

# Circular RNAs in gastric cancer: Biomarkers for early diagnosis (Review)

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**Abstract.** Circular RNAs (circRNAs) are highly conserved and stable closed-loop non-coding RNAs. They are involved in numerous biological functions, including regulating gene transcription or protein translation by interacting with proteins and regulating expression of microRNAs. The aberrant expression of circRNAs has been reported in many cancers, including gastric cancer. By regulating gene expression, circRNAs are able to affect the proliferation, invasion and metastasis of gastric cancer. The current review focused on the characteristics and biological functions of circRNAs, the carcinogenic potential and the possible implications of circRNAs on the diagnosis and treatment of gastric cancer. In conclusion, circRNAs may serve as potential biomarkers for diagnosis, as well as therapeutic targets.

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## 1. Introduction

Gastric cancer is the fifth most common cancer and third leading cause of cancer mortality in the world, according to the International Agency for Research on Cancer in 2018 (1). The morbidity of gastric cancer affected >1 million in 2018, accounting for 5.7% of new cancer cases globally. Worldwide, gastric cancer mortality is ~783,000, accounting for 8.2% of the total global deaths caused by cancer in 2018 (1). Diagnosis of gastric cancer relies on endoscopic examination and analyses of serum biomarkers in the clinical practice (2). However, endoscopy cannot be used for large-scale screening, and detection by serum biomarkers lacks sensitivity and specificity (3). To date, there is no simple and efficient diagnostic method that allows for the early diagnosis of gastric cancer to improve its prognosis.

Circular RNAs (circRNAs) are a group of single-strand closed-loop RNAs that are derived from back-splicing and are widely found in serum and saliva (4,5). circRNAs serve a regulatory role at the transcriptional and/or post-transcriptional level, but some can only function at the transcriptional level. Previous research has found that biological functions of circRNAs include microRNA (miRNA) sponging, regulation of transcription and translation, and interaction with RNA-binding proteins (4,6-8). Additionally, the dysregulation of circRNA expression is suggested to play an important role in the pathogenesis and diagnosis of gastric cancer.

Although little is known about the role of circRNAs in the development of gastric cancer at the molecular level, circRNAs secreted into the extracellular environment can be identified in blood, stool and other body fluids (9-12). Thus, circRNAs might be used as new potential biomarkers for the diagnosis and therapeutic targeting of gastric cancer.

## 2. Biological functions of circRNAs

circRNAs are abnormally expressed in various cancer types, including gastric cancer (13-16), such as circCCDC66, circPIP5K1A, circ-ATAD1 are higher expressed, but circMTO1 expression is lower in gastric cancer (17-20). circRNAs may cause cancer by interacting with tumor-associated miRNAs, proteins and genes, and by participating in pathophysiological activities, including proliferation, invasion

and apoptosis (21-23). CDR1 antisense RNA (CDR1as) is an abundantly expressed circRNA in the mammalian brain with >70 miRNA (miR)-7 binding sites (24). CDR1as/miR-7 is a classical tumor-associated circRNA-miRNA sponge system. CDR1as inhibits miR-7 activity by competing with miR-7, which ultimately upregulates the expression of oncogenes, such as epidermal growth factor receptor, NF- $\kappa$ B, and eventually promotes the development of cancer (25).

Overexpression of CDR1as inhibits the proliferation and invasion of glioma, breast cancer, gastric cancer and colorectal cancer (26-29). By contrast, upregulation of other circRNAs, such as circHIPK3, hsa\_circ\_001569 and circSCAF11, promotes the development of bladder and colorectal cancers, as well as glioma (30-32). In addition, abundant exosome circRNAs in the serum differentiate gastric cancer by transmitting a signal to local and remote cells, such as infiltrating immune cells, stromal cells and endothelial cells. These cells are vital components of the tumor microenvironment and enhance tumor growth, angiogenesis and metastasis (33). Such circRNAs may be useful for early and specific diagnosis of tumors.

