Review

Regulation of lncRNA and Its Role in Cancer Metastasis

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Metastasis is the primary cause of cancer-related death all over the world. Metastasis is a process by which cancer spreads from the place at which it first arose to distant locations in the body. It is well known that several steps are necessary for this process, including cancer cell epithelial–mesenchymal transition (EMT), cell migration, resistance to anoikis, and angiogenesis. Therefore, investigating the molecular mechanism of regulating cancer metastasis progress may provide helpful insights in the development of efficient diagnosis and therapeutic strategy. Recent studies have indicated that long noncoding RNAs (lncRNAs) play important roles in cancer metastasis. lncRNAs are the nonprotein coding RNAs that have a size longer than 200 nucleotides. More and more studies have indicated that lncRNAs are involved in a broad range of biological processes and are associated with many diseases, such as cancer. The role of lncRNAs in cancer metastasis has been widely studied; however, lncRNAs are mainly involved in the EMT process on the current literature. This review focuses on the mechanisms underlying the role of lncRNAs in cancer metastasis.

Key words: Noncoding RNAs; Long noncoding RNAs (lncRNAs); Cancer metastasis; Gene regulation

INTRODUCTION

Cancer metastasis is a complex process involving the spread of a tumor to distant parts of the body from its original site (1). More evidence indicated that metastasis has occurred in 60% to 70% of cancer patients by the time of diagnosis. Cancer metastasis is the most common cause of death in cancer patients. Many molecular mechanisms enable tumor cells to infiltrate the process of cancer metastasis. Besides protein-coding genes, some noncoding RNAs may participate in cancer metastasis, such as microRNAs (miRNAs) and long noncoding RNAs (lncRNAs) (2,3). There have been many reviews about miRNAs in cancer metastasis (4,5). This review will focus on lncRNAs in cancer metastasis.

lncRNAs are non-protein-coding RNA molecules longer than 200 nt in length, are poorly conserved, and capable of regulating gene expression at various levels, including histone modification, transcription, and/or posttranscriptional regulation. They act as activators, decoys, guides, or scaffolds for their interacting proteins, DNA and RNA (6,7). Increasing evidence has suggested that lncRNAs could play critical roles in almost all the biological processes, including stem cell maintenance, cell proliferation, cell apoptosis, cell invasion, and metastasis (8–10). More and more studies have revealed that lncRNAs may be involved in almost all the human cancers (Fig. 1). A well-studied lncRNA HOTAIR is significantly increased in breast cancer patients, whose expression is strongly predictive of cancer metastasis and death (9). HOTAIR could change the cell expression profile involving cancer metastasis, leading to breast cancer metastasis by associating with polycomb repressive complex 2 (PRC2) (11). Besides breast cancer, HOTAIR was also observed to be aberrantly expressed in colon, liver, pancreatic cancers, and gastrointestinal stromal tumors and contributes to their metastasis (12–15). The study of the metastasis-related lncRNAs represents a new approach that may enhance our understanding of the molecular mechanisms modulating the metastatic cascade. This review will focus on lncRNAs in the cancer metastatic process.

