Role of the long non-coding RNA LINC00052 in tumors (Review)

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Abstract. Long intergenic non-protein coding RNA 52 (LINC00052) is a non-coding RNA with >200 nucleotides in length, which exerts important effects on several physiological and pathological processes of the human body. Recent studies have demonstrated that LINC00052 plays key roles in the tumorigenesis, progression and metastasis of multiple types of human cancer, including hepatocellular carcinoma, breast cancer, colorectal cancer, cervical carcinoma and gastric cancer. However, the associations between LINC00052 and these tumors remain unclear. The present review summarizes the biological functions of LINC00052 during the pathogenic process of certain tumors, and discusses its potential therapeutic targets.

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1. Introduction

Long non-coding RNAs (lncRNAs) are functional small RNA molecules that cannot encode proteins (1). Increasing evidence suggest that lncRNAs exert important effects on the physiological and pathological processes of the human body, primarily through transcriptional or post-transcriptional mechanisms (2,3). Long intergenic non-protein coding RNA 52 (LINC00052, National Center for Biotechnology Information reference sequence: NR_026869.1) is 1,786 base pairs in length and is located on human chromosome 15 (4). Abnormal expression of LINC00052 has been observed in several tumors, such as liver cancer (5-7), breast cancer (8) and colorectal cancer (9). The current research on LINC00052 mainly focuses on the effect of LINC00052 on tumorigenesis, cancer progression and metastasis (Table I).

The effect of LINC00052 on tumors was first reported by Xiong et al (5) in 2016, with the help of the gene trapping technique (10). The capture plasmid pU21 was transfected into hepatocellular carcinoma (HCC) cells through a plasmid vector. Subsequently, several single cell clones (for example A1 and A2) were obtained. The wound healing and Transwell assays demonstrated that the migratory and invasive abilities of the pU21 plasmid-obtained monoclonal cells were enhanced in the A26 and A55 cell lines, and slightly weakened in the A18 and A28 cell lines compared with the controls (5). 5'RACE-PCR results demonstrated that the gene trapped by pU21 in the A55 cell line was LINC00052 (5); functional tests demonstrated that LINC00052 has the ability to regulate the invasion and migration of HCC cells (5). Subsequently, several single cell clones (for example A1 and A2) were obtained. The wound healing and Transwell assays demonstrated that the migratory and invasive abilities of the pU21 plasmid-obtained monoclonal cells were enhanced in the A26 and A55 cell lines, and slightly weakened in the A18 and A28 cell lines compared with the controls (5).

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5'RACE-PCR results demonstrated that the gene trapped by pU21 in the A55 cell line was LINC00052 (5); functional tests demonstrated that LINC00052 has the ability to regulate the invasion and migration of HCC cells (5). Subsequently, several studies have reported that LINC00052 is strongly associated with the occurrence and development of several tumors, including breast cancer (8), colorectal cancer (CRC) (9), cervical carcinoma (11) and gastric carcinoma (GC) (12). However, there is no conclusive article on the association between LINC00052 and these tumors. The present review summarizes the biological functions of LINC00052 during the pathogenic process of certain tumors and discusses its potential therapeutic targets.
2. LINC00052 and HCC

HCC is one of the most common types of cancer worldwide. Bray et al (13) reported that HCC ranked sixth among the most diagnosed cancers (841,080 new cases) and was the fourth leading cause of cancer-associated mortality (781,631 deaths) in 2018, among the 38 types of tumors evaluated in 185 countries.

It has been proven that LINC00052 inhibits the invasion and migration of HCC cells (5). Through in-depth investigation of the molecular mechanisms underlying the effects of LINC00052 on the development of HCC, three target genes of LINC00052 were identified: Neurotrophic receptor tyrosine kinase 3 (NTRK3) (5), erythrocyte membrane protein band 4.1-like 3 (EPB41L3) (6) and SRY-related HMG-box gene 9 (SOX9) (7).

