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REVIEW

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LncRNA LINC00460: Function and mechanism in human cancer

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Abstract

Long non-coding RNAs (LncRNAs), which are more than 200 nucleotides in length and with limited protein-coding potential, play vital roles in the pathogenesis, tumorigenesis, and angiogenesis of cancers. Aberrant expression of lncRNAs has been detected in various carcinomas and may be correlated with oncogenesis by affecting related genes expression. Recently, an increasing number of studies have reported on long intergenic non-protein coding RNA 460 (LINC00460) in human tumor fields. LINC00460 is upregulated in diverse cancer tissues and cells. The upregulated expression level of LINC00460 is correlated with larger tumor size, tumor node metastasis (TNM) stage, lymph node metastasis, and shorter overall survival. The regulatory mechanism of LINC00460 was complex and diverse. LINC00460 could act as a competitive endogenous RNA (ceRNA), directly bind with proteins or regulate multiple pathways, which affected tumor progression. Moreover, LINC00460 was also identified to increase drug resistance, and therefore, weaken the effectiveness of tumor treatment. It has become increasingly important to investigate the roles of LINC00460 in various cancers by different mechanisms. Therefore, a more comprehensive understanding of LINC00460 is crucial to expound on the cellular function and molecular mechanism of human cancers. In this review, we refer to studies concerning LINC00460 and provide the basis for the evaluation of LINC00460 as a predicted biomarker or potential therapeutic target in malignancies, and also provide ideas for the future research of lncRNAs similar to LINC00460.

KEYWORDS
cancer, LINC00460, long non-coding RNA, mechanism, oncogene

INTRODUCTION

Cancer is a predominant reason for death worldwide, and the quantities of cancer cases and deaths rapidly grow as populations grow.[1] Eliminating cancer requires not only improved therapies, but also improved methods to detect cancers at an early stage. Molecular technology plays a vital role in cancer detection and prognosis and has gradually received greater attention.[2] Therefore, we are eager to find a new therapeutic biomarker to improve cancer treatment and prognosis.

An increasing number of studies related to long non-coding RNAs (lncRNAs) have been reported because of their high specificity and easy detection in tissues, serum, plasma, urine, and saliva.[3] LncRNAs were a novel class of functional RNAs that were longer than 200 nucleotides, characterized by low levels of sequence conservation and expression.[4] LncRNAs regulate various biological functions at different levels, including the epigenetic, transcriptional, and post-transcriptional levels.[5] Aberrant expressions of lncRNAs in some cancers is associated with tumorigenesis, metastasis, and angiogenesis.[6,7] Therefore, lncRNAs could be potential novel biomarkers for cancer diagnosis and therapy. For instance, lncRNA-differentiation antagonizing non-protein coding RNA (DANCR) could act as a competing

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endogenous RNA (ceRNA) that interacts with messenger RNA (mRNA) sequences to restrain the microRNA (miRNA) suppressive effect on target genes and is involved in various cancers.[8] Additionally, lncRNA HOXA-cluster antisense RNA2 (AS2) has been demonstrated to modulate cellular function and regulate gene expression by complicated regulatory mechanisms.[9]

Recently, RNA sequencing data from several cancers, such as lung adenocarcinoma (LC), head and neck squamous carcinoma (HNSCC), breast cancer, bladder cancer, lung squamous cell carcinoma, and renal cell carcinoma, from The Cancer Genome Atlas (TCGA) data portal and identified differentially expressed RNAs were used to construct the lncRNA-related ceRNA network.[10–17] After analysis the lncRNA-related ceRNA network, a common valuable lncRNA correlated with pathogenesis and tumorigenesis was confirmed, namely, long intergenic non-protein coding RNA 460 (LINC00460).[10] LINC00460 (NR_034119.1, NCBI: https://www.ncbi.nlm.nih.gov) expression was elevated in various cancer types through querying the TCGA database and data analysis of Ensembl database (http://asia.ensembl.org) revealed that LINC00460 has seven transcripts and is located in chr13q33.2 region.[18] The previous studies indicated that the transcripts associated with cancers are mostly LINC00460-202 and LINC00460-203.[18–20] LINC00460-202 transcribed as an 857 nt transcript and has three exons; it has been proved highly expressed in lung cancer.[19] LINC00460-203 transcribed as a 915 nt transcript and has two exons; it has been demonstrated upregulated in HNSCC[18] and gastric cancer (GC).[20] LINC00460 has been demonstrated to be upregulated in many types of cancers and functions as an important oncogene, the exploration of molecular mechanism of LINC00460 is of great concern and the expression of LINC00460 is involved in the development of various tumors, including HNSCC, colorectal cancer (CRC),[21] lung cancer,[22] papillary thyroid cancer (PTC),[23] hepatocellular carcinoma (HCC),[24] glioma,[25] renal cell carcinoma,[16] meningioma,[26] and others. LINC00460 plays a significant role in the pathogenesis and tumorigenesis of diverse cancers and is associated with distant lymph mode metastasis, epithelial-mesenchymal transition (EMT), and poor overall survival.[26,27] Therefore, LINC00460 is one of the most critical regulatory RNAs in human cancers, and it might be a potential and valuable target for therapeutics. In this review, we emphatically discuss the mechanisms and effects of LINC00460 in human cancers (Table 1).

MATERIALS AND METHODS

Search strategy

A systematic literature survey was conducted via electronic searched of PubMed, China National Knowledge Infrastructure (CNKI) and WanFang databases for eligible studies published as of June 1, 2021. The search terms include "long non-coding RNA", "lncRNA", "long intergenic non-coding RNA", "LINC00460", "cancer", "carcinoma", "neoplasm", "tumor", "prognosis", "prognostic", "survival", "overall survival", and "OS". Furthermore, the references in retrieved articles were also manually reviewed for potentially relevant studies.

Inclusive and exclusive criteria

The inclusive criteria were as follows: (1) the expression of LINC00460 was determined; (2) studies on any type of human cancer; (3) for molecular studies; and (4) with full-text. The exclusive criteria were as follows: (1) letter, review, case report, conference abstract, and meta-analyses; (2) non-English papers and non-human studies; and (3) lack of essential information.

Data extraction and quality control

Two investigators independently extracted data from the eligible studies according to the inclusion and exclusion criteria. The third reviewer verified and then any disagreements were resolved by consensus. The following information was collected: first author name, publication year, cancer type, lncRNA, the detection method of lncRNA LINC00460 expression, biological function, miRNAs, RNA-binding proteins (RBPs). The process of the study selection is strictly based on the abovementioned eligibility criteria (Figure 1).

