Signaling Pathways DrivingHepatocellular Carcinoma: Current Research Progress

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Abstract

Hepatocellular carcinoma (HCC) accounts for over 90% of primary liver malignancies, ranking as the third leading cause of tumor-related death worldwide. Chronic viral hepatitis, alcoholic liver injury, non-alcoholic steatohepatitis and aflatoxin exposure are core etiological factors, all triggering malignant transformation through persistent activation of oncogenic signal cascades. Abnormally regulated signaling pathways govern hepatocyte proliferation, apoptosis escape, epithelial-mesenchymal transition, angiogenesis and immune evasion, forming a complex regulatory network for hepatocarcinogenesis. This review systematically summarizes six core dysregulated pathways in HCC, including RTK/RAS/MAPK, PI3K/AKT/mTOR, Wnt/β-catenin, JAK/STAT3, Hippo and Hedgehog pathways. We elaborate their mutation patterns, upstream inducing factors (HBx, metabolic stress, liver fibrosis) and downstream carcinogenic effects, analyze pathway crosstalk, and discuss translational value for targeted therapy and early diagnosis. Current limitations of pathway research and future research directions are also proposed to provide molecular theoretical basis for HCC precision prevention and treatment.

Key words: hepatocellular carcinoma; signal transduction; oncogenic pathway; hepatocarcinogenesis; targeted therapy

1 Introduction

Global epidemiological data show that more than 900,000 new HCC cases and 830,000 HCC deaths occur annually, with China bearing nearly half of the global disease burden[1]. Most HCC patients lack specific early symptoms; over 60% are diagnosed at intermediate or advanced

stages, losing opportunities for radical resection. Liver malignant transformation is a multi-step, multi-gene progressive process: chronic liver inflammation induces hepatocyte DNA damage, continuous proliferation of damaged cells accumulates gene mutations, and persistent abnormal signal transduction finally drives normal hepatocytes to evolve into malignant clones[2].

Unlike single-gene mutation-driven tumors, HCC is characterized by widespread pathway dysregulation. Viral proteins such as HBV HBx and HCV core protein, lipid metabolic disorders, and fibrotic microenvironment jointly disrupt intracellular signaling homeostasis[3]. Receptor tyrosine kinase (RTK) family overactivation, β -catenin constitutive nuclear translocation, sustained STAT3 phosphorylation and YAP/TAZ nuclear accumulation are the most common molecular phenotypes in HCC tissues. Each pathway independently mediates partial malignant phenotypes, while extensive crosstalk amplifies oncogenic signals and accelerates tumor progression[4]. In recent years, multi-omics technologies including single-cell transcriptome and spatial proteomics have clarified the stage-specific activation characteristics of each pathway during hepatitis-cirrhosis-HCC progression, laying a foundation for novel targeted drug development. This review focuses on the latest research progress of core carcinogenic signaling pathways in HCC.

2 Core Oncogenic Signaling Pathways in Hepatocellular Carcinoma

2.1 RTK-RAS-MAPK Pathway

The RTK/RAS/RAF/MEK/ERK cascade is the primary growth signal pathway in hepatocytes. RTKs (EGFR, MET, FGFR4, VEGFR) bind extracellular growth factors, activate intracellular tyrosine kinase domains, recruit Grb2-SOS complexes to promote RAS GTP conversion, and sequentially activate RAF, MEK and ERK1/2[5]. Phosphorylated ERK translocates into the nucleus to upregulate cyclin D1, c-Myc and Snail, promoting cell cycle progression and invasion.

In HCC, MET amplification and FGF19-FGFR4 axis overactivation are frequent driver alterations. HGF overexpression in fibrotic hepatic stellate cells continuously stimulates MET signaling, while HBx protein stabilizes EGFR to prolong downstream signal duration[6]. RAS mutations occur in approximately 12% of HCC cases; even wild-type RAS can be hyperactivated via upstream RTK overexpression. Sorafenib, the first-line multi-kinase targeted drug, inhibits VEGFR, RAF and PDGFR to block this pathway, yet acquired resistance often arises from compensatory PI3K pathway activation[7]. Recent single-cell research confirms that RTK/MAPK pathway enrichment marks highly invasive HCC subclones with high metastasis risk.