**miRNA sponge.** circRNAs can absorb specific miRNAs through numerous miRNA binding sites (Fig. 1A). Conversely, they may serve as highly efficient sponges with miRNA to inhibit the biological functions of miRNAs and prevent them from binding to their target genes (34). For example, Sex-determining region Y, the testis-specific circRNA, inhibits the activity of miR-138 through multiple miR-138 binding sites and potentially regulates expression of miR-138 target genes (35). It is speculated that miRNA sponge effects achieved by circRNA formation are a common phenomenon (35). circ-CEP85L functions as a sponge of miR-942-5p to suppress expression of its target genes NFKBIA (36). In addition, circFGFR4 promotes the differentiation of myoblasts by sponging miR-107 and suppressing its target gene Wnt3 expression (37).

**Interaction with RNA-binding proteins (RBPs).** circRNAs are involved in numerous physiological processes by interacting with a variety of RBPs to form RNA-protein complexes, regulating gene transcription and influencing the formation of circRNAs (Fig. 1B). RBPs affect the expression of downstream target genes and miRNA sponges by competing with miRNAs (6,7). RBPs also act as *trans*-factors to regulate circRNA generation. Modulation of splicing factor muscle blind (MBL) expression affects the biosynthesis of circMBL through specific binding to MBL binding sites within introns of circMBL (38). circMBL regulates parental gene expression by binding to its own pre-mRNA flanking introns binding sites at the transcriptional level. circRNAs have a binding site for the enzyme and its substrate, thus it can directly bind to protein or act as a scaffold between two or more proteins. It has been reported that circ-Amot1l interacts with proto-oncogene c-Myc, STAT3, pyruvate dehydrogenase kinase 1 and AKT1 and affects the expression of its target genes by promoting nuclear translocation of these proteins (39,40). In addition, RBPs are also involved in the post-transcriptional regulation of miRNA expression and interact with miRNA regulators by cooperative and competitive inhibition (41). Pumilioprotein, a cooperative RBP, promotes miRNA binding to target mRNA,

which inhibits protein translation by binding to a specific short sequence in the 3'UTR of target mRNA, leading to altered spatial conformation of mRNA (42).

**Regulation of transcription.** circRNAs derived from exons are located in the cytoplasm and have an open reading frame (ORF) to drive translation (Fig. 1C) (43). In addition, some circRNA protein translation is initiated after being modified by N<sup>6</sup>-methyladenosine (m<sup>6</sup>A), such as circRNAs initiates the protein translation by recruit YTHDF3 and EIf4G2 through the m<sup>6</sup>A modification site (44). circANRIL regulates the expression of INK4/ARF by affecting the binding of ANRIL to polycomb-group complex and inhibiting the transcription of the coding gene INK4 and its variable reading frame genes (45). circPABPN1 reduces the translational efficiency of PABPN1 mRNA by competitively binding the RBP human antigen R (HuR) and prevents HuR binding to PABPN1 mRNA (46). In addition, a small amount of circRNAGFP participates in the translation process as a template (47).

**Regulation of host gene expression.** circRNA sequences are highly similar to their homogenous linear mRNA. circRNAs act as positive regulators of the activity of RNA polymerase II (RNA pol II), affecting expression of parental genes and transcription (Fig. 1D). circEIF3J and circPAIP2, both exon-intron circRNAs (EiRNAs), interact with U1 small nuclear ribonucleoprotein (snRNP) through RNA-RNA interactions to form EiRNA-U1 snRNP complexes. This complex interacts with RNA pol II in the promoter region of host genes to *cis*-regulate the expression of its host genes (48). Additionally, circ-ITCH has common miRNA binding sites with the 3' untranslated region of itchy E3 ubiquitin protein ligase (ITCH). circ-ITCH interacts with miR-7, miR-17 and miR-214 to promote the expression of ITCH (49).

