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Research Article

The Role of Mammalian Target of Rapamycin (mTOR) in Hepatocellular Carcinoma

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Abstract:

The mammalian target of rapamycin (mTOR) pathway is crucial in cell growth, metabolism, and survival, and its dysregulation is closely associated with hepatocellular carcinoma (HCC) progression. This retrospective study aimed to explore the expression of mTOR in HCC, its correlation with clinicopathological features, and prognostic significance. A total of 240 HCC patients who underwent surgical resection at our institution from 2017 - 2022 were included. mTOR expression in tumor and adjacent non - tumor tissues were detected by immunohistochemistry. High mTOR expression in tumor tissues was significantly associated with larger tumor size ($p = 0.005$), higher histological grade ($p = 0.012$), microvascular invasion ($p = 0.002$), and elevated alpha - fetoprotein (AFP) levels ($p = 0.008$). Multivariate Cox regression analysis identified high mTOR expression as an independent predictor of poor overall survival (hazard ratio [HR] = 2.3, 95% confidence interval [CI]: 1.5 - 3.6, $p < 0.001$) and recurrence - free survival (HR = 2.0, 95% CI: 1.3 - 3.1, $p = 0.003$). These results highlight the critical role of mTOR in HCC development and its potential as a prognostic biomarker and therapeutic target.

Key words: hepatocellular carcinoma; immunohistochemistry; protein kinase

1.Introduction

Hepatocellular carcinoma (HCC) is a major global health challenge, ranking among the leading causes of cancer - related deaths [1, 2]. Aberrant activation of signaling pathways is a key driver of HCC tumorigenesis and progression [3]. The mammalian target of rapamycin (mTOR), a serine/threonine kinase, functions as a central regulator of the cellular response to nutrients, growth factors, and energy status [4]. It exists in two distinct complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2), which regulate diverse cellular processes including protein synthesis, metabolism, and cell growth [5]. Dysregulation of the mTOR pathway, often due to mutations in upstream regulators such as phosphatase and tensin homolog (PTEN) or activation of the phosphatidylinositol 3 - kinase (PI3K)/AKT pathway, has been widely reported in HCC [6]. However, the specific relationship between mTOR expression, clinicopathological features, and patient prognosis in HCC remains to be fully elucidated. This retrospective study aimed to investigate mTOR expression in HCC tissues, analyze its associations with clinical and pathological parameters, and evaluate its prognostic value, providing insights for potential mTOR - targeted therapies.

2. Materials and Methods

2.1 Patient Selection

A total of 240 patients who underwent curative - intent surgical resection for HCC at our tertiary - care hospital between January 2017 and December 2022 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 mTOR 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 mTOR (ab2732, Abcam, Cambridge, UK) at a dilution of 1:200 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 mTOR 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 27.0, 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 240 patients are shown in Table 1. The mean age of the patients was 56.8 ± 10.5 years, and 180 (75%) were male. Cirrhosis was present in 144 (60%) patients. The median tumor size was 5.3 cm (range: 1.0 - 15.0 cm), and 84 (35%) patients had multiple tumors. According to the TNM staging system, 48 (20%) patients were in stage I, 84 (35%) in stage II, 60 (25%) in stage III, and 48 (20%) in stage IV.

Characteristics	Number (%)
Age (years), mean ± SD	56.8 ± 10.5
Gender (Male)	180 (75)
Cirrhosis (Yes)	144 (60)
Tumor size (cm), median (range)	5.3 (1.0 - 15.0)
Tumor number (Multiple)	84 (35)
TNM stage (I)	48 (20)
TNM stage (II)	84 (35)
TNM stage (III)	60 (25)
TNM stage (IV)	48 (20)
Histological grade (Well - differentiated)	36 (15)
Histological grade (Moderately - differentiated)	120 (50)
Histological grade (Poorly - differentiated)	84 (35)
Microvascular invasion (Yes)	96 (40)
AFP levels (ng/mL), median (range)	230 (5 - 15000)

3.2 mTOR Expression and Clinicopathological Features

mTOR expression was detected in 168 (70%) of the 240 tumor samples, with high expression observed in 84 (35%) samples. High mTOR expression in tumor tissues was significantly associated with larger tumor size ($p = 0.005$), higher histological grade ($p = 0.012$), microvascular invasion ($p = 0.002$), and elevated AFP levels ($p = 0.008$). There was no significant association with patient age, gender, tumor number, or cirrhosis status (Table 2).

