

REVIEW ARTICLE

LINC00152: A pivotal oncogenic long non-coding RNA in human cancers

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Abstract

In recent years, increasing evidence has shown the potential role of long non-coding RNAs (lncRNAs) in multiple cancers. Deregulation of lncRNAs was detected being closely associated with many kinds of tumours where they can act as a tumour suppressor or accelerator. LINC00152 was identified as an oncogene involved in many kinds of cancers, such as gastric cancer, hepatocellular carcinoma, colon cancer, gallbladder cancer and renal cell carcinoma. Moreover, inhibition of LINC00152 can suppress proliferation, migration and invasion of the cancer cells. Increasing evidence has showed that LINC00152 may act as a diagnostic and prognostic biomarker for the above-mentioned cancers. In our review, we summarize the recent research progress of the expression and role of LINC00152 in various kinds of cancers.

1 | INTRODUCTION

Over the past decade, there has been a more in-depth understanding of genomic complexity in eukaryotes, thanks to the huge technological progress in high-throughput sequencing of DNA and RNA transcripts.¹ This has allowed scientists to shed new light on that beyond protein-coding genes, plenty of transcripts which do not encode for proteins may perform their function through RNA sequences and/or through secondary and tertiary structural modification.^{1,2} Among these non-coding RNAs, microRNAs are well-known regulators of cellular progresses by modulating gene expression. Additionally, long non-coding RNAs (lncRNAs) represent a huge family of RNAs with limited protein-coding potential that are defined by the length of over 200 nucleotides and lack of detectable open reading frame (ORF).³⁻⁷ In the nucleus,

lncRNAs regulate gene expression in various biological conditions by binding to transcription factors,⁸ chromatin-modifying factors^{9,10} or heterogeneous nuclear ribonucleoproteins (hnRNPs),¹¹ or lncRNAs act as a regulator targeting the splicing, stability or translation of host mRNAs by post-transcriptional mechanisms.¹² While in the cytoplasm, lncRNAs are known to act as the endogenous microRNA sponge to regulate the microRNA targets.¹²⁻¹⁴ Studies have shown that some lncRNAs are up-regulated in multiple cancer tissues and cell lines compared with cancer adjacent tissues and normal cell lines, respectively, and perform pro-oncogenic capability, such as CDKN2B antisense RNA 1 (ANRIL)^{15,16} and metastasis-associated lung adenocarcinoma transcript 1 (MALAT1),¹⁷ while some others have reported low expression and play tumour-suppressive roles, for example, maternally expressed gene 3 (MEG3)¹⁸ and growth arrest-specific transcript 5 (GAS5).^{19,20} Furthermore, certain lncRNAs have shown the developmental and tissue-specific expression

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patterns. These characteristics appear critical for their functional analysis and make it possible for application of lncRNAs in diagnosis, prognostic evaluation and treatment of cancer patients. Overall, lncRNA is a major component of epigenetic regulatory networks.

According to GENCODE analysis (www.genencodegenes.org) of the last version (version 25) of the Ensemble human genome annotation (GRCh38, version 25 from March 2016), 27692 transcripts transcribing from 15767 genes can be identified as lncRNAs. Multiple studies have reported that lncRNAs participate in various aspects of cell biological conditions and are closely associated with tumour development, but only a small portion of lncRNAs have been functionally characterized and little of their molecular mechanism was confirmed. Here, we shed light on the cancer-related lncRNA called LINC00152 (long intergenic non-coding RNA 152), a 828 bp lncRNA that maps to chromosome 2p11.2, which was initially detected as differentially hypomethylated during hepatocarcinogenesis,²¹ has been demonstrated to regulate genes by various mechanisms, including epigenetic modifications,²² and lncRNA-miRNA²³ and lncRNA-protein interactions.²²

