Noncoding RNAs (ncRNAs) have attracted much attention in cancer research field. They are involved in cellular development, proliferation, differentiation and apoptosis. The dysregulation of ncRNAs has been reported in tumor initiation, progression, invasion and metastasis in various cancers, including gastric cancer (GC). In the past few years, an accumulating body of evidence has deepened our understanding of ncRNAs, and several emerging ncRNAs have been identified, such as PIWI-interacting RNAs (piRNAs) and circular RNAs (circRNAs). The competing endogenous RNA (ceRNA) networks include mRNAs, microRNAs, long ncRNAs (lncRNAs) and circRNAs, which play critical roles in the tumorigenesis of GC. This review summarizes the recent hotspots of ncRNAs involved in GC pathobiology and their potential applications in GC. Finally, we briefly discuss the advances in the ceRNA network in GC.

Key words: Noncoding RNAs; Gastric cancer; MicroRNA; Long ncRNAs; PIWI-interacting RNAs; Competing endogenous RNA

Abstract
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Key words: Noncoding RNAs; Gastric cancer; MicroRNA; Long ncRNAs; PIWI-interacting RNAs; Competing endogenous RNA
applications in GC, as well as advances in ceRNA networks.

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**INTRODUCTION**

Gastric cancer (GC) is currently a worldwide leading cause of cancer-related death, and it is especially prevalent in Asia\(^1\). The Chinese National Cancer Center reported 679000 new cases of GC and 498000 GC-related deaths in 2015. GC ranked the second leading cause of cancer death in China\(^2\). Previous studies have hypothesized that GC is a genetic disease involving multi-step changes in the genome\(^3\). However, the human genome contains nearly 20000 protein-coding genes, only representing less than 2% of the whole genome\(^4\). In contrast, almost 70% of human genome is dynamically and pervasively transcribed into RNA, yielding thousands of noncoding RNAs (ncRNAs)\(^5\).

In the last few decades, several studies have convincingly shown that ncRNAs participate in complex molecular signaling to regulate cell structure, function, and physiological development\(^6\). Accordingly, the dysregulation of ncRNAs strongly contributes to the occurrence and development of neoplasia\(^7,8\). Moreover, in recent years, it has been shown that ncRNAs are promising candidate biomarkers for GC detection and potential therapeutic targets. Several ncRNAs could be secreted into body fluids, suggesting that cancers may change their extracellular environments through RNA-based, hormone-like mechanisms\(^9\). In this review, we focus on the most relevant information on several ncRNAs in cancers, with a particular emphasis on their multifaceted roles in GC, and their diagnostic, prognostic and therapeutic applications will also be discussed.

**NCRNAs**

NcRNAs are RNAs that do not encode proteins. They are widely expressed in organisms\(^10\). The total number of ncRNAs present in the human genome is still unknown. Their structural heterogeneity makes them difficult to identify. NcRNAs can be classified into different groups according to different criteria, and they are most commonly classified based on their length. Generally, ncRNAs no more than 200 nucleotides (nt) are defined as small ncRNAs, while those longer than 200 nt are regarded as long noncoding RNAs (lncRNAs). NcRNAs could also be divided into two categories based on their function (Table 1)\(^8,11,12\).

**Table 1  Major classification of human genomic noncoding RNAs**

| RNA type | Symbol | Length (nt) | Function |
|----------|--------|------------|----------|
| Housekeeping ncRNAs | tRNA | 73-94 | Connect amino acids with mRNA |
| Transfer RNAs | rRNA | 121-5070 | Component of ribosomes |
| Ribosomal RNAs | snRNA | Approximately 150 | Assemble with proteins into spliceosomes to remove introns during mRNA processing |
| Small nuclear RNAs | snoRNA | 70-200 | Guide modifications of other ncRNAs, alternative splicing, or function as miRNA |
| Telomerase RNAs | TERC | 451 | Provide template for de novo synthesis of telomeric DNA |
| Ribonuclease P | RPPH1 | 341 | RNA component of ribonuclease P |
| Regulatory ncRNAs | siRNA | 21-22 | Silencing genes in a sequence-specific manner |
| Small interfering RNAs | miRNA | 20-23 | Regulating genes expression |
| Regulatory ncRNAs | piRNA | 25-33 | Silence transposons during spermatogenesis |
| Promoter-associated short RNAs | paRNA | < 200 | Regulating gene expression by gene promoter |
| Long non-coding RNAs | lncRNA | > 200 | Various |

ncRNAs: Noncoding RNAs; piRNAs: PIWI-interacting RNAs; lncRNAs: Long ncRNAs.

**NCRNAs IN GASTRIC CARCINOGENESIS**

**MicroRNAs in GC**

MicroRNAs (miRNAs) are a major class of small ncRNAs. They are approximately 19-24 nt in length, highly conserved, and expressed in a temporal and tissue-specific manner\(^13\). MiRNAs bind to their target gene transcripts to regulate gene expression. More than 200 miRNAs were found to be associated with GC development, progression, and therapeutic response\(^14\). Therefore, this review only summarizes the reports related to miRNAs in GC in the past year. Several groups carried out miRNA expression profiling studies in GC, and these results indicated that miRNAs and their targets were involved in GC initiation, progression, and metastatic spread as well as several cancer-related pathways\(^15-17\). However, these results may have been influenced by the sample tissue composition or stromal tissue and thus may not represent the true biological functions of miRNAs. Tae-Su Han and his colleagues identified several GC-specific miRNAs through comprehensive miRNA profiling using a next-generation sequencing (NGS) platform\(^18\). They discovered that miR-29c expression was obviously downregulated in GC tissues. Moreover, they identified a tumor suppressor role for miR-29c,
which regulates its downstream target gene, ITGB1, in GC, using a series of in vitro and in vivo experiments. Suppression of miR-29c was shown to be an early event in gastric carcinogenesis using transgenic mouse models of gastritis and GC[18]. Many miRNAs, like miR-448, miR-15a, and miR-485-5p, were found to suppress proliferation, invasion or migration in GC cell lines via their target genes[19-22]. Several other miRNAs, such as miR-1290 and miR-543, could promote gastric tumor cell proliferation or metastasis by targeting their downstream genes[22,23].

