Long stress-induced non-coding transcript 5: A promising therapeutic target for cancer treatment

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Abstract

Long non-coding RNAs are RNA molecules with a transcript length of more than 200 nucleotides and without protein-coding ability. They regulate gene expression by interacting with protein, RNA and DNA. Their function is closely related to their subcellular localization, with regulation of gene expression at the epigenetic and transcriptional levels occurring in the nucleus, and at the post-transcriptional and translational levels in the cytoplasm. Long stress-induced non-coding transcript 5 (LSINCT5), which is localized in the nucleus, is overexpressed in many types of cancers such as breast cancer, gastric cancer, ovarian cancer, thyroid cancer, and gastrointestinal cancer. Substantial evidence indicates that there is an obvious connection between cancers and LSINCT5, as it inhibits apoptosis and promotes proliferation, invasion and migration of cancer cells, as well as participates in the pathogenesis and progression of cancer by interacting with DNA, protein and RNA. These findings suggest that LSINCT5 could be a novel biomarker and an emerging therapeutic target in human cancers. In the present study, the structure and corresponding biological function of LSINCT5 were summarized in order to clarify its molecular mechanisms in the progression of various malignant tumors.

Key words: LSINCT5, cancers, lncRNA, molecular mechanisms, tumorigenesis

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Introduction

Cancer is caused by dysregulated gene expression that leads to serious illness and death in humans. Less than 2% of all gene sequences in the genome are coding, with mutations in the coding regions leading to the occurrence of most tumors. However, mutations in the non-coding regions of the genome lead to different phenotypes of tumor.[1] Ribonucleic acids (RNAs) are classified as coding RNAs, messenger RNAs (mRNAs) that will be transcribed into protein, and non-coding RNAs (ncRNAs) that are not translated into protein, such as circular RNAs (circRNAs), long non-coding RNAs (lncRNAs) and microRNAs (miRNAs).[2] Recent studies have demonstrated that ncRNAs, identified using high-throughput sequencing technology, are dysregulated in various types of cancer.

Long non-coding RNAs are RNA molecules with a transcript length between 200 nucleotides (nt) and 100 kilobase (kb) pairs that influence the expression of oncogenes and tumor suppressor genes, with many lncRNAs uniquely expressed in differentiated tissues and specific cancer types.[3] Long non-coding RNA is transcribed by RNA polymerase II, capped, polyadenylated, and spliced. It lacks protein-coding sequences and can exert significant regulatory function.[4] The function of lncRNAs depends on their unique subcellular localization. They can form a functional network comprising DNA, protein and RNA, at the epigenetic and transcriptional levels. They also regulate complex cellular processes such as apoptosis, epigenetic changes, genomic imprinting, alternative splicing, gene expression, chromatin modification, and inflammatory pathologies, at the post-transcriptional level.[5,6] Potential roles of lncRNAs have been demonstrated in both oncogenic and tumor-suppressive pathways, with their dysregulation implicated in various pathophysiological processes, especially tumorigenesis.[7] Indeed, the correlation between lncRNA expression and cancer pathogenesis is one of the most promising areas of research for understanding the underlying pathophysiology of human cancers.[6–9]

Long stress-induced non-coding transcript 5 (LSINCT5) is a 2.6-kb polyadenylated transcript which is potentially transcribed by RNA polymerase III, and is located on 5p15.33.[10] The expression of LSINCT5 is found to be increased in multiple cancers, including breast cancer (BRCA), gastric cancer (GC), ovarian cancer (OC), and bladder cancer (BC).[11–14] Long stress-induced non-coding transcript 5 may be an important regulatory RNA in human cancer cell proliferation, cell cycle, survival, migration, and invasion.[15] Furthermore, a dysregulated expression of LSINCT5 has been linked to cancer progression and unfavorable prognosis in various human tumors.[16] The LSINCT5, which is one of 12 stress-induced lncRNAs (LSINCT1-12), is expressed during stress-induced cell formation and has been reported to promote cancer progression by regulating cell proliferation, metastasis and apoptosis.[17,18] Mechanisms of LSINCT5 include the regulation of mRNA metabolism, interaction with proteins, acting as competitive endogenous RNA (ceRNA), and interacting with miRNA. Many of the cancer types promoting cellular processes with LSINCT5 involvement are listed in Table 1. In this article, various functions of LSINCT5 in different types of cancer have been reviewed and the potential of LSINCT5 as a biomarker and therapeutic target in the treatment of cancer has been discussed.

Objectives

All of the literature related to LSINCT5 was reviewed in order to summarize various functions of LSINCT5 in different types of cancer, with the aim of exploring its potential as a biomarker and potential therapeutic target in the treatment of cancer.

