Emerging role of long non-coding RNA in the development of gastric cancer

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Abstract

Gastric cancer is a common, worldwide malignancy and has a poor prognosis due to late diagnosis. Long non-coding RNAs (lncRNAs) are a significant subtype of RNA molecules with a length longer than 200 nucleotides (nt) that rarely encode proteins. In recent decades, deregulation of lncRNAs has been shown to be involved in tumorigenesis and tumor progression in various human carcinomas, including gastric cancer. Accumulating evidence has shown that some lncRNAs may function as diagnostic biomarkers or therapeutic targets for gastric cancer. Thus, exploring the specific functions of lncRNAs will help both gain a better understanding of the pathogenesis and develop novel treatments for gastric cancer. In this review, we highlight the expression and functional roles of lncRNAs in gastric cancer, and analyze the potential applications of lncRNAs as diagnostic markers and therapeutic targets.

Key words: Function; Tumorigenesis; Gastric cancer; Therapeutic target; Long non-coding RNAs; Diagnostic marker

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Core tip: Gastric cancer is a common, worldwide malignancy that has a poor prognosis. The promising regulatory potential of long non-coding RNAs (lncRNAs) in tumorigenesis and cancer development, including gastric cancer, has been widely demonstrated. Thus, exploring the function of lncRNAs can help to both gain a better understanding of the pathogenesis and develop novel treatments for gastric cancer. In this review, we aim to elucidate the expression patterns and functional roles of lncRNAs in gastric cancer, and analyze the latent applications of lncRNAs as diagnostic markers and therapeutic targets.
INTRODUCTION

Gastric cancer is one of the most common malignancies of the digestive tract[1]. Furthermore, there has been consistent growth in the incidence and mortality rates of gastric cancer due to late diagnosis. The 5-year survival rate could reach 90%-97% if patients are diagnosed early and get prompt treatment, either by endoscopy or surgery. Nevertheless, the 5-year survival rate is currently under 20% for terminal cancer patients[2-8]. As a result, prompt diagnosis of gastric cancer would significantly improve prognosis. An exploration of the molecular mechanisms involved in the initiation and development of gastric cancer is needed to help discover credible markers, and further reduce mortality rate, decrease disability and improve prognosis. In the past, most non-coding RNAs were considered “junk RNAs” of the transcriptome. Nevertheless, with the rapid evolution of whole-genome analysis of gene expression, it has been demonstrated that most of the genome is transcribed into RNAs that have no protein-coding functions[9,10]. Although non-coding RNAs do not encode proteins, they regulate gene expression through various mechanisms. Non-coding RNA-mediated gene silencing is an important part of epigenetic changes, which have been demonstrated to be involved in human carcinogenesis[11]. During the last decade, more attention has been paid to the functional significance of non-coding RNAs in oncogenesis and tumor progression[12]. Long non-coding RNAs (lncRNAs), defined as transcripts > 200 nt in length, are an important group of non-coding RNAs[13]. It has been revealed that in various carcinomas, lncRNAs are frequently deregulated, which may indicate their potential role in the initiation of cancers[14-16]. Thus, understanding the roles of lncRNAs will help elucidate the underlying biological events in different cancers, including gastric cancer, and ultimately lead to the development of novel diagnostic tools and targeted therapies. Furthermore, multiple lncRNAs have been shown to be related to diverse biological processes associated with gastric cancer, which enable lncRNAs to serve as diagnostic biomarkers and therapeutic targets. Here, we aim to review the recent progress made in elucidating the function of gastric cancer-related lncRNAs, and to also explore their potential capacity to serve as diagnostic or prognostic biomarkers.

Category of lncRNAs

Thus far, there has been no systematic classification of lncRNAs. In fact, lncRNA entries are a mixture of multiple functions and mechanisms, only a small proportion of which has been functionally annotated. Many lncRNAs cannot be classified into any particular category. As a result, it is difficult to classify lncRNAs based on only one principal.

