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CASE REPORT

Mechanism of Action and Potential Significance of Long Non-Coding RNA-TSPAN12 in Microvascular Invasion of Hepatocellular Carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer and has garnered significant attention due to its rapid progression and aggressive nature. The treatment of HCC primarily involves surgical resection, supplemented by various therapeutic approaches such as targeted therapy, immunotherapy, chemotherapy, and interventional therapy. However, due to its complex pathogenesis and high recurrence rate, the therapeutic effects are often suboptimal.Microvascular invasion (MVI) is one of the important indicators of HCC malignancy and prognosis, closely associated with tumor progression, metastasis, recurrence, and poor prognosis. In recent years, long non-coding RNAs (lncRNAs) have been discovered to possess diverse biological functions and have gradually become a new focus in cancer research. Among them, lnc-TSPAN12, a highly expressed lncRNA in HCC, has been confirmed to be closely related to poor patient survival rates. This article reviews the mechanism of action of lnc-TSPAN12 in HCC, particularly in the context of MVI, and explores its potential as a biomarker for diagnosing HCC with MVI. The aim is to provide new targets and ideas for the treatment of HCC patients.

Keywords Hepatocellular carcinoma(HCC); Long non-coding RNA(lncRNA); Long non-coding RNA-TSPAN12(lnc-TSPAN12);Microvascular invasion(MVI); Mechanism of action;

Introduction

According to the 2022 Global Cancer Epidemiology Report[1], primary liver cancer ranks 6th in incidence among malignant tumors, and the annual mortality due to primary liver cancer is the 3rd leading cause of cancer-related deaths. Primary liver cancer primarily includes three different pathological types, among which HCC is the most common, accounting for 75% to 85% of primary liver cancer cases[2,3,4]. In China, the situation of HCC is particularly severe, and it has become the 4th most common malignant tumor[4]. Currently, the number of HCC cases in China accounts for more than half of the global total, with mortality from HCC ranking second in cancer-related deaths, following lung cancer, posing a serious threat to public health[4]. The causes of HCC are diverse, associated with chronic liver diseases, viral infections, alcohol consumption, aflatoxin exposure, and other

factors[5], with viral hepatitis being the primary cause of liver cancer in China[4], especially hepatitis B and C. In addition, there is a significant difference in the incidence of liver cancer between men and women, with the male-to-female incidence ratio being approximately 3:1, and women typically developing the disease at a later age than men. Currently, surgery remains the primary treatment for HCC, but due to its high recurrence and metastasis rates, the treatment outcomes for HCC are not ideal, making the identification of new therapeutic targets and approaches an urgent issue to address.

The gene product of lnc-TSPAN12 is a long-chain RNA with a length of 1,652 nucleotides, and its function is not yet fully understood. Studies have shown that lnc-TSPAN12 plays an important role in tumor initiation and progression, with its overexpression closely associated with indicators such as tumor malignancy, prognosis, and therapeutic response[6]. This review summarizes the research progress of lnc-TSPAN12 in HCC, aiming to explore whether lnc-TSPAN12 holds promise as a biomarker for diagnosing HCC with MVI and to provide new therapeutic insights for HCC patients.

Overview of Long Non-Coding RNA

Long non-coding RNAs (lncRNAs) are a class of RNA molecules longer than 200 nucleotides that do not possess protein-coding capabilities[7]. They play a key role in epigenetic regulation, transcriptional regulation, and post-transcriptional regulation, thereby playing a crucial role in a wide range of physiological and pathological processes. In particular, in the field of oncology, lncRNAs are deeply involved in the initiation and progression of tumors, acting as either oncogenes or tumor suppressors, showcasing their complex and diverse functional characteristics[8]. Notably, abnormal expression of lncRNAs is closely and intricately linked to cancer risk, prognosis, and disease outcomes. This altered expression pattern not only provides potential molecular markers for early tumor diagnosis but also opens up new perspectives for predicting disease progression and therapeutic responses.

