Research Progress and Application Prospects of Long Noncoding RNAs in Gastric Neoplasms

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Abstract
Long noncoding RNAs (lncRNAs) are noncoding RNAs longer than 200 nt that have almost no function for encoding proteins. As an important regulatory molecule of the human genome, lncRNAs play a regulatory role in the human body. LncRNAs have a variety of functions, such as signaling, guiding, baiting or scaffolding of functional proteins, and are closely related to tumor development. Gastric cancer is one of the most common malignant tumors. It has a high incidence, a low early diagnosis rate, and a poor prognosis, and it seriously threatens human health. Abnormal expression of lncRNAs can affect the occurrence, development, invasion and metastasis of gastric cancer. Therefore, lncRNAs are expected to become important biomarkers and new targets for the diagnosis and treatment of gastric cancer. LncRNAs have a significant potential to guide the diagnosis, treatment and prognosis of gastric cancer. This article reviews lncRNAs and the mechanisms that have been discovered in recent years related to gastrointestinal tumors.

Keywords
LncRNA, gastric cancer, cell proliferation, apoptosis, invasion, metastasis

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Introduction
It has been thought that tumors are caused by mutations in protein-coding genes. In recent years,¹,² more than 80% of tumor-associated single nucleotide polymorphisms in noncoding regions of the genome have been found. Non-coding RNA (ncRNA) is commonly employed for RNA, but this does not mean that such RNAs do not contain information nor have function, including microRNAs and lncRNAs. Although lncRNAs do not participate in protein expression, they regulate gene expression at the transcription and post-transcriptional level. LncRNAs are related to a variety of diseases and are closely related to the occurrence and development of tumors. Many tumor-associated lncRNAs have been found in digestive system diseases.³ Among the known lncRNAs, some of them function as proto-oncogenes and others as tumor suppressors. LncRNAs have become a new hotspot in tumor research after microRNAs because of its potential role in carcinogenesis and suppression of cancer. Every year, nearly 1 million new patients are diagnosed with gastric cancer in China. The morbidity and mortality rates of gastric cancer rank second among all cancers. Gastric cancer is the most common digestive system tumor with a multifactorial and complex pathogenesis.⁴ However, the mechanisms of occurrence and development of gastric cancer have not been clearly elucidated. How to find an effective predictive factor for the occurrence, development and prognosis of gastric cancer and guide clinical treatment have become popular research topic in recent years.

LncRNA
After the completion of the Human Genome Project, the analysis of the genome sequence and its transcripts found that the human genome includes approximately 20,000 protein-coding genes, which account for only approximately 2% of the total

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genes. More than 90% of the transcripts are noncoding RNAs (non-coding RNAs, ncRNAs). NcRNAs do not have open reading frames or protein translation functions. According to their functions, ncRNAs are divided into housekeeping ncRNAs and regulating ncRNAs. The regulating ncRNAs are expressed in cells with strict temporal and spatial regulation. Regulating ncRNAs can be divided into microRNAs and IncRNAs according to their lengths. Okazaki et al. first discovered IncRNAs in large-scale sequencing of mouse full-length cDNA libraries in 2002. IncRNAs are a class of RNA molecules whose transcripts are longer than 200 nucleotides and never encode proteins. MicroRNAs are a class of RNA molecules with transcript lengths ranging from 18 to 25 nucleotides and never encode proteins.

Studies have confirmed that microRNAs not only play a key role in gene regulation but also are important in cancer. LncRNAs have become a popular topic in global biological research after microRNAs. Recent studies have shown that there are approximately 15,000 types of IncRNAs in the human body. Most IncRNAs show different tissue specificities. LncRNA ChIP, northern blotting and high-throughput technology were used to screen out abnormally expressed IncRNAs related to diseases. Further studies have shown that IncRNAs are involved in the regulation of DNA methylation, miRNA precursors, mRNA degradation, phosphorylation, chromatin remodeling and other biological processes.

Recent studies have shown that IncRNAs can be regarded as oncogenes or tumor suppressor genes in tumorigenesis and development. A variety of IncRNAs abnormally expressed in different types of tumors were found by comparing the expression profiles of tumor and normal cells. IncRNAs are expected to become new tumor markers and targets for tumor therapy for the diagnosis, treatment, prognosis and monitoring of tumors. LncRNAs are often in a “deregulated” state in tumor cells compared to that of normal cells, indicating that IncRNAs are potential tumor biomarkers. The expression levels of IncRNAs are related to the efficacy of tumors. In addition, IncRNAs can be used as reference indexes for tumor prognosis. Moreover, the overexpression or downregulation of specific IncRNAs in tumor cells can often trigger apoptosis or make tumor cells sensitive to treatments that induce apoptosis. Therefore, IncRNAs can be used as therapeutic targets for certain types of tumors; for example, LUNAR1 was used as a T-cell acute lymphoblastic molecular marker and a potential therapeutic target for cellular leukemia. In addition, IncRNAs can also regulate tumor metastasis-related signaling pathways and participate in tumor migration and drug resistance. Drug resistance is also critical for the prognosis of patients with gastric cancer, and a lot of researches illuminated that long noncoding RNAs contribute to chemotherapy resistance in various tumors including gastric cancer.

