



2016 Gastric Cancer: Global view

## Emerging roles of non-coding RNAs in gastric cancer: Pathogenesis and clinical implications

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### Abstract

Gastric cancer is a leading cause of cancer-related deaths. However, the mechanisms underlying gastric carcinogenesis remain largely unclear. The association of non-coding RNAs (ncRNAs) with cancer has been widely studied during the past decade. In general, ncRNAs have been classified as small ncRNAs, including microRNAs (miRNAs), and long non-coding RNAs (lncRNAs). Emerging evidence shows that miRNAs and lncRNAs play key roles in the formation and progression of many cancers. In this review, we focus on the regulation of miRNAs and lncRNAs in gastric cancer. miRNAs and lncRNAs appear to be involved in gastric tumor growth, invasion, and metastasis and in establishment of the gastric tumor microenvironment through various mechanisms. Furthermore, we also discuss the possibilities of establishing miRNAs and lncRNAs as potential biomarkers and therapeutic targets for gastric cancer. Taken together, we summarize the emerging roles of ncRNAs in gastric cancer development and their possible clinical significance.

**Key words:** microRNAs; Long non-coding RNAs; Gastric cancer; Cancer invasion; Metastasis

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**Core tip:** Non-coding RNAs (ncRNAs) are recognized as an important player in multiple physiological and pathological processes through diverse mechanisms. This review summarizes the current knowledge on dysregulation of microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) in gastric tumor growth, invasion and metastasis. Moreover, the possibilities of targeting miRNAs and lncRNAs in gastric cancer diagnosis, prognosis and treatment are also discussed.

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## INTRODUCTION

Gastric cancer is one of the leading causes of cancer-related deaths worldwide, with an estimated 951600 new cases and 723100 deaths in 2012<sup>[1]</sup>. The development of medical and surgical therapy has improved the survival rate of gastric cancer patients. However, survival remains unsatisfactory with < 25% overall 5-year survival rates<sup>[2]</sup>. The high mortality of gastric cancer is mainly attributed to delayed diagnosis due to the lack of appropriate biomarkers and specific early symptoms. Therefore, it is important to elucidate the mechanisms of gastric carcinogenesis and explore new biomarkers and therapeutic targets for gastric cancer.

The human genome sequencing project revealed that < 2% of the human genome expresses protein-coding RNAs<sup>[3,4]</sup>. However, several studies have shown that ≥ 90% of the genome is actively transcribed to a diversity of RNAs<sup>[5,6]</sup>. These RNAs without protein-coding capacity are defined as non-coding RNAs (ncRNAs). Generally, ncRNAs are classified as long ncRNAs (lncRNAs) (> 200 nt) and small ncRNAs (≤ 200 nt). Recent studies showed there are many types of small ncRNAs, including microRNAs (miRNAs), small interfering RNAs, piwi-interacting RNAs, small nuclear RNAs and small nucleolar RNAs<sup>[7]</sup>.

ncRNAs contribute to many biological processes, such as cell proliferation, migration, signaling, development and differentiation. Therefore, they are implicated in the pathogenesis of various diseases, including cancers<sup>[8,9]</sup>. Increasing data demonstrate that dysregulation of miRNAs and lncRNAs is involved in the development of many human cancers, such as breast, colorectal, lung, liver and gastric cancer<sup>[10-12]</sup>. Here, we outline our current understanding of the role of miRNAs and lncRNAs in gastric carcinogenesis and highlight their potential clinical value.

