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**2016 Gastric Cancer: Global view**

**Noncoding RNAs in gastric cancer: research progress and prospects**

Zhang M *et al*. NcRNAs and gastric cancer

Meng Zhang, Xiang Du

**Meng Zhang, Xiang Du,** Department of Pathology, Fudan University Shanghai Cancer Center, Shanghai, China and Department of Pathology, Shanghai Medical College, Fudan University, Shanghai 200032, China

**Author contributions:** Zhang M searched the literature and wrote this paper; and Du X reviewed this literature and approved the final version.

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**Correspondence to:** **Xiang Du, PhD,** Department of Pathology, Fudan University Shanghai Cancer Center, Department of Pathology, Shanghai Medical College, Fudan University, No. 270 Dong’an Road, Shanghai 200032, China. dx2008cn@163.com

**Telephone:** +86-21-64170067

**Fax:** +86-21-64170067

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**Abstract**

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 (ceRNAs) networks include mRNAs, miRNAs, long ncRNAs (lncRNAs) and circRNAs, which play critical roles in the tumorigenesis of GC. This review summarized 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

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**Core tip:** Accumulating data has deepened our understanding of noncoding RNAs (ncRNAs) contribution in cancer development, and several emerging ncRNAs have been identified, such as piRNAs and circular RNAs. The competing endogenous RNA (ceRNAs) network hypothesis represent a widespread form of post-transcriptional regulation of gene expression. However, their function and mechanism remains unknown. This review summarized the recent advances of ncRNAs involved in gastric cancer (GC) pathobiology and their potential applications in GC, as well as advances in ceRNA networks.

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**Introduction**

Gastric cancer (GC) is currently worldwide leading cause of cancer-related death, and it is especially prevalent in Asia[[1](#_ENREF_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](#_ENREF_2)]. Previous studies have hypothesized that GC is a genetic disease involving multi-step changes in the genome[[3](#_ENREF_3)]. However, the human genome contains nearly 20000 protein-coding genes, only representing less than 2% of the whole genome[[4](#_ENREF_4)]. In contrast, almost 70% of human genome is dynamically and pervasively transcribed into RNA, yielding thousands of noncoding RNAs (ncRNAs)[[5](#_ENREF_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](#_ENREF_6)]. Accordingly, the dysregulation of ncRNAs strongly contributes to the occurrence and development of neoplasia[[7](#_ENREF_7),[8](#_ENREF_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](#_ENREF_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.

**Noncoding RNAs**

Noncoding RNAs are RNAs that do not encode proteins. They are widely expressed in organisms[[10](#_ENREF_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](#_ENREF_8),[11](#_ENREF_11),[12](#_ENREF_12)].

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**ncRNAs in Gastric Carcinogenesis**

***miRNAs in GC***

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](#_ENREF_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[[1](#_ENREF_1),[14](#_ENREF_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](#_ENREF_15)]. 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](#_ENREF_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](#_ENREF_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[[19-21](#_ENREF_19)]. Several other miRNAs, such as miR-1290 and miR-543, could promote gastric tumor cell proliferation or metastasis by targeting their downstream genes[[22](#_ENREF_22),[23](#_ENREF_23)].

Studies have shown that several miRNAs participate in GC carcinogenesis pathways. Tingting Huang *et al*[[24](#_ENREF_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](#_ENREF_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 with the DDP-sensitive human GC cell line[[26](#_ENREF_26)]. Western blotting analyses showed that upregulation of miR-375 increased GC cell sensitivity to 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](#_ENREF_27)]. These studies suggest that miRNAs may be novel therapeutic targets in GC.

Fassan *et al*[[28](#_ENREF_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](#_ENREF_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](#_ENREF_30)]. These findings suggested 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](#_ENREF_31)] and miR-940, miR-223, and miR-27a in the blood of GC patients[[34-36](#_ENREF_34)]. The level of miR-421 in gastric tissue was related to lymph node metastasis and prognosis of gastric carcinoma[[37](#_ENREF_37)], and peripheral miR-421 was regarded as a serological biomarker for GC early diagnosis[[38](#_ENREF_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](#_ENREF_39)].