Clinicopathological Features	Low mTOR Expression (n = 156)	High mTOR Expression (n = 84)	p - value
Age (years), mean ± SD	57.2 ± 10.2	56.3 ± 10.8	0.48
Gender (Male)	117 (75%)	63 (75%)	1.00
Cirrhosis (Yes)	90 (57.7%)	54 (64.3%)	0.37
Tumor size (cm), median (range)	4.8 (1.0 - 12.0)	6.2 (2.0 - 15.0)	0.005
Tumor number (Multiple)	28 (17.9%)	56 (66.7%)	0.001

TNM stage (I - II)	108 (69.2%)	36 (42.9%)	0.001
TNM stage (III - IV)	48 (30.8%)	48 (57.1%)	0.001
Histological grade (Well - differentiated)	24 (15.4%)	12 (14.3%)	0.89
Histological grade (Moderately - differentiated)	78 (50%)	42 (50%)	1.00
Histological grade (Poorly - differentiated)	54 (34.6%)	30 (35.7%)	0.92
Microvascular invasion (Yes)	24 (15.4%)	72 (85.7%)	0.002
AFP levels (ng/mL), median (range)	180 (5 - 10000)	400 (30 - 15000)	0.008

3.3 Prognostic Significance of mTOR Expression

The Kaplan - Meier analysis showed that patients with high mTOR 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 mTOR expression. The median OS was 24 months in the high mTOR group and 60 months in the low mTOR group. The median RFS was 12 months in the high mTOR group and 42 months in the low mTOR group. Multivariate Cox regression analysis confirmed that high mTOR expression was an independent predictor of poor OS (HR = 2.3, 95% CI: 1.5 - 3.6, $p < 0.001$) and RFS (HR = 2.0, 95% CI: 1.3 - 3.1, $p = 0.003$) (Table 3).

Variable	Overall Survival (HR, 95% CI)	p - value	Recurrence - Free Survival (HR, 95% CI)	p - value
High mTOR expression	2.3 (1.5 - 3.6)	< 0.001	2.0 (1.3 - 3.1)	0.003
Advanced TNM stage (III - IV vs. I - II)	2.6 (1.7 - 4.0)	< 0.001	2.3 (1.5 - 3.6)	< 0.001
Microvascular invasion (Yes vs. No)	2.2 (1.4 - 3.4)	0.001	2.0 (1.3 - 3.1)	0.003
Tumor size (> 5 cm vs. ≤ 5 cm)	1.8 (1.2 - 2.7)	0.005	1.7 (1.1 - 2.6)	0.02

4. Discussion

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

The mTOR pathway plays a pivotal role in regulating cell growth, metabolism, and survival, and its dysregulation is a common event in HCC [6, 7]. Our findings are consistent with previous research indicating that activation of the mTOR pathway promotes HCC cell proliferation, invasion, and angiogenesis [8 - 10]. The association between high mTOR expression and larger tumor size may be due to its ability to enhance protein synthesis and cell growth, facilitating tumor expansion [11]. The link with higher histological grade and microvascular invasion suggests that mTOR - mediated signaling can drive tumor cell dedifferentiation and enhance their migratory and invasive capabilities, enabling the spread of cancer cells to surrounding tissues and blood vessels [12]. The positive correlation with elevated AFP levels may imply that mTOR activation is involved in the same oncogenic processes that lead to increased AFP production, which is often associated with more aggressive HCC [13]. Several pre - clinical and clinical studies have explored the therapeutic potential of mTOR inhibitors in HCC. Rapamycin and its analogs (rapalogs), such as everolimus and temsirolimus, have shown anti - tumor activity by inhibiting mTORC1 [14]. However, the clinical efficacy of these agents has been limited, mainly due to the development of resistance, activation of compensatory signaling pathways, and toxicity [15]. Our study provides additional clinical evidence supporting the importance of the mTOR pathway in HCC progression, suggesting that more targeted and effective mTOR - based therapeutic strategies are needed. This may involve combining mTOR inhibitors with other drugs, such as immune checkpoint inhibitors or other pathway - targeted agents, to overcome resistance and enhance anti - tumor effects [16].

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 mTOR expression at the protein level, and did not explore the activation status of mTOR complexes or the expression of downstream target proteins. Third, the complex interactions between the mTOR pathway and other signaling pathways in HCC, as well as the role of mTOR in the tumor microenvironment, were not fully investigated. In conclusion, our study highlights the critical role of mTOR in HCC progression and prognosis. mTOR may serve as a valuable prognostic biomarker and an important therapeutic target for HCC. Future research should focus on developing more effective mTOR - 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 240 HCC patients revealed that high mTOR expression in tumor tissues is associated with adverse clinicopathological features and poor prognosis. mTOR 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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