune mTOR activation thresholds and contribute to the context-dependent regulation of mTOR signaling during HCC initiation, progression and therapeutic response (31).

Downstream effectors relevant to tumor biology. Activation of mTOR signaling drives a broad spectrum of oncogenic programs that collectively promote hepatocellular carcinoma progression. A central function of mTORC1 is the stimulation of cap-dependent protein translation through phosphorylation of S6K1 and inhibition of 4EBPs, thereby enhancing the synthesis of proteins involved in cell-cycle progression, metabolism, growth and survival (7,19).

mTOR signaling also exerts profound effects on metabolic reprogramming. Through activation of SREBP1/2, mTORC1 promotes *de novo* lipogenesis and membrane biosynthesis required for rapid tumor expansion. In parallel, mTOR coordinates glucose utilization, nucleotide synthesis and mitochondrial metabolism, supporting the increased biosynthetic demands of proliferating cancer cells (32,33). The lipogenesis studies cited here derive partly from non-hepatic systems [a Yes-associated protein (YAP)]-driven tissue-growth model and ovarian cancer) and are extrapolated to HCC.

Another major downstream consequence of mTOR activation is suppression of autophagy. mTORC1 directly phosphorylates and inhibits ULK1, thereby restraining autophagy initiation. Dysregulated autophagy contributes to altered cellular homeostasis, accumulation of damaged organelles, metabolic adaptation and therapeutic resistance during HCC progression (34).

Cell-cycle progression is further enhanced through increased translation of cyclin D1 and activation of cyclin-dependent kinase networks, facilitating G_1-S phase transition and sustained proliferation. Moreover, mTOR signaling promotes angiogenesis by cooperating with HIF-1α to induce vascular endothelial growth factor (VEGF) and other pro-angiogenic mediators that support vascular remodeling within hypoxic tumor regions (35-37).

In addition to these canonical functions, mTOR signaling contributes to epithelial-mesenchymal transition, cancer stem cell maintenance and metastatic dissemination. In particular, mTORC2-mediated phosphorylation of AKT and regulation of cytoskeletal dynamics enhance cell survival, migration and invasive potential (38).

Collectively, these upstream cues, complex-specific functions and downstream effector programs position mTOR as a central integrator of metabolic, proliferative and microenvironmental signals in HCC. Understanding this architecture provides the mechanistic foundation for interpreting how lncRNAs reshape mTOR activity across diverse tumor contexts.

3. Mechanistic core: lncRNA-mTOR circuits

Literature search strategy and selection of exemplar lncRNAs. To identify the mechanistic evidence synthesized in the present review, PubMed (https://pubmed.ncbi.nlm.nih.gov), Scopus (https://www.scopus.com) and Web of Science (https://www.webofscience.com) were searched for the period January 2015-June 2026 using combinations of the terms 'lncRNA', 'long non-coding RNA', 'hepatocellular carcinoma', 'liver cancer', 'mTOR', 'mTORC1', 'mTORC2', 'PI3K/AKT' and 'molecular mechanism'. Terms within a concept group were combined with OR and concept groups were combined with AND. Studies were considered for inclusion if they i) reported a direct biochemical, genetic, or functional link between a specific lncRNA and an mTOR pathway node in HCC or closely related hepatic tumor models, ii) provided mechanistic validation in cellular, xenograft, or orthotopic models and iii) were published in peer-reviewed, English-language journals. Reviews, conference abstracts without primary data and studies restricted to non-hepatic tumor types were excluded unless cited for background context. Titles and abstracts retrieved by the search were screened, followed by full-text assessment of candidate lncRNA-mTOR mechanistic studies. Background references from non-hepatic tumor types, where used, were identified by citation tracking and are labeled in the text as extrapolations. As the aim of the present review article was a focused mechanistic and translational synthesis rather than an exhaustive systematic review, this search informed, rather than exclusively determined, the selection of the exemplar lncRNAs described below; a fully systematic, PRISMA-guided mapping of the entire lncRNA-mTOR literature in HCC remains an important direction for future quantitative synthesis (see Limitations).

The five exemplar lncRNAs were chosen using four explicit criteria: i) Mechanistic evidence, defined as at least one HCC study reporting a functional or biochemical link between the lncRNA and a PI3K-AKT-mTOR pathway node; ii) reproducibility, defined as independent reports from more than one research group; iii) biological relevance, defined as validated effects on proliferation, metabolism, hypoxia adaptation, or immune phenotypes in HCC models; and iv) clinical association, defined as reported correlations with prognosis, recurrence, or treatment response in HCC patient samples. Candidates were then prioritized so that the final set spans the principal mechanistic archetypes [competing endogenous RNA (ceRNA) activity, RNA-protein scaffolding, hypoxia-linked feedback, metabolic coupling and tumor suppression]. These are pragmatic criteria for a narrative review; the selection may favor heavily studied transcripts and other lncRNAs may meet some of the criteria. For each exemplar, the strength of evidence for the lncRNA-mTOR link is graded in Table II (Grades A-D) and statements that are inferred rather than directly demonstrated in HCC are identified as such in the text.

Although numerous lncRNAs have been implicated in PI3K-AKT-mTOR signaling, only a limited subset demonstrates robust mechanistic evidence, *in vivo* validation and clinically meaningful associations in hepatocellular carcinoma (39). This section highlights five representative lncRNAs; highly upregulated in liver cancer (HULC), metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), nuclear paraspeckle assembly transcript 1 (NEAT1), long intergenic non-protein coding RNA 958 (LINC00958) and growth arrest-specific transcript 5 (GAS5), selected for their mechanistic links to key mTOR pathway nodes, validated effects in preclinical HCC models, associations with clinical outcomes or treatment response and potential for therapeutic targeting. Together, these lncRNAs provide a focused framework for examining the mechanistic and translational relevance of lncRNA-mTOR crosstalk in HCC. Fig. 2 summarized the mechanistic circuits through which these exemplar lncRNAs modulate specific nodes of the PI3K-AKT-mTOR pathway.

Mechanistic case studies

HULC: ceRNA-driven amplification of mTORC1 metabolic outputs. HULC is one of the most consistently upregulated lncRNAs in HCC and is best characterized as a ceRNA that sequesters tumor-suppressive miRNAs. In HCC cells and xenografts, HULC sequesters miR-200a-3p to de-repress zinc finger E-box-binding homeobox 1 (ZEB1) and promote epithelial-mesenchymal transition, whereas the patient study that examined HULC together with miR-372

