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REVIEW

Role of circular RNAs in gastric cancer: Recent advances and prospects

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Abstract

Circular RNA (circRNA) is a newly discovered non-coding RNA with special structure, which is widely expressed in eukaryotic organisms and mainly located in the cytoplasm. circRNAs participate in gene regulation by working as miRNA sponges that block the inhibitory effect of miRNA on its target genes. In addition, circRNAs can bind to RNA binding proteins to regulate gene expression. Based on characteristics of stability, expression specificity and participation in gene regulation, circRNAs are expected to be biomarkers for early diagnosis of cancer or potential targets for cancer therapy. With the help of bioinformatics analysis, circRNA microarray analysis and high-throughput sequencing technology, more circRNAs were discovered to participate in the progression of gastric cancer (GC) over the past three years. This article gives an overview of these recent research focusing on the roles of circRNAs in GC and highlights the advances.

Key words: Circular RNA; Gastric cancer; Biomarker; Therapeutic target; Prognosis

Core tip: Gastric cancer (GC) is a common, worldwide malignant tumor with a poor prognosis. An increasing number of circRNAs was discovered to participate in the progression of GC. Therefore, exploring the function of circRNAs will help to achieve a better understanding of the pathogenesis of GC and identify new diagnostic biomarkers and therapeutic targets. This article gives an overview of the recent research focusing on the roles of circRNAs in GC and highlights the advances that were made over the past three years.

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INTRODUCTION

Gastric cancer (GC) is one of the most common human cancers. The number of new cases in 2018 was 1033701, which accounted for 5.7% of all new cancers, and the number of deaths from GC was 782685, which accounted for 8.2% of all cancer deaths; only behind lung cancer[1]. Although diagnostic and therapeutic techniques have been developing rapidly, the prognosis of GC remains poor[2]. The poor prognosis is partly due to an incomplete understanding of the molecular mechanisms of GC occurrence and development. Thus, it is critical to identify some new biomarkers and therapeutic targets to improve the diagnosis and treatment of GC.

Circular RNAs (circRNAs) are newly discovered endogenous non-coding RNAs (ncRNAs) that form covalently closed continuous loops with neither 5′ to 3′ polarity nor a polyadenylated tail[3]. They are generated from backsplicing of exons, introns, or both, and called exonic circRNAs, intronic RNAs and exon-intron circRNAs according to their components (Figure 1). Although circRNAs have been investigated for almost 40 years[4], significant attention has not been received until recent years[5]. circRNAs were found to participate in gene regulation by working as miRNA sponges that block the inhibitory effect of miRNA on its target genes[6], splicing of target genes[7] or interacting with RNA-binding proteins (RBPs)[8]. In addition, some circRNAs can even encode peptides[9,10]. circRNAs have been widely investigated in recent years because they play many important roles in proliferation, apoptosis and metastasis of cancer cells[11-15]. With the help of bioinformatics analysis, circRNA microarray analysis and high-throughput sequencing technology, more circRNAs was discovered to participate in the progression of GC[16-21]. Gu *et al*[20] conducted a circRNA microarray analysis to explore the difference in circRNAs expression between tumor and adjacent nontumorous tissues from six patients with GC. They showed that 440 circRNAs were expressed differently in tumor samples, including 176 upregulated and 264 downregulated circRNAs[20]. Exploration of GC-related circRNAs may provide a new insight into the diagnosis and treatment of GC. In addition, circRNAs are hardly degraded by RNA exonuclease or ribonuclease R[22], making them more stable in tissue or plasma. This feature makes circRNAs a potential use for biomarkers, prognosis predictors, and even therapeutic targets of GC.

We searched MEDLINE and PubMed before January 2019 using the following keywords: circular RNA, circRNA and gastric cancer. The inclusion criteria were as follows: (1) Studies associating circRNAs with GC samples or cancer cells, and discussing their potential use as biomarkers for diagnosis of the disease; (2) Studies associating circRNAs with biological functions or potential pathways in GC; and (3) Studies associating circRNAs with clinical significance of GC. This review highlights recent advances in circRNA in GC, especially focusing on their deregulation, biological function and clinical significance.