The expression levels of IncRNAs in digestive system tumors are divided into those that are up- and downregulated, and most IncRNAs are upregulated. It is speculated that IncRNAs can play a role similar to proto-oncogenes or tumor suppressor genes. IncRNAs can provide new clues for the molecular treatment of digestive system tumors. Although most of the functions of IncRNAs are still unknown, current research has shown that IncRNAs are involved in the pathophysiological process of many diseases, especially in a variety of tumors whose expression is changed and involved in tumorigenesis and development. Mechanism complexity is an important feature of IncRNA. Amounts of IncRNAs may affect the decisive steps in tumor suppression and carcinogenesis. Further exploration of the underlying mechanism of IncRNA will benefit our understanding on the pathogenesis of gastric cancer.

With the continuous discovery of IncRNAs and the interpretation of their functions, researchers have found that IncRNAs exhibit multiple functions, including signaling, guiding, decoying or scaffoldiing molecules of functional proteins. IncRNAs regulate gene expression at multiple levels, and these include chromatin remodeling, gene transcription, translation, and protein modification. IncRNAs also participate in basic physiological processes such as development, immunity, and reproduction.

**Signal Function**

Some IncRNAs combine with specific proteins and locate related complexes to specific targets. The process affects the transcriptional activity and interferes with the transcription mechanism. An IncRNA can silence or activate a gene, a gene family or even the entire chromosome by cis or trans effects. Li et al. found that the IncRNA “Linc-POU3F3”, which is mainly distributed in the nucleus, recruited the histone lysine methyltransferase EZH2 to methylate the histone of the PUU3F3 gene promoter. POU3F3 cannot play a normal physiological role because it cannot translate the corresponding transcription factors, and this eventually leads to the occurrence of esophageal cancer.

**Guidance Function**

IncRNAs can bind specific proteins to form complexes and regulate physiological activities by binding to specific gene regions. Previous studies have shown that X-chromosome inactivation is closely related to the guiding effect of IncRNAs. HOXC transcript antisense RNA (HOTAIR) transcribed from the HOXC gene can form the chromatin remodeling protein complex PRC2 through a multipoint transaction and induce the HOXD gene to produce an inhibitory chromosomal structure. The 40 kb HOXD gene can inhibit the occurrence of transcription.

**Bait Function**

IncRNAs can induce a series of proteins, such as transcription factors, with gene regulatory functions. IncRNAs prevent
proteins from binding to corresponding functional sites and regulate physiological activities. LncRNA PANDA can bind to the transcription factor NF-YA, prevent P53-mediated apoptosis, and negatively regulate the expression of pro-apoptotic genes. NF-YA can transactivate the genes that induce apoptosis. However, the binding of PANDA to NF-YA causes the latter to leave the target gene.29

Scaffold Function
LncRNAs maintain the nuclear speckle structure by forming complexes with 2 or more proteins and regulating the assembly of multiple molecular components. The LncRNA HOTAIR can simultaneously bind to polycomb repressive complex 2 (PRC2) and lysine-specific demethylase 1 (LSD1)/REST corepressor (CoREST)/RE1-silencing transcription factor (REST) to form a histone demethylase complex that regulates the methylation of histone H3 lysine 27 (H3K27). Gene silencing regulates the methylation of histone H3 lysine 27 (H3K27) and the demethylation of histone H3 lysine 27 trimethylation (H3K27me3).30 Studies31 have found that some LncRNAs are strongly associated with multiple chromatin modification complexes. The LncRNA NEAT1-2 can be used as a scaffold for RNA and RNA binding proteins in the nucleus of motor neurons in amyotrophic lateral sclerosis, and it regulates the functions of related RNA binding proteins early in the disease.32

LncRNA and Gastric Cancer
In recent years, accumulating evidence has shown that the abnormal expression of LncRNAs is related to cellular processes and gastric cancer occurrence and development, such as tumor initiation. LncRNAs exhibit regulatory functions, including levels of transcription, post-transcription, and translation, which are considered as potential biomarkers and therapeutic targets in gastric cancer. Numbering studies have suggested that LncRNA can be used as a carcinogenic or tumor suppressor factor to participate in the occurrence and development of gastric cancer, which was found by comparing the LncRNA expression profiles of different tumor cells and normal cells. Gu et al conducted a high-throughput transcript test and revealed that 74 LncRNAs were differentially expressed more than 2 times in gastric cancer tissues compared with adjacent tissues. Among them, 43 were up-regulated and 31 were down-regulated, indicating that LncRNA played an important role in the development of gastric cancer.33 The role of LncRNA in gastric cancer and its regulatory mechanism are complex. It may directly act on mRNA molecules to affect the occurrence and development of gastric cancer, or affect upstream or downstream target genes, inhibit or promote the expression of related genes, or indirectly regulate target genes through signal pathways. LncRNAs ZFAS, PVT1, TUG1, H19, HULC, HOTAIR, MACC1, AK096174, PANDAR, CASC15, TP73-AS1 and GCRL1 play a carcinogenic role in the pathogenesis of GC, and promote cell proliferation, invasion and metastasis. On the contrary, LncRNAs MEG3, GAS5 and MT1JP, acted as tumor suppressor gene, can inhibit cell proliferation and promote apoptosis (Table 1).

