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EDITORIAL

Lipid metabolism-related long noncoding RNAs: A potential prognostic biomarker for hepatocellular carcinoma

Rui-Nan Zhang, Jian-Gao Fan

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Abstract

The incidence rates of hepatocellular carcinoma (HCC) have increased in recent decades. Despite advancements in therapy and early diagnosis improving short-term prognosis, long-term outcomes remain poor. Long noncoding RNAs (lncRNAs) and lipid metabolism play crucial roles in the development and progression of HCC. Enhanced lipid synthesis promotes HCC progression, and lncRNAs can reprogram the expression of lipogenic enzymes. Consequently, lipid metabolism-related (LMR)-lncRNAs regulate lipid anabolism, accelerating the onset and progression of HCC. This suggests that LMR-lncRNAs could serve as novel prognostic biomarkers and therapeutic targets.

Key Words: Long noncoding RNAs; Lipid metabolism; Hepatocellular carcinoma; Prognosis; Biomarker

Core Tip: Lipid metabolism and long noncoding RNAs (lncRNAs) are pivotal in hepatocellular carcinoma (HCC) development. While the prognosis of HCC remains poor and prognostic biomarkers are lacking, lipid metabolism-related lncRNAs may be promising candidates for prognostic biomarkers in HCC.

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INTRODUCTION

Primary liver cancer ranks sixth globally among all malignant tumors and is the third leading cause of cancer-related mortality worldwide. It is also a major cause of death in cirrhosis, with about 80%-90% of primary liver cancers being hepatocellular carcinoma (HCC)[1,2]. The primary causes of cirrhosis leading to HCC include hepatitis B virus infection, hepatitis C virus infection, alcohol-related liver disease, and metabolic dysfunction-associated fatty liver disease[1,3]. The main therapeutic strategies for HCC include surgical resection, radiotherapy, chemotherapy, vascular interventional treatments, and immunotherapy. However, the 5-year survival rate remains unsatisfactory, as many patients are diagnosed at an advanced stage, resulting in a poor prognosis[4,5]. Therefore, identifying new prognostic biomarkers and exploring underlying molecular mechanisms are crucial to improve HCC treatment modalities.

Metabolic reprogramming of lipids, such as fatty acids (FA), is an important marker of liver carcinogenesis and progression. Understanding this mechanism can help elucidate the complexity of HCC pathogenesis[6,7]. Long noncoding RNAs (lncRNAs) also play significant roles in HCC development[8]. Moreover, lncRNAs are key mediators of lipid metabolism and are directly involved in the reprogramming of lipid metabolism in HCC cells. Several studies have shown that lncRNAs such as RP11-386G11.10 and nuclear paraspeckle assembly transcript 1 (NEAT1) regulate the expression of FA synthase (FASN) and adipose triglyceride lipase (ATGL) to promote lipid anabolism, accelerating HCC progression and influencing patient prognosis[9,10]. Lipid metabolism-related (LMR)-lncRNAs may serve as biomarkers for early diagnosis and prognosis of HCC[11].

PROGNOSTIC BIOMARKERS IN HCC

The long-term prognosis for HCC remains poor, with a 5-year survival rate of only 17%[12]. HCC patients often exhibit no symptoms in the early stages, and clinical signs typically manifest only at advanced stages of the disease. Consequently, the prognosis is unsatisfactory, and therapeutic interventions have low efficacy when HCC is diagnosed at advanced stages[13]. There is a significant need for biomarkers to enable early detection and prognosis of HCC.

Serum alpha-fetoprotein (AFP) is the most widely used biomarker for HCC. However, its utility for early detection is limited due to poor sensitivity. To enhance diagnostic performance, serum AFP is often used in combination with AFP lectin fraction (AFP-L3) and des-gamma-carboxy prothrombin[14]. Other biomarkers, such as glypican 3[15], cytokeratin 19[16], midkine[17], Golgi protein 73[18], osteopontin[19], and squamous cell carcinoma antigen[20], as well as liquid biopsies including circulating tumor cells, circulating tumor DNA, microRNA, and extracellular vesicles, also play roles in the diagnosis and prognosis of HCC[21]. However, these markers have not yet been widely adopted in clinical practice.

lncRNAs are defined as RNAs longer than 200 nucleotides that do not encode protein products. Numerous studies have shown that lncRNAs are involved in various biological processes, including cell cycle regulation, proliferation, apoptosis, and cell death, and that they mediate cancer growth, invasion, and metastasis[22,23]. Abnormal lncRNA expression can impact the initiation and development of different diseases[23]. LncRNAs have also been identified as early diagnostic markers for HCC, serving as promising candidates for early biomarkers that enable timely intervention and improve patient outcomes[24]. Additionally, lncRNAs have demonstrated substantial prognostic value in HCC and are associated with HCC progression and poor prognosis, highlighting their prognostic potential[25,26].

