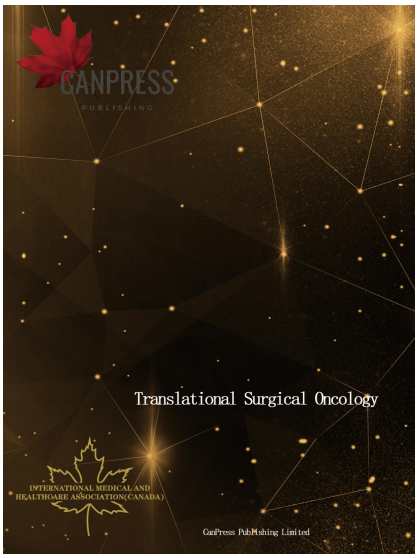
Long noncoding RNA promotes oncogenic pathway to drive stem cell behaviors of hepatocellular carcinoma



Yubo Liang[1], Qingbo Wang[1], Xingming Chen[1], Wanling Luo[1], Yang Ke[1, 2]*, Yan Jiao[3]*

[1] Department of Hepatobiliary Surgery, the Second Affiliated Hospital of Kunming Medical University, Kunming 650101, China.

[2] Department of Surgical Education and Research, the Second Affiliated Hospital of Kunming Medical University, Kunming 650101, China.

[3] Department of Orthopedic Surgery and BME-Campbell Clinic, University of Tennessee Health Science Center, Memphis, TN 38163, USA

*Corresponding authors: Yang Ke, Department of Hepatobiliary Surgery & Department of Surgical Education and Research, the Second Affiliated Hospital of Kunming Medical University, No, 374 Kunrui Road, Wuhua District, Kunming 650101, China.

Yan Jiao, Department of Orthopedic Surgery and BME-Campbell Clinic, University of Tennessee Health Science Center, Memphis, TN 38163, USA

Abstract

Hepatocellular carcinoma (HCC) is a notoriously malignant cancer in the liver that causes high mortality and morbidity. The poor prognosis of HCC patients is largely attributed to recently recognized stem cell behaviors of HCC. Notably, a recent study revealed a novel mechanism by which long noncoding RNA promotes oncogenic pathway to drive stem cell behaviors of HCC. Kinesin Family Member 9-Antisense RNA 1 (KIF9-AS1) is a long noncoding RNA significantly upregulated in HCC patients and its level is correlated with poor prognosis. Furthermore, m6A writer METTL3 is upregulated in HCC patients and promotes the m6A methylation and stability of KIF9-AS1. The stabilized KIF9-AS1 then promotes ubiquitin-specific peptidase 1 mediated deubiquitination of short stature homeobox (SHOX2). The stabilized SHOX2 then drives the transcription of key genes involved in Wnt/β-catenin pathway, TGFβ signaling pathway and other unclear pathways to promote stem cell behaviors of HCC. These findings bring new hope to reduce HCC mortality and morbidity by revealing METTL3/KIF9-AS1/SHOX2 axis as prognostic markers and therapeutic targets.

Keywords: Hepatocellular carcinoma; KIF9-AS1; METTL3; ubiquitin-specific peptidase 1; SHOX2; stem cell

Copyright and usage

Hepatocellular carcinoma (HCC) is a notoriously malignant cancer in the liver that causes high mortality and morbidity. At present, HCC is the fifth most common cancer and the fourth leading cause of cancer-related death worldwide. Hepatitis B virus (HBV) infection is one of the most important risk factors of HCC. Therefore, HCC has been widespread in China in the past decades, mainly due to high prevalence of HBV infection in China [1-3]. With the implement of HBV vaccination and the development of novel anti-HBV drugs, the incidence of HCC has reduced significantly in the past years. However, other risk factors such as obesity, diabetes, and metabolic syndrome cause increasing cases of HCC recently [4,5].