First, LINC00152 is a new lincRNA, which is one of the hot research topics nowadays and in several cancers, it has been verified by large clinical samples. For instance, in colon cancer, large samples of 133 patients were used to verify the conclusion that linc00152 is increased in human colon cancer tissues and is associated with poor prognosis and in gastric cancer. In addition, analysis in a cohort of 97 gastric cancer patients revealed that LINC00152 expression was positively correlated with tumour invasion depth, lymph node metastasis, higher TNM stage and poor survival. Second, the representative mechanisms by which LINC00152 could regulate target genes expression are researched most deeply and all sidedly nowadays, for example it could act as ceRNA in cytoplasm or bind to PRC2 to epigenetically regulate genes' expression in nucleus. Third, the relative expression of LINC00152 in cancers was really high, which indicated the importance of LINC00152 in the occurrence and development of tumours, is even comparable to some star molecule, such as *HOTAIR*, *MALAT1*. So, it is meaningful and essential to study LINC00152 in more depth.

In our review, we summarized the current studies of functional regulation mechanisms and clinical significance of LINC00152 in the evolution and progression of human cancers (Tables 1 and 2).

2 | LINC00152 IN HUMAN CANCERS

2.1 | Gastric cancer

Human gastric cancer, with characteristic of poor prognosis and high death rate, is the second most common cause of cancer-related death over the world.^{16,20,24} Therefore, it is necessary to find original prognostic markers and develop novel therapeutic strategies in countermeasures for gastric cancer.^{24,25}

Studies showed that increased expression of LINC00152 was positively correlated with larger tumour size, tumour invasion depth, lymph node metastasis, higher TNM stage and poor survival.^{22,24,26} Interestingly, LINC00152 levels in gastric juice from patients with gastric cancer were observably higher than those from normal controls.²⁶ Moreover, it is in plasma that LINC00152 can be detected as well and the levels of plasma LINC00152 were significantly increased in gastric cancer patients compared with healthy controls, and one of the possible mechanisms of its stable existence in blood is that it is protected by exosomes.²⁷ Unexpectedly, significant joint effect between LINC00152 and *H. pylori* infection on risk of gastric cancer was also found (OR: 17.49, 95% CI: 4.78-63.92).²⁸ Therefore, LINC00152 has the possibility to be applied in gastric cancer diagnosis as a novel blood-based biomarker for diagnosis of gastric cancer, particularly for those with *H. pylori* infection.

In vitro, LINC00152 in gastric cancer cell lines, BGC-823, MGC-803 and SGC-7901, was significantly higher than those in human normal gastric epithelial cell line GES-1.²⁶ Moreover, LINC00152 knockdown could inhibit cell proliferation and colony formation, promote cell cycle arrest at G₁ phase, trigger late apoptosis, reduce the epithelial to mesenchymal transition (EMT) programme, and suppress cell migration and invasion²⁴ (Figure 1F).

Additionally, subcellular fractionation assay showed that in human gastric cancer cell lines, LINC00152 was present in both the nuclear and the cytoplasmic fractions of BGC-823 cells and SGC-7901 cells; however, it was located mainly in the cytoplasm. LINC00152 overexpression facilitated GC cell proliferation by accelerating the cell cycle by binding to enhancer of zeste homologue 2 (EZH2) and silencing the expression of *p15* and *p21*, and this mechanism may be a new molecular signalling link in gastric cancer²² (Figure 1E). *P15* and *p21*, cyclin-dependent protein kinase inhibitors (CKIs), can contribute to

TABLE 1 Functional characterization of LINC00152 in various tumours

Tumour type	Expression	Functional role	Related gene	Protein binding	Role	References
Gastric cancer	Upregulation	Proliferation, apoptosis, migration, invasion, tumorigenesis and epithelial to mesenchymal transition	<i>p15</i> ; <i>p21</i>	EZH2; H3K27me3	Oncogene	22,24,26
Hepatocellular carcinoma	Upregulation	Proliferation and tumorigenesis	<i>EpCAM</i>	/	Oncogene	38
Colon cancer	Upregulation	Tumorigenesis and chemoresistance	miR-193a-3p/ <i>ERBB4</i>	/	Oncogene	23
Gallbladder cancer	Upregulation	Proliferation, metastasis, apoptosis and tumorigenesis	/	/	Oncogene	50
Renal cell carcinoma	Upregulation	Proliferation, invasion, cell cycle and apoptosis	/	/	Oncogene	57

the regulation of both the GC cell cycle and proliferation.²⁹ In addition, Xia, T. et al.³⁰ have found that LINC00152 may interact with *THBS1* mediated by miR-18a-5p (Figure 1A).