### 3. circRNAs regulate proliferation and progression in gastric cancer

**circRNAs regulate the proliferation and progression as miRNA sponges in gastric cancer.** circRNAs promote malignant cell development, proliferation and metastasis by sponging miRNAs resulting in the dysregulated expression of miRNAs and the disruption of target genes in gastric cancer. Upregulated circPDSS1 expression promotes the expression of NIMA-related kinase 2 (NEK2) in gastric cancer through a miR-186-5p sponge *in vivo* and *in vitro* (Fig. 2) (50). Subsequently NEK2, which is associated with cell centrosome and cell cycle in gastric cancer, enhances cell proliferation and cell cycle by regulating cell mitosis in this type of cancer (51). circPVT1, a potential oncogenic gene, inhibits the activity of miR-125 and promotes the proliferation of gastric cancer through c-Myc (52). In addition, circLARP4 is inversely associated with tumor size and lymph node metastasis in gastric cancer by regulating the target gene large tumor suppressor kinase 1 and Yes-associated protein (YAP) of miR-424, resulting in the inhibition of DNA synthesis, cell proliferation and invasion (Fig. 2) (53). circYAP1 inhibits cellular proliferation, invasion and cell cycle by suppressing cyclin dependent kinase inhibitor 1B. Downregulated circYAP1 in gastric cancer is linked to poor prognosis and low 5 year survival rate (Fig. 2) (53).

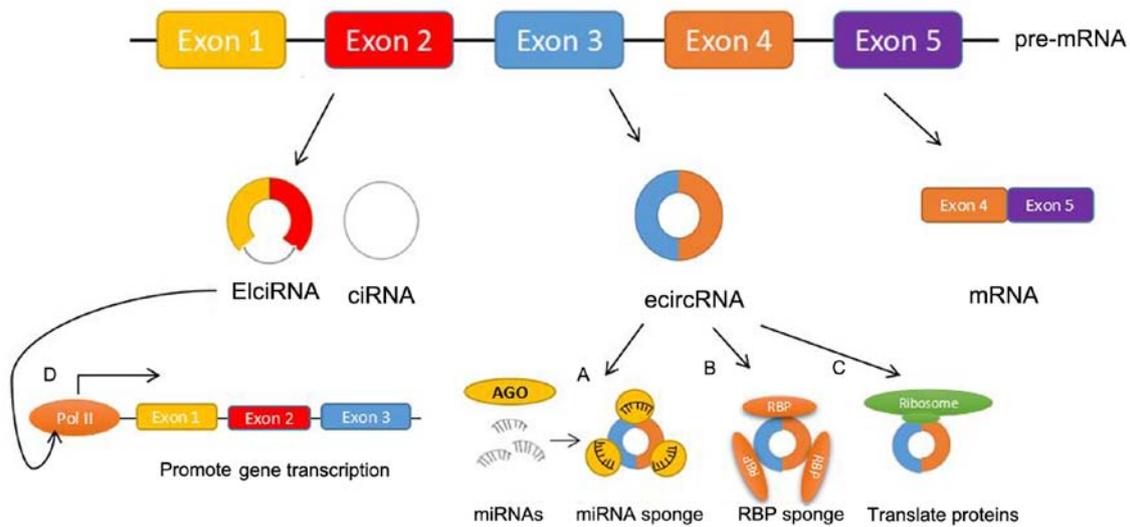


Figure 1. Biological functions of circRNAs. A pre-mRNA is back-spliced, producing three different types of circRNA, including ciRNAs, ecirRNAs and EICIcRNA. The biological functions of circRNAs are regulated by different mechanisms. (A) miRNA sponge. circRNAs absorb specific miRNA to regulate the biological function of miRNA, affecting miRNA target gene expression. (B) RBP sponge. circRNAs interact with a variety of RBPs to form RNA-protein complexes, regulating their cellular localization and activity. (C) Translate proteins. Some circRNAs can be translated into proteins that exert specific biological effects and affect tumor progression. (D) Promote gene transcription. ciRNAs and EICIcRNAs promote the transcription of their parental genes by acting as positive regulators of Pol II activity. AGO, protein argonaute; circRNAs, circular RNAs; ciRNAs, intronic circular RNAs; ecirRNAs, exonic circular RNAs; EICIcRNA, exon-intron circular RNAs; miRNAs, micro RNAs; Pol II, RNA polymerase II; RBPs, RNA binding proteins.