## MIRNAS AND GASTRIC CANCER

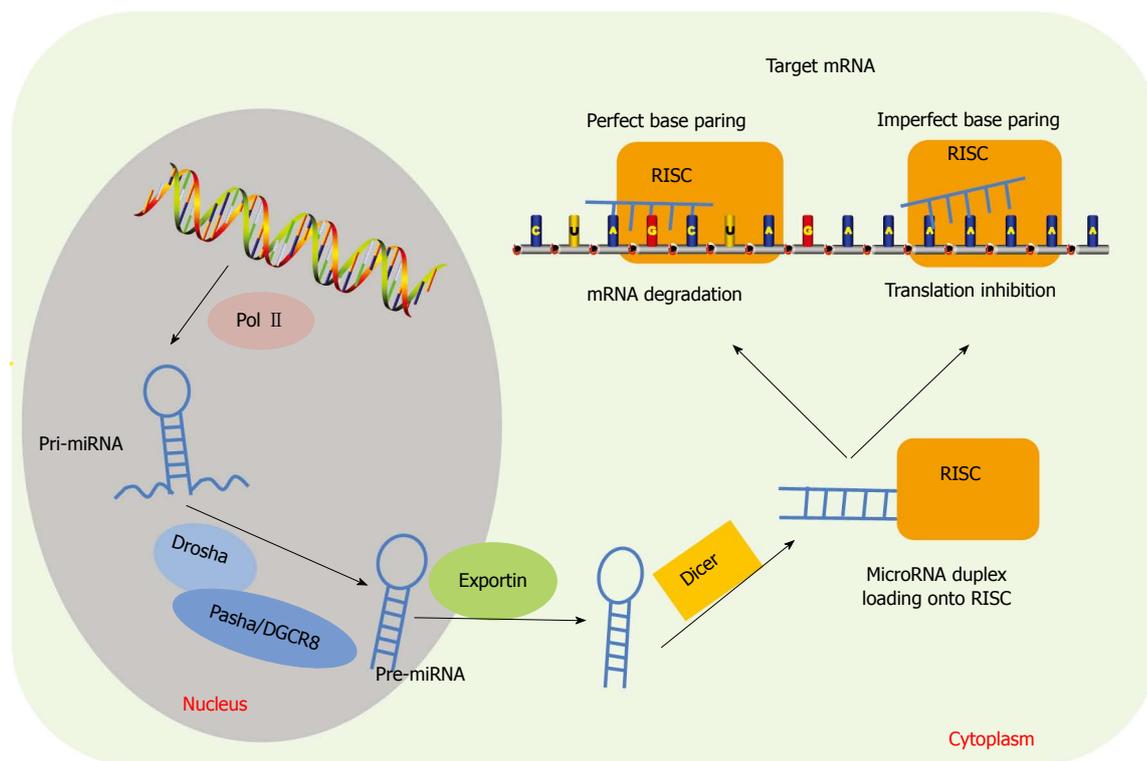
miRNAs are 20-22 nt members of the ncRNA family that regulate genes by triggering mRNA degradation or by translational repression *via* perfect or imperfect base matching between miRNAs and their target mRNAs (Figure 1). Each miRNA has been shown to target up to 200 mRNAs and therefore they influence many cellular processes, such as cell proliferation, apoptosis, migration, invasion and metabolism<sup>[13]</sup>. Many studies have demonstrated that dysregulation of miRNAs is associated with the pathogenesis of various cancers, including gastric cancer, through promoting tumor growth, invasion and metastasis (Supplemental Table 1).

### miRNAs promote tumor growth

In 2011, Hanahan and Weinberg summarized the hallmarks of cancer<sup>[14]</sup>. Some hallmarks, including sustaining proliferative signaling, evasion of growth suppressors, resistance of cell death, and enabling replicative immortality, appear to promote tumor growth<sup>[13]</sup>. In gastric cancer, the activity of numerous miRNAs has been shown to enhance tumor growth through stimulation of these hallmark processes.

The first studies on the role of miRNAs in gastric cancer were on Let-7a, which is downregulated in gastric cancer tissues. Let-7a directly targets RAB40C, which is a member of the small GTPase RAS family, and downregulation of Let-7a results in the suppression of cell proliferation *in vitro* and tumor growth *in vivo* through regulation of RAB40C<sup>[15,16]</sup>. Our group and others found that expression of another miRNA, miR-375, is frequently decreased in gastric cancer tissues<sup>[17-19]</sup>. miR-375 plays a crucial role in gastric cancer growth by inhibiting Janus kinase (JAK)2; a key molecule in the cytokine signaling pathway<sup>[17]</sup>. JAK2 levels are inversely correlated with the levels of miR-375 in gastric cancer tissues. Data from Moriyama's group also indicate that ectopic expression of miR-375 results in the suppression of cell viability *via* the caspase-mediated apoptosis pathway by directly targeting phosphoinositide-dependent kinase 1 and 14-3-3ζ in gastric cancer cells<sup>[18]</sup>. In addition, other groups showed that receptor tyrosine kinase ERBB2 is also targeted by miR-375 in gastric cancer<sup>[19]</sup>. Thus, these data suggest that miR-375 is involved in gastric carcinogenesis by sustaining proliferative signaling.