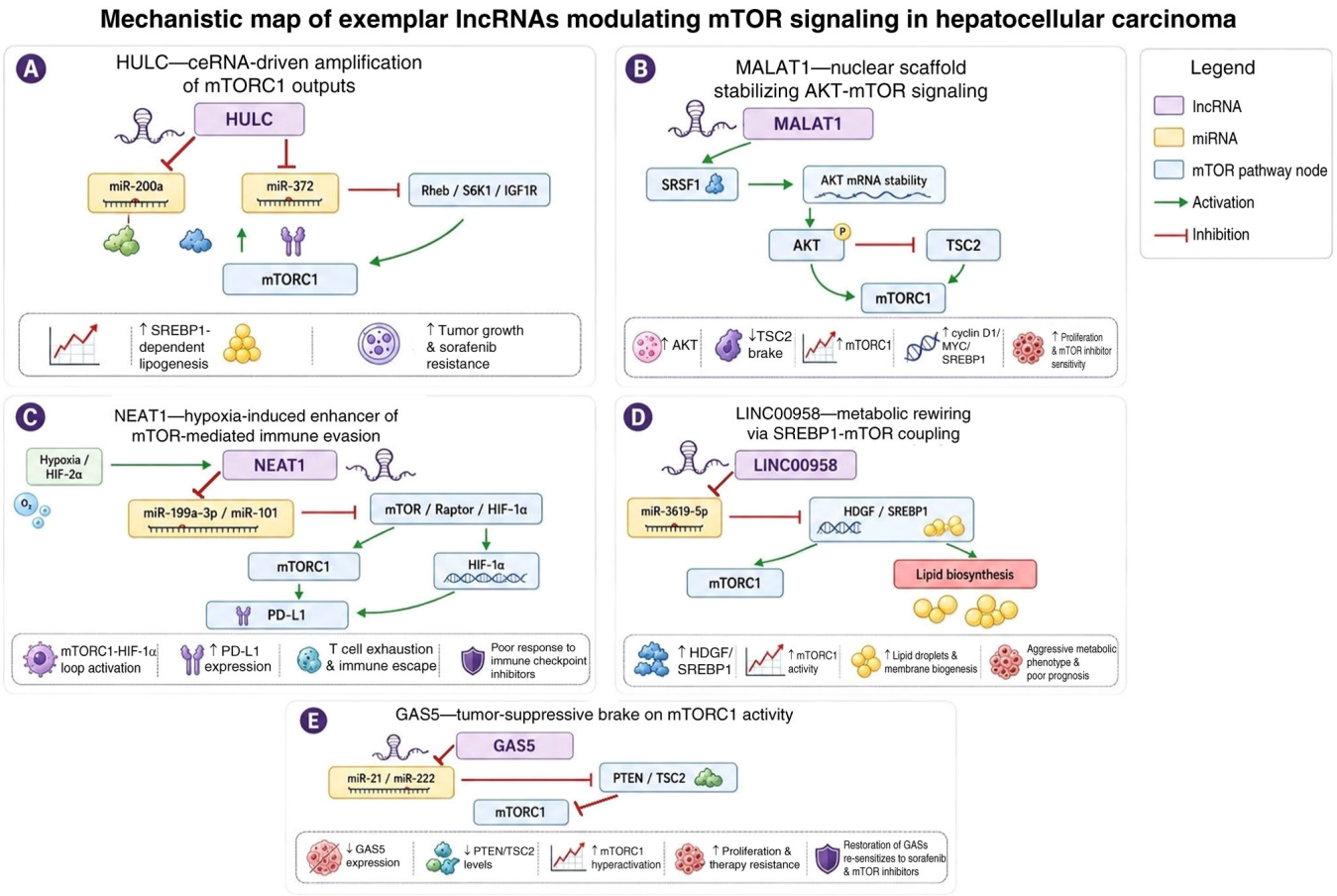


Figure 2. Mechanistic circuits through which exemplar lncRNAs modulate mTOR signaling in hepatocellular carcinoma. Five representative lncRNAs, HULC, MALAT1, NEAT1, LINC00958 and GAS5, engage distinct molecular interactions involving miRNAs, RNA-binding proteins, metabolic regulators and hypoxia-responsive factors to modulate specific nodes of the PI3K-AKT-mTOR pathway. Together, these modules illustrate the diverse mechanisms by which noncoding RNAs amplify, sustain, or restrain mTORC1 activity and shape oncogenic phenotypes in HCC. (A) HULC acts as a ceRNA that sequesters miR-200a-3p (de-repressing ZEB1 and promoting EMT in HCC cells and xenografts) and miR-372; HULC-dependent de-repression of Rheb, S6K1 and IGF1R, leading to mTORC1 activation, SREBP1-dependent lipogenesis, tumor growth and sorafenib resistance, is proposed. (B) MALAT1, a nuclear scaffold, upregulates SRSF1, which promotes alternative splicing of S6K1 and activates mTOR signaling; stabilization of AKT mRNA with AKT-mediated inhibition of TSC2, and downstream induction of cyclin D1, MYC and SREBP1, are proposed. (C) Hypoxia/HIF-2α induces NEAT1; sequestration of miR-199a-3p/miR-101 to enhance mTOR/Raptor and HIF-1α signaling, with PD-L1 upregulation and T-cell exhaustion, is proposed (in HCC, mTOR has been shown to act upstream of NEAT1). (D) LINC00958 sponges miR-3619-5p to increase HDGF and SREBP1-dependent lipid biosynthesis, coupled to mTORC1 outputs; LINC00958-driven mTORC1/p70S6K activation has also been reported. (E) The tumor-suppressive lncRNA GAS5 restrains PI3K-AKT-mTOR signaling by maintaining PTEN (demonstrated in HCC cells); sponging of miR-21/miR-222 to restore PTEN/TSC2 is proposed, and GAS5 loss is associated with mTORC1 hyperactivation, proliferation and therapy resistance. The strength of evidence differs among the depicted links (see Table II for evidence grades and experimental models): the links of HULC to Rheb, S6K1 and IGF1R, of MALAT1 to AKT and TSC2, of NEAT1 to Raptor and mTOR and of GAS5 to TSC2 are proposed rather than directly demonstrated in HCC. Created with BioRender.com. lncRNA, long non-coding RNA; mTOR, mechanistic target of rapamycin; HULC, highly upregulated in liver cancer; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; NEAT1, nuclear paraspeckle assembly transcript 1; LINC00958, long intergenic non-protein coding RNA 958; GAS5, growth arrest-specific transcript 5; miRNA, microRNA; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; mTORC1, mechanistic target of rapamycin complex 1; HCC, hepatocellular carcinoma; Rheb, ras homolog enriched in brain; RNA, ribonucleic acid; S6K1, ribosomal protein s6 kinase β-1; IGF1R, insulin-like growth factor 1 receptor; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; TSC2, tuberous sclerosis complex 2; NEAT1, nuclear paraspeckle assembly transcript 1; HULC, highly upregulated in liver cancer; HIF, hypoxia-inducible factor; PD-L1, programmed death-ligand 1.

evaluated their diagnostic performance and did not establish an mTORC1-directed mechanism (40). The HCC studies cited in the present study do not therefore directly demonstrate that HULC acts through Rheb, S6K1, or IGF1R: HULC-dependent de-repression of these mTORC1-related nodes is a proposed, inferred mechanism that should be tested by miRNA-target reporter assays, rescue experiments and phospho-S6K1/4EBP1 read-outs. Likewise, a role for HULC in SREBP1-dependent lipogenesis and the reported restoration of autophagy after HULC knockdown remain to be validated as mTORC1-mediated effects. HULC knockdown reduces tumor growth *in vivo* and high HULC expression has been associated with vascular invasion and sorafenib resistance in exploratory clinical studies. HULC is detectable in the plasma of HCC patients, with higher detection rates in HBV-positive and higher-grade disease and its comparatively liver-enriched expression makes it a theoretically tractable antisense oligonucleotide target; however, HULC remains an exploratory diagnostic and prognostic candidate rather than a validated biomarker and it has not been targeted therapeutically in HCC patients (41,42).

MALAT1: A nuclear scaffold stabilizing AKT-mTOR signaling. MALAT1 is upregulated in HCC and influences mTOR signaling through RNA-protein interactions and splicing

control. In HCC models, MALAT1 upregulates the oncogenic splicing factor serine/arginine-rich splicing factor 1 (SRSF1), which promotes alternative splicing of S6K1 and thereby activates mTOR signaling; inhibition of SRSF1 or of mTOR abrogated MALAT1-induced transformation. To the best of the authors' knowledge, this is the most direct HCC-specific demonstration of a lncRNA-mTOR link among the five exemplars, although it rests on liver progenitor cell transformation, cell-line and xenograft models. Other reported mechanisms, such as stabilization of AKT mRNA with downstream TSC2 phosphorylation and recruitment of chromatin modifiers to activate cyclin D1, MYC and SREBP1, derive largely from broader or non-HCC literature and have not been confirmed in HCC with RNA-protein interaction or rescue experiments (43). MALAT1 depletion has been reported to reduce phosphorylated (p-)AKT and p-S6K1 levels and to sensitize tumor cells to mTOR inhibitors in preclinical settings, but these observations are largely associative with respect to the specific nodes affected. MALAT1 has been associated with recurrence and microvascular invasion in exploratory clinical studies. MALAT1 can be depleted with locked nucleic acid (LNA)-antisense oligonucleotides (ASOs) despite its nuclear localization, including in data from hematological malignancies that are extrapolated here to HCC; however, its broad expression in normal tissues raises concerns about the therapeutic window (44,45).

NEAT1: Hypoxia-induced enhancer of mTOR-mediated immune evasion. NEAT1 is induced by HIF-2α under hypoxic conditions, a defining feature of advanced HCC and promotes invasion and epithelial-mesenchymal transition in HCC cells; hypoxia-induced NEAT1 also sustains HCC growth through a miR-199a-3p/uridine-cytidine kinase 2axis (46,47). Notably, the HCC study that directly examined NEAT1 and mTOR placed mTOR upstream of NEAT1, reporting that mTOR regulates aerobic glycolysis through NEAT1 and paraspeckle formation (48). A reverse NEAT1 → mTOR/Raptor direction through sequestration of miR-199a-3p or miR-101 and the resulting hypoxia-mTOR feed-forward loop, therefore remain hypotheses that require direct supporting evidence (for example, miRNA-binding, rescue and mTORC1 read-out experiments); the relationship may well be bidirectional. Similarly, NEAT1-dependent regulation of programmed death-ligand 1 (PD-L1) through mTORC1-HIF-1α signaling has not, to our knowledge, been demonstrated in HCC. With regard to immunotherapy, the only clinical data linking NEAT1 to immune checkpoint inhibitors (ICIs) come from melanoma and glioblastoma cohorts, in which higher NEAT1 expression was associated with improved, not worse, outcomes after anti-programmed cell death protein 1/PD-L1 therapy (49). These data neither support a resistance role for NEAT1 nor have they been tested in HCC cohorts; NEAT1 should therefore be regarded as an exploratory candidate whose predictive direction in HCC is unknown.

LINC00958: Metabolic rewiring through SREBP1-mTOR coupling. LINC00958 illustrates how lncRNAs may couple metabolic and signaling networks. In HCC cells, m6A-mediated upregulation of LINC00958 sponges miR-3619-5p to increase hepatoma-derived growth factor (HDGF), which promotes SREBP1-dependent lipogenesis; LINC00958 knockdown reduces lipid droplet formation and tumor growth in xenograft models and nanoparticle-delivered siRNA against LINC00958 showed proof-of-concept efficacy. As SREBP1 is a downstream output of mTORC1 rather than an activator of it, this lipogenic axis should be read as metabolic coupling to mTORC1 outputs and not, by itself, as evidence of mTORC1 activation. A separate HCC study (50) reported that LINC00958 activates the mTORC1/p70S6K pathway to promote epithelial-mesenchymal transition, which provides more direct pathway evidence, although independent replication and *in vivo* confirmation would strengthen this link. LINC00958 expression correlates with aggressive phenotypes and poor prognosis (50-52). Given its strong metabolic signature, LINC00958 is a candidate for preclinical testing of RNA therapeutics combined with mTORC1 or lipogenesis inhibitors.