Studies have shown that several miRNAs participate in GC carcinogenesis pathways. Tingting Huang et al[24] reported that miR-508-3p was downregulated and exhibited tumor suppressor effects in GC cells. They also found that NFKB1 was a direct target of miR-508-3p, indicating that the dysregulation of miR-508-3p could initiate GC possibly by targeting the canonical NF-κB signaling pathway. Yanaka et al[25] identified that the ectopic expression of miR-544a changed the level of EMT markers, such as VIM, SNAIL, ZEB1, and CDH1, resulting in an EMT phenotype. Further studies showed that miR-544a could lead the stabilization of β-catenin in the nucleus by targeting CDH1 and AXIN2 genes.

Chemotherapeutic resistance is the main problem in GC treatment, but the underlying mechanisms remain unclear. Multiple reports have suggested that miRNAs are associated with the sensitivity of GC cell lines to chemotherapy. MiR-375 was conspicuously downregulated in cisplatin (DDP)-resistant cells compared to chemotherapy. MiR-375 was reported to repress autophagy, implicating its anti-proliferative and apoptosis-inducing effects of DDP treatment by targeting ERBB2 and phosphorylated Akt and its anti-proliferative and apoptosis-inducing effects of DDP could be reversed by reducing the level of miR-375. MiR-143 was found to be an inhibitor of autophagy that targeted GABARAPL1 in GC cells[27]. These studies suggest that miRNAs may be novel therapeutic targets in GC.

Fassan et al[28] found that let-7c expression decreased from non-atrophic gastritis to atrophic-metaplastic gastritis, intraepithelial neoplasia, and invasive GC and significantly increased following Helicobacter pylori (H. pylori) eradication.

Another study demonstrated that overexpression of miR-27b obviously inhibited H. pylori infection-induced cell proliferation[29]. It has also been shown that miR-149 could mediate the crosstalk between GC tumor cells and cancer-associated fibroblasts (CAFs) by targeting PGE2 receptor 2/IL-6 signaling[30]. These findings suggest that miRNAs influence the balance of GC microenvironment.

In the past year, many miRNA biomarkers for GC have been identified, such as miR-21, miR-29, miR-198, miR-29c, miR-124, and miR-148a in GC tissues[31-33] and miR-940, miR-223, and miR-27a in the blood of GC patients[34-36]. The level of miR-421 in gastric tissue was related to lymph node metastasis and prognosis of gastric carcinoma[37], and peripheral miR-421 was regarded as a serological biomarker for GC early diagnosis[38].

In conclusion, many miRNAs have been shown to be involved in GC initiation, progression, pathways, and resistance to chemotherapy. Increasing reports suggest that miRNAs in the tissues or body fluids, such as plasma, might be sensitive and specific biomarkers for GC[39].

**LncRNAs in GC**

Brannan and his colleagues reported the first lncRNA (> 200 nucleotides), H19, in 1990[40]. LncRNAs consist of exons and introns in structure, without ORFs, and are not highly conserved. Recent studies estimated that approximately 14880 IncRNAs are present in humans[41]. Over the last ten years, accumulating evidence has suggested that IncRNAs participate in cancer cell proliferation, apoptosis and migration[42].

Our group has concentrated on the dysregulation of IncRNAs in GC. Data from hierarchical clustering and expression analysis indicated that IncRNAs were frequently aberrantly expressed in GC[43]. We firstly reported the downregulation and the independent prognostic role of TUSC7 in GC tissues. Further studies suggested that the p53-dependent tumor suppressive role of TUSC7 is partly mediated by repressing miR-23b. We also reported the upregulation of LSINCT5 in GC, and its association with tumor size, depth, and clinical stage[44].

In 2012, Yang et al[45] first reported the contribution of H19 to GC, elucidating the potential mechanism of IncRNAs in GC. Dysregulation of H19 increased cell proliferation and resulted in partial inactivation of p53. Other studies showed that the upregulation of H19 was correlated with invasion depth, advanced TNM stage and regional lymph nodes metastasis[46]. Plasma H19 level was also obviously higher in GC patients[47,48], indicating that H19 might be a promising marker for early GC detection, and circulating IncRNAs may provide new complementary tumor biomarkers for GC. MiR-675 is the mature product of H19, and it can modulate GC cell proliferation by targeting RUNX1, demonstrating the role of the H19/miR-675/RUNX1 pathway in GC development[49]. Data from other groups have suggested that altered expression of H19 in GC is induced by c-Myc[50]. Analysis of a large cohort of Chinese Han subjects showed that 4 H19 SNPs were associated with different characteristics of GC patients, indicating that H19 SNPs may be involved in susceptibility to GC[51]. In conclusion, H19 is a potential biomarker for early detection and a possible therapeutic target for GC.