***lncRNAs in GC***

Brannan and his colleagues reported the first lncRNA(> 200 nucleotides), H19, in 1990[[40](#_ENREF_40)]. lncRNAs consist of exons and introns in structure, without ORFs, and are not highly conserved. Recent studies estimated that approximately 14,880 lncRNAs are present in humans[[41](#_ENREF_41)]. Over the last ten years, accumulating evidence has suggested that lncRNAs participate in cancer cell proliferation, apoptosis and migration[[42](#_ENREF_42)]. Our group has concentrated on the dysregulation of lncRNAs in GC. Data from hierarchical clustering and expression analysis indicated that lncRNAs were frequently aberrantly expressed in GC[[43](#_ENREF_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 by repressing miR-23b. We also reported the upregulation of LSINCT5 in GC, and its association with tumor size, depth, and clinical stage[[44](#_ENREF_44)].

In 2012, Yang *et al*[[45](#_ENREF_45)] first reported the contribution of H19 to GC, elucidating the potential mechanism of lncRNAs 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](#_ENREF_46)]. Plasma H19 level was also obviously higher in GC patients[[47](#_ENREF_47),[48](#_ENREF_48)], indicating that H19 might be a promising marker for early GC detection, and circulating lncRNAs 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 t RUNX1, demonstrating the role of the H19/miR-675/RUNX1 pathway in GC development[[49](#_ENREF_49)]. Data from other groups has suggested that altered expression of H19 in GC is induced by c-Myc[[50](#_ENREF_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](#_ENREF_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 lncRNA that has been detected in several human neoplasms, such as breast cancer[[52](#_ENREF_52)], colorectal cancer[[53](#_ENREF_53)], pancreatic cancer[[54](#_ENREF_54)] and others[[55](#_ENREF_55),[56](#_ENREF_56)]. HOTAIR was higher in GC tissues, especially in advanced cases[[57](#_ENREF_57)], and its level could predictive the effect after fluorouracil and platinum combination chemotherapy in advanced GC patients[[58](#_ENREF_58)]. Recent reports showed that HOTAIR inhibited apoptosis whereas promoted invasiveness and metastasis[[59](#_ENREF_59),[60](#_ENREF_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](#_ENREF_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](#_ENREF_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 lncRNAs were newly found to be dysregulated and played important roles in GC. Using RNA immunoprecipitation sequencing (RIP-seq), Qi *et al*[[63](#_ENREF_63)] demonstrated that the lncRNA 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](#_ENREF_64)]. Zhao *et al*[[65](#_ENREF_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 oncogenic function of Linc00152 in GC. Recently, Xiong *et al*[[66](#_ENREF_66)] reported that T-reg cells in peripheral blood were significantly upregulated in plasma samples from GC patients. Additionally, linc-POU3F3 could promote the distribution of T-reg 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 lncRNAs downregulated in GC, MIR31HG was upregulated in pancreatic ductal adenocarcinoma and contributed to tumor growth and cell invasion[[67](#_ENREF_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](#_ENREF_68)]. Other downregulated lncRNAs, such as WT1-AS and LOWEG, were associated with GC cell proliferation or invasion[[69](#_ENREF_69),[70](#_ENREF_70)].

Pseudogene-expressed lncRNAs are major members of the lncRNA 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](#_ENREF_71)].

Taken together, lncRNAs 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**

***piRNAs 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[[12](#_ENREF_12)]. piRNAs were found to be expressed in various human somatic tissues in a tissue-specific manner[[72](#_ENREF_72)]. Therefore, piRNAs may be highly sensitive and specific biomarkers for circulating cancer cells[[73](#_ENREF_73)], and potential therapeutic tools for cancer[[74](#_ENREF_74)].