GAS5: A tumor-suppressive brake on mTORC1 activity. GAS5 is a tumor-suppressive lncRNA frequently downregulated in HCC. In HCC cells, GAS5 downregulation promotes proliferation and drug resistance by decreasing expression of phosphatase and tensin homolog (PTEN), a negative regulator of PI3K-AKT signaling; this is the most direct HCC-specific link between GAS5 and the pathway (53). Other proposed mechanisms, namely GAS5 acting as a decoy for the glucocorticoid receptor and GAS5 sponging miR-21 and miR-222 to restore PTEN and TSC2, have been described mainly in non-HCC or non-oncologic settings and HCC-specific primary evidence that GAS5 regulates TSC2 or mTORC1 is lacking (54). GAS5-mediated inhibition of PI3K-AKT-mTOR signaling has been demonstrated in other tumor types, such as esophageal squamous cell carcinoma (55,56). Loss of GAS5 is associated with enhanced proliferation and drug resistance in HCC models and restoration of GAS5 has been reported to sensitize HCC cells to sorafenib (57); however, unchecked mTORC1 activation after GAS5 loss and sensitization to rapalogs have not, to the best of the authors' knowledge, been demonstrated in HCC. GAS5 replacement, via synthetic mimics or CRISPRa, therefore remains a conceptual, preclinical tumor-suppressive RNA strategy (58).

Given the translational relevance of these regulatory circuits, Table II summarized the key lncRNAs governing mTOR pathway dynamics in HCC and highlights their mechanistic class, the mTOR pathway nodes affected, whether each link is direct or indirect, the experimental model used and a graded level of evidence (grading criteria are given below the table).

Cross-mechanism synthesis. Across the exemplar lncRNAs aforementioned, several unifying regulatory principles emerge that collectively define how lncRNAs sculpt mTOR pathway dynamics in hepatocellular carcinoma. A recurring theme in the literature is the proposed convergence on the TSC1/2-Rheb checkpoint, the principal regulator controlling mTORC1 activation. Oncogenic lncRNAs such as HULC and MALAT1 have been proposed to suppress TSC2 or to activate mTORC1 through other nodes, whereas the tumor-suppressive lncRNA GAS5 has been proposed to restore TSC2 expression through miRNA sequestration (59). If confirmed, this convergence would make TSC2 an attractive vulnerability; however, direct

HCC-specific evidence is currently limited [for example, MALAT1 acts through SRSF1-dependent S6K1 splicing in HCC (60)] and TSC2 involvement should be regarded as a hypothesis (53). A second recurring motif is the tight coupling of metabolic rewiring with mTOR activation. LINC00958 and, more tentatively, HULC have been linked to lipid biosynthesis in HCC models and such lncRNAs may participate in self-reinforcing loops with mTORC1 activity that sustain biomass accumulation and proliferative fitness under nutrient stress; evidence that these loops operate through mTORC1 itself remains limited.

A third principle is the integration of microenvironmental stress signals, particularly hypoxia, into mTOR circuitry. NEAT1 illustrates how hypoxia-induced lncRNAs may be integrated into mTOR-HIF circuitry: in HCC, hypoxia induces NEAT1 and mTOR regulates NEAT1, whereas NEAT1-driven amplification of mTORC1 activity and PD-L1 upregulation remain hypotheses. This highlights the importance of spatial context in interpreting lncRNA-mTOR interactions. A fourth insight is the potency of RNA-protein scaffolding as a mechanism for pathway amplification. MALAT1 induces SRSF1 and alters S6K1 splicing in HCC models (60) and reshapes transcriptional programs in other settings, illustrating how nuclear lncRNAs can exert layered control over mTOR signaling (43,61).

Together, these patterns suggest that lncRNAs may not simply modulate isolated nodes of the PI3K-AKT-mTOR axis; rather, they may reconfigure entire signaling-metabolic-microenvironmental modules. This systems-level integration has direct translational implications. ceRNA-type lncRNAs are, in principle, tractable with antisense or siRNA therapeutics, whereas nuclear scaffolds may require LNA-ASOs or CRISPRi approaches. The following applications remain hypotheses: Hypoxia-responsive lncRNAs such as NEAT1 have been proposed as candidate biomarkers for immunotherapy, although the predictive direction in HCC is unknown and metabolic lncRNAs such as LINC00958 could inform combination strategies pairing mTOR inhibitors with lipid-metabolism-targeted agents (62-65). These cross-mechanistic insights form the conceptual foundation for the translational roadmap outlined in subsequent sections.

4. Tumor microenvironment and single-cell perspectives

Recent advances in transcriptomics, single-cell sequencing, spatial transcriptomics and multi-omics integration have further revealed profound heterogeneity in lncRNA-mTOR networks across tumor cells, stromal populations and immune compartments. Rather than functioning as isolated linear pathways, lncRNA-mediated mTOR programs operate within dynamic spatially organized ecosystems shaped by metabolic competition, inflammatory signaling, hypoxia and therapeutic pressure (66,67).

Several caveats govern the interpretation of the single-cell and spatial evidence summarized in this section. The HCC studies cited in the present study (for example, those profiling single-cell and spatial ecosystems of HCC) and a cross-cancer atlas of lncRNA expression at single-cell and spatial resolution were, to the best of the authors' knowledge, not designed primarily to test lncRNA-mTOR regulation and the number of patients profiled in the spatial studies is generally modest relative to the etiological and geographic diversity of HCC; cohort sizes, platforms and analytical pipelines differ among the original studies and are reported there. Technical constraints also limit inference about lncRNA activity: a number of lncRNAs are expressed at low levels and are sparsely detected (high dropout) by droplet-based poly(A)-capture methods; 3'-biased protocols and incomplete annotation can misassign overlapping or isoform-specific transcripts; nuclear-retained lncRNAs such as MALAT1 and NEAT1 are detected more readily than other species, which can bias comparisons; and spot-based spatial platforms average signal across several cells, while probe-based panels frequently omit lncRNAs. Moreover, mTOR pathway 'activity' in these datasets is typically inferred from transcriptional signatures or pathway scores, which reflect gene expression rather than phosphorylation of S6K1, 4EBP1, or AKT. Transcriptional signatures are therefore not direct evidence of mTOR activation without functional validation (for example, phospho-protein staining, spatial proteomics, or perturbation experiments) and the niche- and cell-state-level assignments below should be read as hypotheses.

Immunometabolic crosstalk. HCC develops within a uniquely complex microenvironment characterized by chronic inflammation, fibrosis, metabolic dysfunction and profound immune remodeling. Within this ecosystem, mTOR signaling serves as a critical interface linking nutrient sensing, metabolic adaptation and immune regulation. Emerging, largely indirect evidence suggests that lncRNAs may contribute to this immunometabolic circuitry by modulating mTOR activity across both malignant and nonmalignant cellular compartments (68,69).

Tumor cells exhibiting sustained mTOR activation frequently display enhanced glycolysis, glutamine utilization, lipid biosynthesis and lactate production. These metabolic adaptations reshape the local nutrient landscape, creating competition for glucose, amino acids and oxygen that ultimately impairs antitumor immune responses. Several oncogenic lncRNAs, including HULC, NEAT1 and LINC00958, have been implicated in reinforcing these metabolic programs through activation of PI3K-AKT-mTOR signaling and downstream metabolic effectors such as SREBP1, HIF-1α and MYC (70). Consequently, lncRNA-driven mTOR activation may not only promote tumor growth but also contribute indirectly to immune dysfunction through metabolic exclusion mechanisms (71).

A previous study suggested that lncRNA-mTOR networks influence the phenotype and function of tumor-associated macrophages (TAMs), cancer-associated fibroblasts (CAFs), regulatory T cells and myeloid-derived suppressor cells (72). mTOR-mediated secretion of cytokines, chemokines and extracellular vesicles can promote recruitment of immunosuppressive myeloid populations while limiting effective cytotoxic T-cell infiltration (73). Hypoxia-responsive lncRNAs such as NEAT1 may amplify these effects by enhancing HIF-dependent expression of immune checkpoint molecules, including PD-L1. In parallel, dysregulated lncRNAs can modulate autophagy, ferroptosis susceptibility and oxidative stress responses, thereby altering the release of damage-associated molecular signals that shape local immune activation states (74,75).

These observations are compatible with a model in which lncRNAs act as upstream regulators of immunometabolic adaptation, enabling mTOR signaling to coordinate tumor growth with immune suppression; this model remains largely inferential. Rather than acting solely within malignant cells, lncRNA-mTOR circuits appear to operate across interconnected cellular networks that collectively determine tumor fitness and therapeutic responsiveness (76).

Spatial heterogeneity of lncRNA-mTOR activity. Growing evidence indicates that mTOR pathway activation in HCC is spatially heterogeneous rather than uniformly distributed throughout the tumor mass. Advances in spatial transcriptomics and multiplex imaging have revealed distinct ecological niches characterized by differences in oxygen availability, nutrient access, stromal composition, vascularization and immune infiltration (77,78). These regional microenvironmental conditions strongly influence both lncRNA expression and mTOR signaling activity.

