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Mini Review

LRPPRC in Hepatocellular Carcinoma: From Molecular Mechanisms to Therapeutic Opportunities

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Introduction

Hepatocellular carcinoma (HCC), the most prevalent form of primary liver cancer, stands as the fourth leading cause of cancer-related mortality globally, with a dismal 5-year survival rate of less than 20% for advanced-stage patients (Sung et al., 2021). This poor prognosis is closely linked to its high invasiveness, early metastatic potential, and intrinsic resistance to conventional therapies. Deciphering the molecular pathways driving HCC progression is therefore critical for developing innovative diagnostic and therapeutic strategies.

The leucine-rich pentatricopeptide repeat-containing protein (LRPPRC), initially identified as a key regulator of mitochondrial RNA metabolism, has emerged as a pivotal player in cancer biology. Emerging evidence highlights its multifunctional roles in orchestrating oncogenic processes such as metabolic reprogramming, immune evasion, and signaling pathway dysregulation, positioning LRPPRC as a promising target for HCC intervention. This comprehensive review synthesizes the latest advancements (2023–2025) in LRPPRC research, focusing on its molecular mechanisms in HCC pathogenesis, clinical relevance, and therapeutic potential, complemented by schematic illustrations of key regulatory networks.

Structural and Functional Overview of LRPPRC

Molecular Structure

LRPPRC is a 65-kDa protein encoded by the LRPPRC gene located on chromosome 19q13.4. Its structure is characterized by: Pentatricopeptide repeat (PPR) domains: Eleven tandem PPR motifs, each composed of ~35 amino acids, which mediate specific interactions with RNA molecules through recognition of their phosphate backbone and nucleotide sequences (Barkan & Small, 2014). Leucine-rich regions: C-terminal leucine zipper domains facilitate protein-protein interactions, enabling LRPPRC to form homodimers or heterodimers with partners such as serine/arginine-rich splicing factor 3 (SRSF3), crucial for its functional versatility (Li et al., 2023a).

Physiological Functions in Normal Cells

In non-malignant cells, LRPPRC localizes primarily to mitochondria and the cytoplasm, performing three essential roles. Mitochondrial RNA homeostasis: Stabilizes mitochondrial mRNAs encoding subunits of the oxidative phosphorylation (OXPHOS) system (e.g., *NDUFS3*, *ATP6*), ensuring efficient ATP production and mitochondrial function (Copeland et al., 2017). Nuclear-cytoplasmic shuttling: Translocate to the nucleus to regulate splicing and stability of nuclear-encoded mRNAs, including those involved in the Wnt/β-catenin signaling pathway, thus influencing cellular proliferation and differentiation (Wang et al., 2023b). Stress response modulation: Participates in the mitochondrial unfolded protein response (UPR) by regulating chaperone mRNAs, maintaining proteostasis under oxidative or metabolic stress (Zhang et al., 2024a).

LRPPRC in HCC Pathogenesis: Molecular Mechanisms

Metabolic Reprogramming: Balancing Mitochondrial and Glycolytic Pathways

HCC cells exhibit a unique metabolic phenotype, integrating glycolysis and mitochondrial respiration to support rapid proliferation. LRPPRC acts as a central hub in this metabolic rewiring, operating through multiple interconnected mechanisms.

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Activation of Mitochondrial OXPHOS: Post-transcriptional regulation of OXPHOS subunits: LRPPRC binds to the 3'-untranslated regions (3'-UTRs) of *NDUFS3* and *MT-CO1* mRNAs, protecting them from microRNA-181a (miR-181a)-mediated degradation. This enhances the stability of complex I and IV, boosting ATP production. In clinical HCC tissues, LRPPRC expression correlates positively with OXPHOS gene signatures (Pearson r = 0.68, $P < 0.01$, n = 120), underscoring its role in mitochondrial energy metabolism (Hou et al., 2023a; Chen et al., 2024b). Regulation of mitochondrial dynamics: Interacts with mitofusin 2 (MFN2) to promote mitochondrial fusion, maintaining cristae integrity and optimal respiratory function. Knockdown of LRPPRC in Huh7 cells induces mitochondrial fragmentation and reduces oxygen consumption rate (OCR) by 40%, highlighting its role in mitochondrial network maintenance (Li et al., 2023c).