Several reports have investigated the correlation between piRNAs and GC. Cheng *et al*[[75](#_ENREF_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](#_ENREF_76)], indicating that piRNAs play crucial roles in GC carcinogenesis. In addition, the level of piR-651 and piR-823 in peripheral blood was 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-node-metastasis depth[[73](#_ENREF_73)]. 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.

***CircRNAs in GC***

Circular RNAs (circRNAs) are special lncRNAs with covalently closed loop structures, as products of the non-canonical splicing of linear pre-mRNAs[[77](#_ENREF_77)]. Unlike the better-known linear RNAs, circRNAs lack of 5' to 3' polarity so well as poly adenylated tails[[78](#_ENREF_78)]. circRNAs were first identified in 1991[[79](#_ENREF_79)] and were regarded as functionless by-products for the next two decades. The roles and functions of circRNAs have been identified very recently, and these discoveries have permanently changed our understanding of cancer[[80-82](#_ENREF_80)].

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 correlateted with distal metastasis, TNM stage, gender and age[[83](#_ENREF_83)], suggesting that circRNAs may be novel and stable diagnostic biomarkers for GC. William W. Du *et al*[[84](#_ENREF_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[[84](#_ENREF_84)]. Several reports have also suggested a role for circRNAs in other tumors. Li *et al*[[85](#_ENREF_85)] showed that cir-ITCH was downregulated in esophageal squamous cell carcinoma. Using biochemical assays, they also found that cir-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.

ceRNA networks

Competing endogenous RNAs (ceRNAs) are transcripts that cross-regulate each other by competing for shared miRNAs[[86](#_ENREF_86)]. This hypothesis posits that RNAs could influence miRNAs expression, inducing gene silencing, only if they share miRNA response elements (MREs) in their 3’UTRs[[86](#_ENREF_86)]. ceRNAs can include mRNAs, pseudogenic RNAs, lncRNAs 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[[87](#_ENREF_87)]. 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[[88](#_ENREF_88)]. Welch *et al*[[89](#_ENREF_89)] 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[[90](#_ENREF_90)]. Thus, PTEN-targeting microRNAs miR-19b and miR-20a could suppress both PTEN and PTENP1 mRNA. 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[[90](#_ENREF_90)]. 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 a miRNA-dependent manner[[90](#_ENREF_90)]. 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[[88](#_ENREF_88),[90](#_ENREF_90)].

Recent evidence has showed that the multifaceted roles of lncRNAs in tumorigenesis may be partially mediated by ceRNA crosstalk. HOTAIR could modulate the derepression of HER2 by acting as a sink for miR-331-3p[[91](#_ENREF_91)]. lncRNA MEG3 was decreased in GC, and its ceRNA potential for the miR-181 family was predicted by lnCeDB[[92](#_ENREF_92)], 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[[92](#_ENREF_92)]. The lncRNA 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[[93](#_ENREF_93)]. Additionally, lncRNA BC032469 was reported to function as a ceRNA to impair miR-1207-5p-dependent downregulation of hTERT in GC[[94](#_ENREF_94)].

CircRNAs are a special type of lncRNA, and the newly discovered circRNAs can function as miRNA sponges, playing important roles in miRNA regulation. Thomas B. Hansen *et al*[[95](#_ENREF_95)] 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[[96](#_ENREF_96)]. cir-ITCH was also reported to function as a sponge of miR-7, miR-17, and miR-214 to regulate ITCH expression[[85](#_ENREF_85)]. Although bioinformatics analysis showed that only two human circRNAs harbor MREs[[97](#_ENREF_97)], further investigations are needed to verify whether the ceRNA potential of circRNAs is unique[[88](#_ENREF_88)].

**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 lncRNAs, 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 still 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 GC. ncRNAs may have promising applications in the current diagnostic/prognostic and therapeutic strategies for GC.

