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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 lncRNAs according to their lengths.[5,6] Okazaki *et al*[7] first discovered lncRNAs in large-scale sequencing of mouse full-length cDNA libraries in 2002. LncRNAs 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.[5,8-10] Studies have confirmed that microRNAs not only play a key role in gene regulation but also are important in cancer.[10] LncRNAs have become a popular topic in global biological research after microRNAs. Recent studies have shown that there are approximately 15,000 types of lncRNAs in the human body. Most lncRNAs show different tissue specificities.[11] LncRNA ChIP, northern blotting and high-throughput technology were used to screen out abnormally expressed lncRNAs related to diseases. Further studies have shown that lncRNAs are involved in the regulation of DNA methylation, miRNA precursors, mRNA degradation, phosphorylation, chromatin remodeling and other biological processes.[12]

Recent studies have shown that lncRNAs can be regarded as oncogenes or tumor suppressor genes in tumorigenesis and development. A variety of lncRNAs abnormally expressed in different types of tumors were found by comparing the expression profiles of tumor and normal cells. LncRNAs are expected to become new tumor markers and targets for tumor therapy for the diagnosis, treatment, prognosis and monitoring of tumors.[13] LncRNAs are often in a "deregulated" state in tumor cells compared to that of normal cells, indicating that lncRNAs are potential tumor biomarkers. The expression levels of lncRNAs are related to the efficacy of tumors. In addition, lncRNAs can be used as reference indexes for tumor prognosis. Moreover, the overexpression or downregulation of specific lncRNAs in tumor cells can often trigger apoptosis or make tumor cells sensitive to treatments that induce apoptosis. Therefore, lncRNAs can be used as therapeutic targets for certain types of tumors; for example, LUNAR1 was used as a T-cell acute lymphoblast molecular marker and a potential therapeutic target for cellular leukemia.[14-16] In addition, lncRNAs can also regulate tumor metastasis-related signaling pathways and participate in tumor migration[17] and drug resistance.[18] 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 variety tumors including gastric cancer.[19-21] The lncRNA MRUL (MDR-related and upregulated lncRNA) is a potential target to reverse the multidrug resistance of gastric cancer, which can promote the gene expression of SGC7901 / ADR ABCB1 (ATP-binding cassette, subfamily B, member 1) in adriamycin-resistant gastric cancer cells.[18] The expression levels of lncRNAs in digestive system tumors are divided into those that are up- and downregulated, and most lncRNAs are upregulated. It is speculated that lncRNAs can play a role similar to proto-oncogenes or tumor suppressor genes. LncRNAs can provide new clues for the molecular treatment of digestive system tumors.[22] Although most of the functions of lncRNAs are still unknown, current research[23-25] has shown that lncRNAs 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 lncRNA. Amounts of lncRNAs may affect the decisive steps in tumor suppression and carcinogenesis. Further exploration of the underlying mechanism of lncRNA will benefit our understanding on the pathogenesis of gastric cancer.

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

Signal Function

Some lncRNAs combine with specific proteins and locate related complexes to specific targets. The process affects the transcriptional activity and interferes with the transcription mechanism. An lncRNA can silence or activate a gene, a gene family or even the entire chromosome by cis or trans effects. Li *et al*[26] found that the lncRNA "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

LncRNAs can bind specific proteins to form complexes and regulate physiological activities by binding to specific gene regions. Previous studies[27] have shown that X-chromosome inactivation is closely related to the guiding effect of lncRNAs. 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.[28]

Bait Function

LncRNAs can induce a series of proteins, such as transcription factors, with gene regulatory functions. LncRNAs prevent

Table 1. Summary of lncRNA Mechanisms in GC.

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; upregulatingn miR-124-3p-mediated ZEB1	45-47
TUG1	Oncogenic	regulating PRC2	48-51
H19	Oncogenic	enhancing inflammation induced by NF-κB; 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	30,71-74
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

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] Studies[31] 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).

