Biomedicine & Pharmacotherapy 109 (2019) 1140–1147

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

LncRNA KTN1-AS1 promotes tumor growth of hepatocellular carcinoma by targeting miR-23c/ERBB2IP axis

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ARTICLE INFO

Keywords:
KTN1-AS1
Hepatocellular carcinoma
miR-23c
ERBB2IP
Tumor growth

ABSTRACT

Long non-coding RNAs (lncRNAs) are critical regulators in the tumorigenesis and metastasis of hepatocellular carcinoma (HCC). LncRNA KTN1 antisense RNA 1 (KTN1-AS1) has been reported to play an important role in colorectal cancer and correlates with unfavorable clinical outcomes of head and neck squamous cell carcinoma. However, the clinical significance and functional role of KTN1-AS1 in HCC are still unclear. Here, we found that KTN1-AS1 was a highly expressed lncRNA in HCC according to public available databases and our HCC cohort. Further analyses revealed that higher expression of KTN1-AS1 was observed in HCC tissues with large tumor size, high tumor grade and advanced TNM stage. Analysis of survival data indicated that high KTN1-AS1 expression was prominently correlated with poor clinical outcomes of HCC patients. Functionally, KTN1-AS1 knockdown suppressed cell proliferation and colony formation, and increased apoptosis of SMMC-7721 cells *in vitro*. Furthermore, silencing of KTN1-AS1 restrained tumor growth of HCC *in vivo*. Conversely, forced expression of KTN1-AS1 facilitated Huh7 cell proliferation and inhibited apoptosis. Mechanistically, KTN1-AS1 inversely regulated miR-23c abundance in HCC cells. Further evidence supported that KTN1-AS1 acted as a competing endogenous RNA (ceRNA) by directly sponging miR-23c in HCC cells. Interestingly, erbb2 interacting protein (ERBB2IP), a known target of miR-23c, was positively regulated by KTN1-AS1 and its restoration reversed KTN1-AS1 knockdown attenuated HCC cell growth. To conclude, our study sheds light on the novel function and underlying mechanism of KTN1-AS1 in HCC, which may accelerate the development of cancer therapy.

1. Introduction

Hepatocellular carcinoma (HCC) is a common human malignancy worldwide, and its prevalence in Asia is higher when compared to that in other continents [1,2]. The development and progression of HCC is a multistage process involving the deregulation of genes that are crucial to cellular processes [3]. Long non-coding RNAs (lncRNAs) are transcripts longer than 200 bp that do not have any apparent protein-coding ability [4]. The biological functions of lncRNAs are widely implicated in chromosomal silencing, chromatin modification, transcriptional activation and transcriptional interference [5]. Emerging evidence has indicated that lncRNAs can participate in diverse physiological and pathological processes and affect disparate cellular functions, especially in human cancer [6,7]. Notably, large amount of studies indicate that lncRNAs function as tumor promoting or suppressive factors to regulate tumor growth and metastasis of HCC [8–10]. LncRNAs usually function as competing endogenous RNAs (ceRNAs), which regulate other RNA transcripts by competing for shared microRNA (miRNAs) [11]. Meanwhile, miRNAs are important regulators for the tumorigenesis and progression of HCC [12–15]. LncRNA MIR31HG is recognized as a tumor suppressor, which inhibits tumor growth and metastasis of HCC *via* sponging miR-575 and subsequently enhancing suppression of tumorigenicity 7 like (ST7L) [16]. LncRNA CDKN2B-AS1 functions as a ceRNA by directly sponging let-7c-5p and contributes to HCC progression *via* nucleosome assembly protein 1 like 1 (NAP1L1) [17]. Our previous study shows that lncRNA CASC2 inhibits epithelial-mesenchymal transition (EMT) and tumor metastasis of HCC *via* targeting miR-367/F-box and WD repeat domain-containing 7 (FBXW7) axis [18].

Abbreviations: LncRNA, long non-coding RNA; KTN1-AS1, antisense RNA 1; ceRNA, competing endogenous RNA; HCC, hepatocellular carcinoma; miRNA, microRNA; ST7L, suppression of tumorigenicity 7 like; NAP1L1, nucleosome assembly protein 1 like 1; EMT, epithelial-mesenchymal transition; FBXW7, F-box and WD repeat domain-containing 7; PTTG1, pituitary tumor-transforming 1; CRC, colorectal cancer; HNSCC, head and neck squamous cell carcinoma

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https://doi.org/10.1016/j.biopha.2018.10.105
Received 30 September 2018; Received in revised form 18 October 2018; Accepted 20 October 2018