| LncRNA | Role in GC | Mechanisms | References |
|--------|------------|------------|------------|
| ZFAS   | Oncogenic  | regulating miR-200b-mediated Wnt/β-catenin signaling | 35-37 |
| MEG3   | Tumor suppressor | inhibiting the expression of miR-21; affecting the expression of P53; upregulating the expression of the epithelial marker E-cadherin inhibiting the expression of the mesenchymal markers vimentin and fibronectin | 38-42 |
| GAS5   | Tumor suppressor | negatively regulating miR-222 and regulating the PTEN/Akt/mTOR pathway | 43,44 |
| PVT1   | Oncogenic  | binding to the FOXM1 protein and upregulating FOXM1 after translation; upregulating miR-124-3p-mediated ZEB1 | 45-47 |
| TUG1   | Oncogenic  | regulating PRC2 | 48-51 |
| H19    | Oncogenic  | enhancing inflammation induced by NF-kB; regulating miR-22-3p/Snail1 signaling pathway | 52,53 |
| HULC   | Oncogenic  | regulating miR-9-5p/MYH9 axis; regulating PI3K/AKT and JNK signaling pathways | 54-56 |
| HOTAIR | Oncogenic  | regulating miR-126/CXCR4 axis; regulating the activity of STAT3/Cyclin D1 and the expression of miR-454-3p | 57-62 |
| MACC1  | Oncogenic  | regulating c-Met/AKT/mTOR pathway | 63-69 |
| AK096174 | Oncogenic  | regulating E-cadherin, N-cadherin, ZEB1 and Snail | 70 |
| PANDAR | Oncogenic  | regulating the transcription of the CDKN1A gene through competitive binding with the p53 protein | 71-74 |
| MT1JP  | Tumor suppressor | acting as ceRNA of miR-214-3p and regulate p21 and Bim levels | 75-81 |
| CASC15 | Oncogenic  | regulating CDKN1A in the nucleus by interacting with EZH2 and WDR5; acting as ceRNA of miR-33a-5p | 82 |
| TP73-AS1 | Oncogenic  | regulating the miR-194-5p/SDAD1 pathway; regulating WNT/β-catenin signaling pathway | 83-85 |
| GCRL1  | Oncogenic  | sponging miR-885-3p and actively regulating CDK4 | 86 |

LncRNAs Related to Gastric Cancer Cell Proliferation and Apoptosis

ZFAS. Zinc finger antisense1 (ZFAS1) is a newly discovered LncRNA. Several studies have demonstrated34,35 that ZFAS1 is
MEG3. Maternally expressed gene 3 (MEG3) was first discovered by Miyoshi in 2000, and lncRNA-MEG3 is approximately 1.6 kb and is located on chromosome 14q32. It lacks a complete open reading frame and is considered a tumor suppressor gene in many different types of cancer. Dan et al. found that pcDNA3.1-MEG3 transfected with overexpressed MEG3 can significantly inhibit the proliferation of gastric cancer cells. Mechanistic studies have shown that miR-21, as a target of MEG3, can promote cell proliferation, and the expression of miR-21 is negatively regulated by MEG3. However, the transfection of pcDNA3.1-MEG3 can inhibit the effect of miR-21 on the proliferation of gastric cancer cells. This indicates that MEG3 inhibits the proliferation of gastric cancer cells by inhibiting the expression of miR-21. The overexpression of MEG3 and application of 5-Aza inhibited the proliferation and promoted apoptosis of MGC-803 cells. In gastric cancer tissues, MEG3 is highly methylated to reduce its expression. Once MEG3 expression is restored or its methylation is inhibited, tumor growth can be inhibited in vivo and in vitro. MEG3 may also inhibit the growth and proliferation of gastric cancer by affecting the expression of P53. Jiao et al. showed that the transfection of lncRNA-MEG3 inhibited tumor growth mainly by reducing the expression of vascular endothelial growth factor and increasing the expression of Bel-2. Upregulating the expression of the epithelial marker E-cadherin in gastric cancer cells and inhibiting the expression of the mesenchymal markers vimentin and fibronectin can inhibit epithelial-mesenchymal transition (EMT) and the progression of gastric cancer.

GAS5. Growth arrest-specific 5 (GAS5) is an lncRNA encoded by the gas5 gene. The expression levels of GAS5 were significantly negatively correlated with those of miRNA-106a-5p in gastric cancer tissues and cell lines (a decrease in GAS5 and an increased in miRNA-106a-5p). Overexpression of GAS5 inhibited the proliferation of gastric cancer cell lines and promoted apoptosis, while overexpression of miRNA-106a-5p reversed the effect caused by overexpressing GAS5. Overexpression of GAS5 can inhibit miRNA-106a-5p expression in vitro and in vivo, inactivating the Akt/mTOR pathway and inhibiting tumor growth. Li et al. found that when GAS5 expression was downregulated in gastric cancer cells, miR-222 expression was upregulated; that is, GAS5 inhibited miR-222 expression. Overexpression of GAS5 and knockdown of miR-222 inhibited gastric cancer cell proliferation, increased PTEN protein levels and decreased the protein levels of p-Akt and p-mTOR. GAS5 inhibits the proliferation of gastric cancer cells by negatively regulating miR-222 and regulating the PTEN/Akt/mTOR pathway.