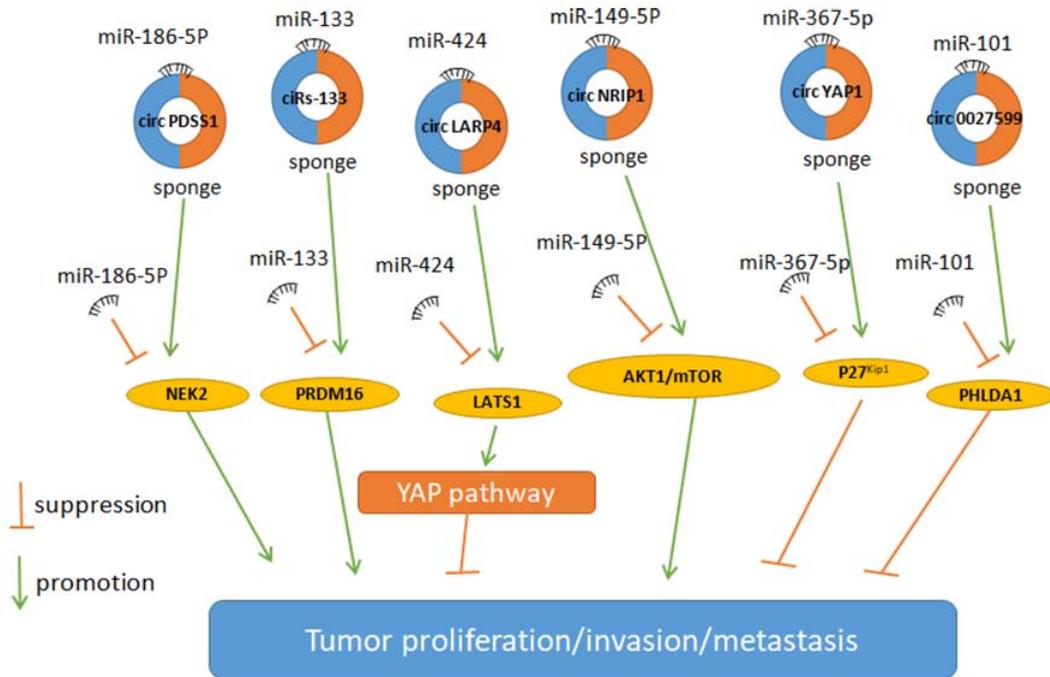


Figure 2. Roles of circRNAs in gastric cancer. circRNAs function as sponges for the indicated miRNAs, which regulate the respective target genes to promote or inhibit tumor proliferation, invasion and metastasis. circRNA, circular RNA; LARP4, La ribonucleoprotein 4; LATS1, large tumor suppressor kinase 1; miR, microRNA; NEK2, NIMA related kinase 2; NRIP1, nuclear receptor interacting protein 1; p27<sup>kip1</sup>, cyclin dependent kinase inhibitor 1B; PDSS1, decaprenyl diphosphate synthase subunit 1; PHLDA1, pleckstrin homology like domain family A member 1; PRDM16, PR/SET domain 16; YAP1, Yes associated protein 1.

circ\_100269 suppresses the p53 signaling pathway by sponging miR-630 to inhibit proliferation and invasion of gastric cancer (54). In addition, circ\_0027599 sponges miR-101 to inhibit the migration and invasion of gastric cancer by targeting pleckstrin homology-like domain family A member 1 gene (Fig. 2) (55). These differential expressions of circRNAs in the different aforementioned cancers play crucial but different

roles in determining cell fate, inducing tumor-suppressive or oncogenic effects by acting as a sponge to multiple different miRNAs, forming a circRNA-miRNA-mRNA axis (50-55). Thus, circRNAs have the ability to participate in many physiological and pathological processes, suggesting that the regulation of circRNAs could offer a potential therapeutic window for gastric cancer.