NTRK3 is a type of neurotrophin receptor that plays an important role in the nervous system, and it may be involved in the initiation, progression and metastasis of several human tumors, such as breast, medullary thyroid, liver, colon, lung and prostate cancers (14-16). Xiong et al (5) demonstrated that LINC00052 inhibits cell proliferation, invasion and migration by upregulating NTRK3 expression through complementary base pairing with microRNA (miRNA/miR)-128 and miR-485-3p. This is a key regulatory mechanism through which lncRNAs regulate target gene expression in tumors by sponging miRNAs, thus reducing their regulatory effect on mRNAs (17) (Fig. 1).

Zhu et al (6) reported that LINC00052 directly acts on EPB41L3 to affect the occurrence and development of HCC by targeting miR-452-5p. EPB41L3, a membrane skeletal protein that belongs to the protein 4.1 family (18), functions as a tumor suppressor in different tumors, such as GC, non-small cell lung cancer and renal clear cell carcinoma (19-21). In addition, Zhu et al (6) confirmed that EPB41L3 is a downstream target gene of LINC00052 via microarray, reverse transcription-quantitative PCR and western blot analyses.

miR-452-5p was predicted to have two binding sites in the sequence of LINC00052 through the bioinformatics databases: DIANA-LncBase, https://bigd.big.ac.cn; miRcode, http://www.mircoder.org and BiBiServ, https://bibiserv.ccbj.umbc.edu. Furthermore, it was demonstrated that miR-452-5p can recover LINC00052 function in HCC cells and inhibit EPB41L3 expression by targeting the 3'-untranslated region of miR-452-5p (Fig. 1). Thus, Zhu et al (6) uncovered a novel LINC00052/miR-452-5p/EPB41L3 regulatory network in HCC.

The third target gene of LINC00052 is SOX9. SOX9 is a member of the SOX transcription factor family, which is associated with early embryonic development (22). SOX9 expression is frequently upregulated, and it is characterized as an oncogene in different types of human cancer, including lung cancer, GC and HCC (23-25). Yan et al (7) reported that LINC00052 promotes miR-101-3p expression by enhancing its promoter activity, and that miR-101-3p can interact with SOX9 to affect the occurrence and development of HCC (Fig. 1).

3. LINC00052 and breast cancer

Breast cancer is the leading cause of cancer-associated mortality among women worldwide (26). Bray et al (13) reported 2,088,849 new cases and 626,679 breast cancer-associated mortalities in 2018, and breast cancer ranked second among the 38 types of tumors investigated in 185 countries. Thus, several studies continue to persistently investigate the pathogenesis and pathogenic genes of breast cancer, in the hope to identify biomarkers associated with its early diagnosis and treatment (27-29). By using RNA isolation, RNA-seq and microarray, Muñoz-Galindo et al (29) identified 221 and 146 dysregulated lncRNAs after 12 and 20 days of three-dimensional culture in breast cancer cells, respectively. It was demonstrated that LINC00052 was the most extensively downregulated lncRNA at two time points: Decreased by 47-fold on the 12th day and 69-fold on the 20th day. These results suggest that LINC00052 is a key target for intervention in tumor diagnosis and treatment.

Triple-negative breast cancer (TNBC), which is characterized by the lack of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 expression, is an extremely aggressive type of breast cancer (30). Lv et al (31) demonstrated that LINC00052 is markedly upregulated in TNBC tissues compared with non-TNBC tissues and may serve as a powerful indicator for diagnosis of TNBC by analyzing the result of the receiver operating characteristic curve (area under the curve, 0.823; 95% confidence interval, 0.637-1.000). These results suggest that LINC00052 may serve as a potential biomarker for differentiating TNBC samples from non-TNBC samples.

Human epidermal growth factor receptor 3 (HER3/ErbB3) family of tyrosine kinase receptors (8). Upregulated HER3 expression has been implicated in the development and progression of different types of cancer (32,33). For example, Salameh et al (8) confirmed that LINC00052 promotes the proliferation of breast cancer cells by increasing HER3 signaling both in vitro and in vivo (Fig. 1). This suggests that LINC00052 may act as a potential biomarker for HER3-targeted cancer therapies.