Currently, most common treatments for HCC include surgery and chemotherapy, and immunotherapy has recently been applied to improve the efficacy of HCC therapy [6-9]. In particular, sorafenib is an effective first-line chemotherapy for HCC due to the ability of sorafenib to inhibit many kinases involved in the progression of HCC. Unfortunately, the prognosis of HCC patients remains poor due to recently recognized stem cell behaviors of HCC, including the development of drug resistance to sorafenib. The “stem cell behaviors" refer to a subset of cancer cells within HCC called "liver cancer stem cells" (LCSCs)” that exhibit properties similar to normal stem cells, including self-renewal, the ability to differentiate into various cancer cell types, resistance to therapy, and the potential to initiate tumor growth, and act as a key driver of tumor progression, metastasis, and recurrence in HCC [10]. Indeed, genes that regulate stemness of HCC have been reported to be associated with the prognosis in HCC patients [11,12].

Interestingly, a recent study showed that a long noncoding RNA called Kinesin Family Member 9-Antisense RNA 1 (KIF9-AS1) was associated with the prognosis of HCC patients and it regulated stem cell behaviors of HCC via a novel mechanism [13]. In detail, the authors found that KIF9-AS1 level was significantly higher in HCC patients than controls, and KIF9-AS1 level was correlated with poor prognosis of HCC patients. Moreover, the expression of m6A writer METTL3 was higher in HCC cells, which could promote m6A modification of KIF9-AS1. Consequently, IGF2BP1 as an m6A reader stabilizes m6A-marked KIF9-AS1 to increase the stability of KIF9-AS1 in HCC cells.

Furthermore, the authors revealed that KIF9-AS1 upregulated ubiquitin-specific peptidase 1 (USP1) to enhance the stability of short stature homeobox (SHOX2). SHOX2 is a significant transcriptional factor that regulates development. Recently, SHOX2 has been proposed as a marker for the diagnosis and prognosis of various types of cancer, including HCC [14-16]. Mechanistically, SHOX2 promotes tumorigenesis via Wnt/β-catenin and TGFβ pathways [17,18]. Therefore, this study provides novel insight into the role of METTL3/KIF9-AS1/SHOX2 axis in the regulation of stem cell behaviors of HCC (Figure 1). METTL3 promotes the m6A methylation of KIF9-AS1 to stabilize it in IGF2BP1 dependent manner. The stabilized KIF9-AS1 then upregulates USP1 in an unclear mechanism. The upregulated USP1 then inhibits the ubiquitination and degradation of SHOX2. The stabilized SHOX2 then drives the transcription of key genes involved in Wnt/β-catenin pathway, TGFβ signaling pathway and other unclear pathways to promote stem cell behaviors of HCC, including but not limited to cell stemness and resistance to chemotherapy. Further studies are needed to explore the unclear mechanism or pathways highlighted in Figure 1 to get better understanding of the role of METTL3/KIF9-AS1/SHOX2 axis in HCC.

Acknowledgement

Supported by the National Natural Science Foundation of China, 82103173 and 82460461; Medical Subject Leader of Yunnan Province (General Surgery), D-2024029; Yunnan Fundamental Research Project for Excellent Young Scholars, 202401AW070003; and the Young and Mid-aged Academic and Technical Leader Reserve Talent Program of Yunnan Province, 202205AC160063.

Conflict of interest

The authors declare that they have no conflict of interest.

References

[1] Wong GL. Updated Guidelines for the Prevention and Management of Chronic Hepatitis B-World Health Organization 2024 Compared With China 2022 HBV Guidelines. J Viral Hepat. 2024;31 Suppl 2:13-22.

[2] Xie D, Shi J, Zhou J, Fan J, Gao Q. Clinical practice guideline and real-life practice in hepatocellular carcinoma: Chinese perspective. Clin Mol Hepatol. 2023;29:206–216.

[3] Yang J, Yang Z, Zeng X, Yu S, Gao L, Jiang Y, Sun F. Benefits and harms of screening for hepatocellular carcinoma in high-risk populations: systematic review and meta-analysis. J Natl Cancer Cent 2023; 3: 175-185.

[4] Chen Le, Ye X, Yang L, Zhao J, You J, Feng Y. Linking fatty liver diseases to hepatocellular carcinoma by hepatic stellate cells. Journal of the National Cancer Center 2024, 4(1): 25-35.

