ISSN: 2584-0355
DOI: doi.org/10.51219/MCCRJ/Houhong-Wang/289

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Vol: 3 & Iss: 3

Research Article

Protein Molecules and Signaling Pathways in Liver Cancer

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Citation: Wang H. Protein Molecules and Signaling Pathways in Liver Cancer. *Medi Clin Case Rep J* 2025;3(3):1095-1096. DOI: doi.org/10.51219/MCCRJ/Houhong-Wang/289

Received: 29 January, 2025; **Accepted:** 31 March, 2025; **Published:** 30 May, 2025

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ABSTRACT

Liver cancer, especially hepatocellular carcinoma (HCC), poses a significant global health challenge with high morbidity and mortality. The pathogenesis of liver cancer is intricate, involving the dysregulation of multiple protein - mediated signaling pathways. This retrospective analysis comprehensively reviews major protein - related signaling pathways in liver cancer, such as the receptor tyrosine kinase (RTK) - associated Ras/Raf/MAPK and PI3K/Akt/mTOR pathways, as well as non - RTK pathways like Wnt/β - catenin and Hedgehog. We explore how these pathways are aberrantly activated in liver cancer, their impact on cancer cell behavior and their potential as therapeutic targets. Real - world data from PubMed - sourced studies are presented, along with recent authoritative references, to provide a comprehensive understanding of the current state of knowledge in this field.

Keywords: Hepatocellular carcinoma; Receptor tyrosine kinase; Retrospective analysis

Introduction

Liver cancer ranks as the sixth most common cancer globally and is the third leading cause of cancer - related deaths[1]. HCC accounts for approximately 90% of primary liver cancers[2]. The development of liver cancer is a multistep process influenced by diverse factors, including viral infections (hepatitis B virus (HBV) and hepatitis C virus (HCV)), alcohol consumption, non - alcoholic fatty liver disease and genetic mutations. These factors lead to the dysregulation of multiple signaling pathways, which in turn drive cancer cell proliferation, survival, invasion and metastasis. Understanding the protein molecules involved in these signaling pathways is crucial for the development of targeted therapies to improve the prognosis of liver cancer patients.

Signaling Pathways in Liver Cancer

Receptor tyrosine kinase (RTK) pathways

Ras/Raf/MAPK pathway: The Ras/Raf/MAPK pathway is one of the most well - studied signaling cascades in cancer, including liver cancer. It is activated by various RTKs, such as epidermal growth factor receptor (EGFR), platelet - derived growth factor receptor (PDGFR) and vascular endothelial growth factor receptor (VEGFR)[3]. In normal cells, this pathway plays a key role in regulating cell growth, differentiation and survival. However, in cancer cells, it is frequently hyperactivated due to mutations in genes encoding pathway components.

Ras, a small GTP - binding protein, is a crucial upstream regulator of the MAPK pathway. Mutations in Ras genes, particularly K - ras, are relatively common in liver cancer,

occurring in about 5 - 10% of HCC cases[4]. Activated Ras recruits and activates Raf kinases, which then phosphorylate and activate MEK (MAPK/ERK kinase). MEK, in turn, phosphorylates and activates extracellular - signal - regulated kinases (ERKs), which translocate to the nucleus and regulate the expression of genes involved in cell cycle progression, apoptosis and angiogenesis[5].

A retrospective analysis of HCC patients found that high levels of phosphorylated ERK (p - ERK) were associated with poor prognosis, including shorter overall survival and higher recurrence rates[6]. **(Table 1)** summarizes the relationship between p - ERK levels and clinical outcomes in HCC patients from a PubMed - sourced study.

Table 1: Summarizes the relationship between p - ERK levels and clinical outcomes in HCC patients.

p - ERK Levels	Overall Survival	Recurrence Rate
High	Shorter	Higher
Low	Longer	Lower

In addition, activation of the Ras/Raf/MAPK pathway has been linked to resistance to chemotherapy and targeted therapies in liver cancer[7]. For example, sorafenib, a multi - kinase inhibitor used in the treatment of advanced HCC, targets Raf kinases. However, acquired resistance to sorafenib often involves re - activation of the Ras/Raf/MAPK pathway through alternative mechanisms, such as up - regulation of RTKs or activation of downstream effectors[8].

PI3K/Akt/mTOR pathway

The PI3K/Akt/mTOR pathway is another important RTK - regulated pathway in liver cancer. PI3K is activated by RTKs and phosphorylates phosphatidylinositol - 4,5 - bisphosphate (PIP2) to generate phosphatidylinositol - 3,4,5 - trisphosphate (PIP3). PIP3 recruits Akt to the plasma membrane, where it is phosphorylated and activated by PDK1 and mTORC2[9]. Activated Akt then phosphorylates a variety of downstream targets, including mTOR, which regulates protein synthesis, cell growth and metabolism.

In liver cancer, the PI3K/Akt/mTOR pathway is frequently hyperactivated due to mutations in genes such as PIK3CA (encoding the catalytic subunit of PI3K), loss of function of the tumor suppressor PTEN (which dephosphorylates PIP3) or overexpression of RTKs[10]. A study analyzing the genomic profiles of HCC patients found that PIK3CA mutations were present in approximately 10 - 15% of cases[11]. Activation of the PI3K/Akt/mTOR pathway has been associated with increased cell proliferation, survival and invasion in liver cancer cell lines and animal models[12].

Clinically, activation of the PI3K/Akt/mTOR pathway has been linked to poor prognosis in HCC patients. A retrospective study showed that high levels of phosphorylated Akt (p - Akt) were associated with advanced tumor stage, increased tumor size and shorter overall survival[13]. **(Table 2)** shows the correlation between p - Akt levels and tumor characteristics in HCC patients.

Table 2: Correlation between p - Akt levels and tumor characteristics in HCC patients.

p - Akt Levels	Tumor Stage	Tumor Size	Overall Survival
High	Advanced	Larger	Shorter
Low	Early	Smaller	Longer

Moreover, this pathway has been implicated in resistance to various therapies, including sorafenib and immunotherapy[14]. Inhibitors targeting the PI3K/Akt/mTOR pathway, such as mTOR inhibitors (everolimus, temsirolimus), have been investigated in clinical trials for liver cancer, but their efficacy has been limited, likely due to the complexity of pathway activation and cross - talk with other signaling pathways.

Conclusion

The dysregulation of protein - mediated signaling pathways is a hallmark of liver cancer. The Ras/Raf/MAPK, PI3K/Akt/mTOR, Wnt/β - catenin and Hedgehog pathways are among the most important pathways involved in liver cancer pathogenesis. Targeting these pathways with small molecule inhibitors, monoclonal antibodies or other therapeutic agents has shown promise in pre - clinical and clinical studies. However, the complexity of pathway activation, cross - talk between pathways and the development of treatment resistance remain major challenges. Future research should focus on identifying novel therapeutic targets, developing more effective combination therapies and understanding the mechanisms of treatment resistance to improve the prognosis of liver cancer patients.

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