LINC00460 IN VARIOUS CANCERS

Head and neck squamous cell carcinoma

HNSCC is the most common malignant lesion in the head–neck region.[57] The main treatment for the majority of patients is the best supportive care in combination with chemotherapy and targeted therapy.[58] Most recurrences or disease-specific deaths occur within the first 2 to 3 years, and half of the patients die within 5 years after diagnosis.[59] Therefore, it is necessary to investigate novel valid regulators to detect the disease in the early stage and improve the prognosis of HNSCC patients.

Cao et al.[60] selected a three-lncRNA panel, including LINC00460, which had the optimal prediction power for HNSCC patients based on analysis. High expression of LINC00460 was detected in HNSCC tissues and was associated with poor survival.[61] In some studies, LINC00460 promoted HNSCC progression by sponging miRNAs and inhibiting their expression.[28–31] Xue et al.[28] found that LINC00460 silencing affected cell cycle distribution and promoted cell apoptosis and autophagy. The levels of activated apoptosis-related proteins including PARP, Bax, and caspase-3 were increased after LINC00460 knockdown. Knockdown of LINC00460 or overexpression of miR-206

TABLE 1 LINC00460 in human cancers

Cancer types	Cell lines	Expression	Phenotype	Clinical feature	Clinical value	Role	Related genes and protein	Reference
Head and neck squamous cell carcinoma	HSC3, Fadu, SAS, WSU-HN4, WSU-HN6, WSU-HN30, SCC-4, SCC-9, SCC-25, CAL27	Up	Proliferation, invasion, migration, apoptosis, autophagy	Tumor recurrence, lymph node metastasis	Diagnosis, prognosis, therapy	Oncogene	STC2, miR-206, cleaved-PARP, Bax, cleaved-caspase-3, PRDX1, miR-612, AKT2, miR-4443, cyclin D1, p21, miR-320a	[18,28–31]
Esophageal squamous cell carcinoma	EC1, EC9706, KYSE70, TE1, TE13	Up	Proliferation, cell cycle, migration, invasion, apoptosis	TNM stage, lymph node metastasis, poor prognosis	Diagnosis, prognosis, therapy	Oncogene	CBP, P300, miR-1224-5p	[32,33]
Lung cancer	A549, H1299, H1975, H460, PC9, SPC-A1, SKLU-1, Calu-3, HCC-78	Up	Proliferation, migration, invasion, apoptosis	Tumor growth, size, volume, weight	Prognosis, therapy	Oncogene	miR-769-5p, EGFR, cleaved caspase-3, Bcl-2, Bax, miR-539, PI3k, Akt, miR-302c-5p, FOXA1, miR-149-5p	[22,34–37]
Papillary thyroid cancer	FTC-133, 8505C, TPC1, BCPAP	Up	Proliferation, migration, invasion, apoptosis	Tumor size, TNM stage, lymph node metastasis	Diagnosis, therapy	Oncogene	miR-485-5p, Raf1, miR-613, SphK2, miR-539, MMP-9, N-cadherin, vimentin, E-cadherin	[23,38,39]
Breast cancer	MCF-7, BT-474, MDA-MB-231, BT-549	Up	Cell viability, migration, invasion	Lymph node stage, worse survival outcome	Diagnosis, prognosis	Oncogene	miR-489-5p, FGF7, AKT	[40]
Gastric cancer	MGC803, BGC823, SGC7901, MKN-28, MKN-45, AGS	Up	Proliferation, migration, invasion, apoptosis	Lymph node metastasis, TNM stage	Prognosis, therapy	Oncogene	EZH2, LSD1, CCNG2, miR-342-3p, KDM2A, c-MYC, β-catenin	[20,41,42]
Hepatocellular carcinoma	HepG2, Hep3B, SNU-449, THLE-3 cells, HCCLM3, Huh-7, LO2 cells	Up	Proliferation, migration, apoptosis	Tumor progression	Diagnosis, therapy	Oncogene	miR-342-3p, AGR2, cyclin D1, CDK4, MMP-3, MMP-9, Bax, Bcl-2, miR-485-5p, PAK1	[24,43,44]
Colorectal cancer	HCT116, SW480, HT-29, LOVO	Up	Proliferation, cell cycle, apoptosis, migration, invasion	Tumor size, advanced tumor stages, lymph node metastasis	Diagnosis, prognosis, therapeutic detection	Oncogene	EZH2, KLF2, CUL4A, miR-149-5p, ERG, WWC2, LIMK2, miR-939-5p, miR-433-3p, ANXA2	[27,45–47]
Osteosarcoma	Saos-2, HOS, U2OS, MG63	Up	Cell viability, proliferation, migration, apoptosis	Tumor size, distant metastasis	Prognosis, therapy	Oncogene	Cyclin D1, CDK4, CDK6, MMP-9, FADS1, miR-1224-5p	[48,49]
Nasopharyngeal carcinoma	SUNE-1, CNE-1, HNE-1, CNE-2, C666-1, HONE-1	Up	Proliferation, migration, invasion,	Poor prognosis	Diagnosis, prognosis, therapy	Oncogene	miR-30a-3p, Rap1A, miR-149-5p, IL6	[50,51]
Ovarian cancer	HO8910, SKOv-3, A2780, ES-2	Up	Proliferation, migration, invasion, apoptosis	Tumor stage, tumor size	Diagnosis, therapy	Oncogene	miR-338-3p	[52]
Bladder urothelial carcinoma	T24, J82, TCCSUP, UM-UC-3	Up	Proliferation, migration, invasion	Tumor range, metastasis, lymph node	Therapy	Oncogene	miR-612, FOXK1	[53]
Pancreatic cancer	PC PANC1, SW1990	Up	Proliferation, migration, invasion	Poor prognosis	Prognosis	Oncogene	miR-491-5p	[54]
Cervical cancer	HeLa, CaSki	Up	Proliferation	Poor prognosis	Therapy	Oncogene	miR-503-5p, miR-361-3p, Gli1	[55,56]

Abbreviations: TNM stage, tumor-lymph node- metastasis stage.

arrested HNSCC cells in the G0/G1 phase of the cell cycle, hindered the cell cycle progression from G1 phase to S phase, and also increased apoptosis. In addition, knockdown LINC00460 or overexpression of miR-206 downregulated the protein expression of STC2 and blocked the activation of the protein kinase B (AKT) signaling pathway. Therefore, the LINC00460/STC2/miR-206 axis is critical in influencing the development and progression of HNSCC.[28] Furthermore, Xie et al.[29] found that AKT2 was predicted to be a miR-612 binding target and the expression of miR-612 was negatively correlated with AKT2 in HNSCC. LINC00460 could regulate the progression of HNSCC by mediating the miR-612/AKT2 axials. In addition, to regulate cell proliferation and migration, cyclin D1, p21, E-cadherin, and N-cadherin were found to be functional targets of LINC00460.