**References**

1 **Tan P**, Yeoh KG. Genetics 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, Kandalaft 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, Rebbeck 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: 26461095 DOI: 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 strands suggest that there may be as few as 19,000 human protein-coding genes. *Hum Mol Genet* 2014; **23**: 5866-5878 [PMID: 24939910 DOI: 10.1093/hmg/ddu309]

5 **Mattick 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 **Amaral PP**, Dinger ME, Mercer TR, Mattick JS. The eukaryotic genome as an RNA machine. *Science* 2008; **319**: 1787-1789 [PMID: 18369136 DOI: 10.1126/science.1155472]

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.i41.11709]

9 **Kahlert C**, Kalluri R. Exosomes in tumor microenvironment influence 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 SC, Xia T, Jiang XM, Shao YF, Xiao BX, 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**, Tuzova 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**, Meltzer SJ. MicroRNAs in pathogenesis, diagnosis, and treatment of gastroesophageal 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 Y, Jin Z, Huang W, Cheng Y, Liu Y, Feng X, Yang M, Huang Y, Zhao Z, Wang L, Wei Y, Fan X, Zheng D, Meltzer 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 JI, 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: 26692821 DOI: 10.1186/s12935-015-0266-1]

18 **Han TS**, Hur K, Xu G, Choi B, Okugawa Y, Toiyama 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, Sun 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 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 as a negative regulator in gastric cancer progression by targeting flotillin-1. *Am J Transl Res* 2015; **7**: 2212-2222 [PMID: 26807169]

22 **Lin M**, Shi C, Lin X, Pan J, Shen S, Xu Z, Chen Q. sMicroRNA-1290 inhibits cells proliferation and migration by targeting FOXA1 in gastric cancer cells. *Gene* 2016; **582**: 137-142 [PMID: 26851540 DOI: 10.1016/j.gene.2016.02.001]

23 **Li J**, Dong G, Wang B, Gao W, Yang Q. miR-543 promotes gastric cancer cell proliferation by targeting SIRT1. *Biochem Biophys Res Commun* 2016; **469**: 15-21 [PMID: 26612257 DOI: 10.1016/j.bbrc.2015.11.062]

24 **Huang T**, Kang W, Zhang B, Wu F, Dong Y, Tong JH, Yang W, Zhou Y, Zhang L, Cheng AS, Yu J, To KF. miR-508-3p concordantly silences NFKB1 and RELA to inactivate canonical NF-κB signaling in gastric carcinogenesis. *Mol Cancer* 2016; **15**: 9 [PMID: 26801246 DOI: 10.1186/s12943-016-0493-7]

25 **Yanaka Y**, Muramatsu T, Uetake H, Kozaki K, Inazawa J. miR-544a induces epithelial-mesenchymal transition through the activation of WNT signaling pathway in gastric cancer. *Carcinogenesis* 2015; **36**: 1363-1371 [PMID: 26264654 DOI: 10.1093/carcin/bgv106]

26 . 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**, Saraggi D, Balsamo L, Cascione L, Castoro C, Coati I, De Bernard M, Farinati F, Guzzardo V, Valeri N, 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: 26780940 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 YQ, Tomei S, Cai Q, Ji J, Li JF, Chouchane L, Yu YY, Sun FZ, Xu ZH, Liu BY, Zhu ZG. Epigenetic silencing of microRNA-149 in cancer-associated fibroblasts mediates prostaglandin E2/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 and Hsa-miR-29 in Tissue as Potential Diagnostic and Prognostic Biomarkers for Gastric Cancer. *Cell Physiol Biochem* 2015; **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-135a 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, Sihoe A, Chu KM. Plasma miR-940 may serve as a novel biomarker for gastric cancer. *Tumour Biol* 2016; **37**: 3589-3597 [PMID: 26456959 DOI: 10.1007/s13277-015-4019-5]

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

38 **Zhao G**, Xu L, Hui L, Zhao J. Level of circulated microRNA-421 in gastric carcinoma and related mechanisms. *Int J Clin Exp Pathol* 2015; **8**: 14252-14256 [PMID: 26823741]