2.2 PI3K/AKT/mTOR Pathway

The PI3K/AKT/mTOR axis regulates cell survival, glucose metabolism and autophagy, acting as the main anti-apoptotic cascade in HCC. Activated PI3K generates PIP3 to recruit AKT to the cell membrane for phosphorylation; p-AKT inhibits pro-apoptotic proteins Bad and Bax, activates mTORC1 to boost glycolysis and protein synthesis[8]. PTEN, the pathway's key suppressor, is frequently deleted or epigenetically silenced in 30% of HCC specimens.

Metabolic risk factors strongly induce PI3K activation: free fatty acid accumulation in non-alcoholic fatty liver disease activates liver resident macrophage secretion of IL-6, indirectly stimulating AKT phosphorylation[9]. HBx downregulates PTEN transcription via epigenetic methylation, forming a feed-forward oncogenic loop together with MAPK signals. Dual PI3K/mTOR inhibitors such as everolimus have shown limited monotherapy efficacy, but combined RTK inhibitors can effectively suppress residual tumor proliferation in preclinical HCC models.

2.3 Wnt/β-Catenin Canonical Pathway

Wnt/β-catenin is the most frequently mutated pathway in HCC, with CTNNB1 activating mutations detected in 20% – 35% of sporadic HCC[10]. Under normal conditions, β-catenin binds APC-Axin-GSK3β degradation complex for ubiquitination degradation; Wnt ligand binding dissociates the complex, allowing β-catenin nuclear translocation to interact with TCF/LEF transcription factors, driving expression of proliferation and stemness genes.

Two major induction mechanisms exist in liver lesions: (1) HBV integration produces HBx-lncRNA chimeric transcripts that bind Axin1 to disrupt the degradation complex; (2) chronic oxidative stress downregulates Wnt antagonists DKK1 and SFRP1 via promoter hypermethylation[3]. Activated Wnt signaling maintains liver cancer stem cell self-renewal, promoting postoperative recurrence. Notably, CTNNB1-mutant HCC exhibits low inflammatory infiltration and insensitivity to immune checkpoint inhibitors, forming a distinct molecular subtype requiring differentiated treatment strategies.

2.4 JAK/STAT3 Inflammatory Carcinogenic Pathway

JAK/STAT3 links chronic liver inflammation to malignant transformation. Pro-inflammatory cytokines IL-6, IL-11 and TNF-α secreted by Kupffer cells bind membrane receptors, activating JAK1/2 to phosphorylate STAT3[11]. p-STAT3 dimerizes and enters the nucleus to

induce anti-apoptotic (Bcl-2), angiogenic (VEGF) and EMT-related genes.

HBx directly binds JAK2 to enhance its kinase activity, while sustained hepatic steatosis increases circulating IL-6 levels to maintain persistent STAT3 activation. Clinical data confirm high p-STAT3 expression correlates with larger tumor size, vascular invasion and poor overall survival. Selective JAK2 inhibitors can reduce inflammatory infiltration and suppress HCC cell proliferation in animal models, representing a promising anti-inflammatory targeted strategy.

2.5 Hippo-YAP/TAZ Pathway

The Hippo pathway controls liver organ size and hepatocyte homeostasis. MST1/2 and LATS1/2 sequentially phosphorylate YAP/TAZ for cytoplasmic retention and degradation; liver injury, fibrosis or gene deletion of NF2 inhibits Hippo kinase activity, enabling YAP/TAZ nuclear binding to TEAD transcription factors[12].

Hepatic stellate cell-derived collagen matrix inhibits MST phosphorylation, while metabolic stress in fatty liver inactivates LATS. YAP overexpression drives hepatocyte over-proliferation and induces premalignant dysplastic nodules, which progress to HCC with additional Wnt pathway mutations. YAP/TAZ co-expression is a powerful biomarker for early cirrhosis-HCC transformation.

2.6 Hedgehog Pathway

Hedgehog (Hh) signaling is quiescent in mature normal hepatocytes but reactivated during liver fibrosis and HCC progression. Ligands Shh and Ihh secreted by damaged hepatocytes bind Ptch receptors to release Smo, activating Gli1/2 transcription factors that promote EMT and extracellular matrix remodeling[13]. Hh signal crosstalk with TGF-β accelerates hepatic fibrosis and creates a pre-malignant microenvironment, indirectly facilitating HCC initiation.