Recently, we and another group discovered that miR-215 is upregulated in gastric cancer tissues and induces cell proliferation by binding tumor suppressor gene retinoblastoma 1; a key cell cycle regulator<sup>[20,21]</sup>. Expression of another miRNA, miR-106a, is also elevated in gastric cancer tissues. miR-106a significantly enhances gastric cancer cell proliferation and prevents apoptosis through interference with the FAS-mediated apoptotic pathway<sup>[22,23]</sup>. Finally, it



**Figure 1 miRNAs biogenesis.** Primary miRNA (pri-miRNA) is transcribed by RNA polymerase II from miRNA genes. The long pri-miRNA is processed by the RNase III proteins Drosha and Pasha/DGCR8 into precursor miRNA (pre-miRNA) in the nucleus. The cleaved pre-miRNA is then exported to the cytoplasm by Exportin 5 and cleaved into about 18-22 nt miRNA duplex by the RNase III Dicer. Only one strand of the miRNA duplex becomes mature and incorporates into the RNA-induced silencing complex (RISC), whereas the other strand is degraded. miRNA regulates gene expression by forming base pairs mainly with the 3'-untranslated region of its target mRNAs. The imperfect and perfect base matching between miRNA and its target mRNAs leads to inhibition of mRNA translation and induction of mRNA degradation, respectively.

has been shown that miR-1182 is downregulated in gastric cancer tissues<sup>[24]</sup>. miR-1182 targets telomerase reverse transcriptase (hTERT). Telomeres are able to promote replicative immortality, which is controlled by hTERT. In turn, overexpression of hTERT facilitates cell immortality, which increases cell proliferation. Taken together, these studies indicate that, in gastric cancer, aberrant expression of miRNAs results in the promotion of tumor growth through evasion of growth suppressors, resistance of cell death and enabling of replicative immortality.

#### **miRNAs enhance tumor invasion and metastasis**

Recent studies indicated that miRNAs are involved in activating tumor invasion and metastasis. These studies showed that miR-21 expression is frequently elevated in gastric cancer tissues compared with corresponding non-cancerous gastric tissues<sup>[24-27]</sup>. Furthermore, miRNA-21 is significantly associated with tumor invasion and metastasis. miR-21 apparently promotes gastric tumor invasion by targeting phosphatase and tensin homolog (PTEN)<sup>[27]</sup>.

Several studies showed that miR-148a is downregulated in gastric cancer tissues and that the expression of miR-148a is significantly correlated with TNM stages, lymph node metastasis, and poor prognosis of gastric cancer patients<sup>[28-31]</sup>. Furthermore,

ectopic expression of miR-148a suppresses gastric cancer cell migration and invasion *in vitro* and lung metastasis *in vivo* by targeting ROCK1 (rho-associated, coiled-coil-containing protein kinase 1)<sup>[28]</sup>. miR-148a represses the expression of DNA methyltransferase (DNMT)1, whereas ectopic expression of DNMT1 results in the silencing of miR-148a through hypermethylation of its promoter region<sup>[29,30]</sup>. These results suggest the existence of a miR-148a/DNMT1 circuit in gastric cancer. In addition, matrix metalloproteinase (MMP)7 and p27, which may contribute to gastric cancer invasion, are also targeted by miR-148a<sup>[32,33]</sup>.

Some miRNAs stimulate the development of gastric cancer through multiple pathways. Our group previously demonstrated that miR-375 is not only involved in tumor growth, but also influences gastric cancer invasion<sup>[34]</sup>. Moreover, miR-375 expression is negatively regulated by Snail, which binds directly to the putative promoter of miR-375. Snail is a key transcription factor for metastasis.

#### **miRNAs and the tumor microenvironment**

The crosstalk between cancer cells and their neighboring stroma is required for invasive tumor growth, metastasis, modulation of inflammation and angiogenesis<sup>[14]</sup>. miRNAs have been shown to play important roles in gastric carcinogenesis induced by *Helicobacter*

