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

Yu H *et al*. Emerging role of LncRNA in the development of gastric cancer

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**Abstract**

Gastric cancer is a common malignancy worldwide 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 do not or rarely encode proteins. In recent decades, deregulation of lncRNAs has been shown to be involved in tumorigenesis and 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 function of lncRNAs will help to gain a better understanding of the pathogenesis and help develop novel treatment 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:** Gastric cancer; Long non-coding RNAs; Function; Tumorigenesis; Diagnostic marker; Therapeutic target

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

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**INTRODUCTION**

Gastric cancer is one of the most familiar malignancies in the digestive tract[1]. Furthermore, there has been a sustainable growth in the incidence and mortality rates of gastric cancer due to late diagnosis. The 5-year survival rate could reach to 90%-97% if the patients are diagnosed early and get prompt treatment, endoscopically or surgically. Nevertheless, the 5-year survival rate is under 20% for terminal cancer patients[2-8]. As a result, prompt diagnosis of gastric cancer would significantly improve prognosis. 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, it has been demonstrated, with the rapid evolution of whole-genome analysis of gene expression, that most of the genome is transcribed into RNAs that has 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 development of novel diagnostic tools and targeted therapies. Furthermore, multiple lncRNAs have been shown to be related to diverse biological processes of 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 also explore their potential capacity to serve as diagnostic or prognostic biomarkers.

***Structure of lncRNAs***

Length of transcript over 200 nts and little protein-coding potential are two of the main characteristics that distinguish lncRNAs from others[17]. Researchers first identified lncRNA when trying to sequence full-length cDNA in mouse[18]. Then, a 2.2 kilobase functional lncRNA termed HOTAIR was shown to be involved in multiple process of epigenetic regulation[19]. In the past decade, with the development of transcriptomics, more lncRNAs have been recognized as an important functional products of the genome[20]. The polyadenylation and transcription of lncRNAs are commonly held by RNA polymerase (RNAP) II[21-23]. The length of lncRNAs varies typically from 1000 to 10000 nts, and some lncRNAs can reach 100000 nts[20]. To date, the sequence and molecular structure of many lncRNAs still need to be elucidated. For sequence elements, some lncRNAs may perfectly match Watson-Crick base pairing in order to function properly, while others would utilize imperfect pairing, where Watson-Crick base pairs are interspersed with non-Watson-Crick pairs[17]. In a previous study, an analysis of 204 lncRNAs and their comparison to protein-coding transcripts showed that a paucity of introns, low GC content and lack of start codons were some of the sequence trait of lncRNAs. Some of the biological features of lncRNAs including nucleus position and less transcription level, are generated from the sequence trait formerly mentioned[24]. The secondary elements and three-dimensional structures of RNA also play a vital role in their action mode, but structural studies of lncRNAs have not been performed.

***Category of lncRNAs***

Thus far, there has been no systematic classification of lncRNAs. Actually, 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 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 5 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) Bidiretional lncRNA is transcribed in a strand while an adjacent protein-coding gene initiates expression in the same strand simultaneously; (4) Intronic lncRNA is transcribed entirely from within introns of protein-coding genes; and (5) Intergenic lncRNA is transcribed from within genomic interval 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). Expression level of adjacent genes can be regulated by cis-lncRNAs, while that of remote genes by trans-lncRNAs[25].

Recent advances in high-throughput transcriptome sequencing technologies have made it feasible to conduct deep mining on 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, researches 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 convened chromatin remodeling complexes to particular region 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 RNA (siRNA) has been shown to be able to mediate deletion of specific lncRNA and further alter the expression lever[30]. In addition to acting through PRC2, some lncRNAs recruit DNA methyltransferases or other complexes directly 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 from within adjacent gene promoters. These lncRNAs can modulate the function of specific gene by interfering the binding of protein factors. For example, non-coding RNA SRG1 is transcribed across the promoter of *SER3* gene, and the expression of SRG1 can remarkably repress SER3, the mechanism of which is that transcription of SRG1 in the promoter area disturbs the binding with activators[36]. LncRNAs can also be transcribed from within distal enhancers and recruit transcription factors to this loci to regulated the expression level of neighboring genes[37]. Furthermore, lncRNAs can act by regulating RNAP Ⅱ activity[38]. Some lncRNAs could regulate the transcription of key apoptotic genes, which is one of the vital pathways for carcinogenesis control[39]. For instance, lncRNA INXS is transcribed from the intron of *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 dimer *in vivo*. The dimer are then spliced into small RNAs, which can balance effect of X-chromosome inactivation through the RNAi-mediated silencing[41]. It has also been demonstrated that some lncRNAs could act as competing endogenous RNAs (ceRNAs). These lncRNAs were able to bind miRNAs (sponging) and diminish the inhibitory effect on their natural targets[42]. LncRNA sponges are widely involved in the tumorigenesis of cancers. For example, in hepatocellular carcinoma, lncRNA CCAT1 could act as 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 further discovered.