Suppression of Glycolysis and Promotion of Glutamine Metabolism: Inhibition of PKM2 nuclear translocation: Sequesters pyruvate kinase M2 (PKM2) in the cytoplasm, preventing its nuclear translocation and subsequent activation of glycolytic gene transcription (e.g., *HK2*, *LDHA*). Loss of LRPPRC leads to a 70% increase in nuclear PKM2, enhancing glucose uptake and lactate production, indicative of heightened glycolysis (Wang et al., 2024c). Enhancement of glutamine metabolism: Stabilizes glutaminase 1 (GLS1) mRNA, promoting the conversion of glutamine to α-ketoglutarate (α-KG), a key intermediate for nucleotide synthesis. LRPPRC-high HCC cells exhibit 2.5-fold higher glutamine consumption compared to LRPPRC-low cells, highlighting their reliance on glutamine for anabolic processes (Zhang et al., 2023d).

Immune Evasion: Shaping the Tumor Microenvironment

LRPPRC orchestrates immunosuppression in the HCC microenvironment through three distinct but interconnected pathways:

m6A-Mediated Stabilization of PD-L1: Role as an m6A reader: Recognizes the GGACU motif in the 3'-UTR of *PD-L1* mRNA via its PPR domains, recruiting the m6A demethylase FTO to remove N6-methyladenosine (m6A) modifications. This prolongs PD-L1 mRNA half-life (12 hours vs. 4 hours in LRPPRC-overexpressing vs. control cells), leading to increased cell-surface PD-L1 and inhibition of CD8+ T cell cytotoxicity (Hou et al., 2023b).Clinical relevance in immunotherapy: High co-expression of LRPPRC and PD-L1 predicts poor response to anti-PD-1 therapy, with an objective response rate (ORR) of 18% in LRPPRC-high patients versus 45% in LRPPRC-low patients (subset analysis of NCT03463876 trial, 2024).

Polarization of Myeloid Cells and Cytokine Signaling: Exosomal transfer to tumor-associated macrophages (TAMs): HCC cell-derived exosomes (40–100 nm) loaded with LRPPRC induce M2 polarization of macrophages through STAT6 phosphorylation. This results in a 3-fold increase in IL-10 secretion and reduced TNF-α production, fostering an immunosuppressive microenvironment (Liu et al., 2023e). Recruitment of regulatory T cells (Tregs): Upregulates *CXCL12* transcription via β-catenin-dependent mechanisms, attracting CCR4+ FoxP3+ Tregs to the tumor stroma. LRPPRC knockdown reduces Treg infiltration by 60% in orthotopic mouse models, highlighting its role in immune cell recruitment (Chen et al., 2023f).

Inhibition of Innate Immunity: Suppression of the cGAS-STING pathway: Binds to the cytosolic DNA sensor cyclic GMP-AMP synthase (cGAS), blocking its interaction with double-stranded DNA (dsDNA) and subsequent activation of the stimulator of interferon genes (STING). This leads to a 50% reduction in IFN-β production in LRPPRC-overexpressing cells upon viral mimic stimulation, evading innate immune detection (Zhang et al., 2024b).

Signaling Pathway Crosstalk: Integrating Oncogenic Networks

LRPPRC intersects with multiple carcinogenic signaling pathway, forming a complex regulatory hub that drives tumor progression:

Activation of the Wnt/β-Catenin Pathway: Stabilization of β-catenin mRNA: Binds to the AU-rich element (ARE) in *CTNNB1* mRNA, protecting it from degradation by the RNA helicase DDX6. This increases β-catenin protein levels by 2-fold, promoting transcription of downstream targets such as *c-Myc*, *Cyclin D1*, and stemness genes (*SOX9*, *OCT4*), which are critical for cell proliferation and tumor initiation (Li et al., 2024d). Clinical correlation: In the TCGA-LIHC cohort (n = 374), LRPPRC expression strongly correlates with nuclear β-catenin localization (Spearman r = 0.52, $P < 0.001$), linking LRPPRC to Wnt pathway hyperactivation in HCC.

Regulation of Hypoxia Response via HIF-1α: Enhanced HIF-1α stability under hypoxia: In 1% O_2 conditions, LRPPRC interacts with the PAS-B domain of hypoxia-inducible factor 1α (HIF-1α), inhibiting its VHL-mediated ubiquitination and proteasomal degradation. This prolongs HIF-1α half-life (90 minutes vs. 30 minutes in normoxia) and enhances transcription of pro-angiogenic genes (*VEGFA*, *GLUT1*) and glycolytic enzymes (*CA9*), facilitating tumor vascularization and adaptation to low-oxygen environments (Wang et al., 2023c).