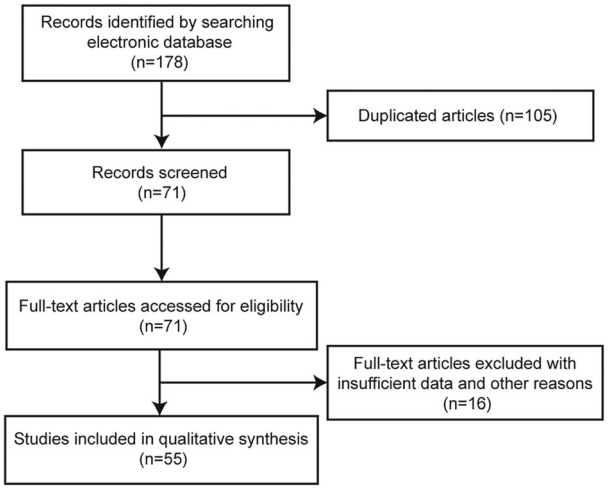

FIGURE 1 Flow diagram of study selection process

The results indicated that knockdown of LINC00460 decreased the expression of cyclin D1 and increased the expression of p21 to regulate cell proliferation, migration and invasion.[29] Furthermore, Li et al.[30] found that miR-4443 might act as a tumor suppressor on account of its effect on proliferation, migration, invasion, and apoptosis was also opposite to LINC00460 in HNSCC cells. In addition, some studies have found that LINC00460 also plays a role by binding with RBPs. Jiang et al.[18] found that PRDX1 is an RBP that binds with LINC00460 to affect cell proliferation, migration and EMT in HNSCC. Silencing PRDX1 decreased the expression of LINC00460, whereas PRDX1 overexpression increased the expression of LINC00460. PRDX1 facilitated the transcription of LINC00460 and EMT-related genes in the nucleus. Knockdown of PRDX1 or LINC00460 remarkably enhanced the level of E-cadherin and reduced the levels of N-cadherin, vimentin, ZEB1, and ZEB2 in HNSCC cells[18] (Figure 2).

Therefore, LINC00460 plays an important role in the development of HNSCC, which is regulated by a variety of mechanisms (specifically sponge miRNAs or directly binds with RBPs). Moreover, the mechanism of LINC00460 involvement in HNSCC needs to be further elucidated, which is of great significance to the application of prognostic and therapeutic target.

Esophageal squamous cell carcinoma

Esophageal cancer (EC) is the eighth most common cancer and the sixth most common cause of cancer-related death worldwide. There are two main histological types of EC: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC).[62] ESCC is one of the most deadly

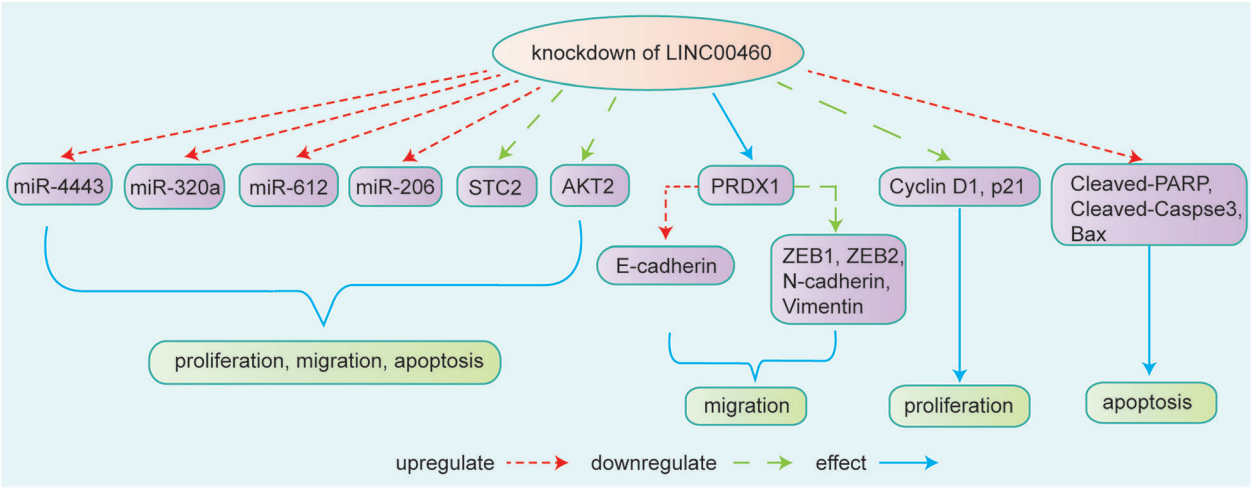

FIGURE 2 Knockdown of LINC00460 decreased STC2 and promoted cell proliferation, migration, and apoptosis of HNSCC by upregulating miR-206 or upregulating the expression of miR-612 by decreasing the expression of AKT or increasing the expression of miR-4443.[28–31] LINC00460 affected HNSCC cell proliferation and migration in a PRDX1-departed manner by regulating the level of E-cadherin and the levels of N-cadherin, vimentin, ZEB1, and ZEB2.[18] Knockdown of LINC00460 affected HNSCC cell migration and invasion by increasing the expression of p21 and decreasing the expression of cyclin D1.[29] Knockdown of LINC00460 promoted cell apoptosis by increasing the expression of cleaved-PARP, Bax, and cleaved caspase-3[28]

forms of human malignancy, and clinical therapy of ESCC remains limited.[63] Hence, it is indispensable for patients to find a valuable and predictable biomarker to improve the prognosis and overall survival.[64]