lncRNA and Malignant Tumors

lncRNAs exhibit differential expression patterns in various tumor tissues, acting both as oncogenes and tumor suppressors. They regulate cell proliferation, apoptosis, and differentiation through epigenetic, transcriptional, and post-transcriptional mechanisms, playing a crucial role in the initiation and progression of tumors[9,10]. These regulatory functions primarily involve DNA methylation or demethylation, RNA interference, histone modifications, and chromatin remodeling in the context of epigenetics. lncRNAs are closely associated with more than 12 types of chromatin regulatory proteins, and they can recruit and guide chromatin-modifying complexes to target gene sites or tumor-specific promoter regions. Through methylation and acetylation processes, lncRNAs regulate target genes, thereby influencing cellular functions such as proliferation, differentiation, apoptosis, and adhesion. Moreover, lncRNAs can also regulate the expression of target genes at the post-transcriptional level by interacting with microRNAs (miRNAs), messenger RNAs (mRNAs), and proteins[11]. Numerous studies worldwide have shown that lncRNAs are aberrantly expressed in breast cancer, gastric cancer, HCC, colorectal cancer, and cervical cancer[12,13,14,15,16], and this abnormal expression is closely associated with the initiation, progression, and prognosis of malignant tumors[17].

The 12 lncRNAs that are currently extensively studied, along with their roles and mechanisms in various tumors, are shown in Table 1.

Table 1: The Role and Mechanism of lncRNA in Different Types of Tumors

LncRNA Name	Tumor Type	Role and Mechanism
HOTAIR	Multiple tumors	Interacts with the PRC2 complex to regulate histone methylation, thereby controlling gene expression. Overexpressed in various tumors, including breast cancer, liver cancer, and lung cancer, and closely associated with tumor initiation, progression, and prognosis.

MALAT1	Lung cancer, breast cancer, etc.	In lung cancer, high expression of MALAT1 is associated with poor prognosis in patients, promoting cell proliferation and migration by regulating cell cycle and apoptosis-related genes. In breast cancer, MALAT1 is also overexpressed, and its expression is linked to tumor progression and metastasis.
H19	Liver cancer, breast cancer, etc.	In liver cancer, H19 promotes cell proliferation and invasion by regulating the expression of genes related to cell proliferation and apoptosis. In breast cancer, H19 acts as a critical regulator of epithelial-mesenchymal transition (EMT) by modulating miRNA expression, thus promoting tumor progression and metastasis.
ANRIL	Glioma, etc.	Regulates the expression of genes associated with the cell cycle and apoptosis, affecting glioma cell proliferation and apoptosis. ANRIL is also associated with angiogenesis and invasion capabilities in glioma.

Continued Table 1: The Role and Mechanism of lncRNA in Different Types of Tumors

LncRNA Name	Tumor Type	Role and Mechanism
PVT1	Breast cancer, ovarian cancer, etc.	PVT1 is overexpressed in both breast and ovarian cancers and is associated with poor prognosis. It promotes tumor cell proliferation and invasion by regulating genes involved in proliferation and apoptosis.
UCA1	Bladder cancer, liver cancer, etc.	In bladder and liver cancers, UCA1 overexpression is associated with tumor cell proliferation, invasion, and metastasis. It promotes tumor initiation and progression by regulating genes related to the cell cycle, apoptosis, and affecting tumor cell metabolism and energy supply.
GAS5	Gastric cancer, ovarian cancer, etc.	Low expression of GAS5 is associated with poor prognosis in gastric and ovarian cancers. GAS5 inhibits tumor progression by regulating genes related to cell proliferation, apoptosis, autophagy, and drug resistance.
LINC00673	Lung cancer	By interacting with miRNAs, LINC00673 regulates the proliferation, migration, and invasion of lung cancer cells. High expression of LINC00673 is associated with poor prognosis in lung cancer patients.
LINC00961	Colorectal cancer	Regulates the Wnt/β-catenin signaling pathway, affecting the proliferation and invasion ability of colorectal cancer cells. High expression of LINC00961 is associated with poor prognosis in colorectal cancer patients.
LINC01296	Breast cancer	Regulates the expression of genes involved in the cell cycle and apoptosis and influences the migration and invasion ability of breast cancer cells, promoting tumor initiation and progression.
NEAT1	Multiple tumors	As a major component of nuclear paraspeckles, NEAT1 participates in regulating gene expression and cell proliferation. High expression of NEAT1 is associated with increased proliferation and invasion abilities in various tumors.
Lnc-DC	Gastric cancer	Regulates immune cell function and activity, affecting the progression and prognosis of gastric cancer. High expression of Lnc-DC is associated with poor prognosis in gastric cancer patients.