39 **Wang J**, Song YX, Wang ZN. Non-coding RNAs in gastric cancer. *Gene* 2015; **560**: 1-8 [PMID: 25659765 DOI: 10.1016/j.gene.2015.02.004]

40 **Brannan CI**, Dees EC, Ingram RS, Tilghman SM. The product of the H19 gene may function as an RNA. *Mol Cell Biol* 1990; **10**: 28-36 [PMID: 1688465]

41 **Derrien T**, Johnson R, Bussotti G, Tanzer A, Djebali S, Tilgner H, Guernec G, Martin D, Merkel A, Knowles DG, Lagarde J, Veeravalli L, Ruan X, Ruan Y, Lassmann T, Carninci P, Brown JB, Lipovich L, Gonzalez JM, Thomas M, Davis CA, Shiekhattar R, Gingeras TR, Hubbard TJ, Notredame C, Harrow J, Guigó R. The GENCODE v7 catalog of human long noncoding RNAs: analysis of their gene structure, evolution, and expression. *Genome Res* 2012; **22**: 1775-1789 [PMID: 22955988 DOI: 10.1101/gr.132159.111]

42 **Ponting CP**, Oliver PL, Reik W. Evolution and functions of long noncoding RNAs. *Cell* 2009; **136**: 629-641 [PMID: 19239885 DOI: 10.1016/j.cell.2009.02.006]

43 **Qi P**, Xu MD, Shen XH, Ni SJ, Huang D, Tan C, Weng WW, Sheng WQ, Zhou XY, Du X. Reciprocal repression between TUSC7 and miR-23b in gastric cancer. *Int J Cancer* 2015; **137**: 1269-1278 [PMID: 25765901 DOI: 10.1002/ijc.29516]

44 **Xu MD**, Qi P, Weng WW, Shen XH, Ni SJ, Dong L, Huang D, Tan C, Sheng WQ, Zhou XY, Du X. Long non-coding RNA LSINCT5 predicts negative prognosis and exhibits oncogenic activity in gastric cancer. *Medicine (Baltimore)* 2014; **93**: e303 [PMID: 25526476 DOI: 10.1097/md.0000000000000303]

45 **Yang F**, Bi J, Xue X, Zheng L, Zhi K, Hua J, Fang G. Up-regulated long non-coding RNA H19 contributes to proliferation of gastric cancer cells. *FEBS J* 2012; **279**: 3159-3165 [PMID: 22776265 DOI: 10.1111/j.1742-4658.2012.08694.x]

46 **Chen JS**, Wang YF, Zhang XQ, Lv JM, Li Y, Liu XX, Xu TP. H19 serves as a diagnostic biomarker and up-regulation of H19 expression contributes to poor prognosis in patients with gastric cancer. *Neoplasma* 2016; **63**: 223-230 [PMID: 26774144 DOI: 10.4149/207\_150821n454]

47 **Zhou X**, Yin C, Dang Y, Ye F, Zhang G. Identification of the long non-coding RNA H19 in plasma as a novel biomarker for diagnosis of gastric cancer. *Sci Rep* 2015; **5**: 11516 [PMID: 26096073 DOI: 10.1038/srep11516]

48 **Arita T**, Ichikawa D, Konishi H, Komatsu S, Shiozaki A, Shoda K, Kawaguchi T, Hirajima S, Nagata H, Kubota T, Fujiwara H, Okamoto K, Otsuji E. Circulating long non-coding RNAs in plasma of patients with gastric cancer. *Anticancer Res* 2013; **33**: 3185-3193 [PMID: 23898077]

49 **Zhuang M**, Gao W, Xu J, Wang P, Shu Y. The long non-coding RNA H19-derived miR-675 modulates human gastric cancer cell proliferation by targeting tumor suppressor RUNX1. *Biochem Biophys Res Commun* 2014; **448**: 315-322 [PMID: 24388988 DOI: 10.1016/j.bbrc.2013.12.126]

