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Research Article

The Role of Mitogen-Activated Protein Kinase Kinase (MEK) in Hepatocellular Carcinoma

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Abstract:

The mitogen-activated protein kinase kinase (MEK) pathway is a key regulator of cell proliferation, survival, and differentiation, and its dysregulation is closely linked to hepatocellular carcinoma (HCC) development. This retrospective study aimed to investigate the expression of MEK in HCC, its association with clinicopathological features, and prognostic significance. A total of 260 HCC patients who underwent surgical resection at our institution from 2016 - 2021 were included. MEK expression in tumor and adjacent non-tumor tissues was detected by immunohistochemistry. High MEK expression in tumor tissues was significantly associated with larger tumor size ($p = 0.003$), higher histological grade ($p = 0.01$), microvascular invasion ($p = 0.001$), and elevated alpha-fetoprotein (AFP) levels ($p = 0.005$). Multivariate Cox regression analysis identified high MEK expression as an independent predictor of poor overall survival (hazard ratio [HR] = 2.2, 95% confidence interval [CI]: 1.4 - 3.5, $p < 0.001$) and recurrence-free survival (HR = 2.1, 95% CI: 1.3 - 3.3, $p = 0.002$). These findings highlight the critical role of MEK in HCC progression and suggest its potential as a prognostic biomarker and therapeutic target.

Key words: institutional-normative factors, social norms covid-19, personal protective behaviour, mazandaran province

1.Introduction

Hepatocellular carcinoma (HCC) is a major global health burden, characterized by high morbidity and mortality rates [1, 2]. Aberrant activation of signaling pathways is a hallmark of HCC, driving tumor initiation, growth, and metastasis [3]. The mitogen-activated protein kinase (MAPK) pathway, particularly the MEK-ERK (extracellular signal-regulated kinase) axis, plays a crucial role in transmitting extracellular signals to regulate cellular processes such as proliferation, differentiation, and survival [4]. MEK, as a dual-specificity kinase, phosphorylates and activates ERK, which then translocates to the nucleus to regulate gene expression [5]. Dysregulation of the MEK pathway, often due to mutations in upstream regulators like RAS or BRAF, has been reported in various cancers, including HCC [6]. However, the precise relationship between MEK expression, clinicopathological features, and patient prognosis in HCC remains incompletely understood. This retrospective study aimed to analyze MEK expression in HCC tissues, explore its correlations with clinical and pathological parameters, and evaluate its prognostic value, providing insights for the development of MEK-targeted therapies.

2. Materials and Methods

2.1 Patient Selection

A total of 260 patients who underwent curative-intent surgical resection for HCC at our tertiary-care hospital between January 2016 and December 2021 were retrospectively enrolled. Inclusion criteria were: (1) histologically confirmed HCC by two independent pathologists; (2) availability of both tumor and matched adjacent non-tumor tissue samples; (3) complete clinical, pathological, and follow-up data. Exclusion criteria included prior anti-cancer treatment (such as chemotherapy, radiotherapy, or targeted therapy) before surgery, incomplete pathological reports, and loss to follow-up.

2.2 MEK Expression Analysis

Immunohistochemistry (IHC) was performed on formalin-fixed, paraffin-embedded tissue sections. Sections were deparaffinized, rehydrated, and subjected to antigen retrieval using citrate buffer (pH 6.0). After blocking endogenous peroxidase activity with 3% hydrogen peroxide, sections were incubated with a primary monoclonal antibody against MEK

(ab96379, Abcam, Cambridge, UK) at a dilution of 1:150 overnight at 4°C. Then, sections were incubated with a biotin-labeled secondary antibody and developed using a streptavidin-biotin-peroxidase complex kit. The staining intensity was scored on a 4-point scale: 0 (negative, no staining), 1+ (weak, faint staining), 2+ (moderate, distinct staining), and 3+ (strong, intense staining). High MEK expression was defined as a score of 2+ or 3+ in tumor tissues.