Materials and methods

Relevant literature was retrieved by searching several databases, including GreenMedical, Spis, China National Knowledge Infrastructure, and PubMed, to identify studies published between January 2000 and July 2021. GreenMedical, Spischolar and PubMed databases were searched using 3 separate sets of keywords, namely "LSINCT5 and cancer", "LSINCT5 and tumor" and "LncRNA and cancers". Keywords used to search the China National Knowledge Infrastructure were "LSINCT5 and tumor". Data were extracted from the articles and entered into Microsoft Word (Microsoft Office 2003; Microsoft Corp., Redmond, USA) for analysis. All figures and tables were prepared manually, according to the protocol of the analysis of the studies.

All studies related to LSINCT5 that were conducted in human subjects, including randomized controlled trials, systematic reviews and meta-analyses, were considered. Additionally, only studies published in the English or Chinese were considered. This resulted in 55 articles being included in the systematic literature review.

LSINCT5 in various tumors

LSINCT5 in gastrointestinal cancer

Xu et al. found that LSINCT5 expression was higher in cancerous tissue than in adjacent healthy tissues in GC and colorectal cancer (CRC).[12] The overexpression of LSINCT5 was also associated with clinical progression and development of these gastrointestinal cancers.[12] Indeed, the expression levels of LSINCT5 in GC and CRC were correlated with patient prognosis, whereby higher expression resulted in significantly worse prognoses than for patients with lower expression levels. Furthermore,

Table 1. Functional characterization of long stress-induced non-coding transcript 5 (LSINCT5) in various cancers

Cancer type	Dysregulation	Functional	Related genes	Role	Reference
Gastrointestinal cancer	upregulated	proliferation, migration, invasion, EMT, tumorigenesis	*E2F1*, *CXCR4*, *IRX2*, *IRX4*	oncogene	12, 19
Liver cancer	upregulated	proliferation, migration, invasion, viability, EMT, tumorigenesis	*HMGA2*, *miR-4516*, *STAT3*, *BclxL*	oncogene	21
Pancreatic cancer	upregulated	proliferation, migration, invasion, cell cycle, tumorigenesis	*P21*, *CyclinB1*, *CyclinE*	oncogene	22
Breast cancer	upregulated	proliferation, migration, invasion, viability, EMT, tumorigenesis	*GAS5*, *B2M*, *miR-30a*	oncogene	11, 26, 27
Lung cancer	upregulated	proliferation, migration, viability, EMT, tumorigenesis	*PI3K*, *Akt*, *p-Akt*, *HMGA2*	oncogene	28–30
Thyroid cancer	upregulated	proliferation, migration, invasion, viability, tumorigenesis	*miR-29c*, *ITGB1*	oncogene	31, 32
Ovarian cancer	upregulated	proliferation, migration, invasion, viability, tumorigenesis	*CXCR4*, *CXCL12*, *SDF-1*, *PSPC1*	oncogene	11, 13
Osteosarcoma	upregulated	proliferation, migration, invasion, viability, apoptosis, tumorigenesis	*APC*, *EZH2*, *CCND1*, *MYC*, *SOX9*, *SOX4*, *TCF1*	oncogene	10, 16, 36
Glioma	upregulated	proliferation, migration, invasion, viability, apoptosis, tumorigenesis	*miR-451*, *Rac1*, *PI3K*, *AKT*, *p65*, *Wnt3a*, *Wnt5a*, *β-catenin*	oncogene	34
Bladder cancer	upregulated	proliferation, migration, invasion, viability, EMT, tumorigenesis	*NCYM*, *β-catenin*, *GSK3b*	oncogene	25, 42
Esophageal squamous cell carcinoma	upregulated	proliferation, migration, invasion, EMT, senescence, apoptosis, tumorigenesis	*ECM*, *MAPK*, *MMP9*, *N-cadherin*, *vimentin*	oncogene	23
Endometrial carcinoma	upregulated	proliferation, apoptosis, migration, invasion, cell cycle, tumorigenesis	*HMGA2*, *Wnt*, *β-catenin*	oncogene	28
Oral squamous cell carcinoma	upregulated	proliferation, apoptosis, migration, invasion, cell cycle, tumorigenesis	*miR-185-5p*, *ZNF703*, *YWHAZ*	oncogene	24

EMT – epithelial–mesenchymal transition.

it was demonstrated that LSINCT5 plays a significant role in GC as an oncogene, as its upregulation significantly promoted tumor cell growth, whereas downregulating had the opposite effect. Therefore, inhibiting the overexpression of LSINCT5 could be an effective way to slow down the progression of GC and CRC (Table 1).