In summary, the mechanisms by which lncRNAs function in tumors involve multiple aspects, including the regulation of cell proliferation, apoptosis, migration, invasion, metabolism, and immunity. Through interactions with DNA, RNA, and proteins, lncRNAs participate in regulating the biological behavior of tumor cells, thereby influencing tumor initiation, progression, and prognosis. However, the specific mechanisms of lncRNAs in tumors are still not fully understood, and further in-depth studies are needed to uncover their complex regulatory networks.

lnc-TSPAN12

lnc-TSPAN12, as one of the long non-coding RNAs, is located in the human chromosome 7q31.2 region and consists of five exons. Overexpression of lnc-TSPAN12 is closely associated with malignant biological behaviors of tumor cells, such as growth, proliferation, invasion, and metastasis. Its abnormal expression pattern can significantly alter the intrinsic characteristics of tumor cells, conferring stronger invasiveness and metastatic potential[6]. Patients with higher expression levels of lnc-TSPAN12 may experience faster tumor progression and relatively poor therapeutic response. Therefore, the expression status of lnc-TSPAN12 can be considered an important prognostic marker for tumors[8].

lnc-TSPAN12 plays a significant role in the initiation and progression of tumors, with its overexpression closely linked to various key indicators such as tumor malignancy, prognosis, and treatment response[6,8,18]. In-depth research on lnc-TSPAN12 not only holds promise for providing new perspectives and methods for tumor diagnosis and prognosis evaluation but may also open new avenues for developing more effective cancer therapies.

lnc-TSPAN12 and HCC

The mechanisms underlying the occurrence and development of HCC are complex, and MVI is a critical pathological feature of HCC. MVI is one of the key indicators of the malignancy and prognosis of HCC, closely associated with tumor progression, metastasis, recurrence, and poor prognosis[19,20]. The detailed mechanisms of MVI in HCC remain unclear, but it is currently believed to be a biological process involving multiple steps and factors. Numerous studies, both domestic and international, have shown that epithelial-mesenchymal transition (EMT) enhances the invasiveness and metastatic potential of tumor cells, playing a crucial role in promoting HCC migration and invasion. EMT is considered a prerequisite for the occurrence and development of MVI[21,22,23].

The expression level of lnc-TSPAN12 is significantly elevated in HCC and is closely associated with poor survival rates[6]. However, the function and mechanisms of lnc-TSPAN12 in regulating EMT and metastasis in HCC remain poorly understood. Li et al.[24]demonstrated that lnc-TSPAN12 positively influences HCC cell migration, invasion, and EMT in vitro, and promotes liver metastasis of HCC in vivo. Lu et al. [25]used high-throughput RNA sequencing to reveal differential expression profiles of lncRNAs and messenger RNAs in four pairs of HCC with MVI and adjacent non-tumor liver tissues. They found that lnc-TSPAN12 was highly expressed in HCC (including HCC with MVI), and its high expression was associated with unfavorable clinical pathological features and poor prognosis. Moreover, multivariate Cox regression analysis confirmed that lnc-TSPAN12 is an independent prognostic factor for overall survival and relapse-free survival[25].

The N6-methyladenosine modification driven by Methyltransferase-like 3 (METTL3) is crucial for the stability of lnc-TSPAN12, which may partially contribute to the upregulation of lnc-TSPAN12[24]. lnc-TSPAN12 exhibits direct interactions with Eukaryotic Translation Initiation Factor 3I (EIF3I) and SUMO1-Specific Peptidase 1 (SENP1), acting as a scaffold that enhances the SENP1-EIF3I interaction. This, in turn, activates the Wnt/β-catenin signaling pathway, promoting EMT and metastasis in HCC. The findings by Li et al.[24]reveal the regulatory mechanism of lnc-TSPAN12 in HCC metastasis and identify the lnc-TSPAN12-EIF3I/SENP1 axis as a novel therapeutic target for HCC.

Additionally, studies have found that silencing lnc-TSPAN12 can inhibit the migration and invasion of HCC cells in vitro[6]. Lu et al.[25]demonstrated through receiver operating characteristic (ROC) curve analysis that lnc-TSPAN12 could serve as a potential diagnostic biomarker for HCC with MVI. Furthermore, other research suggested that lnc-TSPAN12 may

function as an oncogene in the progression of HCC and could serve as a novel diagnostic and prognostic biomarker, as well as a potential therapeutic target for HCC with MVI[25].

The mechanism of action of lnc-TSPAN12 in HCC is illustrated in Figure 1.