*circRNAs regulate the proliferation and progression through the RBP sponge in gastric cancer.* circRNAs not only function as miRNA sponges to regulate miRNA expression, but also serve important roles in regulating protein production (56). circRNAs affect the proliferation and metastasis potential of malignant cells, including gastric cancer cells, by directly interacting with proteins or binding to the miRNA-acting factor to regulate specific downstream target genes (57).

Downregulated circPVRL3 also promotes the proliferation of gastric cancer by promoting protein encoding (58). It might play a role in the assembling of RBP complexes by binding to AGO2, FUS RNA-binding protein, lin-28 homolog A, polypyrimidine tract binding protein and eukaryotic translation initiation factor 4A3. In addition, circPVRL3 contains internal ribosome entry site, ORF and m<sup>6</sup>A modifications, these modifications initiate the protein translation by recruiting ribosomes (59,60). The translational products may exert specific biological effects or interfere with protein-protein interactions to affect tumor progression (44,61). Another study reported that circFAT1(e2), located in cytoplasm and nucleus of gastric cancer cells, is downregulated in gastric cancer (62). circFAT1(e2) directly binds to Y-box binding protein-1 (YBX1) for DNA- and RNA-binding in the nucleus. Upregulated circFAT1(e2) inhibits the growth of gastric cancer by suppressing the expression of three targeted genes of YBX1 (epidermal growth factor receptor, MET proto-oncogene and cell division cycle 25A).

Results from these studies suggest that the stability of circRNA-protein interaction might act as 'scaffolding molecules' in gastric cancer. Consequently, circRNAs acting as scaffolding molecules for protein complexes and network functional modules can modulate protein-protein interactions. circRNAs might work as sequence targeting elements, affecting the function of downstream target genes by simultaneously binding to RBPs.

*circRNAs control the proliferation and progression of gastric cancer cells via regulating cellular metabolism.* Cell glycolytic activity, including in aerobic conditions, is more active in cancer cells compared with normal cells, process known as the Warburg effect (63). In addition, tumor cells exhibit abnormal fatty acid and amino acid metabolism (64). Recent studies demonstrated that circRNAs are closely related to tumor metabolism and these are able to regulate gastric cancer metabolism through miRNA (65-67).

Upregulated circNRIP1 expression promotes the proliferation, invasion and migration of gastric cancer through activating AKT1/mTOR cell pathway by sponging miR-149-5p (Fig. 2) (65). circNRIP1 promotes anabolic activities and prevents metabolic decomposition by maintaining energy homeostasis, suggesting that circNRIP1 plays a crucial role in the regulation of tumor metabolism (66,67).

In gastric cancer, ciRS-133 regulates substance metabolism and organic metabolism through PR domain-containing 16 (PRDM16), enhancing the Warburg effect. ciRS-133 accelerates oxygen consumption and glucose consumption of brown fat cells, promoting white adipose tissue (WAT) burning through enhancing the expression of PRDM16 by adsorbing miR-133 in gastric cancer cells (Fig. 2) (68). Consequently, such effects are known to cause weight loss and systemic

inflammation in patients with poor prognosis. Moreover, knockdown of ciRS-133 reduces cancer cachexia, decreasing oxygen consumption and glucose expenditure in mouse animal models (68). Thus, circRNAs contribute to cancer-associated cachexia and metabolic disorder by sponging miRNA to regulate WAT browning.

