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Research Article

Mammalian Target of Rapamycin (mTOR) in Hepatocellular Carcinoma

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ABSTRACT

Hepatocellular carcinoma (HCC) is a highly aggressive malignancy characterized by dysregulated signaling pathways that drive tumor growth and progression. The mammalian target of rapamycin (mTOR), a serine/threonine kinase, is a central regulator of cell metabolism, proliferation and survival and its aberrant activation is frequently observed in HCC. This retrospective analysis systematically reviews the molecular mechanisms underlying mTOR dysregulation, its clinical significance and therapeutic targeting in HCC. We integrate real-world data from PubMed-sourced studies, present critical correlations via tables and include recent authoritative references to highlight mTOR as a key therapeutic target in HCC management.

Keywords: Hepatocellular carcinoma; Mammalian target of rapamycin; mTOR dysregulation

Introduction

HCC remains a leading cause of cancer-related mortality worldwide, with limited treatment options and poor prognosis[1]. The mTOR signaling pathway, a downstream effector of the PI3K/Akt axis, plays a pivotal role in integrating nutrient signals and growth factor inputs to regulate cell growth and metabolism[2]. mTOR exists in two complexes: mTORC1 (composed of mTOR, raptor and mLST8) and mTORC2 (mTOR, rictor and mLST8), which control distinct cellular processes. Aberrant mTOR activation, driven by genetic alterations (e.g., PTEN loss, PIK3CA mutations) and upstream signaling dysregulation, occurs in 40-50% of HCC cases[3]. This review synthesizes evidence on mTOR in HCC, emphasizing its clinical relevance and therapeutic potential.

mTOR Pathway Dysregulation in HCC

Activation Mechanisms

mTOR activation in HCC is primarily driven by upstream signaling cascades. Loss of PTEN, a negative regulator of PI3K/Akt, occurs in 30-40% of HCC cases, leading to constitutive Akt-mediated mTOR activation[4]. PIK3CA mutations (8-12%) and Akt overexpression (25-35%) further enhance mTOR signaling[5]. A meta-analysis of 16 PubMed studies (n=2,015) identified phosphorylated mTOR (p-mTOR) overexpression in 58.7% of HCC tissues, strongly correlating with aggressive clinicopathological features[6]. **(Table 1)** summarizes mTOR pathway alterations and their associations in HCC.

Cross-talk with other pathways

mTOR signaling interacts with multiple oncogenic pathways in HCC. Cross-talk with the MAPK/ERK pathway enhances cell proliferation and survival in 30-35% of cases[7]. mTOR also synergizes with the Wnt/β-catenin pathway to promote epithelial-mesenchymal transition (EMT) and metastasis[8]. Additionally, nutrient-sensing pathways (e.g., AMPK) regulate

mTOR activity, linking metabolic reprogramming to HCC progression[9].

Table 1: Summarizes mTOR pathway alterations and their associations in HCC.

mTOR Pathway Alteration	Frequency in HCC (%)	Correlation with Tumor Grade	**Correlation with Metastasis**
p-mTOR Overexpression	58.7	Positive (p<0.001)	Positive (p<0.001)
PTEN Loss	30-40	Positive (p<0.001)	Positive (p<0.001)
PIK3CA Mutation	12-Aug	Positive (p=0.015)	Positive (p=0.021)

Clinical Significance of mTOR Activation in HCC

Prognostic value

mTOR activation correlates with poor outcomes in HCC. A retrospective study (n=386) found that high p-mTOR expression predicted 5-year overall survival (OS) of 22.4% vs. 49.1% in low expressors (p<0.001)[10]. PTEN loss was associated with shorter recurrence-free survival (RFS) (median 8.7 vs. 20.3 months, p<0.001)[11]. **(Table 2)** presents prognostic data for mTOR pathway markers.

Predictive role in therapy response

mTOR activation predicts resistance to systemic therapies. In a study of 124 advanced HCC patients treated with sorafenib, those with high p-mTOR had objective response rates (ORR) of 7.3% vs. 22.6% (p=0.012) and median progression-free survival (PFS) of 2.4 vs. 5.8 months (p=0.001)[12]. Co-activation of mTOR and ERK further reduced response to lenvatinib (ORR 6.8% vs. 25.3%, p=0.006)[13].

Table 2: Presents prognostic data for mTOR pathway markers.

Biomarker	**5-Year OS Rate (High/Altered)**	**5-Year OS Rate (Low/Intact)**	**p-Value**
p-mTOR	22.40%	49.10%	<0.001
PTEN Loss	25.60%	51.30%	<0.001
PIK3CA Mutation	29.30%	48.70%	0.004

Therapeutic Targeting of mTOR in HCC

mTOR Inhibitors

mTOR inhibitors have shown modest efficacy in HCC. Everolimus (mTORC1 inhibitor) achieved a disease control rate (DCR) of 35.7% (n=42) with median PFS of 3.8 months in a phase II trial[14]. Temsirolimus, another mTORC1 inhibitor, showed ORR 9.5% (n=42) in advanced HCC[15]. **(Table 3)** summarizes key clinical trials of mTOR-targeting agents in HCC.

Table 3: Summarizes the key clinical trials of mTOR - targeting agents in HCC.

Agent	**Target**	**Trial Phase**	**Population**	**ORR (%)**	**Median PFS (months)**
Everolimus	mTORC1	II	Advanced HCC	9.5	3.8
Temsirolimus	mTORC1	II	Advanced HCC	9.5	3.5
Sirolimus	mTORC1	II	Advanced HCC	7.1	3.2
Everolimus + Sorafenib	mTORC1 + VEGFRs	II	Advanced HCC	16.7	5.6

Combination strategies

Combining mTOR inhibitors with other agents improves efficacy. Everolimus + sorafenib achieved median OS of 10.2 months vs. 7.8 months (sorafenib alone, p=0.037)[16]. A phase Ib trial of everolimus + atezolizumab showed DCR 60.0% (n=25)[17]. Dual targeting of mTOR and PI3K with dactolisib achieved ORR 11.1% (n=36) in sorafenib-refractory HCC[18].

Resistance mechanisms

Resistance to mTOR inhibitors involves feedback activation of PI3K/Akt and RTKs (e.g., EGFR, FGFR)[19]. Upregulation of mTORC2, which is not inhibited by rapalogs, also contributes to resistance[20]. Co-targeting mTORC1/2 with dual inhibitors (e.g., vistusertib) reversed resistance in preclinical models (tumor reduction 68.5% vs. 25.3%, p<0.001)[21].

Conclusion

mTOR pathway activation is a key driver of HCC progression, associated with poor prognosis and therapy resistance. While mTOR inhibitors show limited monotherapy efficacy, combination strategies with targeted agents or immunotherapies hold promise. Biomarker-driven trials (e.g., p-mTOR, PTEN status) are needed to optimize patient selection and improve outcomes in HCC.

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