REGULATION OF lncRNAs

Transcriptional Regulation of lncRNAs

With the development of high-throughput genomic technologies like lncRNA microarray and RNA sequencing, many lncRNAs have been discovered in recent years.
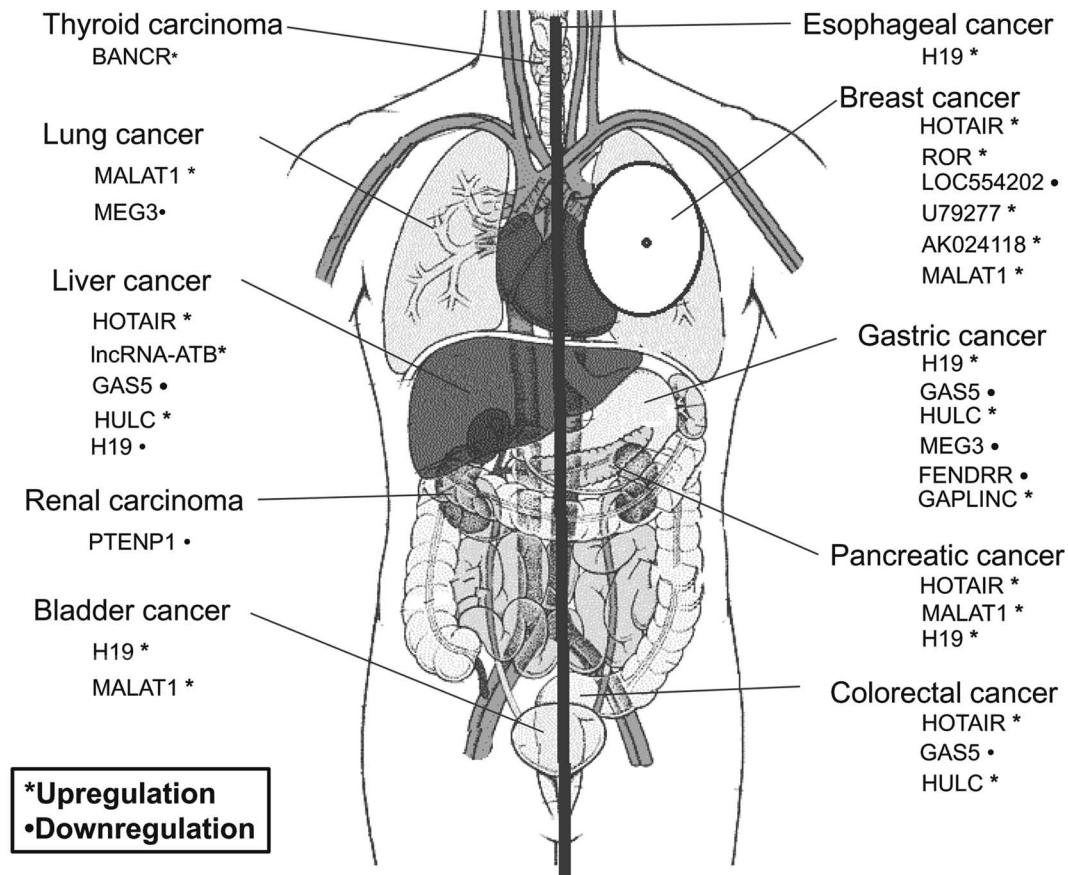
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Figure 1. lncRNAs may be involved in almost all the human cancers.

However, because of the high false-positive rates of predictive algorithms for transcription factor binding sites of lncRNAs, little is known about the transcriptional regulation of the lncRNA genes yet. Based on ChIP-Seq peak lists of transcription factors from ENCODE, some databases for decoding the transcriptional regulation of lncRNA have been developed (http://mlg.hit.edu.cn/tf2lncrna; http://deepbase.sysu.edu.cn/chipbase/). The predicated transcription factors of lncRNAs need to be validated.

DNA Methylation Regulation of lncRNAs

Accumulating evidence has uncovered the underlying cross talk between lncRNAs and DNA methylation regulatory network. lncRNA Dum epigenetically silences its neighboring gene, Dppa2, in *cis* through recruiting methylation enzymes Dnmt1, Dnmt3a, and Dnmt3b. Also, several lncRNAs have been found to be deregulated in cancers due to epigenetic changes. As we all know, the imprinted genes regulated by DNA methylation of either maternal or paternal alleles is very important for embryonic development. Many lncRNAs are imprinted genes such as H19 and MEG3. H19 contains a differentially methylated region (DMR) in its promoter and differentially methylated according to

parental inheritance. Normally, the paternal allele of H19 is silent by DNA methylation, while the maternal allele is activated result from DNA unmethylated. H19 is overexpressed in many human cancers because of DNA methylation regulation, such as esophageal cancer, lung cancer, breast cancer, and bladder cancer (16–21). Besides H19, some tumor-suppressive lncRNAs are downregulated in many cancers with high CpG methylation of the promoter, such as lncRNA MEG3 (22–25) and LOC554202 (26,27). A lncRNA NBAT-1 (neuroblastoma-associated transcript-1) was explored as a prognostic biomarker in neuroblastoma, and the expression of NBAT-1 was regulated by CpG methylation (28). Altogether, lncRNA as an epigenetic regulator in gene expression is deregulated in many malignant diseases due to aberrant DNA methylation. Same as coding genes, there are hypermethylation of tumor-suppressor lncRNAs and hypomethylation of oncolncRNAs contributing to cancer development.

lncRNAs AND CANCER METASTASIS

lncRNAs have been reported to directly regulate the metastatic process both in vitro and in vivo in many human cancers (Table 1).