Hypoxic perinecrotic regions are expected to be enriched for HIF-responsive lncRNAs, including NEAT1 and other stress-associated transcripts that may reinforce mTOR-dependent adaptation programs. By contrast, vascularized tumor margins may show increased expression of proliferation-associated lncRNAs that cooperate with growth factor signaling to sustain mTORC1 activation. Fibrotic stromal regions enriched with activated CAFs may also harbor distinct lncRNA signatures linked to extracellular matrix remodeling, mechanotransduction and nutrient-sensing pathways (79,80). To the best of the authors' knowledge, direct spatial localization of NEAT1, HULC, or LINC00958 together with matched mTOR activity read-outs in human HCC specimens has not yet been reported; the niche assignments in Table III and Fig. 3 are therefore inferred from hypoxia, proliferation and stromal biology and from bulk or cell-line data and should be regarded as hypotheses.

Spatial analyses suggest that lncRNA-mTOR interactions are not restricted to autonomous tumor cell programs but emerge through local cellular neighborhoods. For example, CAF-derived cytokines and growth factors may activate mTOR signaling in adjacent tumor cells, whereas tumor-derived metabolites can reprogram nearby immune populations toward suppressive phenotypes (81,82). Such reciprocal interactions create localized signaling hubs where lncRNA expression, metabolic adaptation and immune remodeling become tightly coordinated.

Importantly, spatial heterogeneity may help explain inconsistent clinical responses to mTOR-targeted therapies. Regions enriched for hypoxia-adapted or stem-like tumor cells may exhibit distinct lncRNA-mediated resistance mechanisms compared with highly proliferative tumor compartments. Consequently, assessment of global tumor expression profiles may underestimate biologically important regional variations in lncRNA-mTOR activity (78,83) (Table III).

Clinical translation and patient stratification using lncRNA-mTOR signatures. Several lncRNAs that have been linked to mTOR signaling (HULC, NEAT1, MALAT1 and LINC00958) have been reported in tumor tissue and, for some, in circulation and have therefore been proposed as biomarker candidates for detection, prognostication and treatment stratification. The strength of this evidence differs markedly among candidates and applications and three distinctions should be kept in mind. First, exploratory biomarker findings (single-center expression or prognostic associations, as for most lncRNAs discussed here) are not equivalent to analytically and clinically validated biomarkers and neither is equivalent to biomarkers with demonstrated clinical utility, that is, those that improve patient outcomes or clinical decisions in prospective studies; to the best of the authors' knowledge, none of the lncRNAs discussed here has reached the latter two categories in HCC. Second, a prognostic association (for example, higher expression with worse survival) does not imply predictive value for a given therapy, which requires a treatment-by-biomarker interaction in comparator-controlled data. Third, tissue specificity differs: HULC has been reported to be comparatively liver-enriched, whereas MALAT1 and NEAT1 are broadly expressed across tissues, which limits their specificity as circulating markers and raises therapeutic-window concerns. For HULC, detection in the plasma of HCC patients has been reported in small studies (84), but robust stability, assay standardization and performance relative to alpha-fetoprotein and imaging have not been established in prospective cohorts; for NEAT1, plasma stability and association with immunotherapy response in HCC have not been demonstrated.

Whether lncRNA-mTOR signatures can refine predictive biomarker strategies for systemic therapies remains an open hypothesis. Although hypoxia-induced NEAT1 has been proposed to enhance mTORC1-HIF-1α signaling and PD-L1 expression, the clinical data relating NEAT1 to ICI outcomes come from melanoma and glioblastoma cohorts, in which higher NEAT1 expression was associated with improved, not worse, response (62); no HCC cohort has addressed this question. The proposal that NEAT1-high HCCs show primary resistance to ICIs therefore lacks supporting evidence and should not be presented as established and the direction of any association in HCC remains to be determined in prospective, treatment-annotated cohorts. Likewise, suppressed GAS5 or elevated MALAT1 may be hypothesized to mark heightened mTORC1 dependency, but this has not been tested against response to mTOR or AKT inhibitors in HCC; given that everolimus, an oral mTOR inhibitor (rapalog) that blocks mTORC1, failed to improve survival in unselected patients (85), any such selection hypothesis would require prospective, biomarker-enriched trials. Integrating lncRNA expression with mTOR pathway activation scores could, in principle, be explored alongside current standards of care (atezolizumab-bevacizumab, durvalumab-tremelimumab, lenvatinib, or sorafenib), but no lncRNA-based treatment selection is supported by current evidence.

Etiology may also shape lncRNA-mTOR networks, but the supporting evidence is thin. Higher HULC detection has been reported in HBV-positive HCC (84), whereas associations of MALAT1 with HBV-related disease, of LINC00958 with MASLD-associated lipogenesis and of NEAT1 with HCV-related immune-metabolic adaptation are, to our knowledge, not supported by HCC cohort data and are presented here as hypotheses for future validation. These possibilities nonetheless motivate etiology-stratified studies and the development of etiology-specific biomarker panels.

Table III. Conceptual model of spatial and single-cell lncRNA-mTOR signatures across major tumor niches in hepatocellular carcinoma (evidence status indicated).

Tumor niche	Dominant lncRNAs	Dominant cell states	Inferred mTOR readout (not directly measured)	Hypothesized biomarker/ therapeutic implication	Evidence status in human HCC	(Refs.)
Hypoxic core (perinecrotic)	NEAT1 (proposed)	Hypoxia-adapted; stem-like; immune-exhausted	↑p-S6K1; ↑HIF-1α; PD-L1 up	Hypothesis: NEAT1 may inform ICI response (direction unknown in HCC); NEAT1 + ICI or HIF/mTOR combinations untested	Hypoxia-NEAT1 induction shown in HCC cells; spatial co-localization with mTOR read-outs not demonstrated	(46,47,134,135)
Vascularized margin	HULC; LINC00958 (proposed)	Proliferative; lipogenic tumor cells	↑p-S6K1; ↑lipogenesis (SREBP1)	Predict mTOR dependence; candidate for mTORC1 + lipogenesis inhibitors	Inferred; spatial distribution of HULC/LINC00958 and mTOR activity not demonstrated	(51)
Fibrotic stroma/CAF niche	None specified (conceptual placeholder)	CAF-activated; ECM-remodeling	Paracrine mTOR activation in adjacent tumor cells	Stratify CAF-targeted + mTOR inhibitor combinations	Conceptual; CAF-associated spatial programs described, but no lncRNA-mTOR link established	(80)
Immune-excluded zones	None specified (conceptual placeholder)	Myeloid-dominant; $SPP1^{+}$ TAMs	mTOR-driven immunosuppressive cytokine signature	Biomarker for myeloid-targeted therapies + mTOR modulation	Conceptual; SPP1+ tumor-associated macrophage niche described in HCC, but lncRNA-mTOR link not established	(11,67, 81,136)

Table III is a conceptual synthesis and not a compilation of directly demonstrated spatial lncRNA-mTOR signatures in human HCC. Niche-level lncRNA assignments are inferred from the biology of each niche and from cell-line or bulk data, mTOR read-outs are inferred rather than measured and entries marked 'conceptual placeholder' indicate that no specific lncRNA has been established for that niche. lncRNA-mTOR HCC, hepatocellular carcinoma; NEAT1, nuclear paraspeckle assembly transcript 1; p-, phosphorylated; S6K1, ribosomal protein S6 kinase β-1; HIF, hypoxia-inducible factor; PD-L1, programmed death-ligand 1; ICI, immune checkpoint inhibitor; CAF, cancer-associated fibroblast; ECM, extracellular matrix; SREBP, sterol regulatory element-binding protein; TAM, tumor-associated macrophage; mTORC1, mechanistic target of rapamycin complex 1; HULC, highly upregulated in liver cancer; LINC00958, long intergenic non-protein coding RNA 958.