PVT1. The plasmacytoma variant translocation 1 (PVT1) gene is a new type of lncRNA located on chromosome 8q24. Studies have found that PVT1 is significantly upregulated in gastric cancer tissues and enhances the proliferation of gastric cancer cells in vitro and in vivo. PVT1 directly binds to the FOXM1 protein and upregulates FOXM1 after its translation. Therefore, PVT1 achieves carcinogenic functions in a FOXM1-mediated manner. Zhao et al. demonstrated that PVT1 was overexpressed in gastric cancer tissues and was significantly associated with a high microvascular density and poor prognosis in gastric cancer. By up- and downregulating the expression of PVT1, the team found that PVT1 not only promotes tumor growth in vivo and in vitro but also significantly induces angiogenesis in tumors. This is because PVT1 directly interacts with the signal transduction activator phospho-STAT3 in the nucleus, and this improves the protein stability of PVT1 by protecting it from polyubiquitination and proteasome-dependent degradation. The combination of PVT1 activates the STAT3 signaling pathway and in turn increases the expression of VEGFA to stimulate angiogenesis. PVT1 expression is upregulated in paclitaxel (PTX)-resistant gastric cancer tissues and cells. By negatively regulating miR-124-3p, silencing PVT1 increased the sensitivity of gastric cancer-resistant cells to paclitaxel. ZEB1 is a direct target of miR-124-3p, and PVT1 upregulation enhances gastric cancer cell resistance to paclitaxel through miR-124-3p-mediated ZEB1.

TUG1. Taurine upregulated gene 1 (TUG1) was originally discovered in a whole-genome screening of mouse retinal cells treated with taurine, and TUG1 expression was upregulated. Zhang et al. found that the overexpression of TUG1 was associated with the prognosis of gastric cancer. Further experiments show that knocking out TUG1 can inhibit cell proliferation in vitro and in vivo. Mechanistic studies have shown that TUG1 plays a key role in cell arrest in G0/G1. In-depth research has proved that TUG1 is related to PRC2 and is required for cyclin-dependent protein kinase inhibitors (including p15, p16, p21, p27, and p57), which help regulate the cell cycle and proliferation of gastric cancer.

H19. H19 was the first cancer-related lncRNA discovered. The H19 gene is located on human chromosome 11p15.5. It has 5 exons and 4 introns. The H19 gene encodes a 2.3 kb noncoding
RNA molecule that is named H19. Some studies have confirmed that H19 is highly expressed in some cancers, including breast cancer, and has carcinogenic effects. There are also some studies that show that H19 is expressed in some cancers, including liver cancer. H19 can show carcinogenic or tumor suppressive effects in different tumors. This duality may be related to the functional diversity of H19 and tissue specificity. Research confirms that H19 promotes the growth of gastric cancer cells caused by a Helicobacter pylori infection by enhancing inflammation induced by NF-kB. Gan et al. found that the downregulation of H19 inhibited the proliferation and EMT of gastric cancer cells in vitro and inhibited the growth of tumors in vivo. H19 was also found to bind to miR-22-3p, and the expression levels of miR-22-3p were inversely related to those of H19 in gastric cancer tissues; in addition, tumor growth and metastasis were promoted through the miR-22-3p/Snail1 signaling pathway.

**HULC.** Highly upregulated in liver cancer (HULC) is a specific and highly expressed lncRNA found in liver cancer that regulates gene expression at the posttranscriptional level. Liu et al. found that HULC was upregulated in gastric cancer, while miR-9-5p was downregulated; both are related to the clinicopathological characteristics of gastric cancer patients. HULC combined with miR-9-5p inhibits miR-9-5p expression. Studies have confirmed that HULC inhibits the progression of gastric cancer by regulating the miR-9-5p/MYH9 axis. Knockdown of HULC can inhibit cell proliferation, promote apoptosis, and inhibit tumor growth of gastric cancer in vivo. Genipin inactivates the PI3K/AKT and JNK signaling pathways by downregulating HULC, inhibits MNK45 cell proliferation and induces apoptosis. Zhang et al. found that silencing HULC can enhance chemotherapy-induced apoptosis of gastric cancer cells.

**LncRNAs Related to Gastric Cancer Invasion and Metastasis**

**HOTAIR.** HOX transcript antisense RNA (HOTAIR) is located in the 12q13.13 HOX gene cluster, is coexpressed with the HOXC gene, and shuttles between chromosomes 12 and 2 through the subunit of polycomb repressive complex 2. HOTAIR participates in the metastasis of malignant tumors through different pathways. By knocking down the Runx3 gene, the reduction in the cell migration induced by HOTAIR-targeted siRNA and the corresponding increase in Claudin1 expression can be significantly attenuated, suggesting that the HOTAIR-Runx3-Claudin1 gene has a role in the aggressiveness of gastric cancer. Uptregulation of HOTAIR is positively correlated with vascular invasion, multiple lymph node metastases, and a lower overall survival in gastric cancer. Knocking down HOTAIR inhibits gastric cancer cell growth, affects cell cycle distribution, and increases the protein levels of P21 and P53. Xiao et al. found a negative correlation between miR-126 and HOTAIR. CXCRI4 is considered a direct target of miR-126. Further research shows that a high expression of HOTAIR promotes the proliferation and metastasis of gastric cancer through the miR-126/CXCRI4 axis and downstream signaling pathways. Knockdown of HOTAIR can inhibit the expression of STAT3 and Cyclin D1 in AGS and SGC7901 cells, indicating that by inhibiting the activity of STAT3/Cyclin D1, downregulating HOTAIR can stimulate miR-454-3p expression and inhibit the development of gastric cancer.