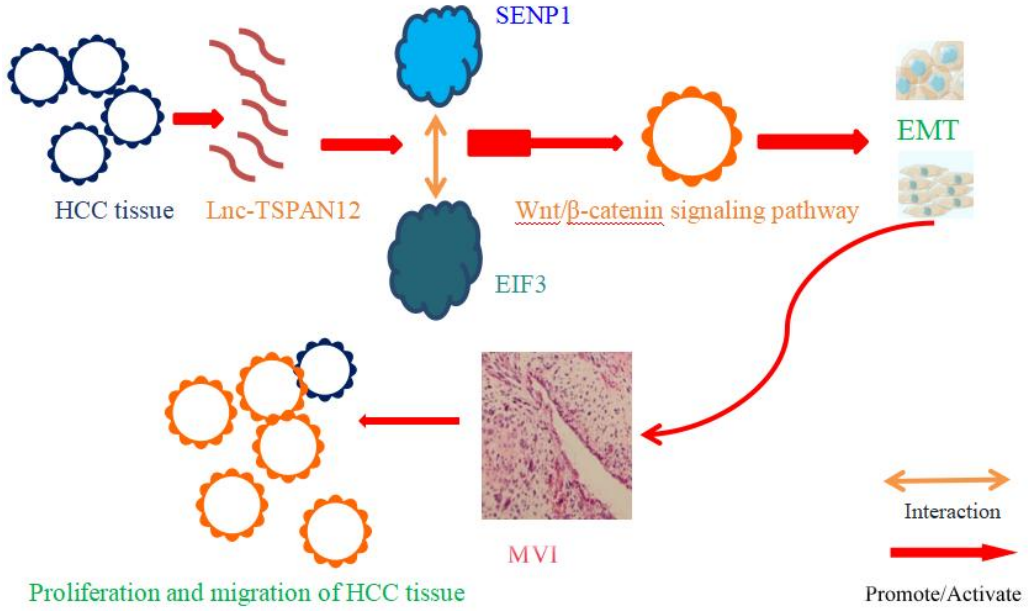

Figure 1: The Mechanism of Action of Lnc-TSPAN12 in HCC (Hepatocellular Carcinoma)

HCC: Hepatocellular Carcinoma ; lnc-TSPAN12: Long Non-coding RNA-TSPAN12 ; IEIF3: Eukaryotic Translation Initiation Factor 3I;SENP1: SUMO1-Specific Peptidase 1;EMT: Epithelial-mesenchymal Transition ; MVI: Microvascular Invasion）

In summary, the malignant progression and prognosis evaluation of HCC are heavily influenced by MVI, the complex mechanisms of which remain to be fully elucidated. EMT is a key process driving HCC migration, invasion, and the occurrence of MVI. lnc-TSPAN12, a long non-coding RNA highly expressed in HCC, is not only closely associated with poor survival rates in patients but also significantly promotes HCC EMT and metastasis by regulating the SENP1-EIF3I interaction and activating the Wnt/β-catenin signaling pathway. Researchers have revealed the central role of lnc-TSPAN12 in HCC metastasis and established the lnc-TSPAN12-EIF3I/SENP1 axis as a novel therapeutic target for HCC. In conclusion, lnc-TSPAN12 holds promise as a biomarker for diagnosing HCC with MVI, providing new perspectives and strategies for early diagnosis, prognosis assessment, and personalized treatment for patients.

Conclusion

lncRNAs, as a class of crucial non-coding RNAs, exhibit highly complex and diverse functional characteristics in the field of tumor biology. Notably, the differential expression patterns of lncRNAs in malignant tumors strongly suggest their potential role as key oncogenes or tumor suppressor genes, deeply involved in the initiation and progression of cancer. Among them, lnc-TSPAN12, a non-coding RNA significantly overexpressed in HCC, is not only closely associated with lower patient survival rates but also accelerates the malignant progression of HCC through a series of complex molecular mechanisms. Further research into lnc-TSPAN12 should focus on exploring its regulatory network and interactions with other molecules, aiming to provide new perspectives and approaches for the treatment strategies and prognosis assessment of HCC patients.

Footnotes

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Authors' contributions SYH and XSL were the

primary author of the manuscript. They are the co-first authors of this article.PYP, MBW, CYP, CWC and WBB searched the literature and data. LYS and QJW assisted in writing the manuscript. All authors have read and approved the final manuscript.

Competing interests The authors declare that they have no competing interests.

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