LMR-LNCRNAS AND HCC

Lipid metabolic reprogramming is significantly altered in various cancer cells, with increasing research highlighting that metabolic dysregulation plays a crucial role in tumorigenesis and progression. Specifically, FA accumulation is associated with membrane synthesis, energy storage, and the generation of signaling molecules. Enhanced lipid synthesis or uptake promotes the rapid growth of cancer cells and induces tumor formation in cancers such as gastric cancer, breast cancer, colorectal adenocarcinoma, and esophageal adenocarcinoma[27]. FA metabolism is also essential in HCC. Increased accumulation of FAs in tumor cells promotes HCC progression by either enhancing FA synthesis or inhibiting FA oxidation. Conversely, inhibiting FA metabolism restricts HCC proliferation[6].

Aberrant lncRNA expression and FA signaling dysfunction both contribute to HCC occurrence and development. Several studies have reported that lncRNAs play a critical role in FA metabolism. Disruption of the CCT3-LINC00326 regulatory network leads to decreased lipid accumulation and increased lipid degradation *in vitro*, as well as reduced tumor growth *in vivo*, correlating strongly with poor HCC prognosis[28]. RP11-386G11.10 functions as a competing endogenous RNA for miR-345-3p, regulating the expression of nucleoprotein HNRNPU and its downstream lipogenic enzymes, such as FASN, leading to lipid accumulation in HCC cells[9]. The LncRNA-NEAT1 disrupts HCC cell lipolysis through ATGL, with the combination of NEAT1 and ATGL showing improved prognostic accuracy for HCC[10]. LncRNA-HR1 reduces lipid metabolism by inhibiting the activity of the SREBP1c promoter and FASN expression[29]. LncRNAs SNHG1 and SNHG7 regulate various FA metabolism-related genes, such as glycerol kinase 2 and carnitine palmitoyl-transferase 2, promoting FA beta-oxidation[22]. These LMR-lncRNAs identified in these studies may serve as promising biomarkers to predict HCC prognosis.

In a recent issue of the *World Journal of Gastroenterology*, Wang *et al*[30] identified LMR-lncRNAs-negative regulator of antiviral response (NRAV), RNA transmembrane and coiled-coil domain family 1 antisense RNA 1 (TMCC1-AS1), and RP11-817I4.1-as predictive markers for HCC patients. Among these, RP11-817I4.1 was strongly correlated with overall survival (OS) and showed potential as a standalone predictive biomarker for HCC. It exhibited the highest correlation

with adenosine triphosphate citrate lyase (ACLY), a key gene involved in lipid synthesis, regulating ACLY expression by acting as a sponge for miR-3120-3p, thereby promoting lipid accumulation in HCC cells. This research highlights that lncRNAs are associated with the development, progression, and prognosis of HCC, and suggests that LMR-lncRNAs, particularly those associated with OS, may serve as novel prognostic biomarkers for HCC.

CONCLUSION

Lipid metabolism and lncRNAs are significantly associated with HCC. Several studies have identified various biomarkers related to lipid metabolism and lncRNAs that are linked to HCC prognosis. However, a definitive prognostic biomarker for HCC remains unmet, and further research is needed. LMR-lncRNAs could serve as potential prognostic biomarkers for HCC, with higher expression levels of lncRNAs (NRAV, TMCC1-AS1, or RP11-817I4.1) correlating with poorer prognoses. LMR-lncRNAs may provide valuable prognostic indicators for HCC and could facilitate the development of new therapeutic drugs and strategies.

FOOTNOTES

Author contributions: Fan JG designed the overall concept and outlined the manuscript; Zhang RN reviewed the literature, wrote and edited the manuscript; Both authors have read and approved the final version to be published.

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