Molecular mechanisms provide additional insight into research of gastric carcinogenesis and strong evidence suggests that LINC00152 may prove a useful biomarker and therapeutic target for GC treatment.

2.2 | Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) ranks the third most common cause of cancer-related death worldwide and the sixth most common cancer malignancies worldwide.^{31–36} However, at an advanced stage, hepatocellular carcinoma is often associated with a poor prognosis due to frequent cancer distant metastasis and clinical recurrence.^{31,37} Therefore, new targets for hepatocellular carcinoma will be of great help to accelerate research on the molecular pathogenesis of HCC and perform untraditional diagnosis, treatments and prognosis.

TABLE 2 Clinical significance of LINC00152 in various tumours

Tumour type	Overexpression of LINC00152	References
Gastric cancer	Poor survival, invasion depth, lymph node metastasis and higher TNM stage	22,24,26
Hepatocellular carcinoma	Tumour size and Edmondson grade	38
Colon cancer	Shorter overall survival and recurrence-free survival	23
Gallbladder cancer	Tumour progression, lymph node invasion and TNM stage advancement	50
Renal cell carcinoma	Advanced TNM stages, shorter overall survival	57

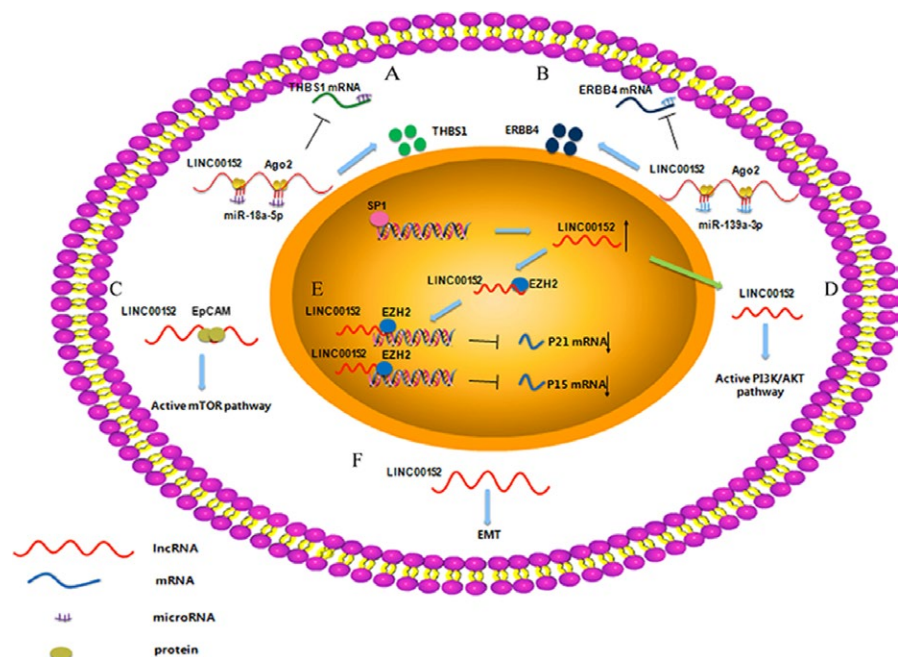
Studies showed that LINC00152 could promote cell proliferation in vitro and tumour growth in vivo.³⁸ In hepatocellular carcinoma, the transcript for LINC00152 was located mainly in the nucleus of MHCC-97H cells. Furthermore, microarray-based analysis demonstrated that LINC00152 could activate the mechanistic target of rapamycin (mTOR) pathway which plays an essential role in the regulation of cancer cell growth, division and tumorigenesis by binding to the promoter of *EpCAM* through a *cis*-regulation, as confirmed by Gal4- λ N/BoxB reporter system^{38,39} (Figure 1C). Thus, LINC00152 might be involved in the oncogenesis of HCC by activating the mTOR signalling pathway and might be a novel biomarker for clinical diagnosis of HCC in the future.