Table 1. Metastasis-Regulating lncRNAs

lncRNA/Properties	Functional Mechanism	Type of Cancer	Reference(s)
HOTAIR			
Promote metastasis	Targets PRC2	Breast cancer	9
Promote metastasis	Reprogramming of PRC2	Colon cancer	12
Promote invasion	Suppress interferon-related genes	Pancreatic cancer	13
Biomarker of recurrence	NA	Liver cancer	42
Promote metastasis	NA	Lung cancer	43
Prognostic marker	NA	Esophageal cancer	44
Biomarkers of poor survival	EMT	Gastric cancer	47
MALAT1			
Promote metastasis	HPV infection	Cervical cancer	36
Promote metastasis	Activating Wnt signaling	Bladder cancer	34,37
Promote metastasis	EMT	Lung cancer	29,38
Biomarker of poor prognosis	NA	Colorectal cancer	35
Promote migration and invasion	EMT	Pancreatic cancer	32
Poor prognosis	NA	Glioma	30
GAS-5			
Prognostic marker	NA	Cervical cancer	71
Prognostic biomarker	Related to p53 expression	Colorectal cancer	74,75
Prognostic biomarker	NA	Hepatocellular carcinoma	73
Prognostic biomarker	Regulating E2F1 and P21 expression	Gastric cancer	72
H19			
Suppress metastasis	Targeting TGFBI	Prostate cancer	62
Promote invasion and migration	Increasing HMGA2-mediated EMT	Pancreatic adenocarcinoma	59
Promote invasion and metastasis	Direct upregulation of ISM1	Gastric cancer	54
Promote migration	EMT	Bladder cancer	64–66
Promote invasion	Deriving miR-675	Glioma	61
Suppress migration and invasion	AKT/GSK-3β/Cdc25A signaling pathway	Hepatocellular cancer	63,67
MEG3			
Relative poor prognosis	NA	Gastric cancer	81
Relative poor prognosis	NA	Pituitary adenomas	78
Poor clinical outcome	NA	Tongue carcinoma	83
Poor clinical outcome	Affecting p53 expression	Lung cancer	84
HULC			
Prognostic biomarker	Interaction with microRNA-372	Liver cancer	88,90
Promote invasion	NA	Gastric cancer	91
LincRNA-RoR			
Promote metastasis	EMT	Breast cancer	95
Promote invasion	Targeting ARF6	Triple-negative breast cancer	96
lncRNA-ATB			
Promote invasion and metastasis	EMT and autocrine induction of IL-11	Liver cancer	97-98
PTENP1			
Reduce invasion and metastasis	Functions as a competing endogenous RNA	Clear cell renal cell carcinoma	100–102
FENDRR			
Prognosis biomarker	Affecting fibronectin1 expression	Gastric cancer	105
GAPLINC			
Prognosis biomarker	Regulates CD44-dependent cell invasiveness	Gastric cancer	106,107
EBIC			
Promote invasion	Binding to EZH2 and repressing E-cadherin	Cervical cancer	108

PRC2, polycomb repressive complex 2; EMT, epithelial–mesenchymal transition.

Metastasis-Associated Lung Adenocarcinoma Transcript 1 (MALAT1)

MALAT1 was first significantly associated with high metastatic potential and poor prognosis in early stage non-small cell lung cancer patients (29). MALAT1 was upregulated in a variety of human cancers including colorectal, pancreatic, prostate, glioma, and bladder cancers (30–35). In cervical cancer, MALAT1 dysregulation was

correlated with HPV infection, and MALAT1 could participate in cervical cancer cell proliferation and invasion (36). The epithelial–mesenchymal transition (EMT) is an important process in cancer metastasis in which epithelial cells lose their properties to become migratory and invasive mesenchymal cells. TGF-β, which is an EMT activator, induces MALAT1 expression in bladder cancer cells (37). MALAT1 decreases the expression of E-cadherin and increases the expression of N-cadherin and fibronectin by associating with suppressor of zeste 12 (SUZ12). Another study found that MALAT1 promoted the EMT process through activating the Wnt signaling pathway in bladder cancer and contributing to this cancer metastasis (34). Besides bladder cancer, MALAT1 is increased in lung cancer and promotes lung cancer brain metastasis by inducing EMT (38). MALAT1 is involved in cancer metastasis mainly through EMT. MALAT1 may participate in cancer migration and invasion by other mechanisms. Miyagawa et al. found that MALAT1 could regulate gene expression in transcriptional and/or posttranscriptional levels in HeLa cells (39). Some studies imply that MALAT1 may participate in the regulation of alternate splicing by modulating the level of active serine/arginine (SR) splicing protein (40), although precisely how this may contribute to tumor metastasis is still unknown.