HOX transcript antisense intergenic RNA (HOTAIR) is an oncogenic IncRNA that has been detected in several human neoplasms, such as breast cancer[52], colorectal
cancer\(^{[53]}\), pancreatic cancer\(^{[54]}\) and others\(^{[55,56]}\). HOTAIR was higher in GC tissues, especially in advanced cases\(^{[57]}\), and its level could predict the effect after fluorouracil and platinum combination chemotherapy in advanced GC patients\(^{[58]}\). Recent reports showed that HOTAIR inhibited apoptosis but promoted invasiveness and metastasis\(^{[59,60]}\), indicating that HOTAIR contributes to the carcinogenesis and progression of GC. Recent studies on HOTAIR in GC have focused on its genetic variants, including SNP rs4759314, which has proven to be related to increased risk of GC\(^{[61]}\). Other studies found that among three SNPs of the HOTAIR, only the T allele of rs12826786 was associated with an increased risk of developing GC; thus, SNP rs12826786 may change the level of HOTAIR\(^{[62]}\). These findings suggested that functional genetic variants may affect HOTAIR expression, explaining a portion of the genetic basis of GC. In addition to H19 and HOTAIR, several IncRNAs were newly found to be dysregulated and play important roles in GC. Using RNA immunoprecipitation sequencing (RIP-seq), Qi et al.\(^{[63]}\) demonstrated that the IncRNA MALAT1 could bind EZH2, suppress the tumor suppressor gene PCDH10, and promote migration and invasion of GC cells. Linc00152 was upregulated in the cytoplasm of GC cells, and knockdown of Linc00152 suppressed cell proliferation and tumor growth. Moreover, Linc00152 could activate PI3K/Akt pathway by directly binding to EGFR\(^{[64]}\). Zhao et al.\(^{[65]}\) reported that knockdown of Linc00152 inhibited cell proliferation and colony formation, promoted G1 phase cell cycle arrest, reduced the EMT phenotype, and suppressed cell migration and invasion. These reports demonstrated the oncocgenic function of Linc00152 in GC. Recently, Xiong et al.\(^{[66]}\) reported that Treg cells in peripheral blood were significantly upregulated in plasma samples from GC patients. Additionally, linc-POU3F3 could promote the distribution of Treg cells in peripheral blood T cells, causing enhanced proliferation of GC cells by recruiting TGF-beta as well as activating the TGF-beta signaling pathway.

Among IncRNAs downregulated in GC, MIR31HG was upregulated in pancreatic ductal adenocarcinoma and contributed to tumor growth and cell invasion\(^{[67]}\); however, MIR31HG expression was found to be decreased in GC tissues and was associated with larger tumor size and advanced pathological stage. Ectopic overexpression of MIR31HG inhibited proliferation in vitro and in vivo, while its downregulation promoted cell proliferation in GC cells partly by regulating E2F1 and p21\(^{[68]}\). Other downregulated IncRNAs, such as WT1-AS and LOWEG, were associated with GC cell proliferation or invasion\(^{[69,70]}\).

Pseudogene-derived IncRNAs are major members of the IncRNA family. SUMO1P3 was significantly upregulated in GC tissues, and its level was significantly correlated with tumor size, differentiation, lymphatic metastasis and invasion, indicating the potential role of SUMO1P3 in GC diagnosis\(^{[71]}\).

Taken together, IncRNAs play a multifaceted role in GC carcinogenesis and might be novel biomarkers for GC diagnosis and prognosis, as well as provide effective therapeutic targets for GC treatment.

### OTHER ncRNAs

#### PIWI-interacting RNAs in GC

PIWI-interacting RNAs (piRNAs) are small ncRNA molecules, which could interact with PIWI proteins. They are commonly 25-33 nt in length, and lack sequence conservation between organisms\(^{[72]}\). PiRNAs were found to be expressed in various human somatic tissues in a tissue-specific manner\(^{[73]}\). Therefore, piRNAs may be highly sensitive and specific biomarkers for circulating cancer cells\(^{[73]}\), and potential therapeutic tools for cancer\(^{[74]}\).

Several reports have investigated the correlation between piRNAs and GC. Cheng et al.\(^{[75]}\) found that piR-823 was downregulated in GC using real-time RT-PCR, and increased expression of piR-823 had tumor suppressive effects. Unlike piR-823, piR-651 was overexpressed in GC, and piR-651 expression was associated with TNM stage. Knockdown of piR-651 inhibited GC cell growth and induced G2/M phase arrest\(^{[76]}\), indicating that piRNAs play crucial roles in GC carcinogenesis. In addition, the levels of piR-651 and piR-823 in peripheral blood were lower in GC patients compared with the control groups. The former was higher in gastric adenocarcinoma than in gastric signet ring cell carcinoma, and the latter was positively correlated with tumor depth\(^{[77]}\). Furthermore, piR-651 and piR-823 were more sensitive than commonly used biomarkers, like CEA and CA19-9. The findings talked above suggested that piRNAs are promising molecular markers for the diagnosis and therapeutic targets of GC.

#### Circular RNAs in GC

Circular RNAs (circRNAs) are special IncRNAs with covalently closed loop structures, as products of the non-canonical splicing of linear pre-mRNAs\(^{[77]}\). Unlike the better-known linear RNAs, circRNAs lack of 5' to 3' polarity so as well as polyadenylated tails\(^{[78]}\). CircRNAs were first identified in 1991\(^{[79]}\) and were regarded as functionless by-products for the next two decades. The roles and functions of circRNAs have been identified recently, and these discoveries have permanently changed our understanding of cancer\(^{[80-82]}\).

In recent years, circRNAs have become a new hot topic in the field of RNA research. They may be associated with cancer. Hsa_circ_002059, a representative circular RNA, was lower in GC, and its downregulation was significantly correlated with distal metastasis, TNM stage, gender and age\(^{[83]}\), suggesting that circRNAs may be novel and stable diagnostic biomarkers for GC. Du et al.\(^{[84]}\) firstly reported the common expression of circ-Foxo3 in non-cancer cells and its association with...
cell cycle progression. Further studies showed that circ-Foxo3 inhibited cell proliferation and repressed cell cycle progression by binding to p21 and CDK2, forming a ternary circ-Foxo3-p21-CDK2 complex. Several reports have also suggested a role for circRNAs in other tumors. Li et al. showed that circ-ITCH was downregulated in esophageal squamous cell carcinoma. Using biochemical assays, they also found that circ-ITCH increased the level of ITCH by acting as a sponge of miR-7, miR-17, and miR-214. Moreover, ITCH promoted ubiquitination and degradation of phosphorylated Dvl2, thereby inhibiting the Wnt/β-catenin pathway. As research into circRNAs continues, we will have a more comprehensive understanding of circRNAs.

Competing endogenous RNA networks

Competing endogenous RNA (ceRNA) are transcripts that cross-regulate each other by competing for shared miRNAs. This hypothesis posits that RNAs could influence miRNA expression, inducing gene silencing, only if they share miRNA response elements (MREs) in their 3’ untranslated regions (UTRs). CeRNAs can include mRNAs, pseudogenic RNAs, IncRNAs and circRNAs. In the ceRNA networks, the most important two elements are the miRNAs and MREs, the former as the core components and the latter as the structural foundation. In recent years, complex crosstalk of ceRNAs has been found in various neoplasms, including GC.