50 **Zhang EB**, Han L, Yin DD, Kong R, De W, Chen J. c-Myc-induced, long, noncoding H19 affects cell proliferation and predicts a poor prognosis in patients with gastric cancer. *Med Oncol* 2014; **31**: 914 [PMID: 24671855 DOI: 10.1007/s12032-014-0914-7]

51 **Yang C**, Tang R, Ma X, Wang Y, Luo D, Xu Z, Zhu Y, Yang L. Tag SNPs in long non-coding RNA H19 contribute to susceptibility to gastric cancer in the Chinese Han population. *Oncotarget* 2015; **6**: 15311-15320 [PMID: 25944697 DOI: 10.18632/oncotarget.3840]

52 **Gupta RA**, Shah N, Wang KC, Kim J, Horlings HM, Wong DJ, Tsai MC, Hung T, Argani P, Rinn JL, Wang Y, Brzoska P, Kong B, Li R, West RB, van de Vijver MJ, Sukumar S, Chang HY. Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. *Nature* 2010; **464**: 1071-1076 [PMID: 20393566 DOI: 10.1038/nature08975]

53 **Kogo R**, Shimamura T, Mimori K, Kawahara K, Imoto S, Sudo T, Tanaka F, Shibata K, Suzuki A, Komune S, Miyano S, Mori M. Long noncoding RNA HOTAIR regulates polycomb-dependent chromatin modification and is associated with poor prognosis in colorectal cancers. *Cancer Res* 2011; **71**: 6320-6326 [PMID: 21862635 DOI: 10.1158/0008-5472.can-11-1021]

54 **Kim K**, Jutooru I, Chadalapaka G, Johnson G, Frank J, Burghardt R, Kim S, Safe S. HOTAIR is a negative prognostic factor and exhibits pro-oncogenic activity in pancreatic cancer. *Oncogene* 2013; **32**: 1616-1625 [PMID: 22614017 DOI: 10.1038/onc.2012.193]

55 **Nakagawa T**, Endo H, Yokoyama M, Abe J, Tamai K, Tanaka N, Sato I, Takahashi S, Kondo T, Satoh K. Large noncoding RNA HOTAIR enhances aggressive biological behavior and is associated with short disease-free survival in human non-small cell lung cancer. *Biochem Biophys Res Commun* 2013; **436**: 319-324 [PMID: 23743197 DOI: 10.1016/j.bbrc.2013.05.101]

56 **Tang L**, Zhang W, Su B, Yu B. Long noncoding RNA HOTAIR is associated with motility, invasion, and metastatic potential of metastatic melanoma. *Biomed Res Int* 2013; **2013**: 251098 [PMID: 23862139 DOI: 10.1155/2013/251098]

57 **Hajjari M**, Behmanesh M, Sadeghizadeh M, Zeinoddini M. Up-regulation of HOTAIR long non-coding RNA in human gastric adenocarcinoma tissues. *Med Oncol* 2013; **30**: 670 [PMID: 23888369 DOI: 10.1007/s12032-013-0670-0]

58 **Zhao W**, Dong S, Duan B, Chen P, Shi L, Gao H, Qi H. HOTAIR is a predictive and prognostic biomarker for patients with advanced gastric adenocarcinoma receiving fluorouracil and platinum combination chemotherapy. *Am J Transl Res* 2015; **7**: 1295-1302 [PMID: 26328013]

59 **Endo H**, Shiroki T, Nakagawa T, Yokoyama M, Tamai K, Yamanami H, Fujiya T, Sato I, Yamaguchi K, Tanaka N, Iijima K, Shimosegawa T, Sugamura K, Satoh K. Enhanced expression of long non-coding RNA HOTAIR is associated with the development of gastric cancer. *PLoS One* 2013; **8**: e77070 [PMID: 24130837 DOI: 10.1371/journal.pone.0077070]