HOX Antisense Intergenic RNA (HOTAIR)

HOTAIR is a noncoding RNA located in the mammalian HOXC locus on chromosome 12, which was found to be overexpressed in metastatic breast cancers (9,41). In hepatocellular cancer, high HOTAIR expression increased the risk of recurrence after liver transplant therapy (42). HOTAIR may represent a novel prognosis marker for non-small cell lung cancer, esophageal squamous cell carcinoma, endometrial carcinoma, and cervical cancer (43–46). HOTAIR could also act as a potential predictor for overall survival in patients with gastric cancer, and knockdown of HOTAIR could reduce invasiveness and reverse the EMT process in gastric cancer cells (47). HOTAIR was demonstrated to be involved in gene expression associated with the PRC2 complex responsible for H3K27 methylation. HOTAIR functions as a guide interacting with PRC2 results in a genome-wide retargeting of the PRC2 complex (9,48). The retargeting of PRC2 silenced the HOXD locus, which is located on chromosome 2 in breast epithelial cells (9). Further study indicated that HOTAIR not only functions as a guide by binding to PRC2, it appears to act as a molecular scaffold by binding at least two distinct histone modification complexes. HOTAIR could modulate H3K27 methylation by binding PRC2 and H3K4 demethylation by binding LSD1 complex (49). In short, HOTAIR has the ability to modulate the cancer epigenome by binding different histone modification complexes and to reprogram chromatin states to promote cancer metastasis.

H19

The H19 gene is a 2.3-kb RNA product that does not code protein (50). It is transcribed by RNA polymerase II, spliced, and polyadenylated. The H19 gene is an imprinting gene that is expressed exclusively in one parental allele (51). H19 is increased in many cancers including esophageal cancer, breast cancer, bladder cancer, ovarian serous epithelial cancer, gastric cancer, and lung cancer (16,18,52–58). H19 is involved in cancer metastasis maybe through EMT progress (59) by antagonizing miRNAs or epigenetic regulation. H19 is a precursor for miR-675, and multiple inducers of EMT upregulate H19 and miR-675 (60–62). TGF-β upregulated Slug, H19, and miR-675 through the PI3K/AKT pathway (63). H19 expression was upregulated remarkably in primary pancreatic ductal adenocarcinoma (PDAC), which subsequently metastasized. H19 increased the expression of HMGA2, which is involved in EMT through antagonizing let-7 and promoted PDAC cell invasion and migration (59). In bladder cancer, H19 levels are remarkably increased in bladder cancer tissues, and H19 may be used as an oncodevelopmental marker for bladder cancer (64). Further study indicated that H19 could activate the Wnt/β-catenin signal pathway and decrease the expression of E-cadherin by associating with enhancer of zeste homolog 2 (EZH2) in bladder cancer cells (65,66). H19 could promote cancer metastasis mainly involving the EMT process.

On the other hand, H19 was downregulated in intratumoral hepatocellular carcinoma (HCC) tissues and predicted HCC prognosis (63). H19 can suppress the expression of EMT markers by activating the miR-200 family and contributing to HCC metastatic inhibition (67). Furthermore, H19 activated miR-200 family expression potentially by increasing histone acetylation associated with the protein complex hnRNP U/PCAF/RNAPol II (68). The unconventional expression patterns of H19 may be due to the tissue specificity, and the mechanism underlying the unconventional expression still needs to be further investigated. Like miRNAs, lncRNA may play different functions in various cancers through different pathways. So a detailed understanding of lncRNA in tumorigenesis is very important.