Qi et al. found that LSINCT5 was upregulated in metastatic GC tissues and promoted GC cell migration and invasion.[19] The LSINCT5 had an impact on epithelial–mesenchymal transition (EMT) in GC cells, a process that has been shown to be critically important in the early events of GC tumor cell metastatic dissemination by inducing cell motility. Furthermore, EMT promotes GC cells to acquire invasion potential, and LSINCT5 can change the malignant phenotype by regulating EMT.[19] Therefore, GC cell migration and invasion could be decreased when EMT is inhibited through decreasing the expression of LSINCT5. Transcription factor E2F1 activates LSINCT5 transcription and increases its expression, with E2F1 and LSINCT5 both found to be overexpressed in GC. Consequently, downregulating E2F1 may be a useful strategy to downregulate the expression of LSINCT5. In conclusion, LSINCT5 could be a novel prognostic indicator and a target for gene therapy in GC (Table 1).

LSINCT5 in hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the most common type of malignant tumor and largely leads to a high occurrence of cancer, with lncRNAs emerging as critical factors for HCC-related gene expression.[20] Li et al. studied the expression pattern and biological function of LSINCT5 in HCC and found it to be upregulated and to predict poor survival through promotion of HCC migration and viability in vivo.[21] They concluded that LSINCT5 might function as a ceRNA of miR-4516.[21] The LSINCT5 stabilizes high mobility group AT-hook protein 2 (HMGA2), which is a master activator of EMT, in order to prevent its degradation.[21] Furthermore, LSINCT5 promotes HCC cells to acquire invasion potential by promoting the progression of EMT. Therefore, the degradation of HMGA2 may stop EMT progression, which could serve as a potential novel therapeutic target for HCC treatment (Table 1).

LSINCT5 in pancreatic cancer

The incidence rate of pancreatic cancer (PC) is increasing year by year globally. Pancreatic cancer leads to the development of a highly malignant tumor with a very poor prognosis. Mei et al. found that the overexpression

Table 2. Clinical significance of long stress-induced non-coding transcript 5 (LSINCT5) in various tumors

Cancer type	Associated clinical features	Prognosis	Reference
Gastrointestinal cancer	OS, DFS, DSS, tumor volume, metastasis, TNM stage	poor	12, 19
Liver cancer	OS, DFS, tumor volume, metastasis, TNM stage	poor	21
Pancreatic cancer	OS, DFS, DSS, tumor volume, metastasis	poor	22
Breast cancer	OS, DFS, tumor volume, lymph node metastasis	poor	11, 26, 27
Lung cancer	OS, tumor size, TNM stage, metastasis	poor	28–30
Thyroid cancer	OS, DFS, tumor volume, metastasis	poor	31, 32
Ovarian cancer	OS, tumor size, TNM stage, lymphatic metastasis	poor	11, 13
Osteosarcoma	OS, DFS, tumor volume, tumor size, lymphatic metastasis, TNM stage	poor	10, 16, 35
Glioma	OS, DFS, tumor volume, tumor size, lymphatic metastasis, TNM stage	poor	34
Bladder cancer	OS, DFS, tumor volume, tumor size, lymphatic metastasis, TNM stage	poor	25, 42
Esophageal squamous cell carcinoma	OS, tumor size, TNM stage, lymph node metastasis, tumor size	poor	23
Endometrial carcinoma	OS, DFS, tumor volume, tumor size, lymphatic metastasis, TNM stage	poor	28
Oral squamous cell carcinoma	OS, DFS, DSS, RFS, tumor volume, tumor size, lymphatic metastasis, TNM stage	poor	24

DFS – disease-free survival; DSS – disease-specific survival; RFS – recurrence-free survival; OS – overall survival; TNM – tumor-node-metastasis.

of LSINCT5 was widespread in PC cells and could promote their proliferation and cell cycle progression, inducing adenocarcinoma cell cycle transformation from G1 to S phase.[22] Furthermore, LSINCT5 could regulate the expression level of key cell cycle factors such as mRNA and protein in PC cells. It was concluded that LSINCT5 serves as an oncogene in the progression of pancreatic adenocarcinoma, and its overexpression indicates a poor prognosis for PC patients. Therefore, decreasing the expression of LSINCT5 could have a therapeutic effect in the treatment of PC (Table 1).

LSINCT5 in esophageal squamous cell carcinoma

Esophageal cancer is one of the most common and deadliest cancers in China; its 2 main types are esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EA).[23] The LSINCT5 was shown to be significantly overexpressed in ESCC cell lines, with next-generation RNA-sequencing indicating that 138 genes were upregulated and 227 were downregulated in LSINCT5-knockdown ESCC cells in vitro.[23] This demonstrated the great impact of LSINCT5 on gene expression as proliferation, migration, invasion, and EMT were suppressed in these cells.[23] Also, LSINCT5 was upregulated in ESCC tissues, which correlated with tumor size, tumor-node-metastasis (TNM) stage and lymph node metastasis.[23] Consequently, LSINCT5 could cause disorders in gene expression which further contribute to the progression of ESCC. This provides additional insight into esophageal cancer carcinogenesis and strong evidence to suggest that LSINCT5 may be a viable chemotherapeutic target for prevention of gene expression disorders in the treatment of esophageal cancer (Table 1).