**MACC1.** Metastasis-associated in colon cancer-1 (MACC1) is a transcriptional regulator of MET, which is closely related to the proliferation, invasion and chemotherapy resistance of a variety of malignant tumors and is a key regulator in tumorigenesis and cancer progression. MACC1 is a key regulator of the HGF/c-MET axis and an important target for tumor therapy. Tong et al. found that the expression of MACC1, c-Met and PD-L1 was upregulated in gastric cancer tissues, and there was a positive correlation between their expression levels. MACC1 regulates PD-L1 expression and tumor immunity in gastric cancer cells through the c-Met/akt/mTOR pathway. Jin et al. used a meta-analysis of 9 studies that included 2103 patients with gastric cancer. The analysis showed that high expression of MACC1 was significantly associated with a poor overall survival and was significantly associated with distant metastases and vascular infiltration. Several studies have shown that antisense lncRNAs have regulatory effects on the expression of their counterparts. MACC1-AS1 is a homologous antisense lncRNA of MACC1. Analysis of the expression of MACC1-AS1 and MACC1 using the TCGA database and patient tumor samples also verified this relationship. MACC1-AS1 is significantly elevated in gastric cancer and has a strong correlation with MACC1 expression, which is closely related to the clinical stage and survival prognosis of patients with gastric cancer. MACC1-AS1 can promote the occurrence and metastasis of gastric cancer in vivo and in vitro. MACC1-AS1 regulates MACC1 expression and promotes metabolism by promoting glycolysis and antioxidant capacity.

**AK096174.** Microarray analysis showed that AK096174 expression was significantly increased in gastric cancer tissues. Downregulating the expression of AK096174 by regulating E-cadherin, N-cadherin, ZEB1 and Snail can suppress EMT and inhibit the migration and invasiveness of SGC-7901 and BGC-823 cells. Further research found that AK096174 was positively correlated with the expression of the WD repeat-containing protein 66 (WDR66) gene at the translation level. Decreasing WDR66 expression can attenuate the promoting effect of AK096174 for the development of gastric cancer.

**PANDAR.** Promoter of CDKN1A antisense DNA damage activated RNA (PANDAR) is a lncRNA that plays an important role in the occurrence and development of various cancers. Studies have found that high expression of PANDAR may play a poor prognostic role in gastric cancer. PANDAR is a gene that induces DNA damage and inhibits apoptosis by inhibiting the function of the nuclear transcription factor Y subunit.
MT1JP. MT1JP is located on chromosome 16 and consists of genes encoding homologous proteins of the metallothionein family. Lv et al. found that MT1JP has a significant inhibitory effect on migration and invasion by regulating the expression of FBXW7 related to the occurrence and development of gastric cancer. MT1JP overexpression can increase the mRNA and protein levels of p21 and Bim and promote tumor migration. MiR-214-3p is a key oncogene in a variety of common cancers (including gastric cancer), and its expression is upregulated in mesenchymal stem cells derived from gastric cancer tissues. In gastric cancer tissues, the expression of miR-214-3p is inversely related to the expression of MT1JP. Transfection of miR-214-3p mimics can reverse the tumor suppressive effect of MT1JP, and anti-miR-214-3p can reverse the tumor-promoting effect of knockdown MT1JP. Xu et al. proved that MT1JP can be used as a competitive endogenous RNA (ceRNA) of miR-214-3p, and this can inhibit gastric cancer cells by competitively binding endogenous miR-214-3p to upregulate p21 and Bim levels, thereby regulating the invasion and migration.

CASC15. Cancer susceptibility 15 (CASC15) is a type of lincRNA located on chromosome 6p22.3. Studies have shown that the high expression of CASC15 is associated with the poor prognosis in patients with gastric cancer. CASC15 regulates CDKN1A in the nucleus by interacting with EZH2 and WDR5 and is involved in the occurrence of gastric cancer. Regulating the expression of CASC15 affects the progression of EMT to inhibit or promote cell migration and invasion. Knocking down CASC15 allows it to compete with miR-33a-5p, triggering the silencing of ZEB1 in the cytoplasm.

TP73 AS1. TP73 antisense RNA 1 T (TP73-AS1), as a ceRNA, promotes gastric cancer cell metastasis by regulating the miR-194-5p/SDAD1 pathway. Wang et al. reduced the expression of TCF4 and β-catenin in gastric cancer cells by downregulating the expression of TP73-AS1, which inhibited the WNT/β-catenin signaling pathway. Therefore, this inhibited the invasion of gastric cancer cells. Silencing TP73-AS1 can reverse Snail-mediated EMT to inhibit the migration and invasion of gastric cancer cells.

GCRL1. Gastric cancer-related lncRNA1 (GCRL1) is one of the subtypes of the intergenic lncRNA LINC01272, which is located on chromosome 20q13.13. GCRL1 promotes cell proliferation and metastasis by sponging miR-885-3p and actively regulates CDK4 in gastric cancer cells. Researchers discovered a new regulatory pathway for gastric cancer cell proliferation and invasion, and this pathway included GCRL1, miR-885-3p and CDK4.

Conclusions and Future Perspectives
As an important component of noncoding RNA, long noncoding RNA (lncRNA) is widely involved in many physiological functions of the human body. Having a core role in regulating gene expression at multiple levels, lncRNAs can affect all aspects of cells, including cell division, proliferation, differentiation, aging and apoptosis. With the development of microarrays and high-throughput screening and RT-PCR techniques, thousands of cancer-related lncRNAs have been discovered as diagnostic markers and targets for drug therapy. With the discovery of an increasing number of disease-related lncRNA transcripts, the field of cancer research is changing. However, the following problems and challenges currently exist. The lncRNA detection method is not stable enough. There are many lncRNAs studied by each research group, but they are scattered. The specific mechanisms of various studies are still unclear, and more in-depth research is needed to reveal the relevant mechanisms. And there is still a long way to go before the results of the study can be promoted clinically.