Growth Arrest-Specific 5 (GAS5)

GAS5 is a lncRNA that was originally isolated from mouse genomic DNA, and this gene is a potential tumor-suppressor gene highly expressed in saturation density-arrested cells (69). GAS5 could fuse to the Bcl6 gene as a result of t(1;3)(q25;q27) in B-cell lymphoma (70). GAS5 is a prognostic biomarker in cervical cancer, colorectal cancer, hepatocellular carcinoma, and gastric cancer (71–74). Although GAS5 has been found as a tumor-suppressor

gene in many cancers, the mechanism of this gene involved in tumorigenesis is still not very clear. A recent study found that GAS5-associated snoRNA levels are related to p53 expression and DNA damage in colorectal cancer (75). The main function of GAS5 in cancer is cell apoptosis, and there has been no study about GAS5 in cancer metastasis until recently.

Maternally Expressed 3 (MEG3)

MEG3 is an imprinted lncRNA gene expressed in the maternal allele. Imprinting of this gene is mediated through cytosine methylation-controlled binding protein CTCF (76). MEG3 is silent in many cancer cells because of DNA methylation (77–79). miR-29 and miR-148 can modulate DNA methyltransferase (DNMT) 1 and 3, increasing expression of MEG3 in hepatocellular cancer and gastric cancer, respectively (80,81). MEG3 is a relatively poor prognosis in gastric cancer, pituitary adenomas, tongue squamous cell carcinoma, and lung cancer (22,82–84). Yin et al. found that the lower expression of MEG3 was remarkably correlated with low histological grade, deep tumor invasion in colorectal cancer (85). However, the mechanism of MEG3 underlying cancer metastasis is not very clear. Further study indicated that MEG3 might suppress tumor proliferation through p53-dependent and/or p53-independent pathways (84,86).

Highly Upregulated in Liver Cancer (HULC)

HULC was first identified in hepatocellular cancer and is also expressed in colorectal carcinomas that metastasize to the liver (87,88). IGF2 mRNA-binding protein 1 (IGF2BP1) could regulate the expression of HULC at the posttranscriptional level (89). HULC was upregulated by PKA pathway or transcriptional factor CREB in liver cancer. Upregulated HULC may function as an endogenous sponge by binding to many miRNAs, including miR-372 (90). miR-372 represses the translation of the kinase PRKACB, leading to increased levels of PRKACB (90). PRKACB activates CREB, which upregulated HULC by phosphorylation, therefore leading to increased expression of HULC. The HULC-miR-372-PRKACB-CREB-HULC regulation loop plays an important role in cancer metastasis. Zhao et al. determined that silencing of HULC effectively reversed the EMT phenotype in human gastric cancer (91).

lncRNA-RoR

lncRNA-RoR is a lncRNA that suppresses p53 translation by direct interaction with the heterogeneous nuclear ribonucleoprotein I (hnRNP I) (92,93). The main function of lncRNA-ROR was the maintenance of induced pluripotent stem cells (iPSCs) and embryonic stem cells or involvement in tumor genesis (8,94). Hou et al. discovered that lncRNA-ROR was increased in breast tumor tissues, and ROR regulated EMT progress by functioning as a competing endogenous RNA for miR-205 in human mammary epithelial cells (95).

Triple-negative (ER⁻, HER2⁻, PR⁻) breast cancer (TNBC) is an aggressive disease with a poor prognosis because of no available therapeutic strategies. Silencing of miRNA-145 may be a defining marker of TNBC. RoR is dramatically upregulated in TNBC and functions as a competitive endogenous RNA sponge for miR-145. ARF6, a target gene of miR-145, is a regulator of breast tumor cell invasion and metastasis. Mechanistically, ARF6 regulates E-cadherin localization and impacts cell–cell adhesion (96). These studies reveal a lincRNA-ROR/miR-145/ARF6 pathway that regulates metastasis in TNBCs. In short, lncRNA-ROR mainly functions as a key competing endogamous miRNA sponge contributing to cancer metastasis.

Other lncRNAs

lncRNA-ATB was first identified in the metastases of hepatocellular carcinoma (HCC) and is activated by TGF-β. lncRNA-ATB could promote cancer cell invasion by competitively binding the miR-200 family. miR-200 could decrease the expression of ZEB1 and ZEB2, which are EMT inducers. lncRNA-ATB promotes cancer cell invasion by inducing EMT process. In addition, lncRNA-ATB could promote the organ colonization of disseminated tumor cells by binding to IL-11 mRNA and triggering the STAT3 signaling pathway (97,98).