#### 4. circRNAs have a potential clinical value in gastric cancer

*Potential application of circRNAs in the diagnosis of gastric cancer.* Several studies have demonstrated that circRNAs are differentially expressed in gastric cancer, as summarized in Table I. circRNAs are widely present in blood and gastric juice, and may have potential value for diagnosis (9-12). Therefore, circRNAs may work as novel biomarker-based screening tools for gastric cancer diagnosis and evaluation.

In gastric cancer, circ\_102958 is closely associated to tumor, node, metastasis (TNM) cancer staging, but inversely associated to age, gender, tumor diameter and differentiation degree in lymph node metastasis (69). In addition, receiver operating characteristic curve analysis indicated that circ\_102958 has a high diagnostic value. Together, these features suggested that circ\_102958 may be a biomarker for early diagnosis of gastric cancer.

Owing to the lack of clinical symptoms and detection methods at the early stages of gastric cancer, the analysis of gastric juice could be advantageous for the detection of this type of cancer (70). For instance, circ\_0014717 is downregulated in gastric juice of chronic atrophic gastritis. Individuals with chronic atrophic gastritis are at high risk of gastric cancer (71). This implies that circ\_0014717 may be used for early screening of gastric cancer (72). In addition, circ\_0000181 is downregulated in the plasma of patients with gastric cancer and is positively associated with the differentiation of gastric cancer cells and the level of carcinoembryonic antigen (CEA), which is a well-known gastric cancer biomarker (73). In addition, the specificity and sensitivity of hsa\_circ\_0000181 is higher than CEA and carbohydrate antigen19-9 in screening gastric cancer, suggesting that hsa\_circ\_0000181 may be a reliable plasma-based biomarker (74).

*circRNAs as a prognosis biomarker in gastric cancer.* circRNAs can potentially be used as a biomarker for the prognosis and the evaluation of treatment efficacy in gastric cancer. It has been demonstrated that circ\_0000467 is highly expressed in tissue and plasma samples of patients with gastric cancer associated with a poor prognosis. Cox multivariate analysis showed that circ\_0000467 might be an ideal independent prognostic factor (75). In addition, a previous study reported that the determination of prognostic factors in gastric cancer using circ\_0000467 along with TNM stage is more accurate compared to that using TNM stage alone (75).

The expression of circ\_KIAA1244 in plasma of patients with gastric cancer is lower than that in healthy patients without gastric cancer, which is inversely associated with TNM stage and lymph node metastasis, as well as a shorter overall survival. This is supported by univariate and multivariate analysis, which demonstrated that the expression of circ\_KIAA1244 may be used as an independent prognostic indicator of the overall survival in patients with gastric cancer (76).

Table I. circRNAs and their functions in gastric cancer.