LSINCT5 in oral squamous cell carcinoma

Oral squamous cell carcinoma (OSCC) is a type of cancer in which 5-year survival is lower than 50%, and which has a close relationship with smoking and drinking. Wang et al. analyzed the role of LSINCT5 in OSCC progression, as well as the molecular mechanisms it adopts.[24] They found that LSINCT5 was overexpressed in OSCC specimens and influenced malignant progression through the miR-185-5p/zinc finger protein 703 (ZNF703) axis. In this regard, the proliferative and migratory capacities of OSCC were inhibited when LSINCT5 was knocked down. Dual-luciferase reporter assay further verified that miR-185-5p was the target of LSINCT5, as miR-185-5p displayed anti-cancer properties on malignant phenotypes of OSCC through the downregulation by LSINCT.[24] Furthermore, the mechanism of the action of miR-185-5p in OSCC cells was shown through the downregulation of the oncogenic gene *ZNF703*.[24] Additionally, survival analysis showed that OSCC patients expressing low levels of LSINCT5 had much longer overall survival in comparison to those expressing high levels of LSINCT5. As such, LSINCT5 was suggested as a prognostic factor for OSCC. In summary, miR-185-5p and *ZNF703* could be targeted to influence the expression of LSINCT5 in OSCC cells. Upregulating the expression of miR-185-5p could downregulate the expression of LSINCT5, which could be a therapeutic strategy for OSCC patients (Table 1).

LSINCT5 in bladder cancer

Bladder cancer is one of the most common malignant tumors of the urinary system. Zhu et al. found that LSINCT5 was specifically upregulated in BC and its overexpression was significantly associated with tumor size, TNM stage and metastasis.[25] Moreover, a significant upregulation

of LSINCT5 was found to be a characteristic change in BC and indicated poor prognosis.[25] Competitive RNA pull-down confirmed the interaction of LSINCT5 with *NCYM*, which is a de novo evolved gene product that acts as an oncogenic factor in cancer.[25] As such, the LSINCT5/*NCYM* axis could promote the progression of BC through the activation of the wingless-related integration site (Wnt)/β-catenin signaling pathway and by promoting EMT.[25] In summary, LSINCT5 was found to contribute to the oncogenic potential of BC, and LSINCT5/*NCYM*/Wnt/β-catenin may be a potential chemotherapeutic target for BC treatment (Table 1).

LSINCT5 in breast cancer

Breast cancer is one of the most common malignancies that leads to the death of women globally. Long non-coding RNAs play crucial roles in the key biological processes of both normal and malignant breast cells, with early studies implicating LSINCT5 in BRCA cell proliferation and migration.[11,26] Silva et al.[11], Zhang et al.[26] and Liang et al.[27] found that LSINCT5 was overexpressed in BRCA and positively correlated with its progression. Indeed, the level of LSINCT5 in metastatic tissues was higher than in nonmetastatic tissues, and these higher levels were indicative of a poor prognosis. Therefore, LSINCT5 could be a biomarker for the progression of BRCA. The LSINCT5 is a molecular sponge for miR-30a in BRCA cells, as a knockdown of LSINCT5 suppressed cell motility by regulating miR-30a in MCF-7 cells.[26] Additionally, LSINCT5 knockdown inhibited BRCA cell proliferation, invasion, EMT, and motility, by inactivating the β-catenin/TCF4/c-Myc pathway in vivo (Table 1).[26] Therefore, the knockdown of LSINCT5 may be a promising way of inhibiting the progression of BRCA.

LSINCT5 in ovarian cancer

Ovarian cancer is one of the most serious malignant tumors among women worldwide. Epithelial ovarian cancer (EOC) is characterized by frequent implantation and metastases in the abdominopelvic cavity.[13] The expression of LSINCT5 in OC tissues and cell lines was significantly increased and its expression in metastatic OC tissues was higher than in nonmetastatic tissues. Furthermore, LSINCT5 levels were positively correlated with the pathological grade of OC, and the increased expression of LSINCT5 was related to poor prognosis. At the same time, the downregulation of LSINCT5 significantly suppressed the C-X-C motif chemokine ligand-12 (CXCL12)/C-X-C chemokine receptor 4 (CXCR4) signaling axis and inhibited the proliferation, migration and invasion of OC cells.[11,13] High expression of LSINCT5 was associated with the presence of lymphatic metastases and the advanced International Federation of Gynecology and Obstetrics (FIGO) stage, but was not associated with patient age, histological subtype, histological grade, or residual tumor diameter.[11] As such, LSINCT5 could be used as a biomarker for the progression of OC (Table 1).