Different classification methods are used according to different features of lncRNAs. For example, based on genomic location and context relative to protein-coding genes, lncRNAs can be divided into five broad categories: (1) Sense lncRNA is transcribed from the sense strand and contains several overlapping exons; (2) Antisense lncRNA, on the contrary, is transcribed from the antisense strand; (3) Bidirectional lncRNA is transcribed on one strand, while an adjacent protein-coding gene initiates expression on the same strand, simultaneously; (4) Intronic lncRNA is transcribed entirely from within the introns of protein-coding genes; and (5) Intergenic lncRNA is transcribed within genomic intervals of neighboring protein-coding genes[21]. According to their effects exerted on DNA sequences, lncRNAs can be classified into cis-lncRNAs (cis-acting lncRNAs) and trans-lncRNAs (trans-acting lncRNAs). The expression levels of adjacent genes can be regulated by cis-lncRNAs, while those of remote genes by trans-lncRNAs[25].

Recent advances in high-throughput transcriptome sequencing technologies have made it feasible to conduct deep mining of both the function and mechanism of more lncRNAs, which will eventually enable us to optimize the
arbitrary classifications of lncRNAs.

**MECHANISMS AND FUNCTION OF LNCRNAS**

With the rapid development of experimental and computational technologies, more and more lncRNAs have been identified, among which only a small proportion has been functionally annotated. However, researchers have shown that the process of chromatin remodeling, transcription and post-transcriptional modification could be regulated by lncRNAs\(^{[20,26-28]}\).

**Chromatin remodeling**

Chromatin remodeling was one of the first identified functions of lncRNAs. It has been elucidated that lncRNAs could alter the structure of chromatin and modulate the expression level of genes\(^{[29]}\). LncRNAs can confine chromatin remodeling complexes to particular regions in the genome, which is frequently achieved by interaction with polycomb repressive complex 2 (PRC2), so as to epigenetically regulate gene expression\(^{[20,26]}\). In association with PRC2, small interfering RNAs (siRNAs) have been shown to mediate deletion of specific lncRNAs and thus further alter their expression levels\(^{[30]}\). In addition to acting through PRC2, some lncRNAs directly recruit DNA methyltransferases or other complexes to modify chromatin conformation\(^{[31-33]}\).

**Transcriptional regulation**

LncRNAs regulate transcription by interfering with the transcription of enhancers and promoters\(^{[34,35]}\). Some lncRNAs are transcribed within adjacent gene promoters. These lncRNAs can modulate the function of specific genes by interfering with the binding of protein factors. For example, the non-coding RNA SRG1 is transcribed across the promoter of the SER3 gene, and the expression of SRG1 can remarkably repress SER3. Mechanistically, the transcription of SRG1 in the promoter area disturbs the binding of activators\(^{[20,26]}\). LncRNAs can also be transcribed within distal enhancers and recruit transcription factors to these loci to regulate the expression level of neighboring genes\(^{[37]}\). Furthermore, lncRNAs can act by regulating RNAII activity\(^{[38]}\). Some lncRNAs could regulate the transcription of key apoptotic genes, which is one of the vital pathways for carcinogenesis control\(^{[20,26]}\). For instance, the lncRNA INXS is transcribed from the intron of the *BCL-X* gene. Under the regulation of INXS, BCL-X can splice into BCL-XS, which is a pro-apoptosis isomer of BCL-X\(^{[40]}\).

**Post-transcriptional regulation**

LncRNAs can recognize complementary sequences, and thus can regulate multiple procedures in the post-transcriptional modification of messenger RNAs (mRNAs). For instance, the complementarity of lncRNA Xist and Tsix can form complex dimers *in vivo*. These dimers are then spliced into small RNAs, which can balance the effect of X-chromosome inactivation through RNAi-mediated silencing\(^{[41]}\). Some lncRNAs could also act as competing endogenous RNAs (ceRNAs). Studies showed that these lncRNAs were able to bind miRNAs (sponging) and diminish the inhibitory effect on their natural targets\(^{[42]}\). LncRNA sponges are widely involved in cancer tumorigenesis. For example, in hepatocellular carcinoma, the lncRNA CCAT1 could act as a molecular sponge for let-7 and de-repress the function of its endogenous targets HMGA2 and c-Myc\(^{[43]}\).

By exploring the function of lncRNAs in various aspects of cell transformation and metastasis, we will finally gain a better understanding of cancer biology. Nevertheless, many other functions of lncRNAs remain to be discovered.