[5] Hwang SY, Danpanichkul P, Agopian V, Mehta N, Parikh ND, Abou-Alfa GK, Singal AG, Yang JD. Hepatocellular carcinoma: updates on epidemiology, surveillance, diagnosis and treatment. Clin Mol Hepatol. 2024 Dec 26. doi: 10.3350/cmh.2024.0824. Epub ahead of print.

[6] Krupa K, Fudalej M, Cencelewicz-Lesikow A, Badowska-Kozakiewicz A, Czerw A, Deptała A. Current Treatment Methods in Hepatocellular Carcinoma. Cancers (Basel). 2024;16(23):4059.

[7] Li YK, Wu S, Wu YS, Zhang WH, Wang Y, Li YH, Kang Q, Huang SQ, Zheng K, Jiang GM, Wang QB, Liang YB, Li J, Lakang Y, Yang C, Li J, Wang JP, Kui X, Ke Y. Portal Venous and Hepatic Arterial Coefficients Predict Post-Hepatectomy Overall and Recurrence-Free Survival in Patients with Hepatocellular Carcinoma: A Retrospective Study. J Hepatocell Carcinoma 2024; 11: 1389-1402.

[8] Yang, B., Chen, K., Liu, X., Liu, W., Ma, Y., Tian, X., & Yang, Y. Advance in Tumor Immunotherapy: Establishing a New Paradigm for Oncological Treatment. Translational Surgical Oncology, 2023;1(2), 30–43.

[9] Yang D. The Potential of Siglec Receptors in Cancer Immunotherapy. Translational Surgical Oncology, 2024;1(3), 76–89.

[10] Fu X, Zhang Y, Luo Q, Ju Y, Song G. Targeting the mechano-microenvironment and liver cancer stem cells: a promising therapeutic strategy for liver cancer. Cancer biology & medicine 2023, 20(11): 816-829.

[11] Balaji N, Kukal S, Bhat A, Pradhan N, Minocha S, Kumar S. A quartet of cancer stem cell niches in hepatocellular carcinoma. Cytokine Growth Factor Rev 2024; 79: 39-51.

[12] Yao X, Lu C, Shen J, Jiang W, Qiu Y, Zeng Y, Li L. A novel nine gene signature integrates stemness characteristics associated with prognosis in hepatocellular carcinoma. BIOCELL 2021; 45: 1425-1448.

[13] Yu Y, Lu XH, Mu JS, Meng JY, Sun JS, Chen HX, Yan Y, Meng K. N6-methyladenosine-modified long non-coding RNA KIF9-AS1 promotes stemness and sorafenib resistance in hepatocellular carcinoma by upregulating SHOX2 expression. World J Gastoentrol 2024; 30(48): 5174-5190.

[14] Hu W, Xin Y, Zhao Y, Hu J. Shox2: The Role in Differentiation and Development of Cardiac Conduction System. Tohoku J Exp Med. 2018 Mar;244(3):177-186.

[15] Zhang YA, Zhou Y, Luo X, Song K, Ma X, Sathe A, Girard L, Xiao G, Gazdar AF. SHOX2 is a potent independent biomarker to predict survival of WHO grade II-III diffuse gliomas. Ebiomedicine. 2016;13:80–9.

[16] Yang T, Zhang H, Cai SY, Shen YN, Yuan SX, Yang GS, Wu MC, Lu JH, Shen F. Elevated SHOX2 expression is associated with tumor recurrence of hepatocellular carcinoma. Ann Surg Oncol. 2013;20 Suppl 3:S644-9.

[17] Carbajo-García MC, Juarez-Barber E, Segura-Benítez M, Faus A, Trelis A, Monleón J, Carmona-Antoñanzas G, Pellicer A, Flanagan JM, Ferrero H. H3K4me3 mediates uterine leiomyoma pathogenesis via neuronal processes, synapsis components, proliferation, and Wnt/β-catenin and TGF-β pathways. Reprod Biol Endocrinol. 2023;21(1):9.

[18] Chen X, Li S, Sun B. Downregulation of short-stature homeobox protein 2 suppresses gastric cancer cell growth and stemness in vitro and in vivo via inactivating wnt/β-catenin signaling. Drug Dev Res. 2024;85(7):e70006.