2.3 | Colon cancer

Colon cancer, one of the most prevalent cancers in the world, is the third most common cancer and the second leading cause of cancer-related mortality worldwide.^{40–43} Besides surgery, the fundamental countermeasures for CRC patients, traditional cytotoxic chemotherapy and/or targeted therapies are routinely used to treat patients who are at high risk of developing recurrent or metastatic disease.⁴⁴ However, similar to most other malignant tumours, lack of molecular biomarkers for tumour cell progression is still one of the challenging obstacle for CRC therapy. Therefore, new discovery of the diagnostic and prognostic biomarkers associated with CRC progression and the clinical outcomes would be of great clinical significance and the molecular alterations in CRC have been studied extensively.⁴⁵

Studies have demonstrated that LINC00152 promoted tumour progression and conferred resistance to oxaliplatin (L-OHP)-induced apoptosis in vitro and in vivo.²³ Moreover, it antagonized the sensitivity of chemotherapy through acting as a competing endogenous RNA (ceRNA) to regulate the expression of miR-193a-3p, and then regulate

FIGURE 1 Underlying regulatory mechanisms of LINC00152 in human cancers. (A) LINC00152 may interact with *THBS1* mediated by miR-18a-5p. (B) LINC00152 may act as a competing endogenous RNA (ceRNA) to regulate the expression of miR-193a-3p, and then regulate *ERBB4*. (C) LINC00152 can activate the mechanistic target of rapamycin (mTOR) pathway by binding to the promoter of *EpCAM*. (D) LINC00152, which can be activated by SP1, can participate in the phosphatidylinositol 3-kinase (PI3K)/AKT signalling pathway. (E) LINC00152 can facilitate GC cell proliferation by accelerating the cell cycle by binding to enhancer of zeste homologue 2 (EZH2) and silencing the expression of *p15* and *p21*. (F) LINC00152 can promote the epithelial to mesenchymal transition (EMT) programme



ERBB4, which is associated with AKT phosphorylation and can result in L-OHP resistance²³ (Figure 1B).

All the data suggest that LINC00152 is a novel molecule related with progression of colon cancer as well as a therapeutic target for enhancing response to oxaliplatin in the treatment of colon cancer and potential prognostic biomarker.

2.4 | Gallbladder cancer

Gallbladder cancer (GBC) is the most common biliary tract cancer and the fifth most common gastrointestinal malignancy.⁴⁶ Distinctly, gallbladder carcinoma (GBC), which is common in India and Pakistan, but rare in the Western world, has a unique global distribution all over the world.^{47,48} Novel therapeutic targets will be of great help in treatments for gallbladder cancer, thanks to the advances in cancer biology, which can lead to better understanding of the mechanism of GBC tumorigenesis.⁴⁹

Cai et al.⁵⁰ demonstrated that the high LINC00152 levels correlated positively with tumour status progression, lymph node invasion and TNM stage advancement. Functionally, studies revealed that LINC00152 dramatically promoted cell proliferation, metastasis and inhibited apoptosis in vitro. Moreover, in vivo, LINC00152 overexpression significantly promoted tumour growth. Mechanistic analyses indicated that LINC00152 could participate in the phosphatidylinositol 3-kinase (PI3K)/AKT signalling pathway. In addition, SP1 directly binds to the LINC00152 promoter and positively regulates its expression in GBC cell (Figure 1D). In summary, the research suggested that LINC00152 contributes to the oncogenic potential of GBC, and SP1/LINC00152/PI3K/AKT may be a potential therapeutic target for GBC.