LSINCT5 in endometrial carcinoma

Endometrial carcinoma (EC) is one of the most common gynecologic malignancies in women, ranking 6th in morbidity and 3rd in mortality worldwide. Jiang et al. found that the amount of LSINCT5 in EC tissues was significantly higher than in healthy controls.[28] The LSINCT5 could promote cell proliferation, migration and invasion of EC cells, as silencing it caused cell cycle arrest and apoptosis.[28] Mechanistically, LSINCT5 may suppress the degradation of HMGA2 to stabilize the protein in EC cells, which could promote EMT by activating the Wnt/β-catenin signaling pathway. Therefore, EC cells acquire the potential for proliferation, migration and invasion, increasing the level of HMGA2 protein through LSINCT5. In turn, this would contribute to the progression of EC (Table 1).

LSINCT5 in lung cancer

Lung cancer is the main cause of cancer deaths globally, of which non-small cell lung cancer (NSCLC) has a dramatically low 5-year survival and accounts for nearly 85% of all lung cancers. Tian et al. found that LSINCT5 may be an important gene regulator in NSCLC as its overexpression predicted poor prognosis for NSCLC patients.[29] The overexpression of LSINCT5 has been shown to markedly increase the viability of NSCLC cells and tumor growth, potentially through its interaction with HMGA2.[29] The LSINCT5 physically interacts with HMGA2 to prevent its proteasome-mediated degradation.[29] Additionally, LSINCT5 promotes the expression and activity of protein kinase B (Akt) in PC9 cells, and can promote the resistance to epidermal growth factor receptor/tyrosine kinase inhibitors (EGFR/TKIs) in lung cancer cells.[28] This means that HMGA2 could promote EMT of lung cancer cells by increasing the activity of Akt proteins. Furthermore, Chen et al. found that the expression of LSINCT5 in NSCLC tissues was higher in erlotinib-resistant cells.[30] Therefore, LSINCT5 may be a target for inhibiting the expression and activity of Akt, and a target for promoting cell sensitivity to erlotinib. The LSINCT5 was also found to be closely related to tumorigenesis and chemoresistance in NSCLC (Table 1).

LSINCT5 in thyroid cancer

Papillary thyroid carcinoma (PTC) is a type of thyroid cancer and is the most common malignant endocrine tumor. Kuang et al. found that LSINCT5 was overexpressed in PTC and that LSINCT5 knockdown decreased cellular proliferation and migration of TPC-1 and KAT-5 cell lines.[31] Bioinformatic predictions, dual luciferase reporter gene and receptor interacting protein detection found that

miR-29c was a target for LSINCT5 binding.[31] Furthermore, the co-transfection with miR-29c inhibited the effect of LSINCT5 on proliferation and metastasis and inhibited the effect of upregulation of integrin subunit beta 1 (ITGB1) by LSINCT5.[31] LSINCT5 serves as an oncogene that promotes proliferation and metastasis of PTC via miR-29c/ITGB1 axis.[32] Therefore, LSINCT5 is closely associated with the progression of PTC (Table 1). Hence, targeting LSINCT5 may slow down the progression of PTC.

LSINCT5 in glioma

Gliomas are a type of aggressive brain tumor that cause brain cancer-related death.[33] Liu et al. showed that LSINCT5 promoted cell viability, migration and invasion, but inhibited the apoptosis of glioma GL15 cells.[34] The LSINCT5 exerted its influence as a molecular sponge for miR-451,[34] which it regulated to promote the growth and metastasis of the cells. Furthermore, the overexpression of miR-451 suppressed the growth and metastasis of glioma GL15 cells through regulation of Rac family small GTPase 1 (Rac1).[34] This LSINCT5/miR-451/Rac1 axis affected the phosphatidylinositol 3-kinase (PI3K)/Akt, Wnt/β-catenin and nuclear factor-jB pathways to promote the progression of glioma.[34] Therefore, breaking the LSINCT5/miR-451/Rac1 axis is a promising way to stop the progression of glioma. In summary, LSINCT5 contributes to the oncogenic potential of glioma, and the LSINCT5/miR-451/Rac1 axis may be a potential therapeutic target (Table 1).

LSINCT5 in osteosarcoma

Liao et al. found that LSINCT5 was identified as an upregulated lncRNA in osteosarcoma (OS), and its overexpression decreased the survival rate of OS patients.[35] Proliferation, invasion, migration ability, and the number of cell membrane penetrations of OS cells were decreased after LSINCT5 knockdown. In addition, LSINCT5 was found to inhibit the transcription of the tumor suppressor gene adenomatosis adenomatous polyposis coli (*APC*) by recruiting enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2).[10] Therefore, the invasion, metastasis and growth of OS cells could be promoted by the inhibition of *APC*. In conclusion, LSINCT5 promotes the invasion, metastasis and growth of OS cells through *APC*. Both of these pathways may prove to be promising targets in the treatment of OS (Table 1).