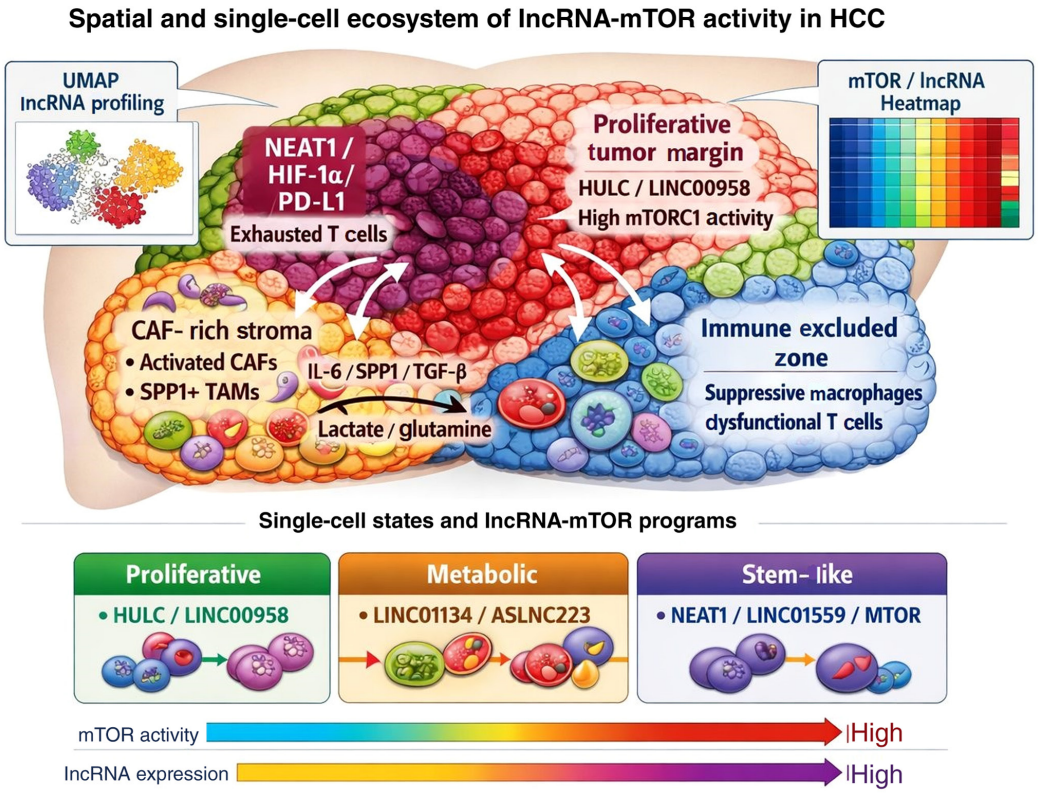


Figure 3. Spatial and single-cell ecosystem of lncRNA-mTOR activity in hepatocellular carcinoma. The schematic depicts major tumor ecological niches, including the vascularized proliferative margin, hypoxic perinecrotic core, CAF-rich stroma and immune-excluded zones, and their dominant cellular states. Hypoxic regions show NEAT1 enrichment and a NEAT1-HIF-mTORC1 feed-forward loop that drives PD-L1 upregulation and T-cell exhaustion, whereas vascular margins contain proliferative tumor cells with high mTORC1 activity and elevated HULC and LINC00958 expression. CAFs and SPP1^{+} TAMs secrete cytokines and metabolites that reinforce local mTOR activation. The bottom panel summarizes major single-cell states (proliferative, metabolic, stem-like) and their associated lncRNA-mTOR programs. Insets (UMAP and heatmap) are schematic and do not depict specific datasets; the lncRNAs labeled in the single-cell panel (LINC01134, ASLNC223 and LINC01559) are illustrative examples and are not established lncRNA-mTOR regulators. Color gradients indicate relative mTOR activity and lncRNA expression and arrows denote inferred regulatory interactions. This figure is a conceptual model rather than a synthesis of published datasets; niche-level assignments are inferred (see Table III). Created with BioRender.com. lncRNA, long non-coding RNA; mTOR, mechanistic target of rapamycin; CAF, cancer-associated fibroblast; NEAT1, nuclear paraspeckle assembly transcript 1; HIF, hypoxia-inducible factor; mTORC1, mechanistic target of rapamycin complex 1; HULC, highly upregulated in liver cancer; LINC00958, long intergenic non-protein coding RNA 958; SPP1^{+} TAM, tumor-associated macrophage; UMAP, Uniform Manifold Approximation and Projection; LINC01134, long intergenic non-protein-coding RNA 1134; ASLNC223, antisense long non-coding RNA 223; LINC01559, long intergenic non-protein coding RNA 1559.

Finally, the integration of lncRNA-mTOR biomarkers into clinical decision frameworks will require standardized assays, prospective validation and harmonization with existing clinical variables such as AFP levels, imaging features and molecular classifications. As spatial transcriptomics and single-cell profiling become increasingly accessible, lncRNA-mTOR signatures may enable microenvironment-aware patient stratification, identifying tumors driven by hypoxia, metabolic stress, or immune exclusion. Collectively, these considerations indicate that lncRNA-mTOR networks are a hypothesis-generating foundation for future biomarker development in hepatocellular carcinoma, not an established basis for clinical decision-making.

Single cell insights into lncRNA-mTOR networks. The emergence of single-cell transcriptomic technologies has transformed understanding of HCC heterogeneity by revealing extensive diversity among malignant, stromal and immune cell populations. These approaches demonstrate that mTOR pathway activation varies considerably between cellular subpopulations and is frequently associated with distinct lncRNA expression programs (86).

Within malignant compartments, single-cell analyses have identified proliferative, metabolic, mesenchymal-like and stem-like cellular states characterized by differential activation of PI3K-AKT-mTOR signaling. Several lncRNAs implicated in HCC progression exhibit preferential expression within specific cellular subpopulations, suggesting that their biological effects may be highly context dependent. For instance, stemness-associated populations have been reported to display elevated expression of lncRNAs linked to mTOR activation, autophagy regulation and metabolic plasticity, whereas more differentiated tumor cells may exhibit alternative regulatory circuits; HCC-specific single-cell data on this point are sparse and part of the supporting evidence is extrapolated from other tumor types (for example, B-cell acute lymphoblastic leukemia) (87,88).

Single-cell profiling has also revealed substantial heterogeneity among TAMs, CAFs, endothelial cells and lymphocyte populations. Distinct immune subsets demonstrate variable expression of mTOR-regulated metabolic programs, cytokine networks and checkpoint pathways (89). Emerging evidence suggests that lncRNAs contribute to this diversity by modulating lineage specification, activation states and

intercellular communication. Through regulation of mTOR signaling, lncRNAs may influence macrophage polarization, T-cell exhaustion, dendritic cell function and endothelial remodeling (90).

Integration of single-cell RNA sequencing with chromatin accessibility, proteomic and spatial datasets further suggests that lncRNA-mTOR interactions operate within dynamic state-transition networks rather than fixed cellular phenotypes. Therapeutic pressure, hypoxia, inflammation and metabolic stress can drive transitions between these states, allowing tumors to adapt and survive under changing environmental conditions (78,91). Fig. 3 provides a conceptual, illustrative model of the spatial and single-cell ecosystem of lncRNA-mTOR activity across major tumor niches in hepatocellular carcinoma; it is not a synthesis of specific published datasets. The lncRNAs shown in the single-cell panel [long intergenic non-protein-coding RNA 1134 (LINC01134), antisense long non-coding RNA 223 (ASLNC223) and LINC01559] are illustrative examples of single-cell lncRNA programs, are not discussed in the present review as validated lncRNA-mTOR regulators and should not be interpreted as established associations.

Implications for therapeutic resistance and biomarker development. Recognition of spatial and cellular heterogeneity within lncRNA-mTOR networks has important implications for precision oncology. One major challenge in HCC therapy is the emergence of adaptive resistance to targeted agents, antiangiogenic therapies and ICIs (92,93). Some evidence suggests that lncRNA-mediated rewiring of mTOR signaling may contribute to these resistance mechanisms, although direct HCC data linking specific lncRNA-mTOR axes to clinical resistance are limited (94).

Activation of alternative growth pathways, compensatory metabolic programs and stress-response networks can maintain mTOR activity despite pharmacologic inhibition. Oncogenic lncRNAs such as HULC, MALAT1, NEAT1 and LINC00958 may facilitate this adaptive rewiring by simultaneously regulating multiple signaling nodes. Furthermore, resistant cellular subpopulations often occupy specialized microenvironmental niches characterized by hypoxia, immune suppression, or nutrient limitation, conditions that favor activation of lncRNA-dependent survival programs (94,95).

These observations support the development of lncRNAs as biomarkers for patient stratification and treatment monitoring. Because some lncRNAs display tissue enrichment, dynamic regulation and detectability in circulating extracellular vesicles, they are candidate analytes for minimally invasive biomarker platforms, although none has yet been clinically validated for this purpose in HCC. Integration of lncRNA signatures with mTOR pathway activity scores, spatial profiling data and single-cell ecosystem analyses could be evaluated for whether they improve prediction of therapeutic response beyond conventional clinicopathologic parameters.

Looking forward, multi-omic approaches combining bulk transcriptomics, single-cell sequencing, spatial transcriptomics and liquid biopsy technologies are expected to enable increasingly precise characterization of lncRNA-mTOR ecosystems. Such strategies may facilitate identification of actionable vulnerabilities, selection of rational drug combinations and real-time monitoring of tumor evolution during therapy. Ultimately, understanding how lncRNA-mTOR circuits operate across heterogeneous cellular and spatial contexts will be essential for translating RNA-based therapeutics and mTOR-targeted interventions into durable clinical benefit for patients with hepatocellular carcinoma.

5. Therapeutic opportunities and translational roadmap

The growing recognition that lncRNAs function as central regulators of mTOR pathway activity has created new opportunities for therapeutic intervention in HCC. Unlike conventional approaches that target individual protein kinases, lncRNA-directed strategies offer the possibility of simultaneously modulating multiple signaling nodes, metabolic programs and microenvironmental interactions that collectively sustain tumor progression. Furthermore, the tissue-restricted expression of some lncRNAs may provide a level of biological selectivity that is difficult to achieve with protein-targeted therapies, although several candidates discussed here (MALAT1 and NEAT1) are broadly expressed (96). As understanding of lncRNA-mTOR circuitry continues to expand, an increasingly sophisticated translational framework is emerging that integrates targeted inhibition of mTOR signaling with RNA-based therapeutics, genome engineering technologies, advanced delivery platforms and biomarker-guided combination strategies (Table IV).

Throughout this section, the present review distinguished three levels of evidence: Proof-of-concept experiments (for example, *in vitro* knockdown or overexpression), preclinical therapeutic efficacy (*in vivo* models) and established clinical applications. For lncRNA-directed therapeutics in HCC, only the first two categories currently apply; the clinical maturity of ASO, siRNA and nanoparticle platforms reflect experience with other targets and indications and should not be extrapolated to lncRNA-mTOR targeting.