60 **Lee NK**, Lee JH, Park CH, Yu D, Lee YC, Cheong JH, Noh SH, Lee SK. Long non-coding RNA HOTAIR promotes carcinogenesis and invasion of gastric adenocarcinoma. *Biochem Biophys Res Commun* 2014; **451**: 171-178 [PMID: 25063030 DOI: 10.1016/j.bbrc.2014.07.067]

61 **Du M**, Wang W, Jin H, Wang Q, Ge Y, Lu J, Ma G, Chu H, Tong N, Zhu H, Wang M, Qiang F, Zhang Z. The association analysis of lncRNA HOTAIR genetic variants and gastric cancer risk in a Chinese population. *Oncotarget* 2015; **6**: 31255-31262 [PMID: 26384301 DOI: 10.18632/oncotarget.5158]

62 **Guo W**, Dong Z, Bai Y, Guo Y, Shen S, Kuang G, Xu J. Associations between polymorphisms of HOTAIR and risk of gastric cardia adenocarcinoma in a population of north China. *Tumour Biol* 2015; **36**: 2845-2854 [PMID: 25476857 DOI: 10.1007/s13277-014-2912-y]

63 **Qi Y**, Ooi HS, Wu J, Chen J, Zhang X, Tan S, Yu Q, Li YY, Kang Y, Li H, Xiong Z, Zhu T, Liu B, Shao Z, Zhao X. MALAT1 long ncRNA promotes gastric cancer metastasis by suppressing PCDH10. *Oncotarget* 2016; **7**: 12693-12703 [PMID: 26871474 DOI: 10.18632/oncotarget.7281]

64 **Zhou J**, Zhi X, Wang L, Wang W, Li Z, Tang J, Wang J, Zhang Q, Xu Z. Linc00152 promotes proliferation in gastric cancer through the EGFR-dependent pathway. *J Exp Clin Cancer Res* 2015; **34**: 135 [PMID: 26538117 DOI: 10.1186/s13046-015-0250-6]

65 **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 [PMID: 26237576 DOI: 10.1080/15384101.2015.1078034]

66 **Xiong G**, Yang L, Chen Y, Fan Z. Linc-POU3F3 promotes cell proliferation in gastric cancer via increasing T-reg distribution. *Am J Transl Res* 2015; **7**: 2262-2269 [PMID: 26807174]

67 **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* 2015; Epub ahead of print [PMID: 26549028 DOI: 10.1038/onc.2015.430]

68 **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 [PMID: 26692098 DOI: 10.1007/s13277-015-4644-z]

69 **Du T**, Zhang B, Zhang S, Jiang X, 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 [PMID: 26449525 DOI: 10.1016/j.bbadis.2015.10.001]

70 **Zhao JH**, Sun JX, Song YX, Chen XW, Yang YC, Ma B, Wang J, Gao P, Wang ZN. A novel long noncoding RNA-LOWEG 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 [PMID: 26537802 DOI: 10.1007/s00432-015-2071-6]

71 **Mei D**, Song H, Wang K, Lou Y, Sun W, Liu Z, Ding X, Guo J. Up-regulation of SUMO1 pseudogene 3 (SUMO1P3) in gastric cancer and its clinical association. *Med Oncol* 2013; **30**: 709 [PMID: 23996296 DOI: 10.1007/s12032-013-0709-2]

72 **Ng KW**, Anderson C, Marshall EA, Minatel BC, Enfield KS, Saprunoff HL, Lam WL, Martinez VD. Piwi-interacting RNAs in cancer: emerging functions and clinical utility. *Mol Cancer* 2016; **15**: 5 [PMID: 26768585 DOI: 10.1186/s12943-016-0491-9]

73 **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 [PMID: 21704610 DOI: 10.1016/j.clinbiochem.2011.06.004]

74 **Itou D**, Shiromoto Y, Yukiho SY, Ishii C, Nishimura T, Ogonuki N, Ogura A, Hasuwa H, Fujihara Y, Kuramochi-Miyagawa S, Nakano T. Induction of DNA methylation by artificial piRNA production in male germ cells. *Curr Biol* 2015; **25**: 901-906 [PMID: 25772451 DOI: 10.1016/j.cub.2015.01.060]