**ROLES OF LNCRNAS IN CANCER**

Aberrant gene expression is the foundation of cancer pathogenesis. Intensive study of the genetic causes of cancer has found that variation in non-coding sequences is responsible for a large proportion of cancer susceptibility\(^{[44]}\). In fact, most single nucleotide polymorphisms (SNPs) associated with malignant tumors are found to be located in non-protein-coding loci. Recent studies have shown that many cancer risk loci are transcribed into non-coding RNAs, particularly lncRNAs, which play vital roles in the process of tumorigenesis and progression.

The underlying mechanisms of the regulatory function of lncRNAs in the progression of cancer remain largely unknown. Evidence to date shows that some lncRNAs can recruit protein factors to particular regions of the genome in order to epigenetically modify chromatin, while others can regulate the protein signaling pathways underlying carcinogenesis. LncRNAs can functionally control cellular growth, division and differentiation, thus making them the focus of current cancer research.

As mentioned above, lncRNAs are key regulators of cancer initiation and progression, suggesting they may have applications in diagnosis and therapeutics. Many lncRNAs are highly correlated with particular cancer states and are useful as diagnostic and prognostic markers. For instance, the lncRNA prostate cancer non-coding RNA 1 (PRNCR1) is upregulated in both prostate cancer and precursor lesion prostatic intraepithelial neoplasia. In addition, PRNCR1 expression levels are elevated in patient urine samples, thus making it a fine noninvasive indicator of prostate cancer\(^{[45]}\).

**Deregulations of lncRNAs in gastric cancer**

The above data showed that lncRNAs have strong correlations with cancer state, and their deregulation can lead to cancer initiation and progression. Many lncRNAs have also been shown to be involved in gastric cancer. Among lncRNAs associated with gastric cancer, some of them function as oncogenes and are upregulated during tumorigenesis, while others are downregulated and
serve as tumor suppressors. In this section, we briefly review some of the well-studied lncRNAs involved in gastric cancer.

**HOX transcript antisense RNA**

Located on chromosome 12, the HOX transcript antisense RNA (HOTAIR) contains 6232 nts and encodes 2.2 kbs of long non-coding RNA. HOTAIR is a non-protein-coding RNA with significant regulatory potential via gene remodeling. High levels of HOTAIR expression are associated with cancer cell proliferation, apoptosis, invasion, and progression in a variety of malignancies, making it a significant predictor of subsequent metastasis and death.

In gastric cancer tissues, HOTAIR expression levels are remarkably elevated, which suggests that HOTAIR functions as an oncogene in gastric cancer. Song et al. observed that HOTAIR was overexpressed in gastric cancer, and that by inhibiting miR-152, HOTAIR was responsible for the elevation of human leukocyte antigen G. Furthermore, Endo et al. elucidated that upregulation of HOTAIR was correlated with lymph node metastasis, invasion into vessels, and reduction of survival time in gastric cancer. Chen et al. also found that HOTAIR was significantly upregulated in gastric cancer tissues, and that its overexpression was associated with migration and invasion.

The mechanism of HOTAIR overexpression in gastric cancer is currently unknown. Previous studies have proposed several potential mechanisms of how deregulated HOTAIR functions in tumorigenesis. Epithelial-to-mesenchymal transition (EMT) is generally considered to be the foundation of metastasis. Liu et al. found that HOTAIR promoted gastric cell EMT and metastasis by inhibiting E-cadherin expression through its interaction with EZH2. The functional SNP rs4759314 of HOTAIR had strong associations with gastric cancer susceptibility. SNP rs4759314, which resides in the promoter region of an intron, has been demonstrated to influence the expression of HOTAIR by interfering with this promoter.

**H19**

The lncRNA H19, discovered in 1991 by Bartolomei, was the first imprinted lncRNA gene identified. H19, residing on chromosome 11p15.5, is transcribed from the H19/IGF2 gene. Similar to mRNA, the H19 gene contains five exons and is transcribed by RNA polymerase II. However, it does not contain a common open reading frame. In general, the high conservation in H19 structure is considered to be responsible for the universality of its functions.