4. LINC00052 and CRC

CRC is a common malignant gastrointestinal tumor (34). Bray et al (13) reported that CRC ranked third among the most diagnosed cancers and second in mortality rate among 38 types of tumors in 185 countries, with 1,096,601 new cancer cases and 551,369 mortalities recorded in 2018. Previous studies have confirmed that lncRNAs are implicated in the occurrence and development of CRC, such as H19 (35), glycolysis-associated lncRNA of colorectal cancer (36) and fez family zinc finger protein 1-antisense RNA 1 (37). Yu et al (9) reported that downregulation of LINC00052 expression promotes the proliferative, migratory and invasive abilities of CRC cells. It was also confirmed that LINC00052 affects the occurrence and development of CRC by modulating the expression of calcium binding and coiled-coil domain 1 (CALCOCO1) through interaction with miR-574-5p (Fig. 1). CALCOCO1 is located on chromosome 12p13 and its different domains can bind with glutamate receptor interacting protein 1 and β-catenin, thereby affecting cell division and apoptosis (38).

5. LINC00052 and cervical carcinoma

Epidemiological statistics indicate that cervical cancer was the fourth most common gynecological malignancy worldwide.
in 2012 (39). Bray et al (13) reported that cervical carcinoma was the fourth most diagnosed cancer and the fourth leading cause of cancer-associated mortality in women among the 38 types of tumors in 185 countries, with 569,847 new cases and 311,365 mortalities reported in 2018. The use of cervical vaccines, early detection and timely treatment have decreased the incidence and mortality rates of cervical cancer (40). Increasing evidence suggest that IncRNAs serve as important regulators in the progression of cervical carcinoma (41). For example, IncRNA papillary thyroid carcinoma susceptibility candidate 3 has been demonstrated to suppress the invasion and proliferation of cervical cancer cells by regulating

![Diagram of LINC00052 in different tumors](image)

**Table I. Targets of LINC00052 in tumors.**

| Tumor type     | miRNA       | Target gene          | Function                               | Refs. |
|----------------|-------------|----------------------|----------------------------------------|-------|
| HCC            | miR-128, miR-485-3p | NTRK3                | Cell invasion and migration             | (4)   |
|                | miR-452-5p  | EPB41L3              | Cell invasion and migration             | (5)   |
|                | miR-101-3p  | SOX9                 | Cell proliferation and metastasis       | (6)   |
| Breast cancer  | -           | HER3/ErbB3           | Cell proliferation                      | (7)   |
| CRC            | miR-574-5p  | CALCOCO1             | Cell metastasis                        | (8)   |
| Cervical carcinoma | -      | STAT3                | Cell metastasis and invasion           | (10)  |
| GC             | -           | Wnt/β-catenin pathway | Cell proliferation and metastasis      | (11)  |
| HNSCC          | miR-608     | EGFR                 | Cell proliferation, migration and invasion | (52)  |
| Glioma         | -           | KLF6                 | Cell proliferation, migration and invasion | (53)  |

LINC00052, long intergenic non-protein coding RNA 52; HCC, hepatocellular carcinoma; CRC, colorectal cancer; GC, gastric carcinoma; HNSCC, head and neck squamous cell carcinoma; miR, microRNA; NTRK3, neurotrophic receptor tyrosine kinase 3; EPB41L3, erythrocyte membrane protein band 4.1-like 3; SOX9, SRY-related HMG-box gene 9; HER3, human epidermal growth factor receptor 3; CALCOCO1, calcium binding and coiled-coil domain 1; STAT3, signal transducer and activator of transcription 3; EGFR, epidermal growth factor receptor; KLF6, kruppel-like factor 6; - , not available.

