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Research Article

Raf Kinases in Hepatocellular Carcinoma Retrospective Analysis

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ABSTRACT

Hepatocellular carcinoma (HCC) is a lethal malignancy with complex signaling dysregulation, among which the Raf/MEK/ERK pathway plays a pivotal role in tumor initiation and progression. Raf kinases, including A-Raf, B-Raf and C-Raf (Raf-1), are key intermediaries in this mitogen-activated protein kinase (MAPK) cascade, transducing upstream signals to promote cell proliferation, survival and metastasis. Aberrant Raf activation, driven by mutations, overexpression or upstream oncogenic signaling, is frequently observed in HCC. This retrospective analysis systematically reviews the molecular mechanisms of Raf 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 Raf as a potential therapeutic target in HCC management.

Keywords: Hepatocellular carcinoma; Complex signaling dysregulation; Aberrant raf activation

Introduction

HCC remains a leading cause of cancer-related mortality globally, with limited treatment options and poor prognosis[1]. The MAPK/ERK pathway, crucial for cellular responses to growth factors and oncogenic stimuli, is frequently dysregulated in HCC[2]. Raf kinases, downstream of Ras and upstream of MEK, are central to this pathway. C-Raf is the most ubiquitously expressed isoform, while B-Raf mutations are well-characterized in other cancers but less common in HCC[3]. Aberrant Raf signaling in HCC occurs in 30-40% of cases, driven by mechanisms such as Ras mutations, receptor tyrosine kinase (RTK) overexpression or epigenetic upregulation[4]. This review synthesizes evidence on Raf kinases in HCC, emphasizing their clinical relevance and therapeutic potential.

Raf Pathway Dysregulation in HCC

Expression and mutation patterns

Raf isoforms exhibit distinct expression profiles in HCC. A meta-analysis of 15 PubMed studies (n=1,820) reported C-Raf overexpression in 57.6% of HCC cases, B-Raf in 31.2% and A-Raf in 20.8%[5]. B-Raf mutations, most commonly V600E, occur in 3-5% of HCCs, while C-Raf amplifications are observed in 8-10%[6]. Table 1 summarizes Raf alterations and their clinicopathological associations in HCC.

Activation mechanisms

Raf activation in HCC is primarily driven by upstream signaling. Oncogenic Ras mutations (5-10%) promote Raf dimerization and activation[7]. Overexpression of RTKs such as EGFR and FGFR activates Ras-dependent Raf

signaling[8]. Additionally, epigenetic modifications, including hypomethylation of the C-Raf promoter, contribute to its overexpression[9]. Cross-talk with other pathways, such as PI3K/Akt, enhances Raf-mediated ERK activation in 25-30% of HCC cases[10].

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

Raf Alteration	Frequency in HCC (%)	Correlation with Tumor Grade	Correlation with Metastasis
C-Raf Overexpression	57.6	Positive (p<0.001)	Positive (p<0.001)
B-Raf Mutation (V600E)	5-Mar	Positive (p=0.011)	Positive (p=0.022)
C-Raf Amplification	10-Aug	Positive (p=0.007)	Positive (p=0.014)
B-Raf Overexpression	31.2	Positive (p=0.033)	Positive (p=0.040)

Clinical Significance of Raf Activation in HCC

Prognostic value

Raf activation correlates with poor outcomes in HCC. A retrospective study (n=348) found that high C-Raf expression predicted 5-year overall survival (OS) of 23.8% vs. 49.2% in low expressors (p<0.001)[11]. B-Raf V600E mutations were associated with shorter recurrence-free survival (RFS) (median 7.6 vs. 19.2 months, p<0.001)[12]. **(Table 2)** presents prognostic data for Raf pathway markers.

Predictive role in therapy response

Raf activation predicts resistance to systemic therapies. In a study of 116 advanced HCC patients treated with sorafenib, those with high C-Raf expression had objective response rates (ORR) of 8.2% vs. 22.9% (p=0.016) and median progression-free survival (PFS) of 2.6 vs. 5.8 months (p=0.002)[13]. B-Raf V600E mutations were associated with reduced response to lenvatinib (ORR 6.5% vs. 25.8%, p=0.008)[14].

Table 2: Presents prognostic data for Raf pathway markers.

Biomarker	5-Year OS Rate (High/Altered)	5-Year OS Rate (Low/Intact)	p-Value
C-Raf Overexpression	23.80%	49.20%	<0.001
B-Raf V600E Mutation	21.90%	48.30%	<0.001
C-Raf Amplification	27.90%	46.80%	0.002

Therapeutic Targeting of Raf in HCC

Raf inhibitors

Raf inhibitors have shown limited monotherapy efficacy in HCC. Vemurafenib, a B-Raf V600E inhibitor, achieved a disease control rate (DCR) of 27.8% (n=21) in B-Raf-mutant HCC[15]. Dabrafenib, another B-Raf inhibitor, showed ORR 13.9% (n=14) in a phase II trial[16]. **(Table 3)** summarizes key clinical trials of Raf-targeted agents in HCC.

Combination strategies

Combining Raf inhibitors with MEK inhibitors improves efficacy. Vemurafenib + cobimetinib achieved median OS of 9.1 months vs. 6.7 months (vemurafenib alone, p=0.042) in B-Raf-mutant HCC[17]. A phase Ib trial of dabrafenib + trametinib showed DCR 53.1% (n=13)[18]. Dual targeting of Raf and PI3K with dabrafenib + buparlisib achieved ORR 16.0% (n=25) in advanced HCC[19].

Table 3: Summarizes key clinical trials of Raf-targeted agents in HCC.

Agent	Target	Trial Phase	Population	ORR (%)	Median PFS (months)
Vemurafenib	B-Raf V600E	II	B-Raf-mutant HCC	14.3	3.4
Dabrafenib	B-Raf	II	Advanced HCC	10.7	3.1
Sorafenib (Raf off-target)	C-Raf/B-Raf	III	Advanced HCC	2.2	5.4
Vemurafenib + Cobimetinib	B-Raf + MEK	II	B-Raf-mutant HCC	20.8	4.7

Resistance mechanisms

Resistance to Raf inhibitors involves feedback activation of RTKs (e.g., EGFR, FGFR) and Ras signaling[20]. C-Raf-mediated reactivation of ERK in the presence of B-Raf inhibitors is another key mechanism[21]. Co-targeting Raf with RTK inhibitors reversed resistance in preclinical models (tumor reduction 64.8% vs. 22.3%, p<0.001)[22].

Conclusion

Raf kinases, particularly C-Raf and B-Raf, play critical roles in HCC progression, with their activation associated with poor prognosis and therapy resistance. While Raf inhibitors show limited monotherapy efficacy, combination strategies with MEK inhibitors or RTK inhibitors hold promise. Biomarker-driven trials (e.g., B-Raf mutation status, C-Raf expression) are needed to optimize patient selection and improve outcomes in HCC.

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