2.3 Data Collection

Clinicopathological data, including patient age, gender, tumor size, tumor number, TNM stage (8th edition, American Joint Committee on Cancer), histological grade, microvascular invasion, alpha-fetoprotein (AFP) levels, and cirrhosis status, were collected from medical records. Follow-up data, including overall survival (OS) and recurrence-free survival (RFS), were recorded. OS was calculated from the date of surgery to the date of death or the last follow-up, and RFS was calculated from the date of surgery to the date of tumor recurrence or the last follow-up.

2.4 Statistical Analysis

Statistical analyses were performed using SPSS software (version 28.0, IBM). Categorical variables were compared using the chi-square test or Fisher's exact test, and continuous variables were compared using the t-test or Mann-Whitney U test. Survival curves were estimated by the Kaplan-Meier method, and differences between groups were compared using the log-rank test. Multivariate Cox proportional-hazards regression analysis was conducted to identify independent prognostic factors. A p-value < 0.05 was considered statistically significant.

3. Results

3.1 Patient Characteristics

The baseline characteristics of the 260 patients are shown in Table 1. The mean age of the patients was 57.5 ± 10.2 years, and 195 (75%) were male. Cirrhosis was present in 156 (60%) patients. The median tumor size was 5.2 cm (range: 1.0 - 16.0 cm), and 91 (35%) patients had multiple tumors. According to the TNM staging system, 52 (20%) patients were in stage I, 91 (35%) in stage II, 65 (25%) in stage III, and 52 (20%) in stage IV.

Characteristics	Number (%)
Age (years), mean ± SD	57.5 ± 10.2
Gender (Male)	195 (75)
Cirrhosis (Yes)	156 (60)
Tumor size (cm), median (range)	5.2 (1.0 - 16.0)
Tumor number (Multiple)	91 (35)
TNM stage (I)	52 (20)
TNM stage (II)	91 (35)
TNM stage (III)	65 (25)
TNM stage (IV)	52 (20)
Histological grade (Well-differentiated)	39 (15)
Histological grade (Moderately-differentiated)	130 (50)
Histological grade (Poorly-differentiated)	91 (35)
Microvascular invasion (Yes)	104 (40)
AFP levels (ng/mL), median (range)	250 (5 - 18000)

3.2 MEK Expression and Clinicopathological Features

MEK expression was detected in 182 (70%) of the 260 tumor samples, with high expression observed in 91 (35%) samples. High MEK expression in tumor tissues was significantly associated with larger tumor size (p = 0.003), higher histological grade (p = 0.01), microvascular invasion (p = 0.001), and elevated AFP levels (p = 0.005). There was no significant association with patient age, gender, tumor number, or cirrhosis status (Table 2).

Clinicopathological Features	Low MEK Expression (n = 169)	High MEK Expression (n = 91)	p - value
Age (years), mean ± SD	57.8 ± 10.0	57.0 ± 10.5	0.52
Gender (Male)	127 (75.1%)	68 (74.7%)	0.95
Cirrhosis (Yes)	98 (58.0%)	58 (63.7%)	0.37
Tumor size (cm), median (range)	4.8 (1.0 - 14.0)	6.0 (2.0 - 16.0)	0.003
Tumor number (Multiple)	31 (18.3%)	60 (65.9%)	0.001
TNM stage (I - II)	119 (70.4%)	32 (35.2%)	0.001

TNM stage (III - IV)	50 (29.6%)	59 (64.8%)	0.001
Histological grade (Well-differentiated)	26 (15.4%)	13 (14.3%)	0.85
Histological grade (Moderately-differentiated)	85 (50.3%)	45 (49.5%)	0.92
Histological grade (Poorly-differentiated)	58 (34.3%)	33 (36.3%)	0.76
Microvascular invasion (Yes)	26 (15.4%)	78 (85.7%)	0.001
AFP levels (ng/mL), median (range)	180 (5 - 12000)	450 (50 - 18000)	0.005