Current status of mTOR inhibitors in HCC. Given the central role of PI3K-AKT-mTOR signaling in hepatocarcinogenesis, mTOR has long been considered an attractive therapeutic target. First-generation mTOR inhibitors, including rapamycin and its analogs (rapalogs) such as everolimus and temsirolimus, demonstrated promising antitumor activity in preclinical HCC models by suppressing mTORC1-dependent protein synthesis, proliferation, angiogenesis and metabolic activity (20,97). However, clinical outcomes have been disappointing. In the phase III EVOLVE-1 trial of 546 patients with advanced HCC whose disease progressed on, or who were intolerant of, sorafenib, everolimus did not improve overall survival compared with placebo (median 7.6 vs. 7.3 months; hazard ratio 1.05, 95% CI 0.86-1.27) (85). The investigators attributed this negative result in part to clinical and biological heterogeneity and called for biomarker-enriched trial designs, a rationale that is directly relevant to the lncRNA-based stratification hypotheses discussed in the present review.

Several studies have shown that mTOR inhibition can transiently reduce tumor growth and delay disease progression, yet durable responses remain uncommon. One major limitation arises from incomplete pathway suppression. Rapalogs primarily inhibit mTORC1 while leaving mTORC2

Table IV. Therapeutic strategies targeting lncRNA-mTOR circuitry in HCC.

Therapeutic modality	Best-fit lncRNA class	Mechanistic rationale	Limitations/challenges	Clinical status/evidence	(Refs.)
LNA-ASOs (including LNA-containing gapmers)	Nuclear scaffolds (such as MALAT1, NEAT1)	Direct nuclear knockdown; disrupt RNA-protein scaffolds and paraspeckle function	Nuclear delivery efficiency; off-target RNase H effects; dosing schedule; broad expression of MALAT1 and NEAT1 in normal tissues (therapeutic window)	Proof-of-concept/preclinical (cell lines, xenografts); no lncRNA-targeted ASO has been tested in HCC patients; ASO platforms are clinically established for other targets	(55,126)
siRNA/shRNA (LNP delivery)	Cytoplasmic ceRNA lncRNAs (such as HULC, LINC00958)	Cytoplasmic RNA degradation; reduce miRNA sponging to restore tumor suppressors	LNP liver tropism is favorable, but hepatocyte vs. tumor-cell uptake, immune activation and durability remain unresolved; hepatocyte-directed GalNAc conjugation is the clinically validated liver-delivery route	Preclinical efficacy in HCC models; the LINC00958 nanotherapeutic study (proof-of-concept) is the most direct HCC-specific evidence; LNP and GalNAc siRNA liver delivery is clinically validated only in non-oncologic indications; no lncRNA-targeted siRNA has been tested in HCC patients	(51,108,137)
CRISPRi/CRISPRa (epigenetic modulation)	Promoter-driven or tumor suppressive lncRNAs (such as GAS5 restoration)	Durable transcriptional repression or activation to reprogram lncRNA expression	Delivery, specificity, regulatory hurdles and potential chromatin effects	Early preclinical; *ex vivo* proof-of-concept only	(138-140)
Nanoparticle co-delivery (lncRNA + small molecule)	Metabolic lncRNAs (such as LINC00958)	Simultaneous knockdown + mTORC1 or lipogenesis inhibitor to prevent compensatory loops	Formulation complexity; PK/PD matching; toxicity	Preclinical: proof-of-concept nanotherapeutic targeting LINC00958 in HCC; combination with mTORC1 or lipogenesis inhibitors untested in HCC; no clinical data	(141-143)
Antibody/small-molecule + lncRNA targeting	Hypoxia-responsive lncRNAs (such as NEAT1)	Combine immune checkpoint or anti-angiogenic agents with lncRNA knockdown to reverse immune evasion.	Need for spatial biomarker stratification; heterogeneity of response	Hypothesis only: no HCC clinical evidence for lncRNA targeting combined with checkpoint or anti-angiogenic agents; part of the rationale is extrapolated from non-HCC tumors (for example, lung cancer) and pan-cancer analyses	(47,123,134, 144)

lncRNA, long non-coding RNA; mTOR, mechanistic target of rapamycin; HCC, hepatocellular carcinoma; LNA, locked nucleic acid; ASO, antisense oligonucleotide; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; NEAT1, nuclear paraspeckle assembly transcript 1; siRNA, small interfering RNA; shRNA, short hairpin RNA; ceRNA, competing endogenous RNA; GalNAc, n-acetylgalactosamine; LNP, lipid nanoparticle; GAS5, growth arrest-specific transcript 5; CRISPRi, CRISPR interference; CRISPRa, CRISPR activation.

activity largely intact, allowing continued AKT activation and compensatory survival signaling. Furthermore, inhibition of S6K1-mediated negative feedback frequently results in paradoxical activation of upstream receptor tyrosine kinases and PI3K signaling, ultimately restoring pathway activity (23,98-100). Intratumoral heterogeneity, on-target toxicities and the compromised hepatic reserve of a number of patients with cirrhosis further narrow the therapeutic window of mTOR inhibition in HCC.

To overcome these limitations, second-generation ATP-competitive mTOR kinase inhibitors capable of simultaneously targeting mTORC1 and mTORC2 have been developed. Dual PI3K-mTOR inhibitors have also demonstrated broader pathway suppression in experimental models. Nevertheless, toxicity, metabolic complications and adaptive resistance continue to limit their clinical efficacy (100,101). These observations suggest that effective suppression of mTOR signaling in HCC may require targeting the upstream regulatory networks that sustain pathway activation, including dysregulated lncRNAs.

It has been hypothesized that lncRNA expression profiles could help identify patient subsets more likely to benefit from mTOR-directed therapies. Tumors characterized by elevated expression of candidate mTOR-associated lncRNAs such as HULC, MALAT1, NEAT1, or LINC00958 may exhibit greater pathway dependence and therefore enhanced sensitivity to rationally designed combination approaches incorporating mTOR inhibition (102,103). This hypothesis has not been evaluated in biomarker-annotated HCC trials of mTOR inhibitors.

Antisense oligonucleotide and siRNA approaches. Among currently available RNA-targeting technologies, ASOs and siRNAs represent the most clinically advanced RNA-targeting platforms; however, clinical experience to date relates to protein-coding or non-oncologic targets and, to the best of the authors' knowledge, no lncRNA-directed ASO or siRNA has been tested in patients with HCC. These approaches offer several advantages, including high sequence specificity, programmable target selection and the ability to inhibit transcripts that lack conventional druggable protein products (104,105).

ASOs are particularly attractive for targeting nuclear-retained lncRNAs. Through RNase H-mediated degradation or steric blockade of functional domains, ASOs can effectively suppress lncRNAs that function as transcriptional regulators, chromatin scaffolds, or RNA-protein interaction hubs. Nuclear oncogenic lncRNAs such as MALAT1 and NEAT1 represent especially promising candidates because their functions depend on structural interactions that can be disrupted by ASO-mediated transcript depletion (43,106). Experimental studies, largely in non-hepatic tumor models (for example, MALAT1-mTOR signaling in breast cancer) and a smaller number of HCC cell-line and xenograft studies, indicate that suppression of these lncRNAs can reduce AKT-mTOR signaling, impair tumor growth and enhance sensitivity to targeted therapies; these findings should be regarded as extrapolations to HCC until confirmed in HCC-specific systems.

By contrast, siRNA-based approaches are particularly effective against cytoplasmic lncRNAs that function through ceRNA activity or post-transcriptional regulation. HULC and LINC00958 exemplify cytoplasmic lncRNAs whose inhibition may restore tumor-suppressive microRNA activity, attenuate mTOR signaling and reverse metabolic reprogramming (107,108). Advances in chemical modification, conjugation chemistry and lipid nanoparticle technology have substantially improved siRNA stability and hepatic delivery, making liver-directed RNA therapeutics particularly feasible.

An important conceptual advantage of RNA therapeutics is their ability to simultaneously disrupt multiple oncogenic outputs downstream of a single lncRNA. Unlike kinase inhibitors that target one signaling node, lncRNA-directed therapies may suppress interconnected programs involving mTOR activation, metabolic adaptation, stemness, angiogenesis and immune evasion. This systems-level effect could potentially generate more durable responses than conventional pathway inhibition alone (96). Pleiotropy also carries risk, however: broad expression of MALAT1 and NEAT1 in normal tissues raises concerns about on-target toxicity and therapeutic window and the potential for more durable responses remains hypothetical.

CRISPR-based targeting of lncRNA-mTOR networks. Genome engineering technologies provide additional opportunities to therapeutically manipulate lncRNA-mTOR circuitry. CRISPR-based approaches are particularly attractive because they can target regulatory DNA elements, transcriptional programs and RNA transcripts simultaneously (109).

CRISPR interference (CRISPRi) utilizes catalytically inactive Cas proteins fused to transcriptional repressors to silence lncRNA expression without introducing permanent DNA damage. This approach is especially useful for oncogenic lncRNAs that function through sustained transcriptional activity. Conversely, CRISPR activation (CRISPRa) can restore expression of tumor suppressor lncRNAs such as GAS5, potentially reestablishing endogenous inhibition of PI3K-AKT-mTOR signaling (96,110).