CIRCRNAS ACT AS MIRNA REGULATORS IN GASTRIC CANCER

As mentioned before, circRNAs primarily act as miRNA sponges to regulate gene expression. Most circRNAs contain a miRNA response element, which can bind with miRNAs and regulate their expression. At present, there are 13 circRNAs that act as miRNA regulators in GC. Some of these are downregulated and serve as tumor suppressors, while others are upregulated during carcinogenesis and serve as oncogenes. All these circRNAs are summarized in Table 1.

hsa_circ_0000993 is downregulated in GC. It can act as a miRNA sponge for miR-214-5p and inhibit the proliferation, invasion and migration of GC cells[23]. Has_circ_000146, a sponge for miR-548g, is significantly downregulated in GC cell lines and tissues, and negatively correlated with survival time of GC patients. Overexpression of has_circ_0001461 can inhibit proliferation, migration and invasion of GC cells. These effects can be reversed by overexpression of miR-548g, which can downregulate expression of runt-related transcription factor 1 (RUNX1). These results suggest that has_circ_0001461 acts as a tumor suppressor in GC cells by regulating the miR-548g/RUNX1 pathway[24]. Liu *et al*[25] reported that has_circ_0002320 level was

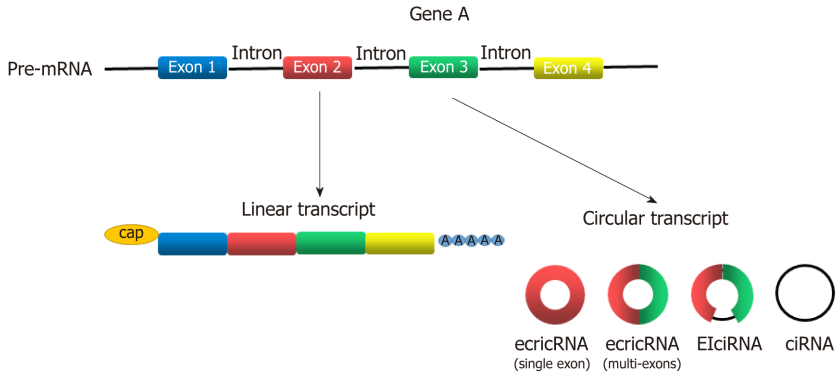

Figure 1 Classification of circRNAs according to their components. EcircRNAs are composed of single or multi-exons. In EIciRNAs, exons are circularized with introns "retained" between exons. CiRNAs are composed of introns.