LncRNAs Related to Gastric Cancer Cell Proliferation and Apoptosis

ZFAS. Zinc finger antisense1 (ZFAS1) is a newly discovered lncRNA. Several studies have demonstrated[34,35] that ZFAS1 is

commonly upregulated in gastric cancer tissues and cell lines as an oncogene. After transfection with si-ZFAS1, the growth of the gastric cancer cell lines BGC823 and SGC7901 was significantly inhibited, and the sensitivity of SGC7901 to cisplatin or paclitaxel chemotherapy drugs was enhanced. Overexpression of ZFAS1 can promote the proliferation of AGS cells. After interfering with the ZFAS1 gene, the apoptosis rates in the gastric cancer cell lines BGC823 and SGC7901 were significantly increased. Overall, ZFAS1 silencing inhibits the growth, proliferation, and cell cycle progression of gastric cancer cells by blocking Wnt/β-catenin signaling. Zhang *et al*[36] further found that upregulation of ZFAS1 expression in gastric cancer tissues was accompanied by the downregulation of microRNA-200b-3p (miR-200b) expression. MiR-200b overexpression can inhibit gastric cancer cell proliferation, cell cycle processes, and Wnt/β-catenin signaling. ZFAS1 can promote the malignant progression by regulating miR-200b-mediated Wnt/β-catenin signaling.

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.[37] Dan *et al*[38] 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*.[39] MEG3 may also inhibit the growth and proliferation of gastric cancer by affecting the expression of P53.[40] Jiao *et al*[41] 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 Bcl-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 a 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.[42] Li *et al*[43] 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.[44] Zhao *et al*[45] 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.[46]

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*[47] 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,[48] and has carcinogenic effects. There are also some studies that show that H19 is expressed in some cancers, including liver cancer.[49] 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.[50] Research confirms that H19 promotes the growth of gastric cancer cells caused by a *Helicobacter pylori* infection by enhancing inflammation induced by NF-κB.[51] Gan *et al*[52] 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*[53] 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.[54] Zhang *et al*[55] 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.[56] 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.[57] Upregulation of HOTAIR is positively correlated with vascular invasion, multiple lymph node metastases, and a lower overall survival in gastric cancer.[58] Knocking down HOTAIR inhibits gastric cancer cell growth, affects cell cycle distribution, and increases the protein levels of P21 and P53.[59] Xiao *et al*[60] found a negative correlation between miR-126 and HOTAIR. CXCR4 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/CXCR4 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.[61]

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.[62,63] MACC1 is a key regulator of the HGF/c-MET axis and an important target for tumor therapy.[64] Tong *et al*[65] 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*[66] 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[67,68] 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.[69] 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 WRD66 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.[70] PANDAR is a gene that induces DNA damage and inhibits apoptosis by inhibiting the function of the nuclear transcription factor Y subunit

(NFYA). Studies have confirmed that PANDAR is a direct transcription target of the p53 protein and is positively regulated by p53.[29] Silencing PANDAR can significantly reduce the expression of the p53 protein. PANDAR downregulates the transcription of the CDKN1A gene through competitive binding with the p53 protein. When combined with a p53 activator (nutlin3), knockdown of PANDAR using CRISPR/Cas9 technology can synergistically inhibit the progression of gastric cancer.[71-73]

MT1JP. MT1JP is located on chromosome 16 and consists of genes encoding homologous proteins of the metallothionein family. Lv *et al*[74] 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.[75] 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.[76-79] Xu *et al*[75] 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.[80]

TP73 AS1. P73 antisense RNA 1 T (TP73-AS1), as a ceRNA, promotes gastric cancer cell metastasis by regulating the miR-194-5p/SDAD1 pathway.[81] Wang *et al*[82] 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.[83]

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.[84]

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.[85] The PCA3 diagnostic test was found only ten years ago, and it is now being clinically used.[86] 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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