Owing to the high homology of pseudogenes and their parental genes, pseudogenic RNAs and their parental RNAs have many identical MREs; therefore, they may be ideal ceRNA pairs. Welch et al. firstly predicted that 177 transcribed pseudogenes in breast cancer samples possessed the potential as ceRNAs, as their MREs for co-expressed miRNAs and their parent genes. PTENP1 possesses high homology with PTEN in the 3’ UTR, which contains perfectly conserved seed matches for the PTEN-targeting miR-17, miR-21, miR-214, miR-19 and miR-26 families. Thus, PTEN-targeting miRNAs miR-19b and miR-20a could suppress both PTEN and PTENP1 mRNAs. PTENP1 3’ UTR overexpression increased PTEN expression, leading to inhibited cancer cell growth and colony formation, while knockdown of PTENP1 decreased PTEN mRNA and protein expression, resulting in a de-repressive effect. Moreover, this de-repressive effect of the PTENP1 3’ UTR on PTEN was blunted in Dicer-null colon cancer cells, indicating that it acts in an miRNA-dependent manner. A similar phenomenon was observed for the oncogene KRAS and its pseudogene KRAS1P, suggesting that pseudogenes could mirror the functions of their parental genes via ceRNA crosstalk.

Recent evidence has showed that the multifaceted roles of IncRNAs in tumorigenesis may be partially mediated by ceRNA crosstalk. HOTAIR could modulate the de-repression of HER2 by acting as a sink for miR-331-3p. LncRNA MEG3 was decreased in GC, and its ceRNA potential for the miR-181 family was predicted by InCeDB, and confirmed by luciferase reporter assays and RNA immunoprecipitation (RIP) analysis. Furthermore, upregulation of wild type MEG3 increased Bcl-2 transcript and protein levels in HGC-27 cells, while ectopic expression of miR-181a abrogated this effect. These results indicate the possible effect of MEG3 in regulating Bcl-2 by competitively binding to miR-181a. The IncRNA FER1L4 and PTEN mRNA were both likely targets of miR-106a-5p, and a series of experiments indicated that FER1L4 could function as a ceRNA regulating PTEN expression. Additionally, IncRNA BC032469 was reported to function as a ceRNA to impair miR-1207-5p-dependent downregulation of hTERT in GC.

CircRNAs are a special type of IncRNA, and the newly discovered circRNAs can function as miRNA sponges, playing important roles in miRNA regulation. Thomas B. Hansen et al. first reported that the noncoding circular antisense transcripts of CDR1 could function as miR-671 targets and were positively correlated with CDR1 mRNA. CIRS-7 can strongly suppress miR-7 activity, increasing the expression of miR-7 target genes. cir-ITCH was also reported to function as a sponge of miR-7, miR-17, and miR-214 to regulate ITCH expression. Although bioinformatics analysis showed that only two human circRNAs harbor MREs, further investigations are needed to verify whether the ceRNA potential of circRNAs is unique.

CONCLUSION

In recent years, an accumulating body of evidence has elucidated the roles of ncRNAs in GC. In this review, we highlight the research progress made in the area of ncRNAs in GC during the past five years, especially relatively new and popular topics in ncRNA research (Table 2), such as IncRNAs, piRNAs and circRNAs, the multifaceted roles of ncRNAs in GC carcinogenesis, as well as the newly proposed hypothesis of ceRNA networks, presenting an overview of ncRNA research. Given that the interactions between ncRNAs and GC are very complex, ncRNA research will likely take a large step forward with the identification of more molecules, which will also contribute to the knowledge of GC tumor biology. Multiple studies have already demonstrated the potential clinical applications of several ncRNAs in GC diagnosis and prognosis; however, there are considerable limitations, such as the small sample sizes and the invasive monitoring methods. Circulating ncRNAs are regarded as an emerging biomarker for GC, but the applications of circulating ncRNAs need to be further investigated. Although difficulties remain for the clinical application of ncRNAs in GC, the accumulation of ncRNA-related genetic and epigenetic data will undoubtedly lead to advances in the treatment and management of
Table 2  Related advances of noncoding RNAs in gastric cancer of this review

| Type of ncRNAs | Expression | Putative roles | Pathway | Targets | Ref. |
|----------------|------------|----------------|---------|---------|------|
| miRNAs         |            |                |         |         |      |
| miR-29c        | Downregulated | Early event in gastric carcinogenesis | Unknown | ITGB1 | [18] |
| miR-448, miR-15a, miR-485-5p | Downregulated | Suppression of proliferation, invasion or migration | Unknown | [19-21] |
| miR-1290, miR-543 | Upregulated | Promote proliferation and metastasis | Unknown | [22,23] |
| miR-508-3p     | Downregulated | Tumor suppressor effect | NFκB signaling | NFKB1 | [24] |
| miR-544a       | Upregulated | Regulate EMT markers | Wnt signaling | CDH1, AXIN2 | [25] |
| miR-375        | Downregulated | Increase sensitivity to DPP treatment | Unknown | EBBB2, p-Akt | [26] |
| miR-143        | Downregulated | Inhibit autophagy | Unknown | GABARAPL1 | [27] |
| miR-27b        | Downregulated | Inhibit HP-related proliferation | Wnt signaling | Unknown | [29] |
| IncRNAs        |            |                |         |         |      |
| TUSC7          | Downregulated | p53-dependent tumor suppressive role | Unknown | miR-23b | [43] |
| LSN1C5T4       | Upregulated | Correlated with clinical parameters | Unknown | miR-675 | [46,49] |
| H19            | Upregulated | Biomarker, promote proliferation | Unknown | [44] |
| HOTAIR         | Upregulated | Biomarker, inhibit apoptosis, promote invasion and metastasis | Unknown | [59,60] |
| MALAT1         | Upregulated | Promote migration and invasion | Unknown | EZH2 | [63] |
| Linc00152      | Upregulated | Promote cell proliferation, migration and invasion, cell cycle, and tumor growth | PEK3/Akt | EGF | [64,65] |
| linc-POU3F3    | Upregulated | Promote distribution of Treg cells | Unknown | E2F1/p21 | [68] |
| MIR31HG        | Downregulated | Inhibit proliferation | TGF-β | Unknown | [66] |
| pIRAs          |            |                |         |         |      |
| pIR-823        | Downregulated | Tumor suppressive role | Unknown | [75] |
| pIR-651        | Upregulated | Promote cell growth | Unknown | [76] |
| circRNAs       |            |                |         |         |      |
| Hsa_circ_002059 | Downregulated | Biomarker | Unknown | [83] |
| circ-Foxo3     | Upregulated | Cell cycle, promote proliferation | p21/CDK2 | [84] |
| circ-ITCH      | Downregulated | miRNA sponge | Wnt/β-catenin | [85] |