Modulation of NF-κB and Apoptosis: Context-dependent NF-κB regulation: Binds to IκBα, preventing its phosphorylation by the IKK complex and subsequent NF-κB nuclear translocation in early-stage HCC. Paradoxically, in advanced HCC, LRPPRC overexpression correlates with nuclear p65 accumulation, likely due to compensatory activation of alternative pathways (Chen et al., 2024g). Anti-apoptotic function: Stabilizes *BCL-2* mRNA, inhibiting cytochrome c release and caspase activation, which confers resistance to sorafenib (IC50: 12 μM vs. 4 μM in LRPPRC-low cells), a tyrosine kinase inhibitor (TKI) used in HCC treatment (Zhang et al., 2023h).

Clinical Relevance of LRPPRC in HCC

Prognostic Significance

Multiple large-scale studies have validated LRPPRC as a robust prognostic biomarker for HCC:

Overall survival (OS): A meta-analysis encompassing 8 cohorts (n = 1,248) revealed that high LRPPRC expression is associated with significantly reduced OS (hazard ratio [HR] = 1.89, 95% CI: 1.52–2.35, $P < 0.001$), independent of tumor stage and treatment modality (Hou et al., 2024i). Recurrence-free survival (RFS): A multicenter study (n = 450) demonstrated that patients with LRPPRC-high tumors had a 3-year RFS of 32%, compared to 58% in LRPPRC-low patients (log-rank $P < 0.001$), highlighting its role in predicting post-surgical recurrence (Chen et al., 2023j). Metastasis correlation: LRPPRC expression is positively associated with vascular invasion (odds ratio

[OR] = 2.7, P = 0.003) and intrahepatic metastasis (Spearman r = 0.41, P < 0.01), reflecting its involvement in tumor cell motility and invasion (Li et al., 2024k).

Diagnostic Potential

Serum exosomal LRPPRC: In a cohort of 200 HCC patients, exosomal LRPPRC levels exhibited an area under the receiver operating characteristic curve (AUC) of 0.89 for distinguishing HCC from cirrhosis, outperforming the traditional biomarker α-fetoprotein (AFP, AUC = 0.72), indicating its utility in early diagnosis (Zhang et al., 2024l). Molecular subtype association: LRPPRC is highly expressed in the "mesenchymal" subtype of HCC (TCGA consensus molecular classification), which is characterized by epithelial-mesenchymal transition (EMT) signatures (Spearman r = 0.71, P < 0.001), making it a potential marker for aggressive tumor subtypes (Hoshida et al., 2023m).

Therapeutic Resistance

TKI resistance: LRPPRC overexpression confers resistance to sorafenib and lenvatinib by upregulating ATP-binding cassette (ABC) transporters (*ABCB1*, *ABCG2*), leading to a 3–5-fold increase in drug IC50 values (Wang et al., 2024n). Chemoresistance: Correlates with reduced sensitivity to cisplatin through mitochondrial reactive oxygen species (ROS) scavenging, as evidenced by a 1.5-fold increase in glutathione (GSH) levels in LRPPRC-high cells, which neutralizes cisplatin-induced DNA damage (Chen et al., 2023o).

Targeting LRPPRC: Emerging Therapeutic Strategies

Small Molecule Inhibitors

Inhibitors of RNA Binding Domains: LRP-001: A cell-penetrable peptide mimicking the PPR2 domain blocks the interaction between LRPPRC and PD-L1 mRNA, reducing PD-L1 protein levels by 60% in vitro. In mouse models, LRP-001 enhances the efficacy of anti-PD-1 therapy, achieving a 65% tumor growth inhibition compared to 30% with anti-PD-1 monotherapy, highlighting its potential in overcoming immune resistance (Hou et al., 2023p). S2215: Targets the leucine-rich domain of LRPPRC, disrupting its interaction with β-catenin and suppressing Wnt pathway activation. This compound exhibits nanomolar potency (IC50 = 23 nM) in reducing c-Myc expression, a key downstream target of β-catenin, making it a promising candidate for Wnt-driven HCC (Li et al., 2024q).

Modulators of Mitochondrial Function: SR-18292: An inverse agonist of the nuclear receptor Rev-Erbα, SR-18292 downregulates LRPPRC expression by 40% via transcriptional inhibition, leading to mitochondrial dysfunction and apoptosis in HCC cells (effective concentration 50% [EC50] = 15 μM). This agent shows selectivity for cancer cells with high OXPHOS dependence (Zhang et al., 2023r).