**Table 1** Dysregulation of lncRNAs in gastric cancer

lncRNAs	Expression	Biological processes	Targets	Ref.
ABDH11-AS1	Up	Unknown	Unknown	[41]
AC138128.1	Up	Unknown	Unknown	[42]
AK058003	Up	Promote migration and invasion	$\gamma$ -Synuclein	[3]
ANRIL	Up	Promote proliferation and tumorigenesis	miR-99a/miR-449a	[44]
CARLo-5	Up	Promote proliferation	Unknown	[45]
CCAT1	Up	Promote proliferation and migration	Unknown	[46,47]
CCAT2	Up	Unknown	Unknown	[48]
GACAT3	Up	Unknown	Unknown	[49,50]
GAPLINC	Up	Promote proliferation, invasion and tumorigenesis	CD44	[51]
GHET1	Up	Promote proliferation and tumorigenesis	c-myc	[52]
H19	Up	Promote proliferation and suppress apoptosis; enhance metastasis	p53, miR-675/RUX1, CALN1	[53-55]
HIF1A-AS2	Up	Unknown	unknown	[56]
HOTAIR	Up	Promote migration, invasion, EMT and metastasis	Snail, MMP1, MMP3, HER2, SUZ12	[57-62]
HULC	Up	Promote proliferation, invasion and EMT; suppress apoptosis	Unknown	[63]
linc00152	Up	Unknown	Unknown	[64]
linc-UBC1	Up	Promote proliferation and invasion	Unknown	[65]
LSINCT5	Up	Promote proliferation	Unknown	[66]
MALAT1	Up	Promote proliferation	SF2/ASF	[67]
MRUL	Up	Promote MDR	ABC1	[68]
PVT1	Up	Promote cell proliferation	p15, p16	[69]
SPRY4-IT1	Up	Promote tumorigenesis	Unknown	[70]
TINCR	Up	Regulate cell proliferation and apoptosis	KLF2	[71]
UCA1	Up	Unknown	Unknown	[72]
LEIGC	Down	Inhibit migration and EMT	Unknown	[73]
FENDRR	Down	Suppress migration, invasion and metastasis	FN1	[74]
AA174084	Down	Unknown	Unknown	[75]
BM742401	Down	Suppress migration, invasion and metastasis	Unknown	[76]
FERIL4	Down	Unknown	miR-106a-5p	[77,78]
GACAT1	Down	Unknown	Unknown	[79,80]
GACAT2	Down	Unknown	Unknown	[50,81]
GAS5	Down	Inhibit proliferation and tumorigenesis	E2F1, p21	[82]
LET	Down	Unknown	Unknown	[83]
MEG3	Down	Inhibit proliferation and promote apoptosis	p53	[54,85]
ncRuPAR	Down	Unknown	PAR1	[86]

*pylori* (*H. pylori*) infections. *H. pylori* infections are a critical risk factor for gastric cancer development. It has previously been shown that downregulation of miR-375 results in the activation of JAK2-signal transducer and activator of transcription (STAT)3 signaling, which promotes *H. pylori*-mediated inflammation. This in turn facilitates gastric cancer progression<sup>[35]</sup>. Another miRNA, miR-874, is also downregulated in gastric cancer tissues. Downregulation of miR-874 contributes to tumor angiogenesis through the STAT3/vascular endothelial growth factor-A pathway<sup>[36,37]</sup>. These results indicate that miRNAs are versatile and involved in the regulation of the tumor microenvironment.

## LNCRNAs AND GASTRIC CANCER

The first lncRNA, H19, was reported by Brannan and colleagues in 1990<sup>[38]</sup>. To date, the ENCODE project has identified tens of thousands of lncRNAs<sup>[5]</sup>. According to their locations and characteristics, lncRNAs can be grouped into five categories: sense, antisense, bidirectional, intronic or intergenic (Figure 2)<sup>[39]</sup>. Increasing data show that lncRNAs may regulate gene expression through diverse mechanisms, including gene activation and suppression, chromatin

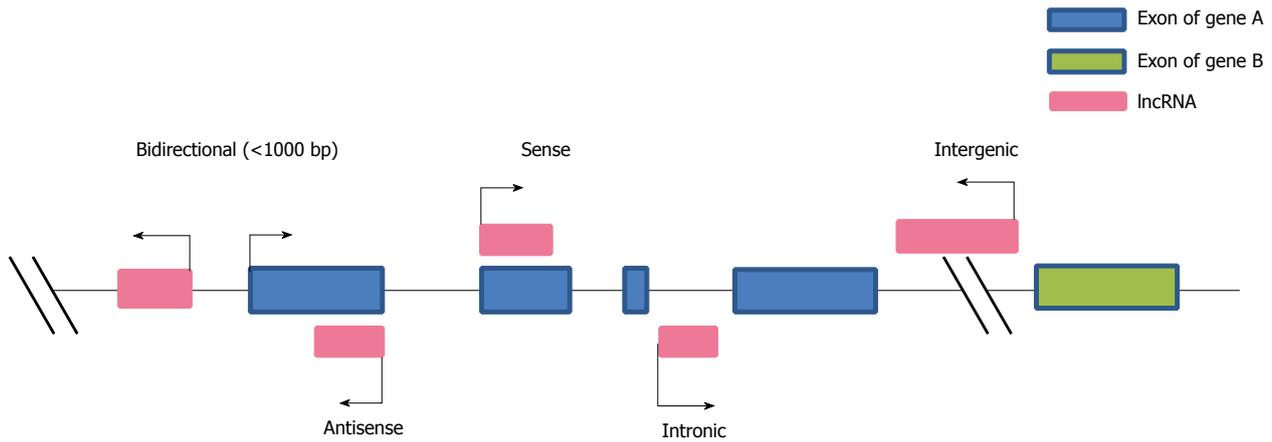
modification and remodeling, splicing modulation, miRNA sponges and translation (Figure 3).