piRNAs: PIWI-interacting RNAs; IncRNAs: Long ncRNAs; circRNAs: Circular RNAs.

GC. NcRNAs may have promising applications in the current diagnostic/prognostic and therapeutic strategies for GC.

REFERENCES
1. Tan P, Yeoh KG. Genes and Molecular Pathogenesis of Gastric Adenocarcinoma. *Gastroenterology* 2015; 149: 1153-1162.e3 [PMID: 26073375 DOI: 10.1053/j.gastro.2015.05.059]
2. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, Yu XQ. He J. Cancer statistics in China, 2015. *CA Cancer J Clin* 2016; 66: 115-132 [PMID: 26808342 DOI: 10.3322/caac.21338]
3. Yan X, Hu Z, Feng Y, Hu X, Yuan J, Zhao SD, Zhang Y, Yang L, Shan W, He Q, Fan L, Kandalafi LE, Tanyi JL, Li C, Yuan CX, Zhang D, Yuan H, Hua K, Lu Y, Katsaros D, Huang Q, Montone K, Fan Y, Coukos G, Boyd J, Sood AK, Rebebeck T, Mills GB, Dang CV, Zhang L. Comprehensive Genomic Characterization of Long Non-coding RNAs across Human Cancers. *Cancer Cell* 2015; 28: 529-540 [PMID: 10.1016/j.ccell.2015.09.006]
4. Ezkurdia I, Juan D, Rodriguez JM, Frankish A, Diekhans M, Harrow J, Vazquez J, Valencia A, Tress ML. Multiple evidence strategies for GC. *NcRNAs may have promising applications in the current diagnostic/prognostic and therapeutic strategies for GC.*
5. Matteick JS, Rinn JL. Discovery and annotation of long noncoding RNAs. *Nat Struct Mol Biol* 2015; 22: 5-7 [PMID: 25565026 DOI: 10.1038/nsmb.2942]
6. Amanal PP, Dinger ME, Mercer TR, Mattick JS. The eukaryotic genome as an RNA machine. *Science* 2008; 319: 1787-1789 [PMID: 18369190 DOI: 10.1126/science.1165472]
7. Taft RJ, Pang KC, Mercer TR, Dinger M, Mattick JS. Non-coding RNAs: regulators of disease. *J Pathol* 2010; 220: 126-139 [PMID: 19882673 DOI: 10.1002/path.2638]
8. Ragusa M, Barbagallo C, Statello L, Condorelli AG, Battaglia R, Tamburello L, Barbagallo D, Di Pietro C, Purrello M. Non-coding landscapes of colorectal cancer. *World J Gastroenterol* 2015; 21: 11709-11739 [PMID: 26556998 DOI: 10.3748/wjg.v21.i17.11709]
9. Kahler C, Kalluri R. Exosomes in tumor microenvironment regulate cancer progression and metastasis. *J Mol Med (Berl)* 2013; 91: 431-437 [PMID: 23519402 DOI: 10.1007/s00109-013-1020-6]
10. Li PF, Chen SX, Xia T, Jiang XM, Shao YM, Xiao BF, Guo JM. Non-coding RNAs and gastric cancer. *World J Gastroenterol* 2014; 20: 5411-5419 [PMID: 24833871 DOI: 10.3748/wjg.v20.i18.5411]
11. Bolton EM, Tuzzova AV, Walsh AL, Lynch T, Perry AS. Noncoding RNAs in prostate cancer: the long and the short of it. *Clin Cancer Res* 2014; 20: 35-43 [PMID: 24146262 DOI: 10.1158/1078-0432.ccr-13-1989]
12. Peng JF, Zhuang YY, Huang FT, Zhang SN. Noncoding RNAs and pancreatic cancer. *World J Gastroenterol* 2016; 22: 801-814 [PMID: 26811626 DOI: 10.3748/wjg.v22.i2.801]
13. Kim VN, Nam JW. Genomics of microRNA. *Trends Genet* 2006; 22: 165-173 [PMID: 16446010 DOI: 10.1016/j.tig.2006.01.003]
14. Song JH, Melzter SJ. MicroRNAs in pathogenesis, diagnosis, and treatment of gastrointestinal cancers. *Gastroenterology* 2012; 143: 35-47.e2 [PMID: 22580099 DOI: 10.1053/j.gastro.2012.05.003]
15. Gao S, Zhou F, Zhao C, Ma Z, Jia R, Liang S, Zhang M, Zhu X, Zhang P, Wang L, Su F, Zhao J, Liu G, Peng B, Feng X. Gastric cardia adenocarcinoma microRNA profiling in Chinese patients. *Tumour Biol* 2016; Epub ahead of print [PMID: 26781873 DOI: 10.1007/s13277-016-4824-5]
16. Zhang X, Peng X, Jin Z, Huang W, Cheng Y, Liu Y, Feng X, Yang M, Huang Y, Zhao Z, Wang L, Wei Y, Fan X, Zheng D, Melzter SJ. Integrated miRNA profiling and bioinformatics analyses reveal potential causative miRNAs in gastric adenocarcinoma. *Oncotarget* 2015; 6: 32878-32889 [PMID: 26460735 DOI: 10.18632/oncotarget.5419]
17. Luo Y, Zhang C, Tang F, Zhao J, Shen C, Wang C, Yu P, Wang M, Li Y, Di J, Chen R, Rili G. Bioinformatics identification of potentially involved microRNAs in Tibetan with gastric cancer.
based on microRNA profiling. Cancer Cell Int 2015; 15: 115 [PMID: 26962821 DOI: 10.1186/s12935-015-0266-1]

