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Research Article

Mitogen-Activated Protein Kinases (MAPK) in Hepatocellular Carcinoma

Dr. Houhong Wang*

Department of General Surgery, The Affiliated Bozhou Hospital of Anhui Medical University, China

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***Corresponding author:** Dr. Houhong Wang, Department of General Surgery, The Affiliated Bozhou Hospital of Anhui Medical University, China

ABSTRACT

Hepatocellular carcinoma (HCC) is a highly aggressive malignancy characterized by dysregulated signaling pathways, with the mitogen-activated protein kinase (MAPK) cascade playing a central role in tumorigenesis and progression. MAPKs, including extracellular signal-regulated kinases (ERK1/2), c-Jun N-terminal kinases (JNK1/2/3), p38 MAPKs and ERK5, transduce extracellular signals to regulate cell proliferation, survival, apoptosis and metastasis. Aberrant MAPK activation, driven by genetic mutations, upstream oncogenic signaling or microenvironmental cues, is a frequent event in HCC. This retrospective analysis systematically reviews the molecular mechanisms of MAPK 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 MAPKs as potential therapeutic targets in HCC management.

Keywords: Hepatocellular carcinoma; Mitogen-activated protein kinase; Oncogenic signaling

Introduction

HCC remains a leading cause of cancer-related mortality globally, with limited treatment options and poor prognosis[1]. The MAPK superfamily constitutes a conserved signaling network that mediates cellular responses to diverse stimuli, including growth factors, cytokines and stress[2]. Among the four major MAPK subfamilies, ERK1/2 is the most extensively studied in HCC, with well-characterized roles in promoting cell proliferation and survival. JNKs and p38 MAPKs, often associated with stress responses, exhibit context-dependent roles in HCC, while ERK5 is emerging as a regulator of tumor angiogenesis and metastasis[3]. Aberrant MAPK activation occurs in 50-60% of HCC cases, making this pathway a key focus for therapeutic development[4]. This review synthesizes evidence on MAPKs in HCC, emphasizing their clinical relevance and therapeutic potential.

MAPK Pathway Dysregulation in HCC

Expression and activation patterns

MAPK subfamilies exhibit distinct activation profiles in HCC. A meta-analysis of 18 PubMed studies (n=2,135) reported phosphorylated ERK1/2 (p-ERK1/2) overexpression in 62.3% of HCC cases, followed by p-JNK (48.7%), p-p38 (41.5%) and p-ERK5 (35.8%)[5]. Genetic alterations in MAPK pathway components are less common but impactful: KRAS mutations (5-10%) drive ERK1/2 activation, while MAP2K1 (MEK1) mutations (2-3%) contribute to pathway hyperactivation[6]. **(Table 1)** summarizes MAPK activation patterns and clinicopathological associations in HCC.

Table 1: Summarizes MAPK activation patterns and their clinicopathological associations in HCC.

MAPK Subfamily	Activation Rate in HCC (%)	Correlation with Tumor Stage	Correlation with Metastasis
ERK1/2	62.3	Positive (p<0.001)	Positive (p<0.001)
JNK	48.7	Positive (p=0.002)	Positive (p=0.005)
p38	41.5	Positive (p=0.012)	Positive (p=0.023)
ERK5	35.8	Positive (p=0.021)	Positive (p=0.034)

Mechanisms of activation

MAPK activation in HCC is driven by multiple mechanisms. Upstream receptor tyrosine kinases (RTKs) such as EGFR and FGFR activate the RAF/MEK/ERK1/2 cascade via RAS[7]. Chronic liver injury, a major HCC risk factor, induces JNK and p38 activation through oxidative stress and cytokine signaling (e.g., TNF-α, IL-6)[8]. Epigenetic modifications, including hypomethylation of MAPK pathway genes, contribute to constitutive activation[9]. Cross-talk with other pathways, such as PI3K/Akt and Wnt/β-catenin, amplifies MAPK-mediated oncogenic effects in 30-40% of HCC cases[10].

Clinical Significance of MAPK Activation in HCC

Prognostic value

MAPK activation correlates with poor outcomes in HCC. A retrospective study (n=386) found that high p-ERK1/2 expression predicted 5-year overall survival (OS) of 23.5% vs. 51.2% in low expressors (p<0.001)[11]. High p-JNK expression was associated with shorter recurrence-free survival (RFS) (median 8.2 vs. 19.7 months, p<0.001)[12]. **(Table 2)** presents prognostic data for MAPK subfamilies.

Table 2: Presents prognostic data for MAPK subfamilies.

MAPK Subfamily	5-Year OS Rate (High Activation)	5-Year OS Rate (Low Activation)	p-Value
ERK1/2	23.50%	51.20%	<0.001
JNK	28.70%	49.80%	0.001
p38	32.40%	48.30%	0.008
ERK5	35.60%	47.90%	0.015

Predictive role in therapy response

MAPK activation predicts resistance to systemic therapies. In a study of 124 advanced HCC patients treated with sorafenib, those with high p-ERK1/2 had objective response rates (ORR) of 8.1% vs. 24.3% (p=0.012) and median progression-free survival (PFS) of 2.5 vs. 5.9 months (p=0.001)[13]. Co-activation of ERK1/2 and JNK was associated with reduced response to lenvatinib (ORR 7.2% vs. 27.5%, p=0.006)[14].

Therapeutic Targeting of MAPK in HCC

MAPK Inhibitors

MAPK inhibitors show varying efficacy in HCC. MEK inhibitors (targeting ERK1/2 upstream) have demonstrated modest activity: trametinib achieved a disease control rate (DCR) of 38.9% (n=36) with median PFS of 4.2 months[15]. JNK inhibitors (e.g., SP600125) are in preclinical development, while p38 inhibitors (e.g., PH-797804) showed limited efficacy in early trials[16]. **(Table 3)** summarizes key clinical trials of MAPK-targeted agents in HCC.

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

Agent	Target	Trial Phase	Population	ORR (%)	Median PFS (months)
Trametinib	MEK1/2 (ERK1/2 upstream)	II	Advanced HCC	11.1	4.2
Selumetinib	MEK1/2	II	Advanced HCC	10.7	3.8
Cobimetinib	MEK1/2	II	Advanced HCC	9.5	3.5
Trametinib + Sorafenib	MEK1/2 + VEGFRs	II	Advanced HCC	16.7	5.8

Combination strategies

Combining MAPK inhibitors with other agents improves efficacy. Trametinib + sorafenib achieved median OS of 11.3 months vs. 7.8 months (sorafenib alone, p=0.023)[17]. A phase Ib trial of cobimetinib + atezolizumab showed DCR 61.5% (n=26)[18]. Dual targeting of ERK1/2 and PI3K with trametinib + buparlisib achieved ORR 15.4% (n=26) in advanced HCC[19].

Resistance mechanisms

Resistance to MAPK inhibitors involves feedback activation of RTKs (e.g., EGFR, FGFR) and alternative pathways (e.g., JAK/STAT)[20]. Upregulation of MAPK phosphatases (e.g., DUSP6) and epigenetic reprogramming also contribute[21]. Co-targeting ERK1/2 with RTK inhibitors reversed resistance in preclinical models (tumor reduction 68.5% vs. 24.3%, p<0.001)[22].

Conclusion

MAPK pathways, particularly ERK1/2, play critical roles in HCC progression, with activation associated with poor prognosis and therapy resistance. While single-agent MAPK inhibitors show limited efficacy, combination strategies with targeted agents or immunotherapies hold promise. Biomarker-driven trials (e.g., p-ERK1/2 status) are needed to optimize patient selection and improve outcomes in HCC.

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