Emerging RNA-targeting CRISPR systems further expand therapeutic possibilities. Cas13-based technologies allow direct degradation of pathogenic RNA transcripts while preserving genomic integrity. Such approaches may be particularly valuable for lncRNAs exhibiting high context specificity and dynamic expression patterns (111). At present, CRISPR-based modulation of lncRNAs in HCC remains at the proof-of-concept stage in cell and preclinical models; *in vivo* delivery of CRISPRi/CRISPRa components to tumor cells, durability, Cas-protein immunogenicity and off-target effects are unresolved (Table IV).

In addition, therapeutic applications, CRISPR-based functional genomics is becoming an essential tool for identifying lncRNA dependencies in HCC (112). Genome-wide screening approaches can systematically map regulatory interactions between lncRNAs and mTOR signaling components, facilitating the discovery of novel biomarkers and therapeutic vulnerabilities. Future precision oncology strategies may increasingly rely on these technologies to identify patient-specific lncRNA-mTOR dependencies that can be therapeutically exploited (113).

Delivery platforms for RNA therapeutics. Efficient and selective delivery remains one of the principal challenges facing

RNA-based cancer therapy. Although the liver is generally considered one of the most accessible organs for nucleic acid delivery, substantial barriers remain, including rapid clearance, nuclease degradation, off-target uptake, tumor fibrosis and intratumoral heterogeneity (56,114).

Lipid nanoparticles (LNPs) currently represent the most mature delivery platform for hepatic RNA therapeutics. Advances in ionizable lipid chemistry have markedly improved nucleic acid encapsulation, endosomal escape and tissue-specific biodistribution. LNP-based systems are capable of delivering siRNAs, ASOs, mRNA constructs and CRISPR components to liver tissues with high efficiency (56,115).

Hepatocyte-directed conjugation to N-acetylgalactosamine (GalNAc) is the clinically validated liver-delivery approach for siRNA and ASO therapeutics: Multivalent GalNAc ligands bind the asialoglycoprotein receptor abundant on hepatocytes, permitting subcutaneous dosing and durable gene silencing and several GalNAc-siRNA drugs are approved for non-oncologic indications (116). Its relevance to HCC is nonetheless uncertain. Receptor expression may be heterogeneous or reduced in poorly differentiated tumors, so that GalNAc-directed agents could preferentially modulate lncRNA expression in non-malignant hepatocytes and 'liver tropism' should not be equated with tumor-selective delivery. Off-target hybridization, innate immune activation, hepatotoxicity (a particular concern in cirrhotic patients) and intratumoral heterogeneity of target expression further constrain translation and must be addressed in preclinical safety packages.

Polymeric nanoparticles, exosome-based carriers and ligand-directed delivery systems are also being actively investigated. Surface modification using hepatocyte-targeting ligands, antibodies, peptides, or glycan-based recognition motifs may further improve selective accumulation within tumor tissues while minimizing systemic toxicity (117).

Emerging multifunctional delivery platforms are increasingly designed not only to transport therapeutic cargo but also to respond dynamically to tumor-specific conditions such as hypoxia, acidic pH, oxidative stress, or enzymatic activity. Such stimuli-responsive systems may allow localized release of RNA therapeutics within specific microenvironmental niches where lncRNA-mTOR signaling is most active (118).

Future delivery technologies will likely integrate molecular targeting, controlled release, imaging capabilities and biomarker-guided patient selection to maximize therapeutic precision.

Rational combination strategies. The biological complexity of HCC suggests that monotherapy approaches are unlikely to achieve durable disease control. Instead, lncRNA-directed interventions may be most effective when incorporated into rational combination regimens designed to simultaneously target complementary vulnerabilities.

One proposed strategy involves combining lncRNA-targeting therapeutics with mTOR inhibitors. Suppression of oncogenic lncRNAs may prevent compensatory pathway reactivation while enhancing the depth and duration of mTOR inhibition. For example, inhibition of MALAT1 or HULC could reduce AKT signaling, thereby limiting adaptive escape mechanisms triggered by rapalog therapy.

Integration with antiangiogenic therapies represents another attractive avenue. Since several mTOR-regulated lncRNAs contribute to hypoxia adaptation and VEGF-driven vascular remodeling, simultaneous inhibition of lncRNA-mTOR circuitry and angiogenic signaling may disrupt reciprocal feedback loops that sustain tumor progression.

Combinations with immune checkpoint blockade are conceptually attractive but remain untested. NEAT1 has been proposed to connect mTOR-HIF signaling to immune suppression and PD-L1 expression, but the HCC evidence currently available places mTOR upstream of NEAT1 in the regulation of glycolysis (70). Whether targeting NEAT1 or similar lncRNAs would enhance antitumor immunity, improve T-cell function, or increase responsiveness to checkpoint inhibitors has not been tested in HCC and remains a hypothesis. Likewise, modulation of immunometabolic pathways could reverse microenvironmental conditions that promote T-cell exhaustion and myeloid-mediated suppression.

Additional opportunities include combining RNA therapeutics with ferroptosis inducers, metabolic inhibitors, autophagy modulators, epigenetic therapies and emerging cell-based immunotherapies. Ultimately, successful combination strategies will likely require biomarker-guided patient stratification informed by molecular, spatial and single-cell profiling.

Mechanisms of resistance. As with virtually all targeted therapies, resistance represents a major obstacle to successful clinical implementation of lncRNA-mTOR-directed interventions. Resistance mechanisms are likely to emerge at multiple biological levels, including signaling pathway adaptation, cellular plasticity, microenvironmental remodeling and therapeutic delivery failure.

One common mechanism involves compensatory activation of parallel signaling pathways such as MAPK, WNT/β-catenin, JAK/STAT, Hippo/YAP and receptor tyrosine kinase networks (119,120) As a number of these pathways interact extensively with mTOR signaling, suppression of one node may simply redirect oncogenic signaling through alternative routes.

Tumor cell plasticity provides an additional challenge. Single-cell studies indicate that HCC contains diverse cellular states capable of dynamically transitioning between proliferative, mesenchymal, stem-like and therapy-tolerant phenotypes. Distinct lncRNA programs may support these adaptive transitions, allowing tumors to evade selective pressure imposed by targeted therapies.

Microenvironmental adaptation also contributes substantially to resistance. Hypoxia, fibrosis, immune suppression, nutrient limitation and stromal signaling can induce alternative lncRNA expression programs that reactivate mTOR signaling or engage compensatory survival mechanisms. Spatially restricted resistant niches may therefore persist despite apparently effective pathway inhibition at the bulk tumor level (121,122).

Finally, therapeutic resistance may arise from inadequate delivery, transcript heterogeneity, alternative splice variants, or incomplete target suppression. These challenges underscore the need for iterative biomarker monitoring using liquid biopsy approaches, serial transcriptomic profiling and spatially

resolved analyses capable of capturing dynamic tumor evolution.

Collectively, these observations suggest that durable therapeutic benefit will require adaptive treatment strategies that account for the ecological and evolutionary complexity of lncRNA-mTOR networks. Future precision oncology approaches will likely combine RNA therapeutics, pathway inhibitors, immunomodulatory agents and biomarker-guided monitoring within an integrated framework designed to suppress both primary oncogenic drivers and emergent resistance mechanisms.

6. Future directions and research agenda

Despite substantial progress in defining interactions between lncRNAs and mTOR signaling in HCC, the field remains in a transitional stage. Most studies have focused on individual lncRNAs and linear signaling relationships, whereas accumulating evidence suggests that lncRNA-mTOR networks operate as dynamic, context-dependent regulatory ecosystems spanning malignant cells, stromal compartments, immune populations and metabolic niches. Translating these discoveries into clinically actionable strategies will require coordinated advances in mechanistic biology, systems-level profiling, biomarker development, therapeutic engineering and clinical trial design.

Future research should therefore move beyond cataloging individual lncRNAs toward constructing predictive models capable of explaining how non-coding regulatory circuits shape mTOR pathway behavior across heterogeneous tumor ecosystems. Achieving this objective will require a phased strategy encompassing mechanistic validation, ecosystem-level modeling, clinical translation and methodological standardization.

Establishing mechanistic precision. The immediate priority is to convert descriptive associations into mechanistic causation with concise, reproducible standards. Candidate lncRNAs should be validated using complementary, orthogonal approaches (CRISPRi/CRISPRa and ASO/siRNA), rescue experiments and direct interaction assays (RNA Immunoprecipitation and Cross-linking Immunoprecipitation or RNA pulldown), with key findings confirmed in orthotopic or patient-derived *in vivo* models. Validation must include isoform-specific controls, cell-type resolution and pathway-focused readouts (phospho-proteomics or single-cell signaling) to distinguish direct mTOR regulators from indirect correlates of tumor progression. Simultaneously, map subcellular mechanisms, nuclear vs. cytoplasmic roles and molecular interactomes, to inform modality choice (such as nuclear ASO vs. cytoplasmic siRNA). Finally, explicitly test context dependence across major HCC etiologies (viral, alcohol-associated, metabolic) and disease stages and systematically characterize bidirectional feedback between mTOR activity and lncRNA expression so that adaptive responses to pathway perturbation can be anticipated.