Mechanisms of LSINCT5 in cancer

Interaction between LSINCT5 and proteins

Many lncRNAs interact with proteins, such as the transcriptional and cell cycle regulator HMGA2, to exert their functions. The HMGA2 has attracted much attention due to its extensive carcinogenic effects, and LSINCT5 has been shown to interact with it to regulate gene expression. This interaction was found to increase the abundance of HMGA2 protein, but had no influence on HMGA2 mRNA levels in NSCLC and EC cells.[28,29] The overexpression of LSINCT5 prevented proteasome-mediated degradation of HMGA2 proteins by suppressing their ubiquitination in NSCLC cells. Furthermore, HMGA2 promoted EMT and increased the rate of cell proliferation, which, in turn, increased the metastatic and invasive potential of tumor cells. Therefore, cancer cell proliferation, metastasis, invasion, EMT, and tumor angiogenesis are promoted when LSINCT5 increases the level of HMGA2 proteins in NSCLC and EC cells.

Interaction between LSINCT5 and RNA

The LSINCT5 has been shown to interact with miRNA and mRNA to exert its influence on the progression of cancer (Fig. 1). Many miRNAs serve as tumor suppressor genes in cancer cells. For example, *miR-185-5p* is a tumor suppressor gene in OSCC, *miR-30a* is a tumor suppressor gene in BRCA cells, *miR-451* is a tumor suppressor gene in glioma cells, *miR-20a-5p* is a tumor suppressor gene in OS cells, *miR-4516* is a tumor suppressor gene in HCC cells, and *miR-29c* is a tumor suppressor gene in PTC. The LSINCT5 could be acting as the ceRNA of these miRNAs to inhibit their tumor-suppressing function. Therefore, cancer cell proliferation, metastasis, invasion, and tumor angiogenesis will be promoted when the tumor-suppressing function of these miRNAs is inhibited by LSINCT5 in OSCC, glioma, OS, HCC, PTC, and BRCA cells. Moreover, v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog (NYCM) could activate the Wnt/β-catenin signaling pathway in order to promote EMT in BC progression.[25] The LSINCT5 binds NYCM to activate the Wnt/β-catenin signaling pathway. The proliferation, metastasis and invasion of BC cells is then promoted by EMT. In addition, CXCR4 and CXCL12 are 2 forms of mRNA in OC cells and LSINCT5 is found to promote the progression of OC by increasing the expression of both mRNA forms.

Interaction between LSINCT5 and DNA

Decreased expression of LSINCT5 influences the expression of multiple genes (Fig. 1). Both iroquois homeobox 4 (*IRX4*) and *IRX2* were shown to be regulated by LSINCT5 and to promote gastrointestinal tumor progression. Moreover, nuclear paraspeckle assembly transcript 1 (*NEAT1*), paraspeckle component 1 (*PSPC1*), epiplakin 1 (*EPPK1*), actin-related protein 2 (*ACTR2*), and *CXCR4* showed a twofold change in LSINCT5 knockdown of BRCA cells. In addition, 138 genes were upregulated and 227 genes

were downregulated in LSINCT5 knockdown of ESCC cell lines in vitro.[23] This suggested that LSINCT5 exerted its influence on ESCC cell lines by interacting with 365 differentially expressed genes that enriched a dozen signaling pathways, further contributing to tumorigenesis and tumor progression in these cells. In conclusion, LSINCT5 has been demonstrated to interact with multiple genes in order to promote tumorigenesis and progression of different cancers.

Interaction between LSINCT5 and EMT

Regulating EMT by LSINCT5 is a common mechanism in different cancers, including GC, BRCA, BC, ESCC, and HCC. The transformation from epithelium to stromal cells during EMT is a central differentiation process that exerts a great impact on cancer initiation and progression, as well as metastasis and tumor angiogenesis. A key to the EMT process in cancer cells is the regulation of the expression of a number of factors by LSINCT5, including E-cadherin, N-cadherin, vimentin, matrix metalloproteinase 2 (MMP-2), and MMP-9. Moreover, HMGA2 is regulated by LSINCT5 and is known to facilitate EMT by inhibiting E-cadherin. As such, HMGA2 could be an important activator during EMT development in different cancers, with LSINCT5 being an important regulator. Therefore, targeting LSINCT5 to stop EMT could exert chemotherapeutic effect on different cancers.

Clinical significance of LSINCT5

LSINCT5 as a biomarker for cancer diagnosis

Early detection of cancer directly contributes to the effect of cancer treatment, and LSINCT5 plays an important role in this process. The overexpression of LSINCT5 was confirmed in EC and PTC, with levels much higher than in adjacent tissues at the early stages of disease. Indeed, higher levels of LSINCT5 in endometrial tissue and thyroid tissue highlighted its potential diagnostic value. However, many types of lncRNA were shown to be overexpressed in adjacent tissues. Therefore, LSINCT5 does not have high specificity or sufficient sensitivity in EC or PTC. Mechanistically, the LSINCT5/HMGA2/Wnt/β-catenin and LSINCT5/miR-29c/ITGB1 axes promote the proliferation, metastasis and invasion of EC and PTC cells. Fortunately, the LSINCT5/HMGA2/Wnt/β-catenin and LSINCT5/miR-29c/ITGB1 axes have higher specificity and greater sensitivity than LSINCT5 alone as a biomarker for the diagnosis of EC and PTC. In summary, LSINCT5 represents a promising diagnostic biomarker detectable in EC and PTC (Table 2).