Liu et al.[65] analyzed the lncRNA expression profile in EC patients' tissue samples from TCGA and gene expression omnibus (GEO)[66] also identified a novel-three lncRNA signature including LINC00460 as a predictor of overall survival and disease-free survival in patients with ESCC. Liang et al.[32] found that LINC00460 was significantly elevated in most of tumor tissues and ESCC cell lines; it was in direct proportion to TNM stage, lymph node metastasis, and poor prognosis. CBP/P300, which were closely related transcriptional coactivators and acetyltransferase enzymes in humans, could directly bind to LINC00460 promoter and active LINC00460 transcribe through histone acetylation. The upregulation of LINC00460 has been demonstrated that promoted ESCC progression through CBP/P300 function.[32] Knockdown of LINC00460 suppressed the metastasis potential and EMT of EC cells by directly binding to miR-1224-5p.[33] Therefore, LINC00460 could as a sponge of miRNAs and histone acetylation to regulate the development of ESCC. LINC00460 might be a candidate biomarker for ESCC diagnosis and have tremendous therapeutic value (Figure 3).

Lung cancer

Lung cancer is the leading malignancy incidence rate and mortality rate.[67] It includes two main types: non-small cell lung cancer (NSCLC) and small cell lung cancer and ~85% of lung cancer consist of NSCLC.[68] Despite advances in health consciousness and systematic treatment, most patients are generally diagnosed at an advanced stage and have a low rate of overall survival.[69]

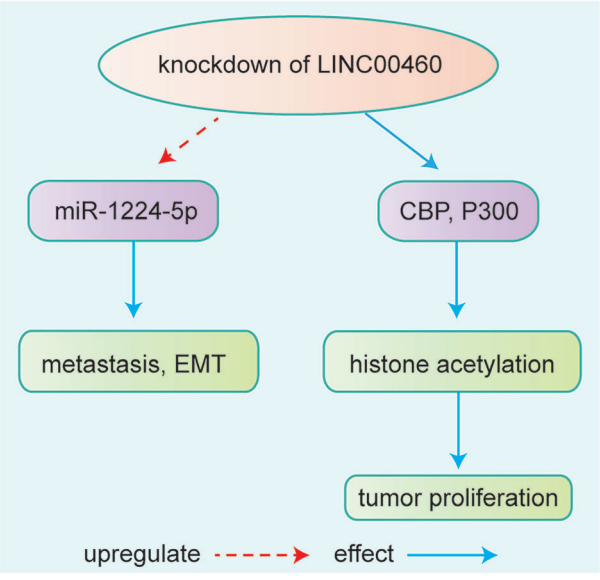

FIGURE 3 Knockdown of LINC00460 suppressed the metastasis and EMT of esophageal cancer cells by directly binding to miR-1224-5p.[33] Knockdown of LINC00460 affected tumor progression and development through CBP/P300 function via influencing histone acetylation[32]

In recent years, research on the molecular mechanism of lung cancer has become a novel method with which to improve diagnosis and prognosis. Li et al.[70] discovered the expression of LINC00460 was remarkably upregulated in NSCLC tissues and was closely related to the TNM stage, lymph node metastasis, and poor prognosis for NSCLC patients. Therefore, it suggested that LINC00460 acts as a valuable target for prognosis and therapy for NSCLC patients.

LINC00460 has emerged as an important regulator of the physiological and pathological processes of NSCLC tumors. Wang et al.[34] indicated that LINC00460 is competitively bound with miR-539 sites to restrain the suppressive effect on NSCLC cell proliferation. In addition, Ma et al.[35] found that LINC00460 is involved in gefitinib resistance in NSCLC cells by targeting epidermal growth factor receptor (EGFR) through sponging miR-769-5p. Zhao et al.[36] discovered that nicotine promoted the development of NSCLC by activating LINC00460 and PI3K/AKT signaling pathway. Specifically, Nicotine affected cell apoptosis mediated by LINC00460 with alterations in Bcl-2, Bax, and cleaved caspase-3; moreover, LINC00460 knockdown inhibited the PI3K/AKT signaling pathway, and the effect was also removed by nicotine.[36]

NSCLC has a major subtype of LC, and the prognosis of LC also remains poor. The upregulated expression of LINC00460 in LC tissues predicted poor prognosis, and silencing of LINC00460 inhibited cell growth in LC.[71] Ye et al.[22] found that LINC00460 promoted LC cell growth partially by upregulating FOXA1, the special target site for LINC00460 and miR-302c-5p, and the effects were partially regulated by the LINC00460/miR-302c-5p/FOXA1 axis. LINC00460 also promoted EGFR-TKI resistance in EGFR-mutated LC by facilitating the release of inflammatory cytokine interleukin 6 (IL-6) via function as a decoy for miR-149-5p and inducing the EMT process[37] (Figure 4).

Therefore, LINC00460 acts as a ceRNA sponging miRNAs and inhibited PI3K/AKT signaling pathway to regulate NSCLC progression. LINC00460 might serve as a prognostic indicator and as an effective therapeutic target in the future.

Papillary thyroid cancer

Thyroid tumors are classified as follicle-derived (thyroid epithelial) neoplasms, other epithelial tumors, non-epithelial tumors, and secondary tumors.[72] The most common subtype of thyroid cancer is PTC.[73] Despite advances in therapeutic methods, the overall survival of patients with local or distant metastasis is still poor.[74] Further detection should be launched by finding a new sensitive target for PTC and improving the prognosis.

It was found that LINC00460 was upregulated in PTC tissues and was associated with poor prognosis,[38] advanced TNM stage, and lymph node metastasis.[39] Li et al.[38] indicated that LINC00460 promoted cell migration, invasion, and EMT of PTC by sponging miR-485-5p to increase the expression of Raf1. Zou et al.[23] also found that LINC00460 knockdown restrained PTC progression by downregulating MMP-9 expression by sponging miR-539. In addition, Feng et al.[39] discovered that LINC00460 regulated sphingosine kinase 2 (SphK2) by sponging miR-613 to partially promote the proliferation, migration, and invasion of PTC cells. Therefore, LINC00460 might be a novel diagnostic and therapeutic target for PTC patients. LINC00460 affected PTC progression mainly by directly binding with miRNAs. Further studies are needed to elucidate the specific mechanisms of LINC000460 in the development of PTC (Figure 5).