Building multi-omic and spatial ecosystem models. With validated regulators in hand, lncRNA biology should be integrated into multi-omic, spatially resolved ecosystem models. Single-cell RNA-seq and ATAC-seq should be combined with spatial transcriptomics and spatial proteomics to localize lncRNA-mTOR activity within tumor niches and to identify niche-specific cell states linked to stemness, metastasis, immune evasion, or resistance. Joint latent factor models, graph-based causal inference and machine-learning approaches should be used to infer emergent regulatory hubs and co-essential modules that connect lncRNAs to mTOR nodes. Predictive perturbation experiments, pooled CRISPRi/CRISPRa and combinatorial screens in organoids and humanized orthotopic models should be prioritized to validate inferred vulnerabilities and to rank rational combinations. Spatially informed biomarkers (tissue and circulating extracellular vesicle lncRNAs) that report on niche-specific mTOR activity and can be used for patient selection and longitudinal monitoring should be developed.

Precision therapeutics and clinical translation. Validated, ecosystem-informed targets should be translated into therapeutics by aligning modality, delivery and combination strategy with biological mechanism and spatial constraints. Therapeutic modality should be matched to subcellular mechanism (ASO/antisense for nuclear targets; siRNA or RNA editing for cytoplasmic targets) and carriers optimized for liver tropism and intratumoral penetration. Biomarker-guided combination regimens that co-target lncRNA modules, mTOR signaling, metabolic adaptation, stroma, or immune checkpoints should be designed to limit compensatory rewiring. Early-phase adaptive trials with integrated spatial and liquid-biopsy monitoring to enable real-time treatment adjustment based on evolving lncRNA-mTOR dependencies should be implemented. Standardize preclinical safety and biodistribution packages (off-target profiling, immunogenicity assessment, biodistribution, GLP toxicology) to support first-in-human studies and conservative, biomarker-driven dose escalation.

Regulatory and safety considerations. Preclinical development of lncRNA-directed therapeutics must include standardized safety and biodistribution packages to support clinical translation. Recommended studies include comprehensive off-target profiling (transcriptome-wide and *in silico* prediction), innate and adaptive immunogenicity assays, dose-range finding and GLP toxicology in two species and quantitative biodistribution with attention to nonparenchymal liver cells and tumor stroma. Early clinical designs should prioritize conservative first-in-human dosing, pharmacodynamic biomarker endpoints (tissue and circulating) and staged escalation with integrated spatial and liquid-biopsy monitoring to detect on-target activity and emergent resistance.

Methodological standards and reproducibility. The rapid expansion of the lncRNA field has generated considerable heterogeneity in experimental design, analytical methodologies and reporting practices. Establishing rigorous methodological standards will therefore be essential for ensuring reproducibility, facilitating cross-study comparisons and accelerating clinical translation.

First, future studies should prioritize accurate lncRNA annotation and transcript validation. Given the complex isoform structures and context-dependent expression patterns

of a number of lncRNAs, precise transcript identification remains critical. Investigators should clearly define transcript variants, genomic coordinates and analytical pipelines used for quantification.

Second, mechanistic claims should be supported by multiple complementary experimental approaches. Correlative expression analyses alone should not be considered sufficient evidence of functional regulation. Robust validation should include gain- and loss-of-function studies, rescue experiments, pathway interrogation and, whenever feasible, *in vivo* confirmation.

Third, experimental systems should more closely reflect the biological complexity of human HCC. Although conventional two-dimensional cell culture models remain useful for mechanistic studies, they fail to capture key metabolic, immunologic and spatial features of native tumors. Greater utilization of patient-derived organoids, orthotopic models, humanized mouse systems and *ex vivo* tissue platforms will improve translational relevance.

Fourth, future investigations should incorporate standardized reporting of patient demographics, etiologic background, molecular subtype, treatment history and clinical outcomes. Such information is essential for interpreting context-dependent effects and identifying clinically meaningful biomarkers.

Finally, increasing emphasis should be placed on open-science practices, including public deposition of sequencing datasets, transparent analytical workflows, reproducible computational pipelines and reporting of negative findings. These measures will facilitate independent validation and accelerate collective progress across the field.

7. Discussion

Despite extensive research into both lncRNAs and mTOR signaling in hepatocellular carcinoma, the existing literature tends to treat these domains as parallel fields rather than components of an integrated regulatory architecture (Table I). Most prior reviews focus on either the PI3K-AKT-mTOR cascade or the oncogenic functions of lncRNAs in isolation, without addressing how these systems converge to shape tumor evolution, metabolic adaptation and therapeutic resistance. By reframing lncRNA-mTOR interactions as multilayered, systems-level circuits that operate across tumor cells, stromal compartments and immune niches, The present review argues for moving beyond linear pathway models toward a more ecological understanding of HCC biology.

A central, though provisional, message of this synthesis is that lncRNAs may influence mTOR signaling at several levels rather than at discrete nodes. The direct HCC evidence is strongest for MALAT1 (SRSF1-dependent S6K1 splicing) and LINC00958 (HDGF-SREBP1 lipogenic axis) and weaker for HULC, NEAT1 and GAS5, for which several proposed links to mTOR nodes remain indirect (Table II); TSC2 convergence is a hypothesis rather than an established vulnerability. Single-cell and spatial transcriptomic studies point to heterogeneity of mTOR-related programs across hypoxic zones, vascularized margins, fibrotic stroma and immune-excluded regions, but direct spatial demonstration of lncRNA-mTOR circuits in human HCC is lacking (Table III). Such heterogeneity may help explain the inconsistent clinical results of mTOR inhibitors, including the negative EVOLVE-1 trial (85) and would argue for microenvironment-aware therapeutic strategies if confirmed.

A related challenge is the translational gap between mechanistic discovery and clinical application: Although numerous lncRNAs have been functionally validated *in vitro* and in xenograft models, few have progressed toward RNA-based therapeutics or biomarker-driven patient stratification, reflecting persistent barriers in tissue-specific delivery, off-target effects and limited understanding of lncRNA dynamics under therapeutic pressure. ceRNA-type lncRNAs such as HULC and LINC00958 appear particularly tractable for antisense or siRNA-based inhibition, whereas nuclear scaffolds such as MALAT1 and NEAT1 may require CRISPRi or LNA-ASO platforms. NEAT1 has been proposed as a biomarker of immunotherapy response, but the available clinical data derive from melanoma and glioblastoma, are not HCC-specific and point in the opposite direction to a resistance hypothesis, while metabolic regulators such as LINC00958 could guide rational combinations of mTOR inhibitors with lipid-metabolism-targeted agents.

Looking ahead, progress will depend on moving from catalogues of individual lncRNAs toward ecosystem-level frameworks that incorporate spatial organization, cellular plasticity and immunometabolic interactions, while retaining strict standards of mechanistic validation. Integrating multi-omic technologies, functional genomics and improved delivery systems may eventually enable biomarker-guided, RNA-directed approaches; at present, however, these remain investigational.

8. Limitations of the present review

The present review has several limitations that should be considered when interpreting its conclusions. First, although informed by a structured literature search, this is a narrative rather than a fully systematic review; formal risk-of-bias assessment and a PRISMA-based flow diagram were not applied and some relevant primary studies may not have been captured. Second, the mechanistic synthesis focuses on five exemplar lncRNAs (HULC, MALAT1, NEAT1, LINC00958 and GAS5) selected for the depth and reproducibility of their mechanistic evidence; this selection, while representative, does not capture the full breadth of lncRNAs implicated in HCC-related mTOR signaling and less-studied transcripts may be under-represented. Third, most of the mechanistic evidence discussed derives from cell-line and xenograft models, which incompletely recapitulate the immune and stromal complexity of human HCC; translational inferences regarding immune evasion and therapeutic combinations should therefore be interpreted as hypothesis-generating rather than clinically validated. Fourth, the spatial and single-cell datasets referenced in Section 4 remain limited in sample size and etiological/geographic diversity, which may constrain generalizability across HCC etiologies (such as HBV- vs. MASLD-driven disease). In addition, the evidence grading in Table II is a qualitative framework devised for the present review and has not been formally validated; the biomarker associations discussed here are exploratory; the spatial and single-cell model in Fig. 3 and Table III is conceptual; and some mechanistic statements are extrapolated from non-HCC

tumor types where HCC-specific data are lacking, as indicated in the text. Finally, because the literature search was restricted to English-language, peer-reviewed publications, relevant findings reported in other languages or in the gray literature may have been omitted. These limitations do not undermine the mechanistic and translational themes synthesized here but should guide the design of future systematic and quantitative syntheses of the lncRNA-mTOR literature in HCC.

9. Conclusion

Current evidence suggests that lncRNAs can regulate PI3K-AKT-mTOR signaling in hepatocellular carcinoma at multiple levels, although direct HCC evidence is stronger for some lncRNAs than for others. Their potential as circulating biomarkers and as targets for RNA-directed therapeutics remains exploratory and preclinical. Prospective clinical validation, spatially resolved mapping in human tumors and liver-directed delivery solutions will be needed before the clinical value of lncRNA-mTOR circuitry can be established.

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BA and PNP performed the investigation and wrote the original draft. WKA conceptualized the review. SRJ, GS and LM designed the figures and tables, made substantial scientific contributions to the review, and wrote, reviewed and edited the manuscript. VA, JR, DP and WKA wrote, reviewed and edited the review. Data authentication is not applicable. All authors read and approved the final manuscript.

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Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, the authors used ChatGPT and Microsoft Copilot to assist in language editing, structuring and improving the clarity of the manuscript, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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