Gastric cancer is one of the most common causes of cancer death. Because there are no reliable molecular detection methods for the early diagnosis of gastric cancer, there are still challenges in clinical practice today. LncRNAs have been found to play important roles in the occurrence, development, metastasis and prognosis of gastric cancer, and some functions have been studied. However, more research is still needed to explore the structure, mode of action, and mechanism of lncRNAs. LncRNA research in gastric cancer is mostly basic research, and there are few clinical research reports. LncRNA research results are rarely used in the clinic as new targets. Currently, a representative example of the clinical application of lncRNA is prostate cancer-specific lncRNA PCA3, which is significantly overexpressed in prostate cancer. The PCA3 diagnostic test was found only ten years ago, and it is now being clinically used. In addition to PCA3, the field of lncRNA-based clinical research is still in its infancy, and further research is needed to make it an integral part of cancer diagnosis and treatment. There are still no large-volume validation data or in-depth molecular mechanism studies for determining which lncRNAs are expected to be used as markers for the diagnosis and prognosis or potential drug targets of gastric cancer. The cause or effect of lncRNAs in the process of gastric cancer is not clear, and further research is needed for confirmation, which will help to develop better diagnosis and treatment strategies for gastric cancer. Therefore, the focus of future research will be using lncRNAs to discover effective tumor markers and therapeutic targets for gastric cancer. How to specifically transfer lncRNAs into gastric cancer cells may become another important aspect to study the relationship between lncRNAs and gastric cancer.
Authors’ Note
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References
1. Fang XY, Pan HF, Leng RX, Ye DQ. Long noncoding RNAs: novel insights into gastric cancer. Cancer Lett. 2015;356(2 Pt B): 357-366. doi:10.1016/j.canlet.2014.11.005
2. Guo X, Xia J, Deng K. Long non-coding RNAs: emerging players in gastric cancer. Tumour Biol. 2014;35(11):10591-10600. doi:10.1007/s13277-014-2548-y
3. Unfried JP, Serrano G, Suarez B, et al. Identification of coding and long noncoding mRNAs differentially expressed in tumors and preferentially expressed in healthy tissues. Cancer Res. 2019;79(20):5167-5180. doi:10.1158/0008-5472.CAN-19-0400
4. Wang SM, Zheng RS, Zhang SW, et al. Epidemiological characteristics of gastric cancer in China, 2015. Zhong Hua Liu Xing Bing Xue. 2019;10(12):1517-1521.
5. Guttmann M, Amit I, Garber M, et al. Chromatin signature reveals over a thousand highly conserved large non-coding RNAs in mammals. Nature. 2009;458(7235):223-227. doi:10.1038/nature07672
6. St Laurent G, Wahlestedt C, Kapranov P. The landscape of long noncoding RNA classification. Trends Genet. 2015;31(5):239-251. doi:10.1016/j.tig.2015.03.007
7. Okazaki Y, Furuno M, Kasukawa T, et al. Analysis of the mouse transcriptome based on functional annotation of 60,770 full-length cDNAs. Nature. 2002;420(6915):563-573. doi:10.1038/nature01266
8. Cao J. The functional role of long non-coding RNAs and epigenetics. Biol Proced. Online. 2014;16(11):10.1186/1480-9221-16-11
9. ENCODE Project Consortium. Birney E, Stamatoyannopoulos JA, et al. Identification and analysis of functional elements in 1% of the human genome by the encode pilot project. Nature. 2007;447(7146):799-816. doi:10.1038/nature05874
10. Nagano T, Fraser P. No-nonsense functions for long noncoding mRNAs. Cell. 2011;145(2):178-181. doi:10.1016/j.cell.2011.03.014
11. Derrien T, Johnson R, Bussotti G, et al. The genome v7 catalog of human long noncoding RNAs: analysis of their gene structure, evolution, and expression. Genome Res. 2012;22(9):1775-1789. doi:10.1101/gr.132159.111
12. Chen J, Miao Z, Xue B, Shan Y, Weng G, Shen B. Long noncoding RNAs in urologic malignancies: functional roles and clinical translation. J Cancer. 2016;7(13):1842-1855. doi:10.7150/jca.15876
13. Renganathan A, Felley-Bosco E. Long noncoding RNAs in cancer and therapeutic potential. Adv Exp Med Biol. 2017;1008:199-222. doi:10.1007/978-981-10-5203-3_7
14. Trimarchi T, Bilal E, Ntziaichristos P, et al. Genome-wide mapping and characterization of notch-regulated long noncoding RNAs in acute leukemia. Cell. 2014;158(3):593-606. doi:10.1016/j.cell.2014.05.049
15. Kumar MS, Armenteros-Monterroso E, East P, et al. HMGA2 functions as a competing endogenous RNA to promote lung cancer progression (retraction of vol 505, pg 212, 2014). Nature. 2015;523(7560):370. doi:10.1038/nature14551
16. Huang Y, Nayak S, Jankowitz R, Davidson NE, Oesterreich S. Epigenetics in breast cancer: what’s new? Breast Cancer Res. 2011;13(6):1-11. ARTN 225. doi:10.1186/bcr2925
17. Gu Y, Chen TX, Li GL, et al. LncRNAs: emerging biomarkers in gastric cancer. Future Oncol. 2015;11(17):2427-2441. doi:10.2217/fon.15.175
18. Wang Y, Zhang DX, Wu KC, Zhao QC, Nie YZ, Fan DM. Long noncoding RNA MRUL promotes ABCB1 expression in multidrug-resistant gastric cancer cell sublines. Mol Cell Biol. 2014;34(17):3182-3193. doi:10.1128/Mcb.01580-13
19. Wang S, Chen W, Yu H, et al. LncRNA ROR promotes gastric cancer drug resistance. Cancer Control. 2020;27(1):1073274820904694. doi:10.1177/1073274820904694
20. Zeng L, Liao Q, Zou Z, et al. Long non-coding RNA xloc_006753 promotes the development of multidrug resistance in gastric cancer cells through the p38/akt/mtor signaling pathway. Cell Physiol Biochem. 2018;51(3):1221-1236. doi:10.1159/000495499
21. Xu YD, Shang J, Li M, Zhang YY. LncRNA DANCR accelerates the development of multidrug resistance of gastric cancer. Eur Rev Med Pharmacol Sci. 2019;23(7):2794-2802. doi:10.26355/eurrev_201904_17554
22. Li GB, Zhang HH, Wan XS, et al. Long noncoding RNA plays a key role in metastasis and prognosis of hepatocellular carcinoma. Biomed Res Int. 2014.05.049
23. Gupta RA, Shah N, Wang KC, et al. Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. Nature. 2010;464(7291):1071-1076. doi:10.1038/nature09875
24. Kim K, Jutooru I, Chadalapaka G, et al. HOTAIR is a negative prognostic factor and exhibits pro-oncogenic activity in pancreatic cancer. Oncogene. 2013;32(13):1616-1625. doi:10.1038/onc.2012.193
25. Yap KL, Li SD, Munoz-Cabello AM, et al. Molecular interplay of the noncoding RNA ANRIL and methylated histone h3 lysine 27 by polycomb CBX7 in transcriptional silencing of INK4a. Molecular Cell. 2010;38(5):662-674. doi:10.1016/j.molcel.2010.03.021
26. Li W, Zheng J, Deng JQ, et al. Increased levels of the long intergenic non-protein coding RNA POU3F3 promote DNA methylation in esophageal squamous cell carcinoma cells.
55. Zhang Y, Song X, Wang X, Hu J, Jiang L. Silencing of lncRNA HULC enhances chemotherapy induced apoptosis in human gastric cancer. *J Med Biochem*. 2016;35(2):137-143. doi:10.1515/jmb-2015-0016