Breast cancer

Breast cancer is the second leading cause of cancer death among women after lung cancer.[75] Treatment for breast cancer is based on TNM stage, distant metastasis, patient age and status, and so on.[76] The 5-year overall survival was connected with early diagnosis; therefore, more valid methods to detect the disease at the early stage and provide potential therapies are needed.

LINC00460 was identified as one of the meaningful lncRNAs from the TCGA database.[12] LINC00460 was overexpressed in breast cancer, and its expression was correlated with distant lymph node metastasis and poor prognosis.[40] Moreover, LINC00460 promoted cell proliferation, migration, and invasion by the miR-489-5p/FGF7/AKT axis in breast cancer.[40] A clear understanding of LINC00460 involved in breast cancer is still confusing needed to be

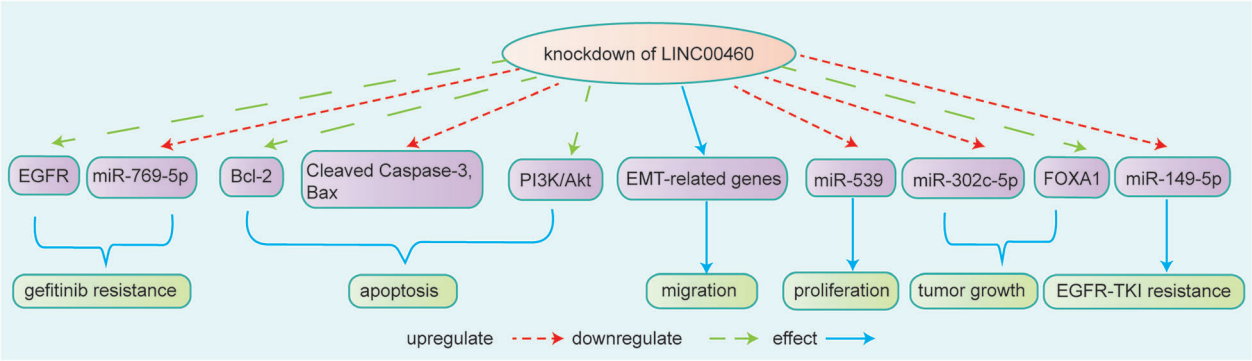

FIGURE 4 Knockdown of LINC00460 decreased EGFR protein expression by increasing the expression of miR-769-5p in NSCLC, which influenced gefitinib resistance.[35] LINC00460 is involved in cell apoptosis by regulating the apoptosis proteins Bcl-2, Bax, cleaved caspase-2, and PI3K/AKT.[36] LINC00460 promoted cell migration and invasion through EMT-related genes. LINC00460 affected cell proliferation via sponging miR-539.[34] Knockdown of LINC00460 influenced lung adenocarcinoma growth by binding to miR-302c-5p and upregulating the expression of FOXA1.[22] LINC00460 also promoted EGFR-TKI resistance in EGFR-mutated lung adenocarcinoma by binding to miR-149-5p[37]

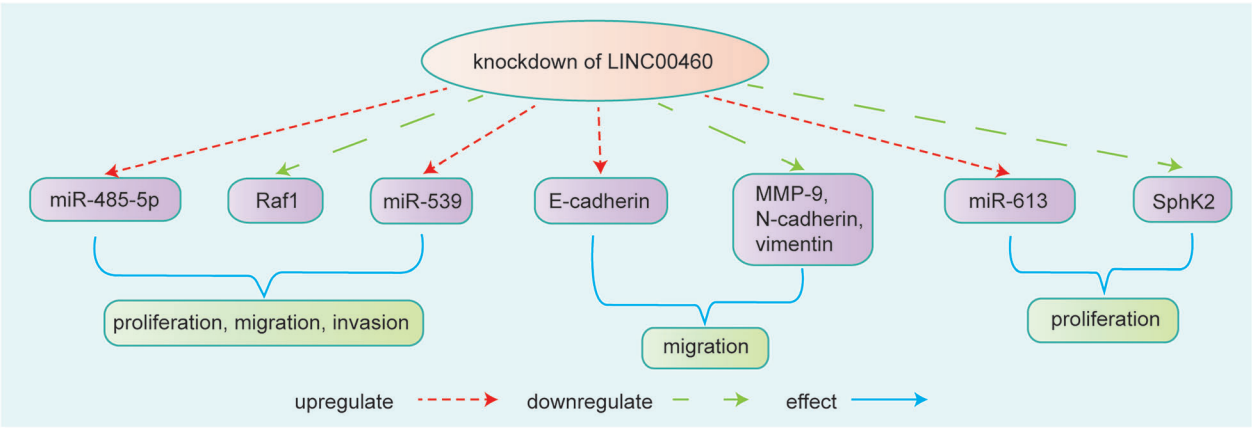

FIGURE 5 Knockdown of LINC00460 inhibited the proliferation, migration, and invasion of PTC cells by downregulating Raf1 and upregulating miR-485-5p.[38] Knockdown of LINC00460 inhibited the migration and invasion of PTC cells by increasing the protein level of E-cadherin and decreasing the levels of MMP-9, N-cadherin, and vimentin. LINC00460 enhanced MMP-9 protein expression by targeting miR-539 to facilitate the proliferation and metastasis of PTC.[23] Knockdown of LINC00460 decreased the expression of SphK2 by upregulating miR-613 to partially affect PTC proliferation[39]

further studied, which will accelerate the application of LINC00460 in diagnosis and prognosis (Figure 6).

Gastric cancer

GC is the second leading cause of cancer-related mortality and is correlated with Helicobacter pylori infection, lifestyle factors, and genetics.[77] Despite the advances in current treatment, unfortunately, most patients are diagnosed at an advanced and unresectable stage.[78] Therefore, new investigations and methods must be considered.[79] There are no valid approaches that could be applied to treat advanced GC, so new predictive and prognostic biomarkers are needed to explore for GC patients.[80]

Yang et al.[20] found that LINC00460 expression was obviously elevated in GC tissues and that high LINC00460 expression had a poor prognosis in GC patients. The results showed that LINC00460 influenced GC cell proliferation and apoptosis by downregulating CCNG2 via recruiting EZH2 and LSD1.[20] Wang et al.[41] found that LINC00460 upregulated the expression of the cell cycle/cell motility-associated proteins CCND1, CDK4, vimentin, MMP-2, and MMP-9 by competitively binding to miR-342-3p; moreover, LINC00460 upregulated KDM2A expression by sponging miR-342-3p to partially affect cell proliferation and metastasis in GC.[41] Furthermore, Zhang et al.[42] showed that LINC00460 knockdown reduced c-Myc and β-catenin expression to inhibit the Wnt/β-catenin signaling pathway, which was reported to affect cell proliferation and invasion in several tumors, including GC.[42] Therefore, LINC00460 affected GC progression not only by directly binding with miRNAs or RBPs, but also through the Wnt/β-catenin signaling pathway. These studies have shown that LINC00460 might be a potential prognostic indicator for GC patients (Figure 7).