**ROLES OF LNCRNAS IN CANCER**

Aberrant expression of genes is the foundation of pathogenesis of cancer. 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 (SNP) associated with malignant tumor is found to be located in the non-protein-coding loci. Recent studies have shown that many cancer risk loci are transcribed into non-coding RNAs, particularly the 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. The evidence to date shows that some lncRNAs can recruit protein factors to particular region of the genome to epigenetically modify the chromatin, while others can regulate the protein signaling pathways underlying carcinogenesis. LncRNAs can functionally control the cellular growth, division and differentiation, thus making them the focus of current cancer research.

As mentioned above, lncRNAs are key regulators in 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 up-regulated in the prostate cancer and precursor lesion prostatic intraepithelial neoplasia, and the expression level of PRNCR1 in the urine samples is elevated, making it a fine noninvasive indicator of prostate cancer[45].

***Deregulations of lncRNAs in gastric caner***

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 been shown to be involved in gastric cancer as well. Among lncRNAs associated with gastric cancer, some of them function as oncogenes and are up-regulated in gastric cancer, while others are down-regulated and serve as tumor suppressors. In this section, we briefly review some of the well-studied lncRNAs in gastric cancer.

***HOX transcript antisense RNA***

Located in chromosome 12, the HOX transcript antisense RNA (HOTAIR) contains 6232 nt and encodes 2.2 kb long non-coding RNA molecule. It is an non-protein-coding RNA with significant regulatory potential through gene remodeling[46]. High levels of HOTAIR expression in a variety of malignancies are associated with cancer cell proliferation, apoptosis, invasion, progression, making it a significant predictor of subsequent metastasis and death[47-50].

In gastric cancer tissues, the expression level of HOTAIR is remarkably elevated, which suggests that HOTAIR functions as an oncogene in gastric cancer. Song *et al*[51] 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*[52] elucidated that up-regulation of HOTAIR was correlated with metastasis of lymph nodes, invasion of vessels and reduction of survival time in gastric cancer. Chen *et al*[53] also found that HOTAIR was significantly up-regulated in gastric cancer tissues, and the overexpression of which 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 the foundation of metastasis. Liu *et al*[54] found that by suppressing HOTAIR, the EMT process could be reversed in the gastric cancer cells. Other research showed that HOTAIR promoted gastric cell EMT and metastasis by inhibiting E-cadherin expression through an interaction with EZH2[53]. The functional SNP rs4759314 of HOTAIR had strong associations with gastric cancer susceptibility. SNP rs4759314, which resides in the promoter area of an intron, has been demonstrated to influence the expression of HOTAIR by interfering with exactly this promoter[55].

***H19***

LncRNA H19, discovered in 1991 by Bartolomei[56], was the first imprinted *lncRNA* gene identified. H19, residing in chromosome 11p15.5, is transcribed from gene H19/IGF2[57,58]. Similar to mRNA, the *H19* gene contains five exons and is transcribed by polymerase II. However, it doesn’t contain a common open reading frame. Generally, the high conservatism in the structure of H19 is considered to be responsible for the universality of its functions[59]. Deregulation of H19 has been reported in various malignancies, such as breast cancer, bladder cancer and cervical carcinomas, which indicates the oncogenic role of H19[60-64]. In gastric cancer, H19 has also been reported to function oncogenetically, and the overexpression may contribute to gastric carcinogenesis. Li *et al*[58] demonstrated the up-regulation of lncRNA H19 in gastric cancer tissues comparing with paired normal tissues and its positive correlation with lymph node metastasis and clinical stage. *In vitro*, up-regulation of H19 could accelerate the proliferation, migration and invasion of gastric cancer cell, while knockdown of H19 caused apoptosis[61,65-67]. Moreover, Hashad *et al*[68] demonstrated that H19 was up-regulated in the plasma of gastric cancer patients, making it a potential non-invasive diagnostic biomarker for gastric cancer.

Multiple previous researches have presented the potential function mechanisms of H19 as an oncogene in gastric cancer. Studies have shown that H19 and miR-675, the primary precursor of which is H19, act together as oncogenes by promoting cell growth and malignant transformation in gastric cancer[58]. H19 expression was negatively related with 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 inhibition relation of H19 and miR-141 plays significant roles in the development of gastric cancer[69]. Other research demonstrated that H19-PEG10 axis is involved in EMT, and the knockdown of axis could induce tremendous changes in the expression of EMT-associated proteins, making it a potential therapeutic target in gastric cancer[70].