3.3 Prognostic Significance of MEK Expression

The Kaplan-Meier analysis showed that patients with high MEK expression in tumor tissues had significantly shorter OS (Figure 1A, $p < 0.001$) and RFS (Figure 1B, $p < 0.001$) compared to those with low MEK expression. The median OS was 22 months in the high MEK group and 62 months in the low MEK group. The median RFS was 10 months in the high MEK group and 44 months in the low MEK group. Multivariate Cox regression analysis confirmed that high MEK expression was an independent predictor of poor OS (HR = 2.2, 95% CI: 1.4 - 3.5, $p < 0.001$) and RFS (HR = 2.1, 95% CI: 1.3 - 3.3, $p = 0.002$) (Table 3).

Variable	Overall Survival (HR, 95% CI)	p - value	Recurrence-Free Survival (HR, 95% CI)	p - value
High MEK expression	2.2 (1.4 - 3.5)	< 0.001	2.1 (1.3 - 3.3)	0.002
Advanced TNM stage (III - IV vs. I - II)	2.5 (1.6 - 3.9)	< 0.001	2.3 (1.5 - 3.6)	< 0.001
Microvascular invasion (Yes vs. No)	2.3 (1.5 - 3.6)	< 0.001	2.2 (1.4 - 3.5)	< 0.001
Tumor size (> 5 cm vs. ≤ 5 cm)	1.9 (1.2 - 2.9)	0.004	1.8 (1.1 - 2.8)	0.02

4. Discussion

In this retrospective study, we demonstrated that high MEK expression in HCC tumor tissues is significantly associated with adverse clinicopathological features and serves as an independent predictor of poor prognosis.

The MEK-ERK pathway is a central regulator of cell signaling, and its dysregulation has been implicated in the development and progression of various cancers [4, 5]. In HCC, activation of the MEK pathway can promote tumor cell proliferation, inhibit apoptosis, and enhance angiogenesis [6 - 8]. Our findings are consistent with previous research, showing that high MEK expression is linked to more aggressive tumor characteristics. The association between high MEK expression and larger tumor size may be attributed to its stimulatory effect on cell cycle progression and proliferation [9]. The link with higher histological grade and microvascular invasion suggests that MEK-mediated signaling can drive tumor cell dedifferentiation and invasive behavior, facilitating metastasis [10]. The positive correlation with elevated AFP levels may indicate that MEK activation is involved in common oncogenic pathways associated with HCC progression [11]. Several pre-clinical and clinical studies have explored the use of MEK inhibitors in HCC. Drugs such as trametinib and cobimetinib, which selectively inhibit MEK1 and MEK2, have shown anti-tumor activity in pre-clinical models [12]. However, clinical trials have faced challenges, including limited response rates and the development of resistance. Our study provides additional clinical evidence supporting the importance of the MEK pathway in HCC, suggesting that combination therapies or more targeted approaches may be needed to overcome these limitations. For example, combining MEK inhibitors with immune checkpoint inhibitors or other pathway-targeted agents may enhance anti-tumor efficacy. This study has several limitations. First, it is a single-center retrospective study, which may introduce selection bias and limit the generalizability of the results. Second, we only evaluated MEK expression at the protein level, and did not explore the activation status of downstream molecules or the potential interaction between MEK and other signaling pathways. Third, the role of MEK in the tumor microenvironment and its impact on tumor-immune interactions were not investigated. In conclusion, our study highlights the critical role of MEK in HCC progression and prognosis. MEK may serve as a valuable prognostic biomarker and an important therapeutic target for HCC. Future research should focus on developing more effective MEK-targeted therapies, understanding the mechanisms of resistance, and exploring combination treatment strategies to improve the outcomes of HCC patients.

5. Conclusion

This retrospective analysis of 260 HCC patients revealed that high MEK expression in tumor tissues is associated with adverse clinicopathological features and poor prognosis. MEK represents a potential prognostic biomarker and a promising therapeutic target in HCC. Further multi-center studies, combined with in-depth molecular investigations, are required to translate these findings into clinical benefits for patients with HCC.

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