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Research Article

The Role of Transcription Factor FOXK2 in Hepatocellular Carcinoma: A Retrospective Analysis

Houhong Wang

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

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

ABSTRACT

This retrospective study comprehensively analyzed the role of transcription factor FOXK2 in hepatocellular carcinoma (HCC). Data from PubMed - related research articles were collected, covering FOXK2's regulatory mechanisms, associations with HCC clinical features, and biomarker potential. FOXK2 is abnormally activated in HCC, and the PIAS4 - FOXK2 axis is crucial for HCC development and chemotherapy resistance. FOXK2 directly regulates multiple genes involved in de novo nucleotide synthesis, and its high expression correlates with poor HCC patient prognosis. Our findings suggest FOXK2 could be a novel HCC diagnostic and prognostic biomarker, and targeting FOXK2 - related pathways may offer new HCC treatment strategies.

KEYWORDS

Hepatocellular carcinoma, FOXK2, Transcription factor, Biomarker, Nucleotide synthesis

INTRODUCTION

Hepatocellular carcinoma (HCC) ranks among the most prevalent malignancies globally, with a high mortality rate. Its development is intricate, involving multiple genetic and epigenetic changes. Understanding these mechanisms is vital for developing effective diagnostic and therapeutic approaches. Transcription factors play a key role in gene expression regulation, and abnormal activation or inactivation of certain transcription factors is linked to cancer development. FOXK2, a member of the forkhead box (FOX) transcription factor family, has emerged as an important factor in cancer biology recently. This study aimed to summarize and analyze current knowledge about FOXK2 in HCC based on a retrospective review of relevant PubMed - sourced literature.

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MATERIALS AND METHODS

Literature Search

A comprehensive search was conducted in the PubMed database using keywords: "FOXK2", "hepatocellular carcinoma", "transcription factor", "nucleotide synthesis", "chemotherapy resistance", "biomarker", and their combinations.

Data Extraction

Two independent reviewers extracted data from the included articles. Information such as study design, sample size, patient characteristics, methods for detecting FOXK2 expression, FOXK2's function in HCC (e.g., gene regulation, impact on cell behaviors), associations between FOXK2 expression and HCC clinical features (e.g., tumor stage, recurrence, survival), and proposed FOXK2 - related mechanisms in HCC were collected. Discrepancies were resolved through discussion with a third reviewer.

RESULTS

FOXK2 Expression in HCC

Multiple studies consistently reported elevated FOXK2 expression in HCC tissues compared to adjacent non - tumor liver tissues. For instance, Wang X. et al. [1] used immunohistochemistry to analyze 120 pairs of HCC and adjacent non - tumor liver samples, revealing a significantly higher FOXK2 protein expression in HCC tissues. The positive rate was 70% in HCC tissues and only 15% in adjacent non - tumor tissues (Table 1). Another study by Li Y. et al. [2] detected higher FOXK2 mRNA levels in HCC cell lines than in normal liver cell lines via quantitative real - time PCR.

FOXK2 and Nucleotide Synthesis in HCC

Research has shown that FOXK2 can directly regulate genes involved in de novo nucleotide synthesis. Zhang Z, et al. [3] employed chromatin immunoprecipitation - sequencing (ChIP - seq) to identify FOXK2's target genes in HCC cells. They found that FOXK2 binds to the promoter regions of genes like phosphoribosyl pyrophosphate synthetase 1 (PRPS1) and carbamoyl - phosphate synthetase 2, aspartate transcarbamylase, and dihydroorotase (CAD), which are key enzymes in the de novo nucleotide synthesis pathway. Knocking down FOXK2 in HCC cells led to a significant reduction in the expression of these genes and intracellular nucleotide levels, as measured by liquid chromatography - tandem mass spectrometry (LC - MS/MS).

Tissue/Cells	Number of Samples	FOXK2 Positive Rate/Expression Level	Detection Method
HCC tissues	120	70% (protein expression)	Immunohistochemistry
Adjacent non - tumor liver tissues	120	15% (protein expression)	Immunohistochemistry
HCC cell lines	8	Higher mRNA levels	Quantitative real - time PCR
Normal liver cell lines	8	Lower mRNA levels	Quantitative real - time PCR

Table 1: FOXK2 expression in different tissues and cell lines.

Association between FOXK2 and HCC Clinical Features

High FOXK2 expression has been associated with poor prognosis in HCC patients. Liu C. et al. [4] followed 180 HCC patients who underwent surgical resection for a median of 6 years. Kaplan - Meier analysis showed that patients with high FOXK2 expression had significantly shorter overall survival (OS) and disease - free survival (DFS) compared to those with low FOXK2 expression. Multivariate Cox regression analysis identified FOXK2 expression as an independent prognostic factor for OS (hazard ratio [HR] = 2.65, 95% confidence interval [CI]: 1.82 - 3.86, P < 0.001) and DFS (HR = 2.15, 95% CI: 1.41 - 3.28, P = 0.002) (Table 2).

Prognosis	FOXK2 High Expression Group	FOXK2 Low Expression Group	HR (95% CI)	P - value
Overall survival	Shorter	Longer	2.65 (1.82 - 3.86)	< 0.001
Disease - free survival	Shorter	Longer	2.15 (1.41 - 3.28)	0.002

Table 2: Association between FOXK2 expression and HCC patient prognosis.

FOXK2 and Chemotherapy Resistance in HCC

Recent studies indicate that the PIAS4 - FOXK2 signal axis is abnormally activated in HCC, and this activation is closely related to chemotherapy resistance. Chen W, et al. [5] demonstrated that overexpression of PIAS4, an E3 SUMO - ligase, promotes the SUMOylation of FOXK2, enhancing its stability and transcriptional activity. In HCC cells treated with chemotherapy drugs such as doxorubicin and cisplatin, knocking down PIAS4 or FOXK2

significantly increased cell sensitivity to chemotherapy, as evidenced by decreased cell viability and increased apoptosis, measured by MTT assay and flow cytometry, respectively.

DISCUSSION

Our literature - based retrospective analysis reveals the crucial role of FOXK2 in HCC. FOXK2 overexpression in HCC tissues and its association with poor prognosis suggest its potential as a biomarker for predicting HCC patient outcomes. FOXK2's regulation of de novo nucleotide synthesis genes offers new insights into HCC development mechanisms. Abnormal activation of nucleotide synthesis pathways can drive increased DNA synthesis and cell proliferation, typical features of cancer cells.

The discovery of the PIAS4 - FOXK2 signal axis in HCC chemotherapy resistance is clinically significant. Chemotherapy resistance remains a major hurdle in HCC treatment. Targeting this axis may be a promising approach to enhance chemotherapy efficacy. For example, developing drugs that inhibit the interaction between PIAS4 and FOXK2 or directly target FOXK2 may increase HCC cell sensitivity to chemotherapy drugs.

However, current research has limitations. Most studies are based on in - vitro cell experiments and animal models. More large - scale clinical trials are needed to validate FOXK2 as a biomarker and therapeutic target. Additionally, the precise molecular mechanisms by which FOXK2 regulates its target genes and interacts with other signaling pathways in HCC require further exploration.

CONCLUSION

In conclusion, FOXK2 plays a significant role in HCC development, prognosis, and chemotherapy response. It has the potential to be a novel diagnostic and prognostic biomarker for HCC, and targeting FOXK2 - related pathways may offer new treatment strategies. Future research should focus on more in - depth and comprehensive studies to fully understand FOXK2's functions and mechanisms in HCC and translate basic research findings into clinical applications.

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