significantly lower in GC tissues than in paired adjacent nontumorous tissues, and the survival time was shorter in GC patients with lower has_circ_0002320 level. By using fluorescence *in-situ* hybridization (FISH) in GC tissues, they found that has_circ_0002320 and miR-367-5p were colocalized in the cytoplasm. Overexpression of has_circ_0002320 upregulated expression of p27 Kip1 in GC cells and inhibited their growth and invasion, and these effects could be reversed by miR-367-5p mimics. These results demonstrate that has_circ_0002320 is a tumor suppressor in GC cells by targeting the miR-367-5p/p27 Kip1 pathway and provides a prediction of survival time in GC patients[25]. Hsa_circ_0027599 was significantly downregulated in GC patients and cells, and its overexpression inhibited proliferation and metastasis of GC cells. Moreover, hsa_circ_0027599 was verified to be a sponge of miR-101-3p.1 (miR-101) by bioinformatic technology and luciferase reporter assays. miR-101 can inhibit the expression of its target gene *PHLDA1* and promote proliferation of cancer cells. Conversely, overexpression of *PHLDA1* decreases the growth and migration of MKN-28 and HGC-27 GC cells. These results suggest that *PHLDA1* is regulated by circ_0027599/miR-101, which inhibits the growth and metastasis of GC cells[26]. Another study, which had different conclusions from the above, has shown that miR-101-3p is a tumor suppressor and overexpression of miR-101-3p inhibits proliferation and invasion of AGS GC cells[27]. Therefore, the functions of miR-101 needs more investigation. miR-630 is one of the newly discovered miRNAs, and its role in cancer has attracted increased attention. miR-630 is dysregulated in many tumors[28,29]. Direct interaction of miR-630 and circRNA_100269 was confirmed by dual-luciferase reporter assays. The level of miR-630 decreased significantly by circRNA_100269 overexpression, which inhibited proliferation of GC cells. These results suggest that the circRNA_100269/miR-630 axis plays an important role in the growth of GC cells[30]. A novel circRNA circ_101057, also termed as circLARP4, was shown downregulated in GC tissues by FISH analysis, and lower circLARP4 expression was associated with poor prognosis. Furthermore, circLARP4 inhibited biological behavior of GC cells[31]. These effects have also been seen in ovarian cancer[32]. circLARP4 was found to sponge miR-424-5p by bioinformatics analysis. miR-424-5p promotes proliferation and invasion of GC cells by targeting *LATS1* gene, and positively correlates with higher clinical stage and worse prognosis of GC patients[31]. However, the function of miR-424-5p is the opposite in breast cancer and esophageal squamous cell carcinoma. Wang *et al*[33] have reported that miR-424-5p acts as a tumor suppressor to regulate proliferation, invasion and migration of breast cancer cells by binding to the functional target Doublecortin Like Kinase 1[33]. Upregulation of miR-424-5p may prevent tumor invasion or metastasis[34]. circ-ZFR is a new circRNA that is markedly downregulated in tumor tissues compared with pair-matched adjacent nontumorous tissues. Moreover, expression of circ-ZFR is significantly lower in GC cell lines HGC-27, AZ521, and AGS than in gastric epithelial cell line GES1. circ-ZFR promotes cell cycle arrest and apoptosis in GC cells by sponging miR-107/miR-130a, and miR-107/miR-130a could bind to the 3′ untranslated region (UTR) of phosphatase and tensin homolog (PTEN)[35]. Many studies have demonstrated that PTEN could be targeted and regulated by miR-107 and miR-130a to influence activities of cancer cells[36,37]. All these results suggest that the circ-ZFR-miR-107/miR-130a-PTEN pathway plays an important role in the progression of GC.

One circRNA hsa_circ_0017639 that is derived from gene *SFMBT2*, also named circ-SFMBT2, shows higher expression level in GC tissues compared with adjacent nontumorous tissues, and is linked to higher tumor stages. The proliferation of GC

Table 1 Deregulated circRNA in gastric cancer: function and potential signaling pathway

circRNA	Deregulation	Function/clinical association	Gene/pathway affected	Ref.
hsa_circ_0000993	Downregulation	Inhibits proliferation, migration and invasion	miR-214-5p	[23]
has_circ_0001461	Downregulation	Inhibits proliferation, migration and invasion; correlates with the clinical stage	miR-548g, RUNX1 in the cytoplasm; YBX1 in the nucleus	[24]
has_circ_0002320	Downregulation	Inhibits proliferation and invasion; correlates with TMN stage and survival time	miR-367-5p, p27	[25]
hsa_circ_0027599	Downregulation	Inhibits proliferation and migration; correlates with TNM stage	miR-101, PHLDA1	[26]
circRNA_100269	Downregulation	Inhibits proliferation; correlates with histological subtype,node invasive number and overall survival time	miR-630	[30]
circRNA_101057	Downregulation	Inhibits proliferation and invasion; correlates with tumor size and lymphatic metastasis and overall survival time	miR-424, LATS1	[31]
circZFR	Downregulation	Inhibits proliferation and promotes apoptosis	miR-130a/miR-107, PTEN	[35]
hsa_circ_0017639	Upregulation	Promotes proliferation; correlates with TNM stage	miR-182-5p, CREB1	[38]
circRNA_0000284	Upregulation	Promotes proliferation; correlates with T stage	miR-124 and miR-29b, COL1A1, COL4A1 and CDK6	[42]
circRNA_001569	Upregulation	Promotes proliferation and inhibits apoptosis; correlates with tumor size, depth of invasion and clinical stage	miR-145, NR4A2	[44]
circPDSS1	Upregulation	Promotes proliferation and inhibits apoptosis;correlates with worse overall survival time	miR-186-5p, NEK2	[45]
circNF1	Upregulation	Promotes proliferation	miR-16, MAP7 and AKT3	[49]
ciRS-7	Upregulation	Promotes proliferation and inhibits apoptosis; correlates with TNM stage and poor overall survival time	miR-7, PTEN/PI3K/AKT pathway	[53]