Author, year	circRNA	Research model in GC	Expression change	Functions	Regulatory network; pathway	(Refs.)
Tian <i>et al.</i> , 2018	Hsa_circ_0003159	Tissue	Downregulation	Biomarker		(99)
Li <i>et al.</i> , 2017	Hsa_circ_0001649	Tissue and serum	Downregulation	Biomarker		(86)
Shao <i>et al.</i> , 2017	Hsa_circ_0014717	Tissue and gastric juice	Downregulation	Biomarker		(72)
Xie <i>et al.</i> , 2018	Hsa_circ_0074362	Tissue and cell lines	Downregulation	Biomarker		(95)
Li <i>et al.</i> , 2018	Hsa_circ_0001017/Hsa_circ_0061276	Tissue and plasma	Downregulation	Biomarker		(90)
Li <i>et al.</i> , 2015	Hsa_circ_002059	Tissue and plasma	Downregulation	Biomarker		(92)
Zhao <i>et al.</i> , 2018	Hsa_circ_0000181	Tissue and plasma	Downregulation	Biomarker		(74)
Huang <i>et al.</i> , 2017	Hsa_circ_0000745	Tissue and plasma	Downregulation	Biomarker	Sponge to miRNA	(88)
Chen <i>et al.</i> , 2017	Hsa_circ_0000190	Tissue and plasma	Downregulation	Biomarker		(100)
Tang <i>et al.</i> , 2019	Hsa_circ_0130810 (circ-KIAA1244)	Tissue, cell lines and plasma	Downregulation	Biomarker		(76)
Lu <i>et al.</i> , 2017	Hsa_circ_0006633	Tissue, cell lines and plasma	Downregulation in tissue/Upregulation in cells	Biomarker		(93)
Sun <i>et al.</i> , 2018	Hsa_circ_0000520	Tissue, cell lines and plasma	Downregulation	Biomarker	Nine miRNAs and nine candidate mRNA (AGO1, AGO2, AGO3, Fus, FMRP, CAPRIN1, DGCR8, PTB, HuR)	(94)
Fang <i>et al.</i> , 2017	Hsa_circ_0058246	Tissue	Upregulation	Biomarker		(91)
Zhang <i>et al.</i> , 2019	Hsa_circ_0067997	Tissue and cell lines	Upregulation	Biomarker	Hsa_circ_0067997/miR-515-5p/XIAP	(79)
Wei <i>et al.</i> , 2019	Hsa_circ_102958	Tissue and cell lines	Upregulation	Biomarker	Sponge to five miRNAs	(69)
Li <i>et al.</i> , 2017	Hsa_circ_104916	Tissue and cell lines	Downregulation	Tumor suppressor	EMT	(87)
Zhang <i>et al.</i> , 2017	Hsa_circ_100269	Tissue and cell lines	Downregulation	Tumor suppressor	Sponge to miR-630	(54)
Liu <i>et al.</i> , 2019	circLARP4	Tissue and cell lines	Downregulation	Tumor suppressor	circLARP4/miR-424-5p/LATS1	(41)
Li <i>et al.</i> , 2017	Hsa_circ_0000096	Tissue and cell lines	Downregulation	Tumor suppressor	Regulating cyclin D1, CDK6, MMP-2 and MMP-9	(89)
Liu <i>et al.</i> , 2018	circYAPI	Tissue and cell lines	Downregulation	Tumor suppressor	circ YAPI/miR-367-5p/p27 axis	(53)
Sun <i>et al.</i> , 2018	Has_circ_0066779 (circPVR1.3)	Tissue and cell lines	Downregulation	Tumor suppressor	Sponge to nine miRNAs	(58)
Li <i>et al.</i> , 2017	circHIPK3	Tissue and cell lines	Downregulation	Tumor suppressor	circHIPK3/miR-124/miR-29b	(30)
Zhong <i>et al.</i> , 2018	Hsa_circ_0000993	Tissue and cell lines	Downregulation	Tumor suppressor	Hsa_circ_0000993/miR-214-5p/ATL2	(97)
Wei <i>et al.</i> , 2018	circZFR	Tissue and cell lines	Downregulation	Tumor suppressor	circZFR/miR-130a/miR-107; PTEN	(98)
Wang <i>et al.</i> , 2018	Hsa_circ_0027599	Tissue and cell lines	Downregulation	Tumor suppressor	Hsa_circ_0027599/miR-101-3p.1/PHLDA1	(55)

Table I. Continued. circRNAs and their functions in gastric cancer.