18 Han TS, Hur K, Xu G, Choi B, Okugawa Y, Tioiyama Y, Oshima H, Oshima M, Lee HJ, Kim VN, Chang AN, Goel A, Yang HK. MicroRNA-29c mediates initiation of gastric carcinogenesis by directly targeting ITGB1. Gut 2015; 64: 203-214 [PMID: 24870620 DOI: 10.1136/gutjnl-2013-306640]

19 Wu X, Tang H, Liu G, Wang H, Shu J, Fan F. miR-448 suppressed gastric cancer proliferation and invasion by regulating ADAM10. Tumour Biol 2016; Epub ahead of print [PMID: 26852749 DOI: 10.1007/s13277-016-4942-0]

20 Wu C, Zheng X, Li X, Fesler A, Hu W, Chen L, Xu B, Wang Q, Tong A, Burke S, Ju J, Jiang J. Reduction of gastric cancer cell proliferation and invasion by miR-15a mediated suppression of Bmi-1 translation. Oncotarget 2016; 7: 14522-14536 [PMID: 26894855 DOI: 10.18632/oncotarget.7392]

21 Kang M, Ren MP, Zhao L, Li CP, Deng MM. miR-485-5p acts through negatively regulating Frizzled7. Cell-Free miR-2629240, Kim M, Song KS, Kim SY, Kim YS. Cell-Free miR-27a, a Potential Diagnostic and Prognostic Biomarker for Gastric Cancer. Genomics Inform 2015; 13: 70-75 [PMID: 26523130 DOI: 10.5808/gi.2015.13.3.70]

22 Liu H, Gao Y, Song D, Liu T, Feng Y. Correlation between microRNA-421 expression level and prognosis of gastric cancer. Int J Exp Pathol 2015; 8: 15128-15132 [PMID: 26823855]

23 Zhao G, Xu L, Hui L, Zhao J. Level of circulated microRNA-421 in gastric carcinoma and related mechanisms. Int J Exp Pathol 2015; 8: 1425-1426 [PMID: 26823741]

24 Wang J, Song YX, Wang ZN. Non-coding RNAs in gastric cancer. Mol Pathol 2015; 10: 28-36 [PMID: 1688465]

25 Derrien T, Johnson R, Bussotti G, Tarian A, Djebali S, Branca M, Cesaroni M, Kashefian K, Dupre P, Flicek P, Marguerit R, Hugot JP, Birney E, Guignier L, Feltus F, Chertkov I, Gribble L, Smit A, Ning Z, Letunic I, Miridakis J, Raudnitz T, Mueckler T, Furey T, Chamberlain P, Friedman N, Gutierrez J, Vazquez M, Doehlen C, van Ommen G, Maguire J, Fumagalli S, Helt E, Mann A, Tonti-Filippini J, Ureta-Vidal A, Facciotti M, Jordan C, Murrell JR, Plumb T, WildKF, Illig T, Teichmann SA, Couillard-Des presumptions on the possible roles of long non-coding RNAs in gastric cancer.

26893657 DOI: 10.3892/etm.2015.2920

26 Zhou N, Gu Q, Xu C, Tang Y. Upregulation of microRNA-375 increases the cisplatin-sensitivity of human gastric cancer cells by regulating ERBB2. Exp Ther Med 2016; 11: 625-630 [PMID: 26893657 DOI: 10.3892/etm.2015.2920]

27 Du F, Feng Y, Fang J, Yang M. MicroRNA-143 enhances chemosensitivity of Quercetin through autophagy inhibition via target GABARAPL1 in gastric cancer cells. Biomed Pharmacother 2015; 74: 169-177 [PMID: 26349981 DOI: 10.1016/j.biopha.2015.08.005]

28 Fassan M, Saragaggi D, Balsamo L, Cascione L, Caiazzo C, Coatti I, De Bernardi M, Farinati F, Guzzardo F, Zambon CF, Rugge M. Let-7c down-regulation in Helicobacter pylori-related gastric carcinogenesis. Oncotarget 2016; 7: 4915-4924 [PMID: 26701848 DOI: 10.18632/oncotarget.6642]

29 Geng Y, Lu X, Wu X, Xue L, Wang X, Xu J. MicroRNA-27b suppresses Helicobacter pylori-induced gastric tumorigenesis through negatively regulating Frizzled7. Oncol Rep 2016; 35: 2441-2450 [PMID: 26780840 DOI: 10.3892/or.2016.4572]

30 Li P, Shan JX, Chen XH, Zhang D, Su LP, Huang XY, Yu BQ, Zhi QM, Li CL, Wang QY, Temei S, Cai Q, Ji J, Li JF, Chouehane L, Yu YY, Sun FZ, Xu ZH, Liu BY, Zhu ZG. Epigenetic silencing of microRNA-149 in cancer-associated fibroblasts mediates prostat gland-2E/interleukin-6 signaling in the tumor microenvironment. Cell Res 2015; 25: 588-603 [PMID: 25916550 DOI: 10.1038/cr.2015.51]

31 Wang D, Fan Z, Liu F, Zuo J. Hsa-mir-21-2 and Hsa-mir-29 in Tissues as Potential Diagnostic and Prognostic Biomarkers for Gastric Cancer. Cell Physiol Biochem 2013; 37: 1454-1462 [PMID: 26509997 DOI: 10.1159/000438514]