***Growth arrest-specific transcript 5***

Growth arrest-specific transcript 5 (GAS5), a long non-coding RNA of approximately 650 nt, was originally isolated when screening for potential tumor suppressor genes during growth arrest[71]. 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 cell cycle, GAS5 managed to arrest the growth of many cancer cell lines[72-74]. 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*[75] found that the decreased GAS5 expression was a common event and that down-regulation of GAS5 was positively correlated to tumor size, tumor stage, invasion depth and regional lymph nodes. Another study also demonstrated low expression level of GAS5 in gastric cancer tissues than non-cancerous tissues and its positive relation with tumor size and clinical stage[76].

The down-regulation of GAS5 in gastric cancer has been generally proved, but the function mechanisms of it remain to be elucidated. Accumulating evidence shows that GAS5 could function by binding with miRNA in the process of tumorigenesis. Li *et a*l[77] found that overexpression of GAS5 could suppress cell proliferation of gastric cancer cells by negatively regulating miR-222, which had been proved to be an oncogenic miRNA. Liu *et al*[78] showed that GAS5 expression in gastric cancer cells was inversely correlated with up-regulated expression of miR-23a, indicating that GAS5 affected biological behavior of gastric cancer by negatively regulating miR-23a expression. GAS5 has also been reported to be further down-regulated in Adriamycin (ADM)-resistant gastric cancer cells. Nevertheless, when ADM-resistant gastric cell lines were transfected for GAS5 overexpression, they were more sensitive to ADM treatment, suggesting that GAS5 may act as a potential therapeutic target in gastric cancer treatment[79].

***Maternally expressed gene 3***

Located in chromosome 14q32.3, maternally expressed gene 3 (*MEG3*) is down-regulated in multiple cancer tissues or cells[80,81]. It has been proved that *MEG3* is a tumor suppressor gene 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 down-regulated in gastric cancer tissues than adjacent non-cancerous tissues. Furthermore, it demonstrated that *MEG3* expression was negatively related to tumor size and positively related with overall survival of gastric cancer[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 prognosis of gastric cancer[82-84].

Increasing evidence reveals that lncRNA might play a crucial role in the occurrence and development of gastric cancer by interacting with miRNAs and then participating in signaling pathways[85,86]. Studies showed that *MEG3* could act as a competing endogenous RNA, which sponged different miRNAs, such as miR-148a, miR-770, miR-181 and miR-141, to regulate the malignant activity in gastric cancer[83,87-89]. 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 in chromosome 2p11.2, long intergenic non-coding RNA 00152 (LINC00152) has a 828 nt-long transcript[90]. In a study 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 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 when knocking-down LINC00152. Moreover, LINC00152 could exert its function by binding with oncogenic driver EGFR and leading to the subsequent activation of EGFR, which is a significant step in the tumorigenesis of gastric cancer[94]. Huang *et al*[92] 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 exerted its biological effects in the development of gastric cancer through the LINC00152/miR-193a-3p/MCL1 pathway[92]. LINC00152 could also bind to the enhancer of zeste homolog 2 (EZH2), which might lead to the repression of p15 and p21 and then induce gastric cancer cell cycle progression[95].

***Urothelial carcinoma-associated 1***

Researcher first discovered urothelial carcinoma-associated 1 (UCA1) in urinary bladder carcinoma. UCA1 was then shown to be an oncogenic long non-coding RNA[96,97]. Deregulation of UCA1 has been reported in a variety of human malignancies besides urinary bladder cancer, such as melanoma, breast cancer, colorectal cancer, tongue squamous cell carcinomas[98-100]. Recently, UCA1 has constantly been proved to play significant roles in the pathogenesis of gastric cancer. In a previous study that detected UCA1 expression in 112 tumorous and adjacent normal tissues 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 cell invasion of gastric cancer cells, and silencing of UCA1 inhibits tumor growth. Gu *et al*[102] found that UCA1 might function by negatively regulating miR-590-3p expression and activating the expression of its downstream target CREB1. The UCA1/miR590-3p/CREB1 may be a potential target for treatment of gastric cancer[102]. Another study indicated that knowdown of UCA1 reduced the EMT-related protein level, and 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 under TGFβ1 induction[103]. Moreover, Shang *et al*[104] demonstrated that the chemotherapy resistance to ADM in gastric cancer cells was depressed and the half maximal inhibitory concentration (IC50) of ADM was also strongly decreased by silencing UCA1, making it a potential target of chemotherapy 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 nt. In response to growth signals, MALAT1 could bind to unmethylated PRC 2 proteins and thus activate the growth control program[105]. At first, researchers found that MALAT1 could function as metastatic biomarker for early-stage lung carcinoma[106]. Recently, overexpression of MALAT1 has been observed in a variety of solid carcinomas, including gastric cancer, indicating that MALAT1 played an important role in the development and metastasis of malignancies[107-112]. By analyzing expression level of MALAT1 in gastric cancer tissues and paired non-cancerous tissues, researchers revealed the up-regulation of MALAT1 and the positive correlation between expression level and local invasion, lymph node invasion, peritoneal metastasis and short overall survival time[113,114]{Feng, 2017 #301;Okugawa, 2014 #329;Li, 2017 #333}. Another study showed that MALAT1 was aberrantly highly expressed in gastric cancer patients with distant metastasis compared to those without metastasis. Furthermore, functional studies demonstrated that EMT would be prevented when epigenetically silencing MALAT1, thus inducing the inhibition of cancer cell migration and invasion[115,116]. According to these evidences, the diagnostic potential of MALAT1 for gastric cancer is unequivocal.