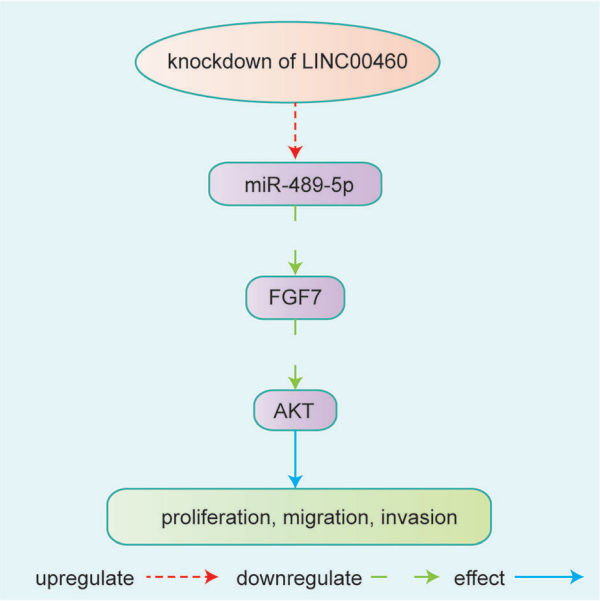

FIGURE 6 Knockdown of LINC00460 affected breast cancer by inhibiting the expression of miR-489-5p, miR-489-5p inhibited FGF7-AKT signaling. LINC00460 affected cell proliferation, migration and invasion through the miR-489-5p/FGF7/AKT axis[40]

Hepatocellular carcinoma

HCC is the most common primary hepatic malignancy in the world, with an increasing worldwide prevalence.[81] Diagnosis of HCC at the earliest possible stage is crucial. Unfortunately, most HCC patients often miss the early diagnosis, leading to poor prognosis and low overall survival.[82] To improve the diagnostic and therapeutic effects, further valid measures should be investigated.

Previous studies indicated that LINC00460 was upregulated in HCC tissues and related to the progression of HCC.[43,44]

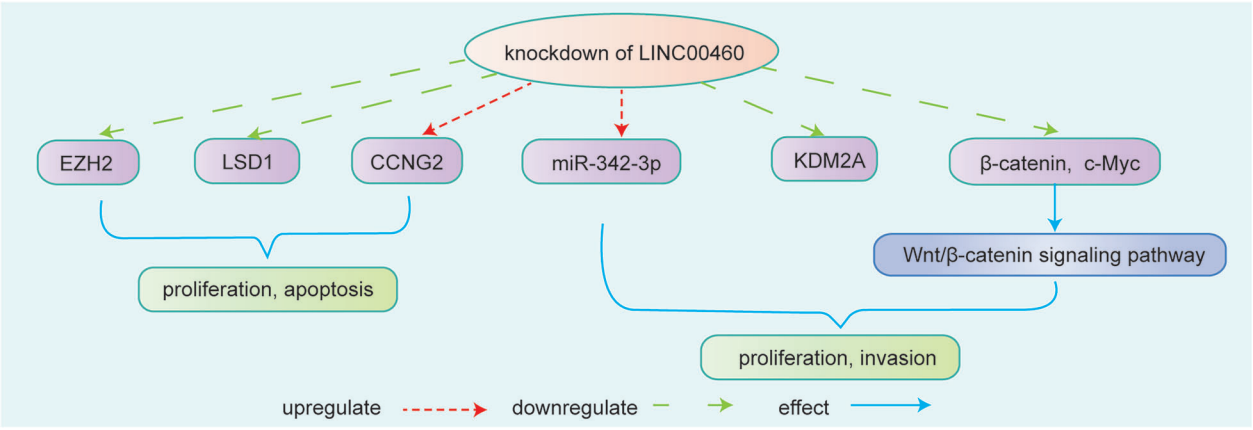

FIGURE 7 LINC00460 knockdown affected GC cell growth by inhibiting the binding between EZH2 and LSD1, and the inhibitory effect on CCNG2 expression of LINC00460 could be achieved by recruiting EZH2 and LSD1.[20] LINC00460 regulated cell proliferation and invasion by upregulating KDM2A through sponging of miR-342-3p.[41] LINC00460 knockdown efficiently inhibited cell proliferation and the Wnt/β-catenin signaling pathway by reducing c-Myc and β-catenin expression[42]

Specifically, knockdown of LINC00460 could suppress the expression of cell cycle-related proteins cyclin D1/CDK4 and the cell migration-related proteins MMP-3/MMP-9.[43] Moreover, knockdown of LINC00460 inhibited anterior gradient homolog 2 (AGR2) expression by targeting miR-342-3p to affect cell proliferation, migration, and apoptosis of HCC.[43,44] Furthermore, Tu et al.[24] predicted that the LINC00460/miR-485-5p/PAK1 axis is involved in HCC development. The results showed that LINC00460 may be a potential diagnostic marker and valuable therapeutic target for HCC patients (Figure 8).

Colorectal cancer

CRC is the second-most in women and third-most common cancer in men,[83] and CRC ranks second in terms of mortality.[84] The risk of CRC is closely related to genetic and environmental factors. Substantial changes in lifestyle, smoking behavior, alcohol intake, and weight management can improve the risk of CRC.[83] Despite advances in therapeutic methods, patients with CRC present with metastatic disease up to 50% at the time of diagnosis.[85] Lech et al.[86] examined molecular biomarkers correlated with CRC screening, early detection of disease recurrence, and prognostic and predictive factors. Therefore, it is necessary to find valuable biomarkers to better predict diagnosis and improve prognosis.