PTENP1 is a pseudogene of the tumor-suppression gene PTEN (99). PTENP1 is downregulated in clear cell renal cell carcinoma (ccRCC) due to DNA methylation (100). PTENP1 was deleted in human melanoma (101). PTENP1 and PTEN are direct targets of miR-21, and their expression is suppressed by miR-21 in ccRCC cell lines (102). The expression of PTENP1 and PTEN in tissues is correlated, and both expressions are inversely correlated with miR-21 expression. Patients with ccRCC with no PTENP1 expression have a lower survival rate. Overexpression of PTENP1 in cells expressing miR-21 reduces cell proliferation, invasion, tumor growth, and metastasis, recapitulating the phenotypes induced by PTEN expression.

lncRNA LOC554202 is a host gene of miR-31. miR-31 and LOC554202 are both down expressed in the TNBC cell lines because of promoter methylation (26). Inhibition of Loc554202 could decrease the migration and invasion of breast cancer cell (27).

U79277, AK024118, BC040204, and AK000974 have been identified using lncRNA expression profiling, and the expression of these four lncRNAs are associated with the survival times for breast cancer patients (103).

lncRNA FENDRR is an essential regulator of heart and body development in mouse (104). This lncRNA was downregulated in gastric cancer tissues resulting from histone deacetylation, and this downregulation

was correlated with tumor invasion and lymphatic metastasis. Further study indicated that FENDRR could suppress gastric cancer cell invasion and migration by decreasing the expression of FN1 and MMP2/MMP9, which are all metastasis-related genes (105).

GAPLINC (gastric adenocarcinoma predictive long intergenic noncoding RNA) is overexpressed in gastric cancer tissues, and GAPLINC overexpression defines a subgroup of patients with very poor survival. Mechanistic investigations revealed that GAPLINC regulates CD44 as a molecular decoy for miR-211, a microRNA that targets both CD44 and GAPLINC (106,107).

lncRNA-EBIC (EZH2-binding lncRNA in cervical cancer) was upregulated in cervical cancer. lncRNA-EBIC could promote the migration and invasion of cervical cancer cells by binding to EZH2. EBIC/EZH2 decreases the expression of E-cadherin, which is a key molecular in cervical cancer metastasis (108).

lncRNA AND miRNA INTERACTIONS IN CANCER METASTASIS
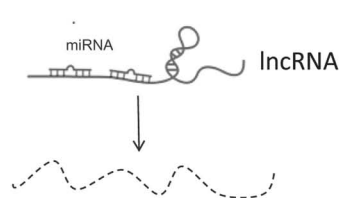
miRNA-Triggered lncRNA Decay

miRNAs and lncRNAs are all noncoding RNAs, and the abundance of numerous lncRNAs is controlled by miRNAs (Fig. 2A). More evidence indicated that miRNAs can regulate over one third of the protein-coding genes by binding to their 3′ untranslated region (UTR); more studies indicated that miRNAs can also target lncRNAs and trigger lncRNA decay. The lethal-7 (let-7) gene family was first discovered as a key developmental regulator and is a direct regulator of oncogene RAS in human cancers (109). Except for Ras gene, let-7 could also regulate lncRNAs. H19 is regulated by four let-7 genes (let-7a, let-7b, let-7g, let-7i) (110,111). Another lncRNA HOTAIR was decreased by let-7, and this regulation is recruited to the RNA-binding protein HuR; this suggested that the mechanism of lncRNA decay through HuR-enhanced microRNA interactions may be widespread. Another most studied miRNA, miR-21, has been found as an oncogene in various types of cancers (112). Zhang et al. found that lncRNA GAS5 is regulated by miR-21 through the pathway involving the RNA-induced silencing complex (RISC) in breast cancer cells (113). lncRNA MALAT1 is targeted by miR-9 also involving the RISC (114). lncRNAs and miRNAs are noncoding RNAs involved in gene regulation. A better understanding of the interactions between microRNAs and lncRNAs will provide new insights into mechanisms underlying various aspects of tumor process including metastasis.
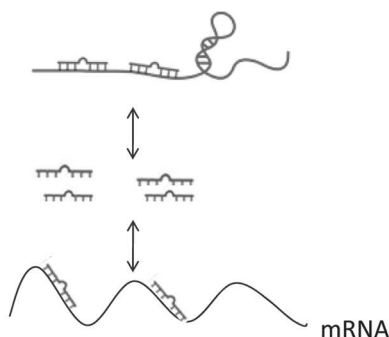
lncRNAs: Reservoir of miRNAs