An *in vitro* study confirmed that MALAT1 was negatively correlated with the expression level of miR-1297, which could promote cell proliferation and invasion by targeting HMGA2. Moreover, silencing MALAT1 could reduce the protein level of HMGA2 by eliminating the inhibition of miR-1297, indicating that MALAT1 functioned as an oncogenic lncRNA partly by modulating HMGA2 expression[113]. Another report illustrated that MALAT1 inhibited the expression of tumor suppressor PCDH10 by binding to EZH2, leading to migration and invasion of gastric cancer cell[117]. 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, thus promoting chemo-induced autophagy and chemoresistance of gastric cancer cells. These findings revealed that MALAT1 could function as therapeutic target for gastric cancer[118].

In addition to the well-documented lncRNAs discussed above, many other lncRNAs play important pathological roles in gastric cancer (Table 1). ANRIL is an antisense lncRNA located in the *INK4* gene area. ANRIL has been shown to be overexpressed in gastric cancer and positively related to tumor size, TNM stage and decreased survival. ANRIL regulated the development of gastric cancer by modulating miR-99a/miR-449a through mTOR and CDK6/E2F1 pathway[119-121]. FENDRR is one of the lncRNAs that play significant roles in tumorigenesis. Researchers have demonstrated down-regulation of FENDRR and its correlation with invasion depth, metastatic lymph nodes and poor prognosis of patients. FENDRR exerted its function by targeting FN1 and MMP2/MMP9[122]. Other lncRNAs found to be overexpressed in gastric cancer include AFAP1-AS1, Sox2ot and CCAT2, while Linc00261, SNHG5 and LincRNA717 were down- regulated in gastric cancer[123-129].

**CONCLUSION**

In summary, with the rapid development of various bioinformatic techniques, thousands of lncRNAs have been discovered. Thus far, various studies have proven the significant functions of lncRNAs in tumorigenesis of gastric cancer.Aberrantly expressed lncRNAs might be used as diagnostic biomarkers, prognosis markers and therapeutic targets for gastric cancer. However, our current understanding of lncRNAs related to gastric cancer remains limited. As a result, more investigations are necessary to gain a better understanding of lncRNAs and their mechanisms in gastric cancer.

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

|  |  |  |  |
| --- | --- | --- | --- |
| **LncRNA** | **Deregulation** | **Biological roles** | **Ref.** |
| HOTAIR | Up-regulated | Induces EMT and promoted metastasis | [46-55] |
| H19 | Up-regulated | Promotes cell growth, proliferation, invasionPromotes EMT | [56-70] |
| GAS5 | Down-regulated | Suppresses cell proliferationSensitizes cell to ADM treatment | [71-79] |
| MEG3 | Down-regulated | Suppresses cell proliferation and metastasis | [80-89] |
| LINC00152 | Up-regulated | Promotes cell proliferation and tumor growth | [90-95] |
| UCA1 | Up-regulated | Promotes cell proliferation, invasion, metastasisDepresses resistance to ADM treatment | [96-104] |
| MALAT1 | Up-regulated | Promotes cell proliferation and invasionPromotes chemo-induced autophagy and chemoresistanse | [105-118] |
| ANRIL | Up-regulated | Promotes tumor growth and metastasis | [119-121] |
| FENDRR | Down-regulated | Inhibits migration and invasion  | [122] |
| AFAP1-AS1 | Up-regulated | Promotes cell proliferation and cell cycle progression | [123,124] |
| Sox2ot | Up-regulated | Promotes cell growth and motility | [125] |
| CCAT2 | Up-regulated | Promotes EMT | [126] |
| Linc00261 | Down-regulated | Represses metastasisInhibits EMT | [127] |
| SNHG5 | Down-regulated | Suppresses cell proliferation and metastasis | [128] |
| LincRNA717 | Down-regulated | Inhibits tumor growth and invasion | [129] |

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