Research over the last 10 years has accumulated evidence that lncRNAs are important regulators in cell proliferation, apoptosis, migration and differentiation<sup>[40]</sup>. Similar to miRNAs, lncRNAs are associated with many processes in gene regulation, therefore it may not be surprising that dysregulation of lncRNAs results in tumor growth, invasion and metastasis (Table 1)<sup>[41-86]</sup>.

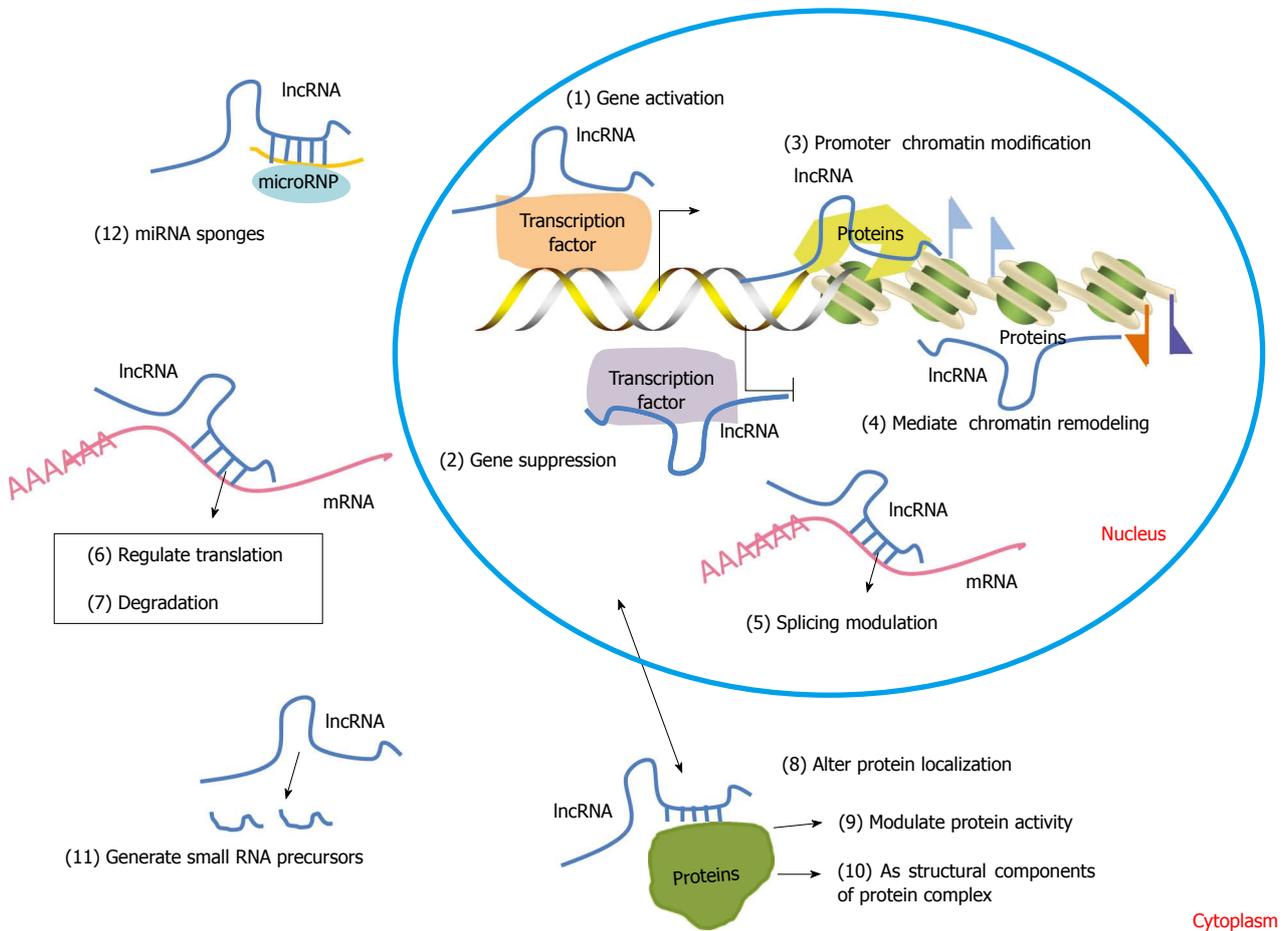
### *lncRNAs involved in tumor growth*

H19 is a paternally imprinted gene that is highly expressed during embryogenesis but almost completely downregulated shortly after birth<sup>[87,88]</sup>. Previous studies have shown that H19 is upregulated in gastric cancer and that it is significantly correlated with poor prognosis of gastric cancer patients<sup>[53-55]</sup>. Furthermore, H19 has been shown to promote gastric cancer cell proliferation, invasion and metastasis through various mechanisms, including processing into miR-675. miR-675 has many targets, such as calneuron 1 and tumor suppressor runt domain transcription factor 1<sup>[54,55]</sup>.