Deregulation of H19 has been reported in various malignancies, such as breast cancer, bladder cancer and cervical carcinomas, which indicates its oncogenic role. H19 has also been reported to function as an oncogene in gastric cancer, and its overexpression may contribute to gastric carcinogenesis. Li et al. demonstrated the upregulation of lncRNA H19 in gastric cancer tissues compared with paired normal tissues, and its positive correlation with lymph node metastasis and clinical stage. In vitro, upregulation of H19 could accelerate the proliferation, migration and invasion of gastric cancer cells, while knockdown of H19 caused apoptosis. Moreover, Hashad et al. demonstrated that H19 was upregulated in the plasma of gastric cancer patients, making it a potential non-invasive diagnostic biomarker for gastric cancer.

Multiple previous researchers have presented the potential functional mechanisms of H19 as an oncogene in gastric cancer. Studies have shown that H19 and miR-675, the primary precursor of H19, act together as oncopgenes by promoting cell growth and malignant transformation in gastric cancer. H19 expression was negatively related to the expression of miR-141 in gastric cancer. The proliferation and invasion of gastric cancer could be accelerated by H19, but suppressed by miR-141. The competitive inhibitory relationship between H19 and miR-141 plays significant roles in the development of gastric cancer.

**Growth arrest-specific transcript 5**

Growth arrest-specific transcript 5 (GAS5), a long non-coding RNA of approximately 650 nts, was originally isolated when screening for potential tumor suppressor genes during growth arrest. The aberrant expression of GAS5 has been found in a variety of human malignancies, including prostate cancer, renal cell carcinoma, and breast cancer. Furthermore, by regulating apoptosis and the cell cycle, GAS5 managed to arrest the growth of many cancer cell lines. Given the statistics above, the potential tumor suppressor role of GAS5 is clear. In a study that retrospectively analyzed the expression of GAS5 in 89 patients with gastric carcinoma, Sun et al. found that the decreased GAS5 expression was a common event, and that downregulation of GAS5 was positively correlated with tumor size, tumor stage, invasion depth and regional lymph nodes. Another study also demonstrated lower expression levels of GAS5 in gastric cancer tissues vs non-cancerous tissues, and its positive relation to tumor size and clinical stage.

The downregulation of GAS5 in gastric cancer has been generally proven, however the functional mechanisms of it remain to be elucidated. Accumulating evidence shows that GAS5 could function by binding with miRNA during the process of tumorigenesis. Li et al. found that overexpression of GAS5 could suppress cell proliferation in gastric cancer cells by negatively regulating miR-222, which was proven to be an oncogenic miRNA. Liu et al. showed that GAS5 expression in gastric cancer cells was inversely correlated with upregulated expression.
of miR-23a, indicating that GASS affected the biological behavior of gastric cancer by negatively regulating miR-23a expression. GASS has also been reported to be further downregulated in Adriamycin (ADM)-resistant gastric cancer cells. Nevertheless, when ADM-resistant gastric cell lines were transfected to promote GASS overexpression, they were more sensitive to ADM treatment, suggesting that GASS may act as a potential therapeutic target in gastric cancer treatment[79].

Maternally expressed gene 3
Located on chromosome 14q32.3, maternally expressed gene 3 (MEG3) is downregulated in multiple cancer tissues and cells[80,81]. It has been proven that MEG3 is a tumor suppressor gene involved in various types of cancers, including gastric cancer. A previous study that detected MEG3 expression in 31 patients with gastric cancer showed that MEG3 was significantly downregulated in gastric cancer tissues vs adjacent non-cancerous tissues. Furthermore, it demonstrated that MEG3 expression was negatively-related to tumor size and positively-related to overall survival rates of gastric cancer patients[82]. Accumulating studies demonstrated that overexpression of MEG3 could inhibit proliferation and metastasis, and that MEG3 was strongly correlated with deep tumor invasion, advanced metastasis and poor gastric cancer prognosis[82-84].