RUNX1: Runt-related transcription factor 1; YBX1: Y-box binding protein-1; PHLDA1: Pleckstrin homology like domain family A member 1; LATS1: Large tumor suppressor kinase 1; PTEN: Phosphatase and tensin homolog; CREB1: cAMP response element binding protein 1; COL1A1: Collagen type I α1 chain; COL4A1: Collagen type IV α1 chain; CDK6: Cyclin-dependent kinase 6; NR4A2: Nuclear receptor subfamily 4 group A member 2; NEK2: NIMA related kinase 2; MAP7: Microtubule associated protein 7.

cells is significantly suppressed when circ-SFMBT2 is knocked down. Luciferase reporter assay revealed that miR-182-5p mimics induced a lower luciferase level in circ-SFMBT2 WT group than in the normal control group. Furthermore, it has been demonstrated that circ-SFMBT2 acts as a sponge of miR-182-5p to regulate expression of cAMP response element binding protein (CREB)1 and promotes proliferation of GC cells[38]. circHIPK3 (circRNA_0000284) that is derived from the homeodomain-interacting protein kinase-3 (*HIPK3*) gene sponges multiple miRNAs and serves as an oncogene in multiple cancers[39-41]. In GC tissues, circHIPK3 level is significantly higher than it in paired adjacent nontumorous tissues. Moreover, it negatively regulates expression of miR-29b/miR-124 and is associated with T stage of GC. Three candidate genes (*CDK6, COL1A1* and*COL4A1*) can be regulated by miR-29b and miR-124, suggesting that these genes may play important roles in GC though circHIPK3-miR-29b/miR-124 axes[42]. circRNA_001569 was firstly discovered to act as a positive regulator in cell proliferation and invasion of colorectal cancer[43]. Recently, it was found upregulated in tissues and cells of GC. circRNA_001569 overexpression significantly decreases expression of miR-145, while circRNA_001569 knockdown has the opposite effect. Moreover, circRNA_001569 knockdown decreases cell viability

dramatically and promotes apoptosis, but these effects of circRNA_001569 knockdown are reversed when cells are cotransfected with miR-145 inhibitor. The online microRNA.org predicted that miR-145 could bind with NR4A2 3′ UTR. miR-145 overexpression significantly decreased NR4A2 expression and cell viability, and promoted apoptosis. However, cotransfection with NR4A2 abolished the above effects[44]. All these results indicate that circRNA_001569 serves as an oncogene by regulating expression of the miR-145/NR4A2 axis. circPDSS1 was recently discovered to be highly expressed in GC tissue and cell lines. Patients with higher circPDSS1 expression have worse overall survival. CircPDSS1 knockdown significantly inhibits cell proliferation[45]. The expression of miR-186-5p, a tumor suppressor gene[46], is decreased by circPDSS1 overexpression. In luciferase reporter assays, luciferase activity was decreased by cotransfection of miR-186-5p mimics and wt-NEK2. This suggests that *NEK2*, an oncogene[47,48], is a target of miR-186-5p. Moreover, miR-186-5p inhibits *NEK2* expression, while miR-186-5p inhibitor reverses this effect[45]. In summary, circPDSS1/miR-186-5p/NEK2 pathway may play an important role in GC cancer progression, and may be a target for gene therapy. circNF1 is upregulated in GC tissues and cell lines. Functional studies have demonstrated that circNF1 serves as an oncogene and significantly promotes cell proliferation. Furthermore, luciferase reporter assays have shown that circNF1 acts as a sponge to miR-16, thereby affecting its downstream target mRNAs, AKT3 and MAP7[49]. ciRS-7 is a well-known circRNA due to its promotion of carcinogenesis in a variety of cancers[50-52]. In GC, the ciRS-7 level is significantly higher than in nontumorous tissues, and higher ciRS-7 is associated with worse survival. miR-7 overexpression increases expression of PTEN, decreases PI3K and Akt phosphorylation, and inhibits tumor growth, while ciR-7 attenuates these effects[53]. These results indicate that ciRS-7 might be a promising therapeutic target through modulation of mir-7/PTEN/PI3K/AKT pathway in GC.