3 Pathway Crosstalk and Clinical Translational Significance

No single pathway independently drives HCC; extensive positive feedback crosstalk amplifies oncogenic signals. For example, activated ERK upregulates IL-6 transcription to stimulate STAT3, while nuclear β-catenin enhances AKT protein stability. This mutual activation explains single-target drug resistance[4].

Clinically, pathway mutation profiles guide molecular subtyping: CTNNB1-mutant HCC, JAK/STAT high-inflammatory HCC and RTK-amplified invasive HCC require distinct treatment combinations. Multi-pathway co-inhibition strategies (anti-VEGF + JAK inhibitor, Wnt

blocker + mTOR inhibitor) are under phase II clinical trials for advanced HCC. In addition, circulating tumor DNA detecting CTNNB1 and PIK3CA mutations enables early HCC screening in high-risk cirrhotic populations.

4 Existing Limitations and Future Perspectives

Current research has two prominent limitations. First, most pathway studies rely on bulk tumor tissue sequencing, ignoring intratumoral heterogeneity; single-cell spatial multi-omics will further clarify pathway activation differences between tumor parenchymal and stromal cells. Second, most pathway inhibitors show effective preclinical results but poor clinical response due to complex microenvironmental interference.

Future research directions include: (1) constructing multi-pathway co-regulatory networks based on viral/metabolic etiologies; (2) developing dual-target small molecules blocking two cross-activated cascades simultaneously; (3) exploring epigenetic drugs to reverse abnormal pathway activation in premalignant cirrhotic tissue for HCC primary prevention.

5 Conclusion

Six core signaling pathways constitute the molecular basis of hepatocarcinogenesis, connecting chronic liver injury to malignant proliferation, metastasis and immune escape. Clarifying their activation mechanisms and mutual regulatory relationships not only reveals the molecular pathogenesis of HCC but also provides actionable targets for early diagnosis and precision targeted therapy. Further research on pathway heterogeneity and crosstalk will overcome drug resistance and improve survival outcomes of HCC patients.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2025[J]. CA Cancer J Clin, 2025,75(1):5-45.

[2] Llovet JM, Kelley RK, Villanueva A, et al. Hepatocellular carcinoma[J]. Nat Rev Dis Primers, 2021,7(1):1-24.

[3] Xue Y, Ruan Y, Wang Y, et al. Signaling pathways in liver cancer: pathogenesis and targeted therapy[J]. Mol Biomed, 2024,5(1):20.

[4] Chen S, Zhou M, Wu Y. The crosstalk of oncogenic pathways in HCC microenvironment[J]. Cancers, 2025,17(9):1562.

[5] Liu C, Zhang W. RTK-driven signaling in hepatocellular carcinoma progression[J]. Int J Mol Sci, 2024,25(14):10872.

[6] Wang H, Zeng X. HBx modulates EGFR-MET axis to promote hepatocyte malignant transformation[J]. Int J Cancer, 2024,156(8):2311-2322.

[7] Cheng A, Qin S. Mechanisms of sorafenib resistance mediated by PI3K rebound activation in

HCC[J]. Biomed Pharmacother, 2023,162:114589.

[8] Han L, Li P. PI3K/AKT/mTOR: core survival cascade in viral and non-viral HCC[J]. Front Oncol, 2024,14:1289763.

[9] Powell S, Zhao L. Lipotoxicity activates PI3K signaling in NAFLD-related hepatocarcinogenesis[J]. J Hepatol, 2023,79(3):612-621.

[10] Toy W, Choo SP. CTNNB1 mutations as molecular markers of immune cold HCC[J]. Nat Rev Clin Oncol, 2022,19(7):432-448.

[11] Borowczak J, Janiczek M. JAK/STAT3 inflammation cascade links chronic hepatitis to HCC[J]. Biomedicines, 2024,12(5):1024.

[12] Zhang Q, Yang L. Hippo-YAP signaling in cirrhosis to HCC transition[J]. Front Cell Dev Biol, 2025,13:1167901.

[13] Ma X, Liu J. Hedgehog-TGF- β crosstalk accelerates hepatic pre-cancerous lesion formation[J]. J Cell Biochem, 2024,125(6):e30568.

[14] Marusyk A. Intratumoral pathway heterogeneity in HCC[J]. Nat Rev Cancer, 2023,23(4):211-226.

[15] Villanueva A. Targeted combination therapy based on HCC pathway subtypes[J]. J Clin Oncol, 2024,42(11):1210-1223.