Increasing evidence reveals that IncRNA might play a crucial role in the occurrence and development of gastric cancer by interacting with miRNAs and promoting signaling pathways[85,86]. Studies showed that MEG3 could act as a competing endogenous RNA that sponges different miRNAs, such as miR-148a, miR-770, miR-181 and miR-141, to regulate the malignant activity of gastric cancer[85,87-89]. Other studies showed that overexpression of MEG3 promoted the expression of p53 in gastric cancer cell lines, indicating that MEG3 may suppress the proliferation and metastasis of gastric cancer via p53-dependent transcription pathways[82].

Long intergenic non-coding RNA 00152
Located on chromosome 2p11.2, long intergenic non-coding RNA 00152 (LINC00152) has an 828 nt-long transcript[90]. In a study in which the expression level of LINC00152 was detected in 71 gastric cancer tissues and their paired non-cancerous tissues, Pang et al[91] found remarkable overexpression of LINC00152 in gastric carcinoma, making it a potential novel biomarker for predicting gastric cancer. Moreover, high expression of LINC00152 was positively-correlated with tumor size, invasion depth and prognosis[92].

Functional analysis showed that silencing LINC00152 could inhibit cell proliferation, arrest cell cycle at the G1 phase, induce late apoptosis, suppress EMT and inhibit cell migration and invasion[93]. Another study demonstrated that gastric cancer cell proliferation could be remarkably inhibited by knocking down LINC00152. Moreover, LINC00152 could exert its function by binding to the oncogenic driver epidermal growth factor receptor (EGFR), leading to subsequent EGFR activation, which is a significant step in the tumorigenesis of gastric cancer[94]. Huang et al[95] discovered that LINC00152 was inversely-related to miR-193a-3p, which could significantly reduce gastric cancer cell proliferation and inhibit tumor growth by targeting MCL1. Thus, LINC00152 exerts its biological effects in gastric cancer development through the LINC00152/miR-193a-3p/MCL1 pathway[96]. LINC00152 could also bind to the enhancer of zeste homolog 2 (EZH2), which might lead to the repression of p15 and p21, thereby inducing gastric cancer cell cycle progression[97].

Urothelial carcinoma-associated 1
Researchers first discovered urothelial carcinoma-associated 1 (UCA1) in urinary bladder carcinoma. UCA1 was then shown to be an oncosgenic long non-coding RNA[98,99]. Deregulation of UCA1 has been reported in a variety of additional human malignancies as well, such as melanoma, breast cancer, colorectal cancer, and tongue squamous cell carcinoma[98-100]. Recently, UCA1 has consistently been proven to play significant roles in the pathogenesis of gastric cancer. In a previous study, which analyzed UCA1 expression in 112 tumor and adjacent normal tissue samples from gastric cancer patients, researchers found that UCA1 was dramatically overexpressed in gastric cancer tissues and cell lines. Further clinicopathological analysis showed that the expression level of UCA1 was positively related to tumor size, invasion depth, TNM stage and poor overall survival[101].

Functional studies revealed that UCA1 expression could enhance cell proliferation, colony formation, and invasion of gastric cancer cells, and that silencing of UCA1 inhibits tumor growth. Gu et al[102] found that UCA1 might function by both negatively regulating miR-590-3p expression and activating the expression of its downstream target CREB1. UCA1/miR590-3p/CREB1 may be a potential target for the treatment of gastric cancer[103]. Another study indicated that knockdown of UCA1 reduced EMT-related protein levels, and that this effect could be partially rescued by treatment with transforming growth factor β1 (TGFβ1). Hypothetically, UCA1 might promote the proliferation, invasion and metastasis of gastric cancer upon TGFβ1 induction[103]. Moreover, Shang et al[104] demonstrated that chemotherapeutic resistance to ADM in gastric cancer cells was depressed, and that the half maximal inhibitory concentration (IC50) of ADM was also strongly decreased by silencing UCA1, thus making it a potential chemotherapeutic target for gastric cancer.