Some lncRNAs are involved in cancer metastasis by generating miRNAs (Fig. 2B). H19 can generate miR-675, a process that is repressed by HuR in mice (115,116).
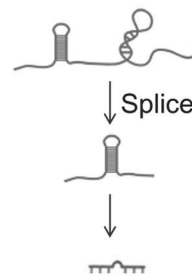

A. Let7 target H19, HOTAIR
   miR-21 target GAS5
   miR-9 target MALAT1

B. H19 generate miR-675
   LOC554202 encode miR-31
   Linc-MD1 generate miR-206, miR-133b

C. HULC as sponge of miR-372
   linc-ATB as sponge of miR-200s
   PTENP1 as sponge of miR-21

Figure 2. lncRNA and miRNA interactions in cancer metastasis. (A) Numerous lncRNAs are controlled by miRNAs and trigger lncRNA decay. (B) lncRNAs could generate miRNAs. (C) lncRNAs can compete with miRNAs for binding to target mRNAs.

H19 could promote cancer metastasis by deriving miR-675, including prostate cancer, gastric cancer, and glioma (61,62,117,118). In contrast, down expression of H19 and miR-675 could promote the migration and invasion of human hepatocellular carcinoma cells (63). Similarly, lncRNA LOC554202 could encode miR-31, and promoter methylation of lncRNA LOC554202 leads to decreased miR-31 and thus contributes to breast cancer invasion and metastasis (26,119). Linc-MD1 generates miR-206 and miR-133b from an intron and an exon, respectively. miR-206 could suppress the migration of breast cancer cells by direct targeting of coronin 1C, which is an actin-binding protein (120). miR-133b is a potential new prognostic marker for human colorectal cancer (121). All of these studies confirm that some lncRNAs serve as a reservoir of miRNAs and could have a dual regulatory output. Besides generating miRNAs, lncRNA can also regulate the miRNA biogenesis. Liz et al. found that lncRNA Uc.283+A regulated pri-miRNA-195 maturation at the level of Drosha processing (122).

lncRNAs: Sponge of miRNAs

lncRNAs could generate miRNAs, and lncRNAs could also compete with miRNAs for binding to target mRNAs (Fig. 2C). miRNAs binding to lncRNAs could result in lncRNA decay or just as a miRNA sponge. Lnc-MD1 enhanced the expression of MAML1 and MEF2C mRNAs by functioning as an endogenous sponge for miR-133, and miR-135 triggered muscle differentiation in mouse and human myoblasts (123). HULC was found to function as a miRNA sponge, contributing to hepatic cancer metastasis (90). lncRNA-ATB could stimulate EMT through sequestering miR-200s in liver cancer (97). PTENP1 is a pseudogene of tumor-suppressor gene PTEN, and they share similar 3′ UTR for the same miRNAs. PTENP1 could decrease the effect of posttranscriptional inhibition of PTEN by functioning as competing endogenous RNA (99,100). In human melanoma, specific mutations in 3′ UTR of PTENP1 could affect the expression of PTEN, contributing to cancer metastasis (101).

In sum, expanding evidence had revealed that lncRNAs and miRNAs work together to regulate gene expression by complex posttranscriptional mechanisms. All of these studies highlighted the increasing complexity of ncRNA-mediated regulatory networks. More examples of lncRNAs regulating gene expression by competing or cooperating with miRNAs are expected to emerge. Together, microRNAs and lncRNAs contribute to a robust and dynamic control of cancer metastasis.

lncRNAs AS DIAGNOSTICS AND THERAPEUTIC BIOMARKERS IN CANCER

Cancer is one of the diseases with a high mortality rate because of metastasis. It is very hard to look for early diagnosis and therapeutic targets for this disease. With the development of molecular mechanism studies, personalized medicine is entering into the era for cancer. More and more accurate and meaningful diagnosis and prognosis markers for cancer are coming because of greater understanding of molecular alterations. In addition to genetic changes, additional epigenetic alterations including DNA methylation, histone modification, and microRNA and lncRNA expression can provide other clinical information. lncRNA as an epigenetic regulator may participate in gene regulation at the transcriptional or posttranscriptional level, and lncRNA may be a potential marker for cancer diagnosis and therapy.