LINC00460 regulated the cellular processes of CRC by promoting cell proliferation, migration, invasion, and affecting apoptosis or the cell cycle.[21] Lian et al.[45] found that LINC00460 was remarkably upregulated in CRC tissues and was related to larger tumor sizes, advanced tumor node metastasis stages, lymph node metastasis and shorter overall survival in CRC patients. Importantly, LINC00460 promoted CRC cell proliferation by binding to the enhancer of zeste homolog 2 (EZH2) and repressing Krüppellike factor 2 (KLF2); LINC00460 also promoted the expression level of cullin 4A (CUL4A) by competing for miR-149-5p to enhance cell proliferation.[45]

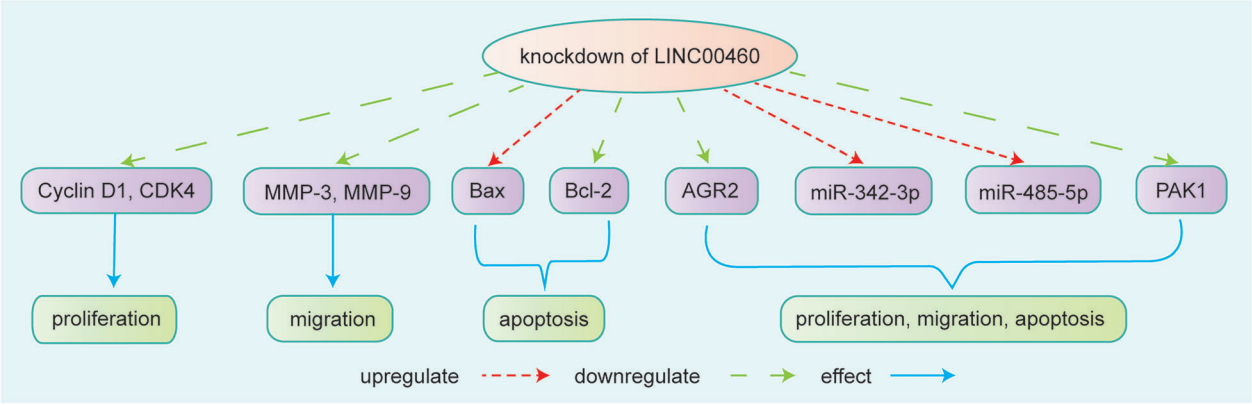

FIGURE 8 Knockdown of LINC00460 suppressed the expression of the cell proliferation-related proteins cyclin D1 and CDK4 in HCC, inducing obvious cell cycle arrest. The expression of the cell migration-related proteins MMP-3 and MMP-9 was also greatly suppressed after LINC00460 knockdown.[43] Knockdown of LINC00460 affected cell apoptosis by elevating the expression of Bax and reducing the expression of Bcl-2. Knockdown of LINC00460 suppressed AGR2 expression by targeting miR-342-3p to affect cell proliferation, migration, and apoptosis of HCC.[44] LINC00460 knockdown inhibited PAK1 levels by sponging miR-485-5p to affect cell proliferation, migration, and apoptosis[24]

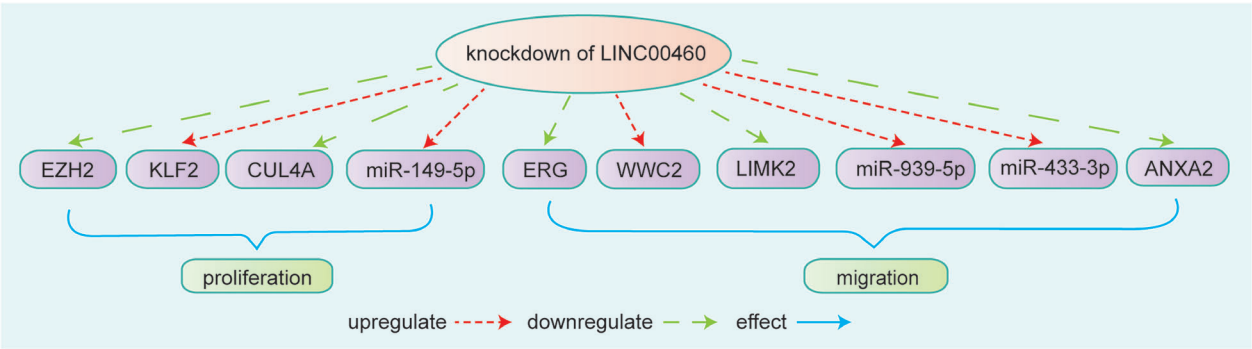

FIGURE 9 Knockdown of LINC00460 suppressed CRC cell proliferation by upregulating KLF2 via binding to EZH2. Knockdown of LINC00460 inhibited cell proliferation by decreasing the expression of CUL4A and increasing the expression of miR-149-5p.[45] Knockdown of LINC00460 suppressed CRC cell metastasis by upregulating WWC2 via ERG.[47] Knockdown of LINC00460 inhibited CRC cell metastasis by decreasing the expression of LIMK2 and miR-939-5p sponging.[46] Knockdown of LINC00460 inhibited cell migration by targeting miR-433-3p and downregulating the expression of ANXA2 in colon cancer[27]