2.5 | Renal cell carcinoma

Renal cell carcinoma (RCC) is one of the most common kidney cancers worldwide and the morbidity and lethality remain increasing although great advantages have been made in the past decades.²⁴ Clinically, RCC is refractory to conventional cytotoxic agents. With therapeutic approaches, immunotherapy or targeted therapies such as tyrosine kinase inhibitors, mTOR inhibitors instead of favouring surgery, a significant proportion of patients will yet undergo disease recurrence and metastases.⁵¹⁻⁵⁴ It is therefore critical to develop novel therapeutic tactics in countermeasures for renal cell carcinoma by finding particularly biomarkers for the early detection and prognosis of RCC, for prioritization of asymptomatic individuals and for the identification of patients with greater risk for progression.^{55,56}

Wu et al.⁵⁷ found that LINC00152 expression was significantly upregulated in renal cancerous tissues compared with normal counterparts, and high LINC00152 expression was closely associated with advanced TNM stage. Moreover, LINC00152 was found to be able to serve as an independent predictor of overall survival. Further experiments verified that LINC00152 expression was obviously upregulated in renal cancer cell lines and overexpression of LINC00152 can promote cell proliferation and invasion, inhibit cell cycle arrest in G₁ phase and dramatically decrease apoptosis in both Caki-2 and 786O

cell lines, whereas the opposite results were observed with down-expression of LINC00152. Overall, the data suggest that LINC00152 is a novel molecule related with progression of renal cell carcinoma as well as a potential prognostic biomarker and therapeutic target.

2.6 | Future directions

Recently, an increasing number of lncRNAs are deregulated in diverse human cancers and associated with disease progression. For instance, prostate cancer antigen 3 (PCA3), which is highly expressed in prostate cancer can promote cancer cell proliferation by modulating the androgen receptor signal pathway.⁵⁸ A highly conserved lncRNA named metastasis associated in lung adenocarcinoma transcript 1 (MALAT1), also referred to as NEAT2 (nuclear-enriched abundant transcript 2), which is overexpressed in many kinds of cancers, especially in non-small cell lung carcinoma (NSCLC), can promote cancer cell migration by regulating the expression of targeted genes.¹⁷ These aberrantly expressed lncRNAs are expected to become novel molecular biomarkers for developing novel therapeutic strategies in treatments for diagnosis and prognosis of various kinds of cancers.

There is no doubt that upregulation of LINC00152 affects various cancer-related aggressive phenotypes, signalling pathways and has a critical role in cancer development, and the dysregulated LINC00152 found in tumours suggests that it may represent an effective target for diagnostic, prognostic and therapeutic purposes.^{22-24,26,28,57} However, while we know that LINC00152 knockdown could suppress cancer cell proliferation and colony formation, promote cell cycle arrest at G₁ phase, trigger late apoptosis, reduce the epithelial to mesenchymal transition (EMT) programme and suppress cell migration and invasion,²⁴ the molecular mechanism of LINC00152 remains to be further explored. Most interesting is that the location of LINC00152 in part of cells was specific in different cell lines and it is hard to conclude that where is LINC00152 locate primarily. For example, in human gastric cancer cell lines, LINC00152 was present in both the nuclear and the cytoplasmic fractions of BGC-823 cells and SGC-7901 cells; however, it was located mainly in the cytoplasm. In hepatocellular carcinoma, the transcript for LINC00152 was located mainly in the nucleus of MHCC-97H cells. So, further more researches are needed to explore the location in different cell lines. In addition, current understanding of the role of LINC00152 in tumour biology is still in an early stage, and these discoveries have not been applied for tumour patients in clinical practice. Hence, further more large-scale researches are needed to expound the exact molecular mechanisms by which LINC00152 is involved in tumorigenesis.

In conclusion, LINC00152 is expected to become molecular markers for cancer diagnosis and prognosis in the future with the detailed molecular mechanism explored, and large case-control studies are needed to prove the sensitivity and specificity of LINC00152 as a serum marker to monitor disease biological behaviour and response to treatment.

COMPETING INTERESTS

The authors have declared that no competing interest exists.

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