CircRNAs ACT AS DIAGNOSTIC BIOMARKERS OF GASTRIC CANCER

The 5-year survival rate of early GC can exceed 92%[54,55]. However, if GC develops to a late stage, the survival rate is significantly decreased[56]. Therefore, stable and effective diagnostic markers for the early diagnosis of GC need to be identified. Over the past three years, many circRNAs have been found to have specific differences between GC and normal gastric tissue, and these differences have helped circRNAs to become potential markers of early diagnosis or predictors of prognosis[38,57-72]. All these circRNA are summarized in Table 2. We will cover in detail those circRNA with an area under the curve (AUC) > 0.75.

Hsa_circ_0000096 level was found to be lower in GC tissues and cell lines than paired adjacent nontumorous tissues and normal gastric epithelial cells. Furthermore, the cutoff value (ΔCt value) of hsa_circ_0000096 was 12.9 with an AUC of 0.82. Hsa_circ_0000096 was also linked to several clinicopathological features such as invasion and TNM stage[57]. Hsa_circ_0000181 levels in plasma from GC patients and tissues were significantly decreased compared with those from healthy individuals and paired adjacent nontumorous tissues. In addition, its level in plasma of GC patients was associated with differentiation and carcinoembryonic antigen (CEA) level. The AUC of hsa_circ_0000181 in plasma was 0.582 with a specificity of 20.6% and sensitivity of 99.0%. Moreover, hsa_circ_0000181 levels in GC tissues were associated with tumor diameter, lymphatic metastasis, distant metastasis, and carbohydrate antigen (CA)19- 9 level. The AUC of hsa_circ_0000181 in tissues was 0.756 with a specificity of 85.2% and sensitivity of 53.9%[58]. Hsa_circ_0000190 was firstly discovered to be downregulated in plasma and tissues samples from GC patients. Its levels in tissue were significantly associated with TNM stage and CA19-9 level. The AUC of hsa_circ_0000190 in tissue was 0.75. The sensitivity and specificity were 72.1% and 68.3%, respectively[59]. hsa_circ_0000520 expression was significantly downregulated in GC tissue, plasma and cell lines (BGC-823, MKN-45, AGS and MGC-803). In plasma, the AUC was 0.8967, and the sensitivity and specificity were 82.35% and 84.44%, respectively[60]. The limitation of this study was the small number of samples. There were only 56 paired GC tissues, 45 preoperative GC plasma and 17 healthy plasma samples used for analysis, thus indicating the need and necessity to expand the sample size to verify the efficacy of hsa_circ_0000520 as a biomarker for GC. Hsa_circ_0001895 levels were lower in 69.8% of GC tissues than in paired adjacent nontumorous tissues and were also downregulated in five GC cell lines (HGC-27, BGC-823, AGS, SGC7901 and MGC-803). In addition, its level was linked to tissue CEA expression, Borrmann type and cell differentiation. The AUC of hsa_circ_0001895 in tissue was 0.792. When the optimal cutoff value of hsa_circ_0001895

