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Long non-coding RNA LINC00461/miR-149-5p/LRIG2 axis regulates hepatocellular carcinoma progression

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ABSTRACT

Long noncoding RNAs (lncRNAs) have been acknowledged as vital regulators in tumorigenesis of human cancers, including hepatocellular carcinoma (HCC). LINC00461 has been found to promote progression of glioma and breast cancer. Nevertheless, the function of LINC00461 in HCC is still unknown. Here, we found that LINC00461 was upregulated in HCC tissues and positively correlated with advanced stage and metastasis. Furthermore, LINC00461 overexpression in HCC patients predicts unfavorable prognosis. Loss-of-function assays showed that LINC00461 silencing suppressed the proliferation, migration and invasion of HCC cells *in vitro*, and impeded tumor growth *in vivo*. Mechanistically, LINC00461 inversely regulates miR-149-5p abundance in HCC. Further investigation indicated that LINC00461 was a competing endogenous RNA (ceRNA) by directly sponging miR-149-5p in HCC cells. Moreover, LRIG2 was identified as the downstream target of miR-149-5p and its expression was regulated by LINC00461/miR-149-5p axis. Restoration of LRIG2 reversed LINC00461 knockdown attenuated HCC cell proliferation, migration and invasion. In summary, our findings revealed that LINC00461 is an oncogene in HCC through regulating miR-149-5p/LRIG2 pathway.

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common and deadly cancers around the world [1]. Many factors, such as hepatitis B or C viruses, alcohol abuse and genetic mutation, could lead to HCC occurrence [2]. Although great effort has been made to treat HCC, the five-year overall survival rate of HCC patients is still rather poor because of recurrence and invasiveness [3]. Thus, it is extremely required to investigate the underlying molecular mechanism and pathogenesis of HCC.

Long noncoding RNAs (lncRNAs) are a subgroup of noncoding RNAs and characterized by a length of over 200 nucleotides and lacking protein-coding ability [4]. Emerging studies have demonstrated that lncRNAs are involved in gene pathogenesis of various diseases, including cancer [5,6]. Through regulating cell proliferation, migration, invasion or differentiation, lncRNAs could act as oncogenes or tumor suppressors [7,8]. For example, lncRNA TINCR as an oncogene promotes chemo-resistance and epithelial-mesenchymal transition (EMT) of breast cancer [9]. LncRNA PTENP1 upregulation inhibits growth and invasion of glioma cells [10]. LncRNA LINC00483 initiates growth and invasion of colorectal cancer cells through regulating FMNL2 [11]. Additionally, lncRNA SNHG8 was reported to regulate HCC metastasis and prognosis [12]. These evidences confirm that lncRNAs are pivot molecules in cancer.

Previously, LINC00461 was found to promote progression of glioma, myeloma and breast cancer [13–15]. However, whether LINC00461 exerts a similar role in HCC remains unclear. In this study, we found that LINC00461 expression was significantly increased in HCC tissues and cells. LINC00461 silencing suppressed HCC growth and metastasis in *vitro*. Xenograft experiment further demonstrated that LINC00461 knockdown impaired HCC growth *in vivo*. Mechanistically, we demonstrated that LINC00461 modulates miR-149-5p/LRIG2 axis in HCC. Collectively, our research revealed a novel regulatory signaling, which may be exploited as a potential therapeutic target for HCC treatment.

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