Accumulating evidence indicates that a number of lncRNAs, including antisense ncRNA in the INK4 locus



**Figure 2 Categories of lncRNAs.** lncRNAs are usually classified into five categories: (1) sense; or (2) antisense, when overlapping one or more exons of another transcript on the same, or opposite strand; (3) bidirectional, when the expression of lncRNA and a neighboring coding transcript on the opposite strand is initiated in close genomic proximity; (4) intronic, when lncRNA is derived wholly from within an intron; and (5) intergenic, when lncRNA lies within the genomic interval between two genes.



**Figure 3 Functions of lncRNAs.** Individual lncRNA transcription occurs at a specific time and place to integrate developmental cues, interpret cellular context, or respond to diverse stimuli. A number of lncRNAs bind to and titrate away transcription factors to activate or suppress gene expression (1, 2); some lncRNAs guide site-specific recruitment of chromatin-modifying complexes to genomic sites to induce epigenetic changes and regulate gene expression (3); several lncRNAs serve as scaffolds for chromatin-modifying complexes (4); some lncRNAs specifically interact with complementary mRNAs that modulate various processes of post-transcription, such as splicing, translation and degradation (5-7). A number of lncRNAs are able to alter protein localization, regulate protein activity, or act as components of protein complex (8-10). Some lncRNAs appear to generate small RNA precursors or function as miRNA sponges (11, 12).

(ANRIL), gastric carcinoma high expressed transcript 1 (GHET1), metastasis associated lung adenocarcinoma transcript 1 (MALAT1), *PVT1* oncogene (*PVT1*) and *SPRY4* intronic transcript 1 (*SPRY4-IT1*), are significantly upregulated in gastric cancer tissues compared with paired non-cancerous tissues, and they are therefore associated with the prognosis of gastric cancer patients<sup>[44,52,67,69,70]</sup>. ANRIL enhances gastric cancer cell proliferation by silencing miR-99a/miR-449a *via* binding to polycomb repressive complex 2<sup>[44]</sup>. Ectopic expression of ANRIL increases the expression of transcription factor E2F1 through repression of miR-449a. Simultaneously, E2F1 promotes ANRIL expression, thus forming a positive feedback loop. GHET1 has been demonstrated to increase the stability of *c-myc* mRNA by enhancing the physical interaction between *c-myc* mRNA and insulin-like growth factor 2 mRNA binding protein 1. Stabilization of *c-myc* mRNA was shown to promote gastric cancer cell growth<sup>[52]</sup>. MALAT1, a lncRNA associated with metastasis of many cancers, facilitates gastric cancer cell proliferation by recruiting SF2/ASF (serine/arginine-rich splicing factor 1)<sup>[67]</sup>. *PVT1* represses the expression of tumor suppressor genes *p15* and *p16*, which promotes gastric cancer cell proliferation *via* binding to the zeste homolog 2 enhancer<sup>[69]</sup>. Finally, *SPRY4-IT1* has been found to increase the proliferation, colony formation, and invasion of gastric cancer cells, partially by increasing the expression of MMP-related genes and cyclin D<sup>[70]</sup>.

Other lncRNAs, such as growth arrest-specific transcript (GAS)5 and maternally expressed gene (MEG)3, are frequently downregulated in gastric cancer tissues. They are correlated with poor prognosis of gastric cancer patients<sup>[82,84,85]</sup>. Ectopic expression of GAS5 decreases gastric cancer cell proliferation and induces apoptosis, partially *via* regulating E2F1 and p21 expression<sup>[82]</sup>. Expression of MEG3 is regulated by miR-148a *via* DNMT1, which inhibits gastric cancer cell proliferation<sup>[84,85]</sup>.

#### ***lncRNAs regulate invasion and metastasis***

Several studies have shown that lncRNAs are involved in the regulation of tumor invasion and metastasis. The lncRNA Hox transcript antisense intergenic RNA (HOTAIR) is elevated in human cancers, including gastric cancer, and enhances tumor invasion and metastasis<sup>[57-62,89]</sup>. Knockdown of HOTAIR reverses the epithelial-mesenchymal transition (EMT) process and inhibits invasion by suppressing the expression of MMP1 and MMP3<sup>[57]</sup>. Furthermore, HOTAIR functions as a competing endogenous RNA and effectively represses HER2 expression through competition for miR-331-3p binding in gastric cancer<sup>[59]</sup>.