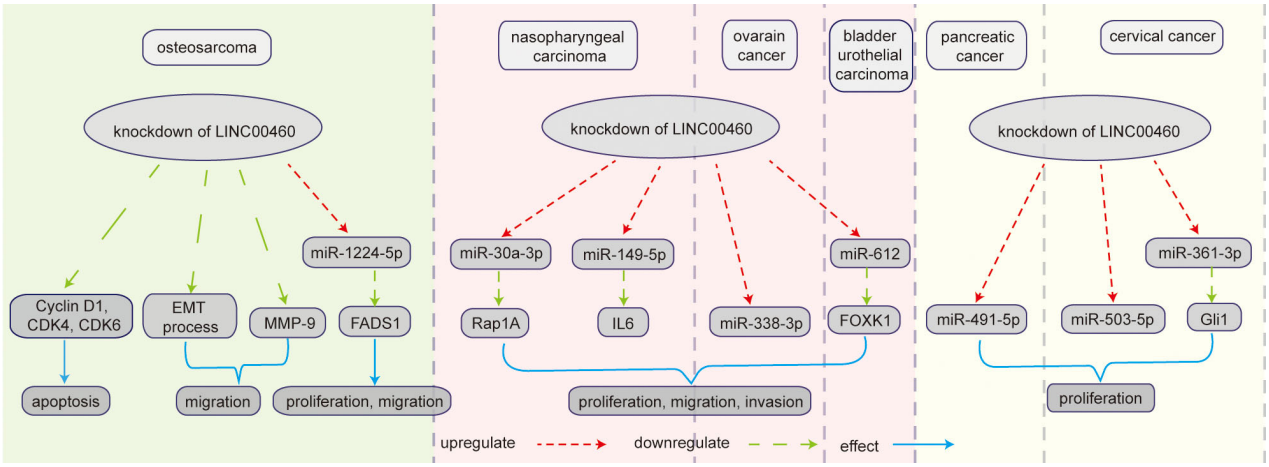

FIGURE 10 Knockdown of LINC00460 affected OS progression by inducing the cell apoptosis via the decreasing the expression of cyclin D1, CDK4, and CDK6. Knockdown of LINC00460 inhibited cell migration through decreasing the MMP-9 activity and suppressing the EMT process.[48] Knockdown of LINC00460 decreased the expression of FADS1 and increased miR-1224-5p regulating the cell proliferation and migration in OS.[49] Knockdown of LINC00460 suppressed NPC cell proliferation, migration, and invasion by targeting miR-30a-3p/Rap1A and miR-149-5p/IL6[50,51]; LINC00460 promoted OC progression by binding miR-338-3p[52]; LINC00460 prompted bladder urothelial carcinoma progression via sponging of miR-612 by elevating FOXK1 expression[53]; LINC00460 accelerated pancreatic cancer by binding to the suppressor miR-491-5p[54]; knockdown of LINC00460 suppressed proliferation cervical cancer cells by targeting miR-503-5p and miR-361-3p/Gli1 axis[55,56]

LINC00460 could also act as a ceRNA and sponge miRNAs in CRC progression. Zhang et al.[46] found that LINC00460 promoted CRC cell metastasis by regulating the miR-939-5p/LIMK2 axis. Additionally, knockdown of LINC00460 partially suppressed cell proliferation, migration, invasion, and EMT of CRC by upregulating WWC2 via ERG.[47] Zhang et al.[87] also found that hypomethylated oncogenic LINC00460 could promote CRC metastasis. LINC00460 is also involved in ionizing radiation-induced radioresistance by mediating EMT processes.[88] In addition, LINC00460 is highly expressed in colon cancer (CC) tissues by targeting miR-433-3p and upregulating the expression of ANXA2 to promote cell carcinogenicity[27] (Figure 9).

Therefore, LINC00460 could directly bind with miRNAs or RBPs to promote the development of CRC. The studies suggested that LINC00460 could promote CRC progression and might be a diagnostic and prognostic marker for CRC patients. Moreover, LINC00460 might be a potential therapeutic value for CRC radiotherapy.

Other cancers

The expression of LINC00460 was also upregulated in osteosarcoma (OS), nasopharyngeal carcinoma (NPC), ovarian cancer (OC), bladder urothelial carcinoma, pancreatic cancer (PC), and cervical cancer, which might be a valuable prognostic and curative biomarker and potential therapeutic target.

LINC00460 affected cell viability, cell cycle, apoptosis, migration, invasion, and EMT process by regulating the expression of cyclin D1, CDK4/CDK6 and MMP-9 in OS.[48] Lian et al.[49] found that LINC00460 facilitated OS cell proliferation, migration, and invasion by regulating FADS1 as a molecular sponge for miR-1224-5p in OS. The high expression of LINC00460 was predicted to be associated with poor prognosis in NPC patients, and LINC00460 overexpression facilitated cancer cell migration, invasion, and EMT by targeting miR-30a-3p/Rap1A[50] or miR-149-5p/IL6 axis.[51] For the OC study, the upregulated expression of LINC00460 was in OC tissues and were associated with tumor stage and tumor size, moreover, LINC00460 promoted OC progression by binding miR-338-3p.[52] For bladder urothelial carcinoma, Li et al.[53] indicated that the high expression of LINC00460 was associated with poor survival, promoted cell proliferation and migration, and LINC00460 prompted tumor progression via miR-612/FOXK1 axis. Moreover, LINC00460 accelerated PC by binding to miR-491-5p.[54] For cervical cancer, LINC00460 affected tumor progression by targeting miR-503-5p,[55] or by mediating the miR-361-3p/Gli1 axis.[56] Therefore, LINC00460 acts as a ceRNA in the pathogenesis and tumorigenesis of cancers base on the above research. This provides the possibility for LINC00460 in the diagnostic and prognostic application (Figure 10).

Summary

More and more evidence suggested that LINC00460 acts as an oncogene in diverse tumors and plays a crucial regulatory role in tumorigenesis. LINC00460 was found to be highly expressed in various tumors tissues and cell lines; moreover, LINC00460 was reported to play vital roles in cellular functions such as proliferation, cell cycle, migration, invasion, autophagy, apoptosis, and others. The regulatory mechanism of LINC00460 was complex and involve many steps, including directly binding with proteins; binding to miRNA to act as a miRNA sponge; or activating signaling pathways,

such as PIK3/AKT, Wnt/β-catenin, etc. The most common mechanism of action of LINC00460 in various tumors is the specific absorption of miRNA as ceRNA. lncRNA-miRNA-mRNA regulatory network and key genes are the important steps of tumorigenesis and development, which provides ideas for the exploration of the regulatory mechanisms of LIN00460 in human cancers.

LINC00460 expression was often related to important clinical features such as tumor size, recurrence, TNM stage, lymph node metastasis, or poor prognosis in various cancers, so it might become a potential diagnostic and prognostic biomarker. Furthermore, the research results on LINC00460 provide a preliminary basis for whether it might be a potential target for cancer therapy in the future.

With the development of genomic studies, the role of LINC00460 gradually faded from mystery. However, the exploration of LINC00460 is still in the early stage and further molecular mechanism of LINC00460 should be elucidated.

CONCLUSIONS

With further exploration of the molecular mechanism of lncRNAs, additional knowledge of how lncRNAs affect tumor growth has been reported. LINC00460 is highly expressed in human cancers, and may be a potential biomarker for cancer diagnosis, prognosis, or therapy. As an oncogene, LINC00460 can promote tumor progression and play the role in cell proliferation, migration, invasion, EMT, apoptosis, cell cycle, autophagy, chemoresistance, or radioresistance in various tumors. The mechanisms of the LINC00460 effect are complex. Clarifying the mechanism of LINC00460 is helpful to further study the relationship between lncRNAs and tumor, and is of great value to clarify the pathogenesis of tumors.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts interests.

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