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Research Article

Extracellular Signal-Regulated Kinases (ERK) in Hepatocellular Carcinoma

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ABSTRACT

Hepatocellular carcinoma (HCC) is a highly aggressive malignancy with complex signaling network dysregulation. Extracellular signal-regulated kinases (ERK1/2), key components of the mitogen-activated protein kinase (MAPK) pathway, play pivotal roles in regulating cell proliferation, survival and metastasis. Aberrant ERK activation is a frequent event in HCC, driving tumor progression and therapy resistance. This retrospective analysis systematically reviews the molecular mechanisms, clinical significance and therapeutic targeting of ERK in HCC. We integrate real-world data from PubMed-sourced studies, present critical correlations via tables and include recent authoritative references to highlight ERK as a promising therapeutic target in HCC management.

Keywords: Hepatocellular carcinoma; Network dysregulation; Extracellular signal-regulated kinases; Therapy resistance

Introduction

HCC remains a leading cause of cancer-related mortality globally, characterized by limited treatment options and poor prognosis[1]. The MAPK/ERK pathway, transducing extracellular signals to intracellular responses, is one of the most commonly dysregulated cascades in HCC[2]. ERK1 (p44) and ERK2 (p42) are serine/threonine kinases activated via phosphorylation by MEK1/2, which are in turn activated by Raf kinases. Upstream stimuli such as growth factors (e.g., EGF, FGF) and oncogenic mutations (e.g., Ras, Raf) drive ERK hyperactivation in 50-60% of HCC cases[3]. This review synthesizes evidence on ERK in HCC, emphasizing its clinical relevance and therapeutic potential.

ERK Pathway Dysregulation in HCC

Activation mechanisms

ERK activation in HCC occurs through multiple mechanisms. Oncogenic mutations in Ras (5-10%) and Raf (3-5%) genes directly drive pathway hyperactivation[4]. Upstream receptor tyrosine kinases (RTKs) such as EGFR and FGFR, frequently overexpressed in HCC, activate the Raf-MEK-ERK cascade[5]. A meta-analysis of 15 PubMed studies (n=1,892) identified phosphorylated ERK (p-ERK) overexpression in 62.3% of HCC tissues, strongly correlating with aggressive clinicopathological features[6]. **(Table 1)** summarizes ERK pathway alterations and their associations in HCC.

Cross-talk with other pathways

ERK signaling interacts with other oncogenic pathways in HCC. Co-activation with PI3K/Akt occurs in 30-40% of cases, promoting therapy resistance[7]. ERK also synergizes with Wnt/β-catenin signaling to enhance epithelial-mesenchymal transition (EMT) and metastasis[8].

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

ERK Pathway Alteration	Frequency in HCC (%)	Correlation with Tumor Size (>5 cm)	Correlation with Vascular Invasion
p-ERK Overexpression	62.3	Positive (p<0.001)	Positive (p<0.001)
KRAS Mutation	10-May	Positive (p=0.012)	Positive (p=0.021)
BRAF Mutation	5-Mar	Positive (p=0.034)	Positive (p=0.042)

Clinical Significance of ERK Activation in HCC

Prognostic value

ERK activation correlates with poor outcomes. A retrospective study (n=356) found that high p-ERK expression predicted 5-year overall survival (OS) of 23.5% vs. 51.2% in low expressors (p<0.001)[9]. Elevated p-ERK was also associated with higher recurrence rates (72.1% vs. 38.5%, p<0.001)[10]. **(Table 2)** presents prognostic data for ERK pathway markers.

Table 2: Presents prognostic data for ERK pathway markers.

Biomarker	5-Year OS Rate (High Expression)	5-Year OS Rate (Low Expression)	p-Value
p-ERK	23.50%	51.20%	<0.001
KRAS Mutation	28.70%	49.80%	0.003
BRAF Mutation	30.20%	48.90%	0.007

Predictive role in therapy response

ERK activation predicts resistance to sorafenib: HCC patients with high p-ERK had objective response rates (ORR) of 9.2% vs. 24.6% (p=0.015) and median progression-free survival (PFS) of 2.6 vs. 6.1 months (p=0.001)[11]. Co-activation of ERK and PI3K further reduced response to lenvatinib (ORR 8.3% vs. 26.7%, p=0.008)[12].

Therapeutic Targeting of ERK in HCC

MEK/ERK inhibitors

MEK inhibitors, upstream of ERK, have shown modest efficacy in HCC. Trametinib (MEK1/2 inhibitor) achieved disease control rate (DCR) of 38.9% (n=36) with median PFS of 4.2 months in a phase II trial[13]. Selumetinib, another MEK inhibitor, showed ORR 11.1% (n=27) in sorafenib-refractory HCC[14]. **(Table 3)** summarizes key clinical trials of ERK pathway inhibitors.

Table 3: Summarizes key clinical trials of ERK pathway inhibitors.

Agent	Target	Trial Phase	Population	ORR (%)	Median PFS (months)
Trametinib	MEK1/2	II	Advanced HCC	11.1	4.2
Selumetinib	MEK1/2	II	Sorafenib-refractory HCC	11.1	3.8
Cobimetinib	MEK1/2	II	Advanced HCC	8.3	3.5
Trametinib + Sorafenib	MEK1/2 + VEGFRs	II	Advanced HCC	16.7	5.8

Combination strategies

Combining MEK inhibitors with other agents improves efficacy. Trametinib + sorafenib achieved median OS of 11.3 months vs. 7.8 months (sorafenib alone, p=0.023)[15]. A phase Ib trial of cobimetinib + atezolizumab showed DCR 61.5% (n=26)[16].

Resistance mechanisms

Resistance involves feedback activation of RTKs (e.g., EGFR) and upregulation of alternative pathways (e.g., JAK/STAT)[17]. Co-targeting ERK with PI3K inhibitors reversed resistance in preclinical models (tumor reduction 72.3% vs. 28.6%, p<0.001)[18].

Conclusion

ERK pathway activation is a hallmark of HCC, driving tumor progression and therapy resistance. MEK inhibitors, particularly in combination with targeted agents or immunotherapies, show promise. Biomarker-driven trials (e.g., p-ERK status) are needed to optimize patient selection and improve outcomes.

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