Another lncRNA, fetal-lethal noncoding developmental regulatory RNA (FENDRR), is downregulated in gastric cancer tissues. FENDRR inhibits gastric cancer cell migration and invasion *via* repressing the expression of fibronectin 1 and MMP2/MMP9. Reduced

FENDRR expression is significantly correlated with metastasis, TNM stages and poor prognosis of gastric cancer patients<sup>[74]</sup>.

## **CLINICAL IMPLICATIONS OF NCRNAS IN GASTRIC CANCER**

The high mortality of gastric cancer is mainly attributed to failure of early detection and the lack of an effective therapy. Early gastric cancer is either asymptomatic or presented with non-specific symptoms. Also, endoscopic screening is not a common practice in less-developed countries<sup>[90]</sup>. The current diagnostic biomarkers, including the serological markers carbohydrate antigen (CA)19-9 and carcinoembryonic antigen (CEA), have a low specificity and sensitivity for gastric cancer diagnosis. Thus, there is an urgent need for the discovery of new biomarkers for non-invasive early detection.

#### ***ncRNAs and gastric cancer diagnosis***

Emerging data indicate that gastric cancer patients have different ncRNA serum profiles compared with the healthy controls<sup>[91-94]</sup>. These profiles appear to be specific in cancer patients and show a higher sensitivity than conventional tumor biomarkers such as CEA and CA19-9. A signature of five specific serum miRNAs (miR-1, miR-20a, miR-27a, miR-34 and miR-423-5p) was able to detect gastric cancer with a sensitivity of 80% and a specificity of 81%. Furthermore, a profile of the three serum lncRNAs CUDR (cancer up-regulated drug resistant), LSINCT-5 (long stress-induced non-coding transcript 5) and PTENP1 (phosphatase and tensin homolog pseudogene 1) showed a better diagnostic accuracy [area under the curve (AUC): 0.92, 95%CI: 0.807-0.974] compared with CEA (AUC: 0.574, 95%CI: 0.432-0.708) and CA19-9 (AUC: 0.580, 95%CI: 0.438-0.713)<sup>[94]</sup>. These data indicate that ncRNAs may be promising new targets for the development of gastric cancer diagnostic tools.

#### ***ncRNAs and gastric cancer prognosis***

The expression levels of ncRNAs have been significantly associated with gastric cancer clinical features such as tumor size, invasion and metastasis. For instance, elevated expression of miRNAs such as miR-27a, miR-335, miR-196a and miR-142-5p is associated with a high frequency of recurrence and poor survival of gastric cancer patients<sup>[95-98]</sup>. Similarly, expression levels of the lncRNAs H19, ANRIL, GHET1, HOTAIR, GAS5, LET, GAPLINC and FENDRR are significantly correlated with the 5-year survival rate of gastric cancer patients<sup>[54,44,52,58,82,83,51,74]</sup>. Therefore, ncRNAs may be good indicators in gastric cancer prognosis.