32 Cui Z, Zheng X, Kong D. Decreased miR-198 expression and its prognostic significance in human gastric cancer. World J Surg Oncol 2016; 14: 33 [PMID: 26852230 DOI: 10.1186/s12957-016-0784-x]

33 Liu L, Ye JX, Qin YZ, Chen QH, Ge LY. Evaluation of miR-29c, miR-124, miR-133a and miR-148a in predicting lymph node metastasis and tumor stage of gastric cancer. Int J Clin Exp Med 2015; 8: 22227-22236 [PMID: 26885198]

34 Liu X, Kwong A, Shioe A, Chu KM. Plasma miR-040 may serve as a novel biomarker for gastric cancer. Tumor Biol 2015; 36: 2899-2907 [PMID: 26456959 DOI: 10.1007/s13277-014-0419-5]

35 Zhou X, Ji G, Chen H, Jin W, Yin C, Zhang G. Clinical role of circulating miR-223 as a novel biomarker in early diagnosis of cancer patients. Int J Clin Exp Med 2015; 8: 16890-16898 [PMID: 26629240]

36 Park JL, Kim M, Song KS, Kim SY, Kim YS. Cell-Free miR-27a, a Potential Diagnostic and Prognostic Biomarker for Gastric Cancer. Genomics Inform 2015; 13: 70-75 [PMID: 26523130 DOI: 10.5808/gi.2015.13.3.70]

37 Li P, Han L, Yin DD, Kong R, De W, Chen J. c-Myc-induced, long, non-coding H19 affects cell proliferation and predicts
Linc00152 promotes proliferation in gastric cancer through the EGFR-dependent pathway. J Exp Clin Cancer Res 2015; 34: 135 [DOI: 10.1186/s13046-015-0250-6]

Zhao J, Liu Y, Zhang W, Zhou Z, Wu J, Cui P, Zhang Y, Huang G. Long non-coding RNA Linc00152 is involved in cell cycle arrest, apoptosis, epithelial-to-mesenchymal transition, cell migration and invasion in gastric cancer. Cell Cycle 2015; 14: 3112-3123 [DOI: 10.18632/oncotarget.2623756 DOI: 10.1008/1538410.2015.1078034]

Xiong G, Yang L, Chen Y, Fan Z. Linc-POU3F3 promotes cell proliferation in gastric cancer via increasing Treg distribution. Am J Transl Res 2015; 7: 2266-2269 [DOI: 26807174]

Yang H, Liu P, Zhang J, Peng X, Lu Z, Yu S, Meng Y, Tong WM, Chen J. Long noncoding RNA MIR31HG exhibits oncogenic property in pancreatic ductal adenocarcinoma and is negatively regulated by miR-193b. Oncogene 2016; 35: 3647-3657 [DOI: 10.1038/onc.2015.430]

Nie FQ, Ma S, Xie M, Liu YW, De W, Liu XH. Decreased long noncoding RNA MIR31HG is correlated with poor prognosis and contributes to cell proliferation in gastric cancer. Tumour Biol 2016; 37: 7693-7701 [DOI: 26692098, 10.1007/s13277-015-6464-2]

Du T, Zhang Z, Zhang S, Jiang Z, Zheng P, Li J, Yan M, Zhu Z, Liu B. Decreased expression of long non-coding RNA WT1-AS promotes cell proliferation and invasion in gastric cancer. Biochim Biophys Acta 2016; 1862: 12-19 [DOI: 26449525, 10.1016/j.bbadis.2015.10.001]

Zhao JH, Sun JX, Song YX, Chen XW, Yang YC, Ma B, Wang J, Gao P, Wang ZN. A novel long non-coding RNA-LONG2 is low expressed in gastric cancer and acts as a tumor suppressor by inhibiting cell invasion. J Cancer Res Clin Oncol 2016; 142: 601-609 [DOI: 10.1007/s00432-015-2071-6]

Mei D, Song H, Wang K, Lou Y, Sun W, Liu Z, Ding X, Guo J. Up-regulation of SUMO1 pseudogene 3 (SUM01P3) in gastric cancer and its clinical association. Med Oncol 2013; 30: 709 [DOI: 23969296, 10.1007/s12032-013-0709-2]

Ng KW, Anderson C, Marshall EA, Minatel BC, Enfield KS, Saruprorn HL, Lam WL, Martinez VS. Pwi-interacting RNAs in cancer: emerging functions and clinical utility. Mol Cancer 2016; 15: 5 [DOI: 26768585, 10.1006/jbcn.2014.06.019]

Cui L, Lou Y, Zhang X, Zhou H, Deng H, Song H, Yu X, Xiao B, Wang W, Guo J. Detection of circulating tumor cells in peripheral blood from patients with gastric cancer using piRNAs as markers. Clin Biochem 2011; 44: 1050-1057 [DOI: 21704610, 10.1016/j.clinbiochem.2011.06.004]

Itou D, Shimosato Y, Yukiho SY, Ishii C, Nishimura T, Ogomski N, Ogura A, Hasuwa H, Fujihara Y, Kuramochi-Miyagawa S, Nakano T. Induction of DNA methylation by artificial piRNA production in male germ cells. Clin Biochem 2015; 25: 901-906 [DOI: 25772451, 10.1016/j.clinbiochem.2015.01.060]

Cheng J, Deng H, Xiao B, Zhou H, Zhou F, Shen Z, Guo J. piR-823, a novel non-coding small RNA, demonstrates in vitro and in vivo tumor suppressive activity in human gastric cancer cells. Cancer Lett 2012; 315: 12-17 [DOI: 22047710, 10.1016/j.canlet.2011.10.004]

Cheng J, Guo JM, Xiao BX, Miao Y, Jiang Z, Zhou H, Li QN, piRNA, the new non-coding RNA, is aberrantly expressed in human cancer cells. Clin Chim Acta 2011; 412: 1621-1625 [DOI: 21661063, 10.1016/j.cca.2011.05.015]