56. Emadi-Andani E, Nikpour P, Emadi-Baygi M, Bidmisheskipoor A. Association of HOTAIR expression in gastric carcinoma with invasion and distant metastasis. *Adv Biomed Res*. 2014;3:135. doi:10.4103/2277-9175.133278

57. Xue M, Chen LY, Wang WJ, et al. HOTAIR induces the ubiquitination of runx3 by interacting with m6x3b and enhances the invasion of gastric cancer cells. *Gastric Cancer*. 2018;21(5):756-764. doi:10.1007/s10120-018-0801-6

58. Endo H, Shiroki T, Nakagawa T, et al. Long non-coding RNA HOTAIR promotes gastric cancer proliferation and metastasis via targeting miR-126 to activate CXCR4 and RhoA signaling pathway. *Cancer Med*. 2019;8(15):6768-6779. doi:10.1002/cam4.1302

59. Jiang D, Li H, Xiang H, et al. Long chain non-coding RNA (lncRNA) HOTAIR knockdown increases miR-454-3p to suppress gastric cancer growth by targeting STAT3/Cyclin D1. *Med Sci Monit*. 2019;25:1537-1548. doi:10.12659/MSM.913087

60. Xiao J, Lai H, Wei SH, Ye ZS, Gong FS, Chen LC. LncRNA HOTAIR promotes gastric cancer proliferation and metastasis via targeting miR-126 to active CXCR4 and RhoA signaling pathway. *Cancer Med*. 2019;8(15):6768-6779. doi:10.1002/cam4.1302

61. Jiang D, Li H, Xiang H, et al. Long chain non-coding RNA (lncRNA) HOTAIR knockdown increases miR-454-3p to suppress gastric cancer growth by targeting STAT3/Cyclin D1. *Med Sci Monit*. 2019;25:1537-1548. doi:10.12659/MSM.913087

62. Hu XW, Sood AK, Dang CV, Zhang L. The role of long non-coding RNA HOTAIR in the diagnosis and prognosis of gastric cancer: a meta-analysis. *Int J Biol Markers*. 2019;34(1):27-32. doi:10.1186/1475-2867-13-68

63. Bai F, Feng Y, et al. MicroRNA-214 regulates gastric cancer cell proliferation, migration and epithelial-mesenchymal transition of runx3 axis. *Cell Physiol Biochem*. 2018;46(6):2445-2459. doi:10.1159/000489651

64. Hu XW, Sood AK, Dang CV, Zhang L. The role of long non-coding RNAs in cancer: the dark matter matters. *Curr Opin Genet Dev*. 2018;48:8-15. doi:10.1016/j.gde.2017.10.004

65. Bhan A, Soleimani M, Mandal SS. Long noncoding RNA and cancer: a new paradigm. *Cancer Res*. 2017;77(15):3965-3981. doi:10.1158/0008-5472.CAN-16-2634

66. Stein U, Walther W, Arlt F, et al. MacC1, a newly identified key regulator of hgf-met signaling, predicts colon cancer metastasis. *Nat Med*. 2009;15(1):59-67. doi:10.1038/nm.1889

67. Xin R, Bai F, Feng Y, et al. MicroRNA-214 promotes peritoneal metastasis through regulating pten negatively in gastric cancer. *Clin Res Hepatol Gastroenterol*. 2016;40(6):748-754. doi:10.1016/j.clinre.2016.05.006