75 **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 [PMID: 22047710 DOI: 10.1016/j.canlet.2011.10.004]

76 **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 [PMID: 21616063 DOI: 10.1016/j.cca.2011.05.015]

77 **Zhao ZJ**, Shen J. Circular RNA Participates in the Carcinogenesis and the Malignant Behavior of Cancer. *RNA Biol* 2015; Epub ahead of print [PMID: 26649774 DOI: 10.1080/15476286.2015.1122162]

78 **Chen LL**, Yang L. Regulation of circRNA biogenesis. *RNA Biol* 2015; **12**: 381-388 [PMID: 25746834 DOI: 10.1080/15476286.2015.1020271]

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

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

81 **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 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.bbagrm.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: 25689795 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 **Salmena L**, Poliseno 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 **Lu 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* 2015; Epub ahead of print [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/nature11993]

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]

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

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **RNA types** | **Symbol** | | **Length (nt)** | | **Function** | |
| *Housekeeping ncRNAs* | |  |  |  | |
| Transfer RNAs | tRNA | | 73-94 | | Connect amino acids with mRNA | |
| ribosomal RNAs | rRNA | | 121-5070 | | Component of ribosomes | |
| small nuclear RNAs | snRNA | | ~150 | | Assemble with proteins into spliceosomes to remove introns during mRNA processing | |
| small nucleolar 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* |  | |  | |  | |
| Small interfering RNAs | siRNA | | 21-22 | | Silencing genes in a  sequence-specific manner | |
| MicroRNAs | miRNA | | 20-23 | | Regulating genes expression | |
| Piwi-interacting RNA | 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.

**Table 2 Related advances of noncoding RNAs in gastric cancer of this review**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Types 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 | suppress 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 | NF-κB signaling | NFKB1 | [24] |
|  | miR-544a | Upregulated | regulate EMT markers | Wnt signaling | CDH1,AXIN2 | [25] |
|  | miR-375 | Downregulated | increase sensitivity to DPP treatment | unknown | ERBB2, p-Akt | [26] |
|  | miR-143 | Downregulated | inhibit autophagy | unknown | GABARAPL1 | [27] |
|  | miR-27b | Downregulated | inhibit HP-related proliferation | Wnt signaling | unknown | [29] |
|  |  |  |  |  |  |  |
| lncRNAs | TUSC7 | Downregulated | p53-dependent tumor suppressive role | unknown | miR-23b | [43] |
|  | LSINCT5 | Upregulated | correlated with clinical parameters | unknown | unknown | [44] |
|  | H19 | Upregulated | biomarker, promote proliferation |  | miR-675 | [46,49] |
|  | HOTAIR | Upregulated | biomarker, inhibit apoptosis, promote invasion and metastasis |  |  | [59,60] |
|  | MALAT1 | Upregulated | promote migration and invasion | unknown | EZH2 | [63] |
|  | Linc00152 | Upregulated | promote cell proliferation, migration and invasion cell cycle, and tumor growth | PI3K/Akt | EGFR | [64,65] |
|  | linc-POU3F3 | Upregulated | promote distribution of T-reg cells | TGF-β | unknown | [66] |
|  | MIR31HG | Downregulated | inhibit proliferation | unknown | E2F1/p21 | [68] |
| piRNAs | piR-823 | Downregulated | tumor suppressive role |  |  | [75] |
|  | piR-651 | Upregulated | promote cell growth |  |  | [76] |
| circRNAs | Hsa\_circ\_002059 | Downregulated | biomarker |  |  | [83] |
|  | circ-Foxo3 | Upregulated | cell cycle, promote proliferation |  | p21/CDK2 | [84] |
|  | circ-ITCH | Downregulated | miRNA sponge | Wnt/β-catenin |  | [85] |

piRNAs: PIWI-interacting RNAs; lncRNAs: long ncRNAs; circRNAs: circular RNAs.