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TOPIC HIGHLIGHT

2016 Gastric Cancer: Global view

Noncoding RNAs in gastric cancer: Research progress and prospects

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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 (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

Core tip: Accumulating data have deepened our understanding of the contribution of noncoding RNAs (ncRNAs) in cancer development, and several emerging ncRNAs have been identified, such as PIWI-interacting RNAs and circular RNAs. The competing endogenous RNA (ceRNA) network hypothesis represents a widespread form of post-transcriptional regulation of gene expression. However, their function and mechanism remain unknown. This review summarizes 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 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			
Transfer RNAs	tRNA	73-94	Connect amino acids with mRNA
Ribosomal RNAs	rRNA	121-5070	Component of ribosomes
Small nuclear RNAs	snRNA	Approximately 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.

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[1,14]. 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[19-21]. 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 down-regulated in cisplatin (DDP)-resistant cells compared with the DDP-sensitive human GC cell line[26]. Western blot 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]. 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 lncRNAs are present in humans[41]. Over the last ten years, accumulating evidence has suggested that lncRNAs participate in cancer cell proliferation, apoptosis and migration[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]. 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 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]. 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 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 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 lncRNA 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 lncRNAs 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 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]. 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 oncogenic 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 lncRNAs 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 lncRNAs, such as WT1-AS and LOWEG, were associated with GC cell proliferation or invasion[69,70].

Pseudogene-derived 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].

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

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[12]. PiRNAs were found to be expressed in various human somatic tissues in a tissue-specific manner[72]. 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 G_2/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[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.

Circular RNAs 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]. Unlike the better-known linear RNAs, circRNAs lack of 5′ to 3′ polarity so 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 very 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[84]. Several reports have also suggested a role for circRNAs in other tumors. Li *et al*[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.

Competing endogenous RNA networks

Competing endogenous RNA (ceRNA) are transcripts that cross-regulate each other by competing for shared miRNAs[86]. 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)[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]. 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]. Welch *et al*[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]. 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[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 an miRNA-dependent manner[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[88,90].

Recent evidence has showed that the multifaceted roles of lncRNAs 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[91]. LncRNA MEG3 was decreased in GC, and its ceRNA potential for the miR-181 family was predicted by lnCeDB[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]. 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]. Additionally, lncRNA BC032469 was reported to function as a ceRNA to impair miR-1207-5p-dependent downregulation of hTERT in GC[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] 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]. cir-ITCH was also reported to function as a sponge of miR-7, miR-17, and miR-214 to regulate ITCH expression[85]. Although bioinformatics analysis showed that only two human circRNAs harbor MREs[97], further investigations are needed to verify whether the ceRNA potential of circRNAs is unique[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 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	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 Treg 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.

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

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