68. Wang CL, Wen ZW, Xie JM, et al. MacC1 mediates chemotherapy sensitivity of 5-Fu and cisplatin via regulating mct1 expression in gastric cancer. *Biochem Biophys Res Co*. 2017;485(3):665-671. doi:10.1016/j.bbrc.2017.02.096

69. Zhao Y, Liu YJ, Lin L, et al. The IncRNA macC1-as1 promotes gastric cancer cell metabolic plasticity via ampk/lin28 mediated mRNA stability of macC1. *Mol Cancer*. 2018;17(1):69. ARTN 69. doi:10.1186/s12943-018-0820-2

70. Zhang Q, Yu ST, Zhang ZZ, Zhao G, Xu J. Long non-coding RNA ak096174 promotes cell proliferation and invasion in gastric cancer by regulating wdr66 expression. *Biosci Rep*. 2018;38(4):BSR20180277. ARTN Bsr20180277. doi:10.1042/BSR20180277

71. Hu XW, Sood AK, Dang CV, Zhang L. The role of long non-coding RNA HOTAIR in the diagnosis and prognosis of gastric cancer: a meta-analysis. *Int J Biol Markers*. 2019;34(1):27-32. doi:10.1186/1475-2867-13-68

72. Liu J, Ben Q, Lu E, et al. Long noncoding RNA pandar blocks cdkn1a gene transcription by competitive interaction with p53 protein in gastric cancer. *Cell Death Dis*. 2018;9(2):168. doi:10.1038/s41419-017-0246-6

73. Han L, Zhang EB, Yin DD, et al. Low expression of long non-coding RNA pandar predicts a poor prognosis of non-small cell lung cancer and affects cell apoptosis by regulating bcl-2. *Cell Death Dis*. 2015;6(2):e1665. doi:10.1038/cddis.2015.30

74. Kotake Y, Kitagawa K, Ohhata T, et al. Long non-coding RNA, pandar, contributes to the stabilization of p53 tumor suppressor protein. *Anticancer Res*. 2016;36(4):1605-1611.

75. Lv Z, Zhang Y, Yu X, Lin Y, Ge Y. The function of long non-coding RNA mt1jp in the development and progression of gastric cancer. *Pathol Res Pract*. 2018;214(8):1218-1223. doi:10.1016/j.prp.2018.07.001

76. Ding Z, Lan HT, Xu R, Zhou X, Pan Y. LncRNA TP73-AS1 inhibits gastric cancer cell proliferation and invasion by targeting pten. *Cancer Cell Int*. 2019;19(1):10.1186/s12935-019-1218-7

77. Yang TS, Yang XH, Wang XD, Wang YL, Zhou B, Song ZS. MiR-214 regulate gastric cancer cell proliferation, migration and invasion by targeting pten. *Cancer Cell Int*. 2013;13(1):68. doi:10.1186/1475-2867-13-68

78. Penna E, Orso F, Taverna D. Mir-214 as a key hub that controls cancer networks: small player, multiple functions. *J Invest Dermatol*. 2015;135(4):960-969. doi:10.1038/jid.2014.479

79. Wang M, Zhao C, Shi H, et al. Deregulated microRNAs in gastric cancer tissue-derived mesenchymal stem cells: novel biomarkers and a mechanism for gastric cancer. *Br J Cancer*. 2014;110(5):1199-1210. doi:10.1038/bjc.2014.14

80. Wu Q, Xiang S, Ma J, et al. Long non-coding RNA casc15 regulates gastric cancer cell proliferation, migration and epithelial mesenchymal transition by targeting cdkn1a and zeb1. *Mol Oncol*. 2018;12(6):799-813. doi:10.1002/1878-0261.12187

81. Ding Z, Lan HT, Xu R, Zhou X, Pan Y. LncRNA TP73-AS1 accelerates tumor progression in gastric cancer through regulating miR-194-5p/SDAD1 axis. *Pathol Res Pract*. 2018;214(12):1199-1210. doi:10.1016/j.prp.2018.09.006

82. Wang Y, Xiao S, Wang B, Li Y, Chen Q. Knockdown of lncRNA TP73-AS1 inhibits gastric cancer cell proliferation and invasion via the wnt/beta-catenin signaling pathway. *Oncof Lett*. 2018;16(3):3248-3254. doi:10.3892/ol.2018.9040
83. Zhang W, Zhai YJ, Wang WB, Cao M, Ma CJ. Enhanced expression of lncRNA TP73-AS1 predicts unfavorable prognosis for gastric cancer and promotes cell migration and invasion by induction of EMT. *Gene*. 2018;678:377-383. doi:10.1016/j.gene.2018.08.055

84. Lin Z, Zhou Z, Guo H, et al. Long noncoding RNA gastric cancer-related lncRNA1 mediates gastric malignancy through miRNA-885-3p and cyclin-dependent kinase 4. *Cell Death Dis*. 2018;9(6):607. doi:10.1038/s41419-018-0643-5

85. Bussemakers MJ, van Bokhoven A, Verhaegh GW, et al. Dd3: a new prostate-specific gene, highly overexpressed in prostate cancer. *Cancer Res*. 1999;59(23):5975-5979.

86. Lee GL, Dobi A, Srivastava S. Prostate cancer: diagnostic performance of the pca3 urine test. *Nat Rev Urol*. 2011;8(3):123-124. doi:10.1038/nrurol.2011.10