Table 2 Deregulated circRNA in gastric cancer: diagnostic or predictive biomarker

circRNA	Deregulation	Cut-off value (ΔCt)	AUC	Sensitivity	Specificity	Clinical association	Ref.
hsa_circ_0000096	Downregulation	12.9	0.82	-	-	Gender, invasion and TNM stage	[57]
hsa_circ_0001181	Downregulation	9.4	0.756	85.2%	53.9%	Tumor diameter, lymphatic metastasis, distal metastasis, and CA19-9 (tissue)	[58]
		7.27	0.582	20.6%	99%	CEA and differentiation (plasma)	
hsa_circ_0001190	Downregulation	6.83	0.75	72.1%	68.3%	Tumor diameter, TNM stage and CA19-9 (tissue)	[59]
		3.07	0.6	41.4%	87.5%	CEA (plasma)	
hsa_circ_0000520	Downregulation	-	0.6129	53.57%	85.71%	TNM stage (tissue)	[60]
		-	0.8967	82.35%	84.44%	CEA (plasma)	
hsa_circ_0000745	Downregulation	-	0.683	85.5%	45%	Tumor differentiation (tissue) and TNM stage (plasma)	[61]
hsa_circ_0001895	Downregulation	9.53	0.792	67.8%	85.7%	Tumor differentiation, Borrmann type, and tissue CEA	[62]
hsa_circ_0000164 9	Downregulation	0.227	0.834	71.1%	81.6%	Tumor differentiation	[63]
hsa_circ_002059	Downregulation	12.9	0.73	81%	62%	TMN stage, distal metastasis, gender and age	[64]
hsa_circ_0003159	Downregulation	12.31	0.75	85.2%	56.5%	Gender, distal metastasis, and TMN stage	[65]
hsa_circ_0006633	Downregulation	8.17	0.741	60%	81%	Distal metastasis and CEA	[66]
hsa_circ_0014717	Downregulation	12.14	0.696	59.38%	81.25%	Tumor stage; distal metastasis; CEA; CA199	[67]
has_circ_0066779	Downregulation	-	0.6726	90.3%	56.4%	TNM stage overall survival time	[68]
hsa_circ_0074362	Downregulation	12.17	0.63	84.3%	36.2%	CA19–9 and lymphatic metastasis	[69]
hsa_circ_0130810	Downregulation	1.443	0.7481	77.42%	68%	TNM stage and overall survival time	[70]
hsa_circ_0000467	Upregulation	-	0.79	70.5%	64.8%	TNM stage	[71]
hsa_circ_0017639	Upregulation	11.46	0.7585	80.56%	63.89%	TNM stage	[38]
hsa_circ_0066444	Upregulation	-	0.7328	70.75%	68.87%	Lymphatic metastasis	[72]

AUC: Area under the curve; CA19-9: Carbohydrate antigen 19-9; CEA: Carcinoembryonic antigen.

was set at 9.53, the sensi-tivity and specificity were 67.8% and 85.7%, respectively[62]. Hsa_circ_0001649 is a well-known prognostic biomarker or tumor suppressor in multiple cancers[73-77]. Hsa_circ_0001649 levels in GC tissues were significantly lower than those in paired nontumorous tissues. The AUC was 0.834 with a sensitivity of 71.1% and specificity of 81.6%. Compared with plasma collected preoperatively, has_circ_0001649 level was significantly upregulated in plasma samples collected

postoperatively[63]. This suggests that has_circ_0001649 could be used as an index of postoperative follow-up. Whether the nonelevation or redecline of has_circ_0001649 level is related to poor prognosis or recurrence of GC needs further exploration. Compared to paired adjacent nontumorous tissues, hsa_circ_0003159 expression was recently found to be significantly downregulated in GC tissues. Moreover, its levels were negatively related to gender, distant metastasis, and TNM stage. The cutoff value was 12.31 with an AUC of 0.75. The sensitivity and specificity were 85.2% and 56.5%, respectively[65].