LSINCT5 as a biomarker for cancer prognosis

The expression of LSINCT5 may also be used to predict cancer prognosis, as different expression levels indicate varying prognoses in a number of cancers. In patients with OSCC, GC or CRC, higher expression levels of LSINCT5 always predicted a significantly worse prognosis, with lower disease-free survival and shorter overall survival. Therefore, LSINCT5 could be an independent prognostic factor for OSCC, GC and CRC patients. Higher expression of LSINCT5 was found to promote OSCC, GC and CRC cells to acquire more invasive ability. Moreover, a higher expression of LSINCT5 was found to promote more lymph node metastases and distant metastases of OSCC, GC and CRC cells. As a result, a higher expression of LSINCT5 deteriorates the progression of OSCC, GC and CRC patients by strengthening the proliferative and migratory capacities of OSCC, GC and CRC cells. In summary, a high expression of LSINCT5 predicts unfavorable prognosis and poor outcome for OSCC, GC and CRC patients, and has a good prognostic value in these patients (Table 2).

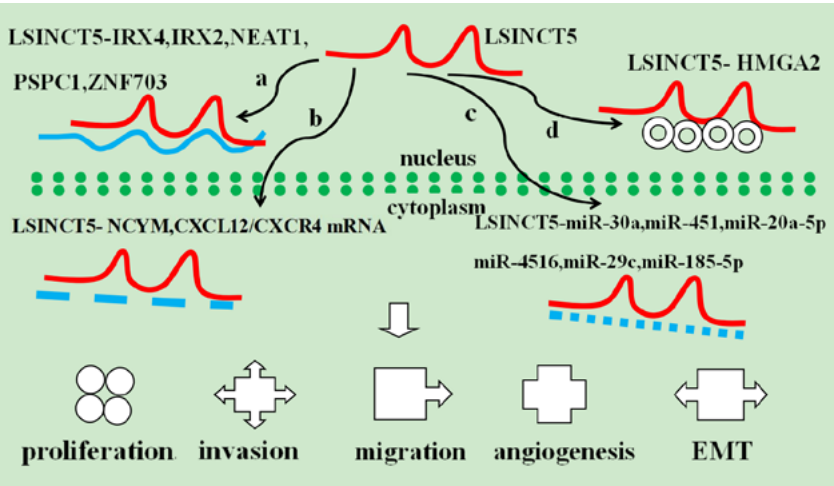

Fig. 1. Graphical representation of interactions between long stress-induced non-coding transcript 5 (LSINCT5) and DNA, RNA, and protein targets – and their role in the multistep development of cancers. A. The LSINCT5 is shown to interact with iroquois homeobox 4 (IRX4), IRX2, nuclear paraspeckle assembly transcript 1 (*NEAT1*), paraspeckle component 1 (*PSPC1*), and zinc finger protein 703 (ZNF703); B. The LSINCT5 is shown to interact with NCYM, C-X-C motif chemokine ligand-12 (CXCL12)/C-X-C chemokine receptor 4 (CXCR4) and mRNAs; C. The LSINCT5 is shown to interact with miR-30a, miR-451, miR-20a-5p, miR-4516, miR-29c, miR-185-5p, and other miRNAs; D. The LSINCT5 is shown to interact with high-mobility group AT-hook protein 2 (HMGA2) protein targets. The LSINCT5 plays an important role in cancer cell proliferation, metastasis, invasion, epithelial–mesenchymal transition (EMT), and tumor angiogenesis

LSINCT5 as a target for cancer treatment

The LSINCT5 is overexpressed in NSCLC, BC, BRCA, glioma, OC, and HCC. Likewise, cancer cell proliferation, metastasis, invasion, EMT, and tumor angiogenesis are inhibited when the expression of LSINCT5 is downregulated. Therefore, LSINCT5 shows promise as a chemotherapeutic target for pharmacological intervention.

Promoting cell proliferation, metastasis, invasion, and EMT of NSCLC was found to be achieved through stabilizing HMGA2 by LSINCT5. Therefore, targeting LSINCT5 to lower its expression level could promote the degradation of HMGA2 as a mean of halting EMT and cancer progression.