Many studies have found that lncRNAs were aberrantly regulated in many cancers and associated with cancer metastasis. lncRNAs can be potential novel biomarkers for cancer diagnosis and therapy. Using lncRNA array or RNA sequencing, many lncRNAs have been found as cancer prognosis markers. lncRNA-ATB was activated by TGF-β in HCC, and the expression of lncRNA-ATB was associated with cancer prognosis. Higher HOTAIR expression increased the risk of recurrence after liver transplant therapy. GAPLINC overexpression defines a subgroup of patients with gastric cancer with very poor survival. These lncRNA expressions are associated with cancer patient prognosis and are all detected in tumor tissues. Like circulating miRNAs, lncRNAs are also detectable in the sputum, blood, and urine of cancer patients. For example, lncRNA DD3, which is specifically expressed in the prostate, has been developed as a marker for prostate cancer, and this lncRNA has higher specificity than serum prostate-specific antigen (PSA) (124–126). Similarly, the lncRNA HULC, which is highly expressed in liver cancer, can be detected in the blood of cancer patients (87). These lncRNAs may be potential noninvasive diagnosis targets for cancer.

Use of lncRNAs as therapeutic targets for cancer is just beginning (127). Although the exact function of lncRNA in cancer is not very clear, some lncRNAs are candidates for therapeutic intervention. Many lncRNAs may form a secondary structure and play important roles by binding to a protein complex; this may provide a means of intervention (128). HOTAIR regulates gene expression by binding to PRC2 or LSD1 complexes; preventing this binding will decrease the metastatic potential of breast cancer cells (129). lncRNAs function as a tumor suppressor or oncogene by interaction with DNA, miRNA, and protein. It has been suggested that RNA-induced transcriptional gene silencing (TGS) or activation could be a potential therapeutic strategy (130).

lncRNAs are dysregulated in many human cancers, and this may provide a therapeutic target for transgene-mediated treatment. Among these lncRNAs, H19 is overexpressed in many cancers (60,117,131). So a series of studies want to regulate the expression of H19 for cancer treatment primarily

in bladder cancer. BC-819 is a double-stranded DNA plasmid that carries the gene for diphtheria toxin-A under regulation of the H19 promoter sequence. Most clinical trials have investigated the efficacy and toxicity of BC-819 for bladder cancer treatment (132). A phase IIb clinical trial in patients with intermediate risk nonmuscle invasive bladder cancer treated with BC-819 reported that BC-819 could prevent new tumor growth and ablate marker lesions (133). In order to improve the therapeutic efficacy, a double promoter plasmid with H19 and IGF2-P4 regulatory sequences was constructed. The double promoter plasmid exhibited enhanced anticancer activity compared to the single promoter expression vector in bladder cancer (134,135). Besides bladder cancer, BC-819 was used to treat other cancers, such as pancreatic cancer, ovarian cancer, and heterotopic cancer (136–138). In short, combining conventional chemotherapy and lncRNA transgene treatment might be a new therapeutic option for cancer patients.

Collectively, these studies indicated that lncRNA may be a potential target for cancer diagnostics and therapies.

CONCLUSIONS

Recently, with the development of high-throughput array technologies, such as microarray and RNA sequencing, something important hidden in the variety of noncoding RNAs makes researchers deeply investigate the pathogenesis of cancer. lncRNA is dysregulated in many human cancers, and this may be a new hallmark in cancer. Although there are more and more studies about lncRNAs in cancer, the exact function of lncRNA in cancer genesis is still unsolved. Cancer metastasis is the leading cause of cancer patient death, and lncRNAs participate in cancer metastasis. In this review, we highlight the character of lncRNA in cancer metastasis. lncRNAs participate in cancer metastasis mainly by interaction with miRNAs, epigenetic gene regulation, and involvement in EMT progress. Finally, we note that lncRNA may be a potential diagnostic and therapeutic marker in cancer. Thus, more effects are needed to better elucidate the function and critical mechanisms of cancer-specific lncRNAs in the progression of cancer metastasis. In the future, integration of lncRNA biology into cancer biology may further deepen our understanding of the mechanisms of cancer metastasis and provide novel applications for efficient, rapid, and specific diagnosis and treatments.

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