#### ***ncRNAs and gastric cancer treatment***

Several studies have reported that ncRNAs could affect

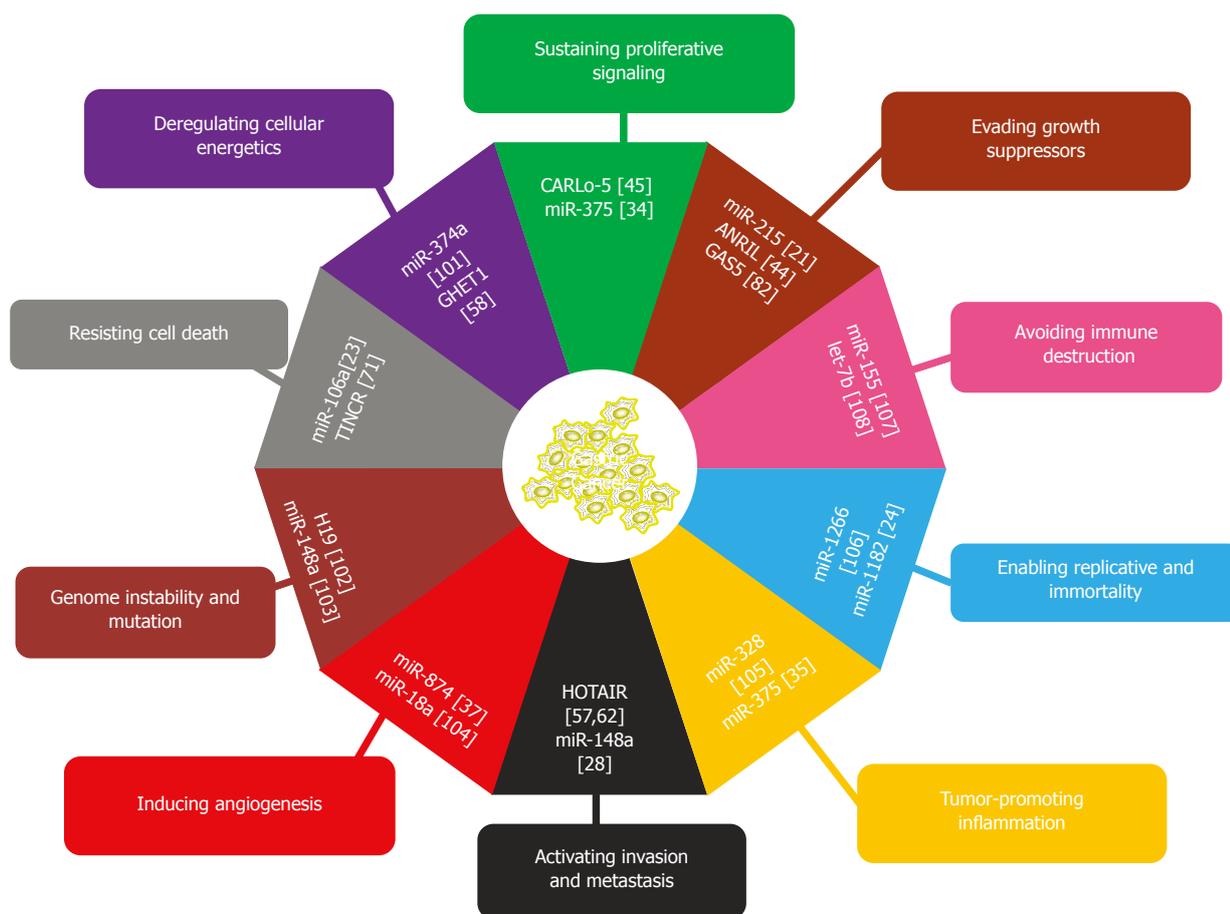


Figure 4 miRNAs and lncRNAs regulate the hallmarks of gastric cancer<sup>[21,23,24,28,34,37,45,58,71,101-108]</sup>.

the resistance of gastric cancer to chemotherapy. For instance, inhibition of miR-21 and miR-223 markedly suppresses gastric cancer cell proliferation by increasing cisplatin sensitivity<sup>[99,100]</sup>. Furthermore, knockdown of multidrug-resistance-related and upregulated lncRNA increases chemosensitivity of multidrug-resistant gastric cancer cell sublines by facilitating the expression of ABCB1 (ATP-binding cassette, subfamily B, member 1)<sup>[68]</sup>. Therefore, ncRNAs may be valuable new targets to include in future gastric cancer treatments.

## CONCLUSION AND FUTURE PERSPECTIVES

In the last decade, increasing numbers of ncRNAs, including miRNAs and lncRNAs, have been documented to affect gastric cancer. These ncRNAs are aberrantly expressed in gastric cancer tissues, play critical roles in the gastric carcinogenesis, and have potential applications in the diagnosis, prognosis or treatment of gastric cancer. Since tumor progression is a complex and multistep process, several hallmarks have been described that enable normal cells to become tumorigenic and malignant during tumor pathogenesis<sup>[14]</sup>. A large number of

miRNAs and lncRNAs are involved in the regulation of these hallmarks (Figure 4). Aberrant expression of some ncRNAs, including miR-375, ANRIL, miR-106a, miR-1182 and miR-374a, results in gastric cancer growth by promoting hallmark processes such as sustaining proliferative signaling, evasion of growth suppressors, resistance of cell death, enabling replicative immortality and deregulation of cellular energetics. Other ncRNAs, such as miR-328, miR-874 and let-7b, are involved in the interaction between gastric cancer cells and their neighboring stroma and activate invasion and metastasis by facilitating tumor-promoting inflammation, inducing angiogenesis and avoiding immune destruction. Furthermore, genome instability and mutations appear to drive or exacerbate these hallmarks in gastric cancer.

Even though aberrant expression of a number of ncRNAs has been described to stimulate gastric cancer, the underlying molecular mechanisms on the function of these ncRNAs in gastric carcinogenesis are not well understood. Most of the current studies on ncRNAs in gastric cancer focus on their expression profiles. The role of mutations in ncRNAs involved in gastric carcinogenesis should be determined in future studies. New technologies, such as next-generation DNA sequencing and CRISPR-Cas9 genome editing, will

further help us to find and characterize the exact role of ncRNAs in gastric cancer.

Clinical applications for ncRNAs in gastric cancer are also in their infancy. Although some ncRNAs may show potential as therapeutic targets, many obstacles, including stability, reliable delivery systems and off-target effects, have to be overcome before clinical trials could commence.

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