Hsa_circ_0000467 levels were significantly higher in GC tissue compared with adjacent nontumorous tissue. Moreover, its level in tissue was positively related to TNM stage. Similar results of hsa_circ_0000467 expression was obtained in AGS, MGC-803, HGC-27 and NUGC-3 compared with GES-1 cell lines. Furthermore, hsa_circ_0000467 knockdown markedly inhibited the proliferation, invasion and migration, and promoted apoptosis of GC cells *in vitro*. The AUC of hsa_circ_0000467 in plasma was 0.790. Its levels in plasma of the same patient obviously declined after surgery[71]. However, the small number of samples was a limitation in this study. More samples are needed to increase the accuracy. At present, none of the AUCs that were obtained using a single circRNA as a diagnostic marker for GC was > 0.9. Therefore, some scholars have suggested that the combined application of > 2 circRNAs may help to improve the accuracy of early diagnostic markers for GC. Li *et al*[78] reported that hsa_circ_0061276 and hsa_circ_0001017 were both downregulated in GC plasma and tissues. Patients with low plasma hsa_circ_0061276 or hsa_circ_0001017 levels had worse overall survival than those with high levels. The AUC of hsa_circ_0061276 and hsa_circ_0001017 in plasma was 85.1% and 84.9%, respectively. When these two plasma biomarkers of GC were used together for analysis, the AUC increased to 0.912, with a sensitivity of 84.7% and specificity of 96.6%[78]. Another similar study also found that the AUC was increased to 0.91 with the combination of hsa_circ_002509 and hsa_circ_0000096[57]. These are the top two highest AUC in all current research.

FUTURE PROSPECTS

Studies of circRNAs in GC are just at the beginning compared with coding RNAs, miRNAs and long ncRNAs. Although more functional circRNAs have been discovered and characterized in GC, most of the studies have focused on their relationship with pathological characteristics. For most of these circRNAs, their biogenesis, cellular location, and mechanism of regulation still need to be explored. In recent years, exosomes have been identified to play an important role in the progression of cancer[79]. One recent study showed that ciRS-133 was delivered into preadipocytes by exosomes derived from GC cells, promoting the transformation of preadipocytes into brown-like cells by suppressing miR-133 and activating *PRDM16*. Additionally, silence of ciRS-133 expression can reduce cachexia in tumor-implanted mice[80]. Therefore, exosome-delivered circRNAs are involved in white adipose tissue browning and play an important role in cancer-related cachexia. In the future, more in-depth studies about the roles of exosome-delivered circRNAs will help to prevent the occurrence of cachexia, improve the prognosis of GC, and prolong the survival time of patients. Some scholars have reported that circRNAs may participate in the process of epithelial–mesenchymal transition (EMT)[81,82], which plays a critical role in cancer metastasis[83]. Further studies on the regulation effect of circRNAs on EMT will be helpful to reveal the mechanism of circRNAs in cancer metastasis. Moreover, how to transfer circRNAs or si-circRNAs efficiently to the accurate lesion site without side effects needs to be resolved urgently for clinical applications. We hope that more basic research about circRNAs will be carried out with the advances in molecular biology and biological informatics technology to reveal the pathological and physiological functions of circRNAs, and to develop circRNA-based therapeutic strategies that can safely and successfully integrate into clinical practice.

CONCLUSION

Many circRNAs are dysregulated in GC tissues, plasma and cell lines. Moreover, their dysregulation is associated with clinicopathological features and prognosis of GC. By working as miRNA sponges or interacting with RBPs, these circRNAs regulate the expression of miRNAs and target proteins that are associated with cell proliferation, apoptosis, invasion and metastasis. Based on their characteristics of stability, expression specificity and participation in gene regulation, circRNAs are expected to be potential biomarkers for early diagnosis, prognostic predictors, and therapeutic

targets of GC.

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