Figure 1. Schematic overview of role of LINC00052 in different tumors. LINC00052, long intergenic non-protein coding RNA 52; HCC, hepatocellular carcinoma; NTRK3, neurotrophic receptor tyrosine kinase 3; EPB41L3, erythrocyte membrane protein band 4.1-like 3; SOX9, SRY-related HMG-box gene 9; miR, microRNA; STAT3, signal transducer and activator of transcription 3; HER3, human epidermal growth factor receptor 3; CALCOCO1, calcium binding and coiled-coil domain 1; GC, gastric carcinoma; HNSCC, head and neck squamous cell carcinoma; CRC, colorectal cancer.
miR-574-5p expression (41), whereas IncRNA nuclear paraspeckle assembly transcript 1 regulates the proliferation and invasion of cervical cancer cells by targeting the PI3K/AKT pathway (42). Lin et al (11) demonstrated that LINC00052 expression is significantly downregulated in both cervical cancer tissues and cells. Overexpression of LINC00052 inhibits the proliferation, migration and invasion of cervical cancer cells. In addition, signal transducer and activator of transcription 3 (STAT3) protein expression is downregulated following overexpression of LINC00052 (11), suggesting that LINC00052 inhibits tumorigenesis of cervical cancer by suppressing the STAT3 pathway (Fig. 1).

6. LINC00052 and GC

GC is the fifth most common cancer and the third most common cause of cancer-associated mortality worldwide, with over one million estimated new cases and 782,685 deaths in 2018 (13,43). Recent studies have reported that IncRNAs are associated with the occurrence and development of GC (44-46).

Shan et al (12) demonstrated that LINC00052 is highly expressed in GC tissues, which is associated with tumor progression and poor prognosis. The underlying molecular mechanisms of LINC00052 on the occurrence and development of GC were investigated, and the results demonstrated that LINC00052 maintains the stability of β-catenin by promoting β-catenin methylation to activate the Wnt/β-catenin pathway (Fig. 1). This suggests that LINC00052 may promote the proliferation and metastasis of GC cells by activating the Wnt/β-catenin pathway. However, some human GC cell lines (MGC-803, BGC-823 and SGC-7901) may be contaminated with HeLa cells (47), thus authenticated cell lines or animal models should be performed accordingly.

7. LINC00052 and other cancers

Tongue squamous cell carcinoma (TSCC) is the most common type of oral squamous cell carcinoma, which is characterized by marked invasiveness, early lymph node metastasis and poor prognosis (48,49). To further investigate the molecular mechanism underlying the development and progression of TSCC, Zhang et al (50) identified a total of 1,867 mRNAs, 828 IncRNAs and 81 miRNAs that are aberrantly expressed in TSCC tissues compared with normal tissues via RNA sequence data processing, expression profile analysis and statistical analysis. It was predicted that LINC00052 is significantly associated with the overall survival rate of TSCC (50).

Pancreatic cancer is an aggressive malignant tumor with a poor prognosis (51). LINC00052 has been demonstrated to act as a tumor suppressor by negatively modulating miR-330-3p expression to affect the occurrence and progression of prostate cancer (52). In addition, LINC00052 may regulate the miR-608/EGFR axis to promote the progression of head and neck squamous cell carcinoma (53), and suppresses the proliferation, migration and invasion of glioma cells by upregulating kruppel-like factor 6 expression (54) (Fig. 1). Taken together, these results suggest that LINC00052 regulates a broad range of tumors.

8. Conclusions and perspectives

In the present review, the potential molecular mechanisms of action of LINC00052 in the pathological process of several tumors, such as HCC, breast cancer, CRC, prostate cancer and GC, were described (Table 1). LINC00052 may represent a functional research hotspot in multiple tumors. LINC00052 can affect the tumor biological processes by regulating tumor cell proliferation, invasion, metastasis and migration. LINC00052 may serve as a miRNA sponge, competing with other genes for miRNA binding, and thus decrease mRNA transcription of targeted genes. However, further studies are required to validate the molecular mechanism of LINC00052. The tumorigenic mechanism of IncRNA is intricate and more information on the regulation of LINC00052 in response to malignant transformation is required to elucidate its complicated role in different tumors. In addition, the network of IncRNA/miRNA/target genes requires further investigation to determine the association between IncRNA expression and the occurrence and development of tumors. In conclusion, the present review summarizes the potential biomarkers or targets for novel therapeutic strategies.

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DX, DW and YC were involved in the conception of the present review. DX drafted the initial manuscript. DW and YC critically revised the manuscript for important intellectual content. DX and YC confirmed the authenticity of all the raw data. All authors have read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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