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Research Article

Mitogen-Activated Protein Kinase Kinases (MEK) in Hepatocellular Carcinoma

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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. Mitogen-activated protein kinase kinases (MEK1/2), key intermediaries in the Raf/MEK/ERK pathway, transduce upstream signals to activate ERK1/2, thereby regulating cell proliferation, survival and metastasis. Aberrant MEK activation, driven by genetic mutations, upstream oncogenic signaling or epigenetic dysregulation, is frequently observed in HCC. This retrospective analysis systematically reviews the molecular mechanisms of MEK 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 MEK as a potential therapeutic target 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/ERK pathway, pivotal for cellular responses to growth factors and oncogenic stimuli, is frequently dysregulated in HCC[2]. MEK1 and MEK2 (collectively MEK1/2) are dual-specificity kinases that act as the only known activators of ERK1/2, making them critical nodes in this pathway[3]. Aberrant MEK signaling in HCC occurs in 40-50% of cases, driven by mechanisms such as Raf overexpression, MEK1 mutations or receptor tyrosine kinase (RTK) activation[4]. This review synthesizes evidence on MEK1/2 in HCC, emphasizing their clinical relevance and therapeutic potential.

MEK Pathway Dysregulation in HCC

Expression and mutation patterns

MEK1/2 exhibit distinct activation profiles in HCC. A meta-analysis of 16 PubMed studies (n=2,012) reported phosphorylated MEK1/2 (p-MEK1/2) overexpression in 56.8% of HCC cases[5]. MEK1 mutations, primarily in the kinase domain, occur in 2-3% of HCCs, while MEK2 mutations are rare (<1%)[6]. **(Table 1)** summarizes MEK alterations and their clinicopathological associations in HCC.

Activation mechanisms

MEK activation in HCC is primarily driven by upstream signaling. Raf kinases, particularly C-Raf and B-Raf, phosphorylate and activate MEK1/2 upon stimulation by Ras[7]. Overexpression of RTKs such as EGFR and FGFR activates

the Raf-MEK-ERK cascade[8]. Epigenetic modifications, including hypomethylation of the MEK1 promoter, contribute to its overexpression[9]. Cross-talk with the PI3K/Akt pathway enhances MEK-mediated ERK activation in 30-35% of HCC cases[10].

Table 1: Summarizes MEK alterations and their clinicopathological associations in HCC.

MEK Alteration	Frequency in HCC (%)	Correlation with Tumor Stage	Correlation with Vascular Invasion
p-MEK1/2 Overexpression	56.8	Positive (p<0.001)	Positive (p<0.001)
MEK1 Mutation	3-Feb	Positive (p=0.013)	Positive (p=0.024)
MEK1 Amplification	7-May	Positive (p=0.008)	Positive (p=0.017)

Clinical Significance of MEK Activation in HCC

Prognostic value

MEK activation correlates with poor outcomes in HCC. A retrospective study (n=364) found that high p-MEK1/2 expression predicted 5-year overall survival (OS) of 24.3% vs. 48.7% in low expressors (p<0.001)[11]. MEK1 mutations were associated with shorter recurrence-free survival (RFS) (median 8.1 vs. 19.5 months, p<0.001)[12]. **(Table 2)** presents prognostic data for MEK pathway markers.

Table 2: Presents prognostic data for MEK pathway markers.

Biomarker	5-Year OS Rate (High/Altered)	5-Year OS Rate (Low/Intact)	p-Value
p-MEK1/2 Overexpression	24.30%	48.70%	<0.001
MEK1 Mutation	22.60%	47.90%	<0.001
MEK1 Amplification	28.50%	46.30%	0.003

Predictive role in therapy response

MEK activation predicts resistance to systemic therapies. In a study of 122 advanced HCC patients treated with sorafenib, those with high p-MEK1/2 had objective response rates (ORR) of 8.2% vs. 23.5% (p=0.016) and median progression-free survival (PFS) of 2.5 vs. 5.8 months (p=0.002)[13]. MEK1 mutations were associated with reduced response to lenvatinib (ORR 7.1% vs. 26.8%, p=0.009)[14].

Therapeutic Targeting of MEK in HCC

MEK Inhibitors

MEK inhibitors have shown modest efficacy in HCC. Trametinib, a MEK1/2 inhibitor, achieved a disease control rate (DCR) of 38.9% (n=36) with median PFS of 4.2 months[15]. Selumetinib, another MEK inhibitor, showed ORR 11.1% (n=27) in a phase II trial[16]. **(Table 3)** summarizes key clinical trials of MEK-targeted agents in HCC.

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

Agent	Target	Trial Phase	Population	ORR (%)	Median PFS (months)
Trametinib	MEK1/2	II	Advanced HCC	11.1	4.2
Selumetinib	MEK1/2	II	Advanced 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)[17]. A phase Ib trial of cobimetinib + atezolizumab showed DCR 61.5% (n=26)[18]. Dual targeting of MEK and PI3K with trametinib + buparlisib achieved ORR 15.4% (n=26) in advanced HCC[19].

Resistance mechanisms

Resistance to MEK inhibitors involves feedback activation of RTKs (e.g., EGFR, FGFR) and upregulation of alternative pathways (e.g., JAK/STAT)[20]. Mutations in MEK1/2 (e.g., P124L) that reduce inhibitor binding also contribute[21]. Co-targeting MEK with RTK inhibitors reversed resistance in preclinical models (tumor reduction 67.3% vs. 23.5%, p<0.001)[22].

Conclusion

MEK1/2 play critical roles in HCC progression, with their activation associated with poor prognosis and therapy resistance. While single-agent MEK inhibitors show limited efficacy, combination strategies with targeted agents or immunotherapies hold promise. Biomarker-driven trials (e.g., p-MEK1/2 status) are needed to optimize patient selection and improve outcomes in HCC.

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