Another mechanism by which the overexpression of LSINCT5 was found to promote proliferation, invasion and EMT, was by sponging miR-30a in BRCA cells.[26] The LSINCT5 promoted the progression of BRCA by regulating the Wnt/β-catenin pathway and promoted EMT by activating the Wnt/β-catenin pathway. Therefore, lowering the expression level of LSINCT5 could increase the expression levels of miR-30a, which would suppress proliferation and invasion of BRCA cells and halt EMT. Similar mechanisms have been shown in HCC, BC and glioma, with lower expression levels of LSINCT5 helping to prevent cancer progression. Indeed, lower expression levels of LSINCT5 increased the expression of miR-4516 in HCC cells, which led to a reduction in proliferation and invasion. Similarly, lowering the expression of LSINCT5 suppressed EMT in HCC cells and BC cells. Furthermore, targeting LSINCT5 to lower its expression levels increased the expression of miR-451, which suppressed proliferation and invasion of glioma cells.[34]

Overexpressed LSINCT5 promoted the progression of OC cells through regulation of the CXCL12/CXCR4 signaling axis by increasing the expression of the *CXCR4* gene.[13] Therefore, targeting LSINCT5 to lower its expression level could decrease the expression level of *CXCR4* and lead to suppressed proliferation and invasion of OC cells.

In summary, LSINCT5 is highly expressed in NSCLC, BC, BRCA, glioma, OC, and HCC, and is a promising target for cancer treatment. Targeting LSINCT5 for cancer treatment has some advantages. First, LSINCT5 may be a gene-specific epigenetic regulator and could be targeted to inhibit epigenetic aberrations and stop the process of carcinogenesis. Second, targeting LSINCT5 could result in reduced side effects, as it is a ncRNA. Third, LSINCT5 has been detected in secreted exosomes, which may be used as a safer route for gene delivery. Taken together, the characteristics of LSINCT5 demonstrate its role as a promising target for cancer treatment (Table 2).

Limitations

This systematic review has a number of limitations. First, the precise mechanisms of LSINCT5 in some cancers, such as ESCC and PC, have yet to be fully clarified. Indeed, the targets of LSINCT5 in these cancers are still unclear. Moreover, evidence of the anti-cancer effect of targeting LSINCT5 is weak, as it has not been proven experimentally and no related articles were found. Furthermore, LSINCT5 has only been linked to 13 types of cancer and its precise mechanisms of action are still unclear. Had there been more data from large trials available, statistical analysis and conclusions would be more persuasive. In addition, there are not enough data and materials available for The Cancer Genome Atlas pan-cancer expression of LSINCT5 to be completed. Therefore, targeting LSINCT5 may provide a novel and effective therapeutic approach for anti-cancer therapies. However, because of the current lack of proper animal and clinical data, it cannot be considered as a definitive target for cancer therapy.

Conclusions

Critical roles for LSINCT5 in tumorigenesis and the mechanisms it adopts are worth exploring, as LSINCT5 is differentially abundant in different cancer types. Indeed, LSINCT5 is closely related to tumorigenesis, metastasis, tumor stage, aggressiveness, invasiveness, poor survival, and other processes through interactions with tumor related DNA, RNA and proteins. Therefore, LSINCT5–DNA, LSINCT5–RNA and LSINCT5–protein interactions are promising approaches for cancer diagnosis and treatment.[43]

The LSINCT5 serves as an oncogene to facilitate tumor cell proliferation, metastasis and invasion, inhibit apoptosis, and induce tumor formation in various types of cancer. It achieves this through regulating gene expression and protein functionality at multiple levels, and its deregulation plays a key role in tumorigenesis.[19,48] Furthermore, LSINCT5 is a novel molecular target in cancer therapy due to its strong predictive and specific expression patterns. In addition, the characterization of LSINCT5 will highlight its potential clinical applications in cancer prevention and diagnosis.

There are several possible approaches for targeting LSINCT5, such as silencing, functional blockage and structure disruption.[51] Targeting LSINCT5 seems to be promising in the fight against cancer and may be available clinically after overcoming certain obstacles.[54] These obstacles include a lack of suitable delivery vehicle, poor cellular uptake and cytotoxicity of antisense oligonucelotides.[52] Furthermore, suitable animal models, significant patient cohorts and clinical experimentation are still required to evaluate the clinical significance of LSINCT5 in cancer progression.

Targeting LSINCT5 as a therapeutic strategy must be based on the identification and functional characterization of LSINCT5. As such, an efficient detection of LSINCT5 and tissue-specific delivery methods are critical to the success of LSINCT5 as a therapeutic target.

The use of the emerging technology, namely clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9 for gene knockout, knock-in and point mutations, may facilitate the development of LSINCT5-based targeted cancer therapy.

This review broadens our understanding of LSINCT5 in the malignant transformation of various cancers and its potential therapeutic application in cancer therapy.[53–55] The LSINCT5 is a potential novel therapeutic target for cancers and a promising and sensitive biomarker for tumor diagnosis and prognosis, as well as personalized cancer treatments. Targeting LSINCT5 may provide a novel and effective therapeutic approach for LSINCT5-based anticancer therapies.

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