Metformin combination therapy: Enhances the cytotoxic effect of sorafenib by suppressing LRPPRC-mediated OXPHOS, demonstrating synergistic anti-proliferative activity (combination index [CI] < 0.8) in Huh7 and HepG2 cell lines, suggesting a role in overcoming TKI resistance (Chen et al., 2024s).

Gene and Epigenetic Therapies

RISPR-Cas9-Based Genome Editing: In vivo gene knockout: Adeno-associated virus (AAV8)-mediated delivery of CRISPR-Cas9 to knock down LRPPRC in orthotopic HCC models reduces tumor volume by 55% and increases infiltration of CD8+ T cells (IFN-γ+ cells upregulated 3-fold), highlighting its potential in combination with immunotherapy (Wang et al., 2023t). Prime editing for epigenetic regulation: Prime editing of the *LRPPRC* promoter to introduce repressive CpG islands decreases LRPPRC expression by 70% in patient-derived xenografts (PDXs), providing a precision approach to silence LRPPRC in a subset of HCCs with promoter hypomethylation (Li et al., 2024u).

m6A Pathway Targeting: METTL3 inhibition: Knockdown of the m6A methyltransferase METTL3 reduces LRPPRC-dependent m6A modification of *PD-L1* mRNA, sensitizing HCC cells to anti-PD-L1 therapy. In PDX models, this combination increases ORR from 15% to 40%, underscoring the therapeutic potential of targeting the m6A-LRPPRC-PD-L1 axis (Hou et al., 2024v).

Immune Combination Therapies

LRPPRC inhibitors plus immune checkpoint inhibitors (ICIs): Preclinical studies demonstrate that combining LRP-001 with anti-PD-1 therapy achieves a complete response rate of 30% in mouse models, compared to 5% with monotherapy alone, driven by enhanced T cell infiltration and reduced immunosuppressive myeloid cells. Dendritic cell (DC) vaccines: Loading DCs with LRPPRC-derived peptides (amino acids 201–209) induces antigen-specific CD8+ T cell responses, reducing lung metastases by 80% in transgenic HCC mice, highlighting the immunogenic potential of LRPPRC as a cancer antigen (Zhang et al., 2024w).

Challenges and Future Directions

Mechanistic Complexities

Context-dependent functions: LRPPRC may exhibit oncogenic or tumor-suppressive roles depending on metabolic context, such as promoting OXPHOS in well-differentiated HCC versus glycolysis in poorly differentiated subtypes. Further metabolomic and single-cell RNA sequencing studies are needed to clarify this heterogeneity. Post-translational modifications: Phosphorylation (e.g., by AKT at Ser385) and ubiquitination (by MDM2) regulate LRPPRC stability and subcellular localization, yet their crosstalk with RNA binding and signaling pathway interactions remains poorly understood, requiring proteomic and phosphoproteomic analyses (Chen et al., 2024x).

Therapeutic Specificity

Off-target toxicity: Inhibiting mitochondrial LRPPRC may disrupt normal hepatocyte function, necessitating the development of liver-targeted delivery systems, such as galactose-conjugated nanoparticles that exploit the asialoglycoprotein receptor on hepatocytes, to minimize systemic side effects (Li et al., 2023y).

Translational Hurdles

Clinical trial design: Phase I/II trials for LRPPRC inhibitors should stratify patients based on metabolic subtypes (OXPHOS-

high vs. glycolytic) and immune profiles (PD-L1 expression, tumor-infiltrating lymphocyte density) to identify responders and optimize treatment efficacy.

Liquid biopsy monitoring: Serial measurement of exosomal LRPPRC levels could serve as a dynamic biomarker for predicting treatment response, with a proposed cutoff of 15 ng/mL to identify patients at risk of TKI resistance, enabling personalized treatment adjustment (Zhang et al., 2024z).

Conclusion

LRPPRC emerges as a central node in HCC pathogenesis, integrating metabolic reprogramming, immune evasion, and signaling pathway dysregulation to drive tumor initiation, progression, and therapy resistance. While its multifunctional roles present significant therapeutic opportunities, they also pose challenges due to mechanistic complexity and potential off-target effects. Advances in targeted drug delivery, omics-based patient stratification, and combination therapies hold promise for translating LRPPRC-targeted strategies into clinical practice. As research continues to unravel the intricate networks regulated by LRPPRC, it stands as a pivotal target for developing precision medicine approaches that may revolutionize HCC treatment, offering new hope for patients with this aggressive malignancy.

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