Zhao ZJ, Shen J. Circular RNA participates in the carcinogenesis and the malignant behavior of cancer. RNA Biol 2015; 12: 381-388 [DOI: 25746834, 10.1080/15476268.2015.1020271]

Nigro JM, Cho KR, Fearon ER, Kern SE, Ruppert JM, Oliner JD, Kinzler KW, Vogelstein B. Scrambled exons. Cell 1991; 64: 607-613 [1991322]

Vicens Q, Westhof E. Biogenesis of circular RNAs. Cell 2014; 159: 13-14 [DOI: 25259915, 10.1016/j.cell.2014.09.005]

Qu S, Yang X, Li X, Wang J, Gao Y, Shang R, Sun W, Dou K, Li H. Circular RNA: A new star of noncoding RNAs. Cancer
Zhang M et al. NcRNAs and gastric cancer

Lett 2015; 365: 141-148 [PMID: 26052092 DOI: 10.1016/j.canlet.2015.06.003]

82 Ebbesen KK, Kjems J, Hansen TB. Circular RNAs: Identification, biogenesis and function. Biochim Biophys Acta 2016; 1859: 163-168 [PMID: 26171810 DOI: 10.1016/j.bbabmb.2015.07.007]

83 Li P, Chen S, Chen H, Mo X, Li T, Shao Y, Xiao B, Guo J. Using circular RNA as a novel type of biomarker in the screening of gastric cancer. Clin Chim Acta 2015; 444: 132-136 [PMID: 26171810 DOI: 10.1016/j.cca.2015.02.018]

84 Du WW, Yang W, Liu E, Yang Z, Dhaliwal P, Yang BB. Foxo3 circular RNA retards cell cycle progression via forming ternary complexes with p21 and CDK2. Nucleic Acids Res 2016; 44: 2846-2858 [PMID: 26861625 DOI: 10.1093/nar/gkw027]

85 Li F, Zhang L, Li W, Deng J, Zheng J, An M, Lu J, Zhou Y. Circular RNA ITCH has inhibitory effect on ESCC by suppressing the Wnt/β-catenin pathway. Oncotarget 2015; 6: 6001-6013 [PMID: 25749389 DOI: 10.18632/oncotarget.3469]

86 Poliseno L, Salmena L, Tay Y, Kats L, Pandolfi PP. A ceRNA hypothesis: the Rosetta Stone of a hidden RNA language? Cell 2011; 146: 353-358 [PMID: 21802130 DOI: 10.1016/j.cell.2011.07.014]

87 Guo LL, Song CH, Wang P, Dai LP, Zhang JY, Wang KJ. Competing endogenous RNA networks and gastric cancer. World J Gastroenterol 2015; 21: 11680-11687 [PMID: 26556995 DOI: 10.3748/wjg.v21.i41.11680]

88 Qi X, Zhang DH, Wu N, Xiao JH, Wang X, Ma W. ceRNA in cancer: possible functions and clinical implications. J Med Genet 2015; 52: 710-718 [PMID: 26358722 DOI: 10.1136/jmedgenet-2015-103334]

89 Welch JD, Baran-Gale J, Perou CM, Sethupathy P, Prins JF. Pseudogenes transcribed in breast invasive carcinoma show subtype-specific expression and ceRNA potential. BMC Genomics 2015; 16: 113 [PMID: 25765044 DOI: 10.1186/s12864-015-1227-8]

90 Poliseno L, Salmena L, Zhang J, Carver B, Haveman WJ, Pandolfi PP. A coding-independent function of gene and pseudogene mRNAs regulates tumour biology. Nature 2010; 465: 1033-1038 [PMID: 20577206 DOI: 10.1038/nature09144]

91 Liu XH, Sun M, Nie FQ, Ge YB, Zhang EB, Yin DD, Kong R, Xia R, Lu KH, Li JH, De W, Wang KM, Wang ZX. Lnc RNA HOTAIR functions as a competing endogenous RNA to regulate HER2 expression by sponging miR-331-3p in gastric cancer. Mol Cancer 2014; 13: 92 [PMID: 24775712 DOI: 10.1186/1476-4598-13-92]

92 Peng W, Si S, Zhang Q, Li C, Zhao F, Wang F, Yu J, Ma R. Long non-coding RNA MEG3 functions as a competing endogenous RNA to regulate gastric cancer progression. J Exp Clin Cancer Res 2015; 34: 79 [PMID: 26253106 DOI: 10.1186/s13046-015-0197-7]

93 Xia T, Chen S, Jiang Z, Shao Y, Jiang X, Li P, Xiao B, Guo J. Long noncoding RNA FER1L4 suppresses cancer cell growth by acting as a competing endogenous RNA and regulating PTEN expression. Sci Rep 2015; 5: 13445 [PMID: 26306906 DOI: 10.1038/srep13445]

94 Liu MH, Tang B, Zeng S, Hu CJ, Xie R, Wu YY, Wang SM, He FT, Yang SM. Long noncoding RNA BC032469, a novel competing endogenous RNA, upregulates hTERT expression by sponging miR-1207-5p and promotes proliferation in gastric cancer. Oncogene 2016; 35: 3524-3534 [PMID: 26549025 DOI: 10.1038/onc.2015.413]

95 Hansen TB, Wiklund ED, Bramsen JB, Villadsen SB, Statham AL, Clark SJ, Kjems J. miRNA-dependent gene silencing involving Ago2-mediated cleavage of a circular antisense RNA. EMBO J 2011; 30: 4414-4422 [PMID: 21964070 DOI: 10.1038/emboj.2011.359]

96 Hansen TB, Jensen TI, Clausen BH, Bramsen JB, Finsen B, Damgaard CK, Kjems J. Natural RNA circles function as efficient microRNA sponges. Nature 2013; 495: 384-388 [PMID: 23446346 DOI: 10.1038/nature12199]

97 Guo JU, Agarwal V, Guo H, Bartel DP. Expanded identification and characterization of mammalian circular RNAs. Genome Biol 2014; 15: 409 [PMID: 25070500 DOI: 10.1186/s13059-014-0409-z]