Metastasis-associated lung adenocarcinoma transcript 1
Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), encoded on chromosome 11q13.1, is a long non-coding RNA with a length of more than 8000 nts. In response to growth signals, MALAT1 could bind to unmethylated PRC2 proteins and thus activate the
growth control program. At first, researchers found that MALAT1 could function as a metastatic biomarker for early-stage lung carcinomas. Recently, MALAT1 overexpression has been observed in a variety of solid carcinomas, including gastric cancer, indicating that MALAT1 plays an important role in cancer development and metastasis. By analyzing expression levels of MALAT1 in gastric cancer tissues and paired non-cancerous tissues, researchers revealed the upregulation of MALAT1 and the positive correlation between expression level and local invasion, lymph node invasion, peritoneal metastasis and short overall survival time. Another study illustrated that MALAT1 could also serve as a competing endogenous RNA for miR-23b-3p and diminish its inhibitory effect on ATG12, which is a significant regulator of autophagy. This would thus promote chemo-induced autophagy and chemoresistance in gastric cancer cells. These findings revealed that MALAT1 could function as a therapeutic target for gastric cancer.

In addition to the well-documented IncRNAs discussed above, many other IncRNAs play important pathological roles in gastric cancer (Table 1). ANRIL is an antisense IncRNA located in the INK4a gene area. ANRIL has been shown to be overexpressed in gastric cancer and positively-related to tumor size, TNM stage and decreased survival. ANRIL regulates the development of gastric cancer by modulating miR-99a/miR-449a through the mTOR and CDK6/E2F1 pathways. FENDRR is one of the IncRNAs that plays significant roles in tumorigenesis. Researchers have demonstrated the downregulation of FENDRR and its correlation with invasion depth, metastatic lymph nodes and poor patient prognosis. FENDRR exerts its function by targeting FN1 and MMP2/MMP9. Other IncRNAs found to be overexpressed in gastric cancer include AFAP1-AS1, Sox2ot and CCAT2, while Linc00261, SNHG5 and LincRNA717 were downregulated in gastric cancer.

Table 1 Deregulations of long non-coding RNA associated with gastric cancer in this review

| LncRNA       | Deregulation | Biological roles                                        | Ref. |
|--------------|--------------|--------------------------------------------------------|------|
| HOTAIR       | Upregulated  | Induces EMT and promotes metastasis                     | [46-55]|
| H19          | Upregulated  | Promotes cell growth, proliferation, invasion           | [56-70]|
|              |              | Promotes EMT                                           |      |
| GAS5         | Downregulated| Suppresses cell proliferation                           | [71-79]|
| MEG3         | Downregulated| Suppresses cell proliferation and metastasis            | [80-89]|
| LINC00152    | Upregulated  | Promotes cell proliferation and tumor growth            | [90-95]|
| UCA1         | Upregulated  | Promotes cell proliferation, invasion, metastasis       | [96-104]|
| MALAT1       | Upregulated  | Promotes cell proliferation and invasion                | [105-118]|
| ANRIL        | Upregulated  | Promotes tumor growth and metastasis                    | [119-121]|
| FENDRR       | Downregulated| Inhibits migration and invasion                         | [122]|
| AFAP1-AS1    | Upregulated  | Promotes cell proliferation and cell cycle progression   | [123, 124]|
| Sox2ot       | Upregulated  | Promotes cell growth and motility                       | [125]|
| CCAT2        | Upregulated  | Promotes EMT                                           | [126]|
| Linc00261    | Downregulated| Represses metastasis                                    | [127]|
| SNHG5        | Downregulated| Suppresses cell proliferation and metastasis            | [128]|
| LincRNA717   | Downregulated| Inhibits tumor growth and invasion                       | [129]|

EMT: Epithelial-to-mesenchymal transition; ADM: Adriamycin; LncRNA: Long non-coding RNA.

CONCLUSION

In summary, with the rapid development of various bioinformatic techniques, thousands of IncRNAs have been discovered. Thus far, various studies have proven the significant functions of IncRNAs in tumorigenesis of gastric cancer. Aberrantly-expressed IncRNAs might be used as diagnostic biomarkers, prognostic markers, and therapeutic targets for gastric cancer. However, our current understanding of IncRNAs in relation to gastric cancer remains limited. As a result, more investigations are necessary to gain a better understanding of IncRNAs and their mechanisms in gastric cancer.
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A. Prognostic significance of drug-regulated genes in high-grade spectrum of human carcinomas.

B. RNA is a marker for murine hepatocellular carcinomas and a Expression profile of microRNAs in c-Myc induced mouse mammary tumors. Breast Cancer Res Treat 2009; 118: 185-196

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