Author, year	circRNA	Research model in GC	Expression change	Functions	Regulatory network; pathway	(Refs.)
Fang <i>et al.</i> , 2019	Hsa_circ_0001461 [circFAT1(e2)]	Tissue and cell lines	Downregulation	Tumor suppressor	circFAT1 (e2)/miR-548g/YBX1	(62)
Chen <i>et al.</i> , 2017	circPVT1	Tissue and cell lines	Upregulation	Tumor promoter	circPVT1/miR-125/E2F2	(52)
Pan <i>et al.</i> , 2018	ciRS-7 (CDR1as)	Tissue and cell lines	Upregulation	Tumor promoter	ciRS-7/miR-7/PTEN/PI3K; AKT	(78)
Rong <i>et al.</i> , 2018	Hsa_circ_0066444	Tissue and cell lines	Upregulation	Tumor promoter	Sponge to 5 miRNAs and 15 corresponding target mRNAs	(96)
Zhang <i>et al.</i> , 2019	Hsa_circ_0010522 (ciRS-133)	Tissue and plasma	Upregulation	Tumor promoter	ciRS-133/miR-133/PRDM16	(68)
Ouyang <i>et al.</i> , 2019	circPDSS1	Tissue and cell lines	Upregulation	Tumor promoter	circPDSS1/miR-186-5p/NEK2	(50)
Shen <i>et al.</i> , 2019	Hsa_circ_001569	Tissue and cell lines	Upregulation	Tumor promoter	Hsa_circ_001569/miR-145/NR4A2	(103)
Zhou <i>et al.</i> , 2018	Hsa_circ_0023642	Tissue and cell lines	Upregulation	Tumor promoter	EMT	(101)
Zhang <i>et al.</i> , 2019	circNRIP1	Tissue and cell lines	Upregulation	Tumor promoter	circNRIP1/miR-149-5p/AKT1/mTOR	(65)
Lu <i>et al.</i> , 2019	Hsa_circ_0000467	Tissue, cell lines and plasma	Upregulation	Tumor promoter		(75)
Sun <i>et al.</i> , 2018	circ-SFMBT2	Tissue, cell lines and plasma	Upregulation	Tumor promoter	circ-sFMBT2/miR-182-5p/CREB1	(102)

circRNAs, circular RNAs; GC, gastric cancer; miR, microRNA.

*circRNA as a therapeutic target biomarker in gastric cancer.* More recently, with the development of molecular biology and in-depth pathogenesis studies, the mechanistic function of circRNAs in metabolic and signal transduction pathways has also been investigated for gastric cancer. ciRS-7 possesses about 70 binding sites for miR-7 and has significant functions in several types of tumors, including gastric cancer, where it is highly expressed (77). ciRS-7 is able to enhance proliferation and migration of gastric cancer cells by upregulating PTEN/PI3K/AKT signaling pathway through sponging of miR-7 (78). Overexpression of ciRS-7 is also shown to promote the growth of xenograft tumors *in vivo* exhibiting a promising therapeutic value for gastric cancer (78). Therefore, developing inhibitors that can efficiently target ciRS-7 may be an important approach for therapy.

Highly expressed circ\_0067997 promotes tumor growth in gastric cancer by sponging miR-515-5p, which results in the regulation of x-linked inhibitor of apoptosis (XIAP) expression (79,80). Suppressing circ\_0067997 by siRNA blocks a variety of apoptosis-related pathways and reduces cell viability, colony formation, proliferation and invasion of gastric cancer cell lines *in vitro*. circ\_0067997 siRNAs treated MGC-803 cells inhibits the growth of tumors *in vivo* compared with si-NC treated cells, also suggesting a potential therapeutic target (81).

Finally, using Gene Ontology functional term and Kyoto Encyclopedia of Genes and Genomes signaling pathway analyses, gastric cancer was found to be linked to circRNAs in several important physiological processes, such as extracellular matrix degradation, binding to cell adhesion molecules and reaction with transforming growth factor  $\beta$  (82).

Data from these studies demonstrated that circRNAs may contribute to the occurrence and development of gastric cancer, and its application in tumor therapy presents a valuable prospect. circRNAs may also be used as a therapeutic target for inhibiting tumor proliferation and metastasis.

## 5. Future prospects

Increasing evidence demonstrates that the expression of circRNAs affect the development and progression of gastric cancer and may exhibit great potential in diagnosis, prognosis and treatment of gastric cancer. Research within the mechanistic function of circRNAs is an emerging scientific field with an enormous potential. The differential expression of circRNAs in gastric cancer compared to non-cancer samples enables the use of these circRNAs as potential biomarkers (41,83,84). circRNAs are have a stable structure and are widely expressed in various body fluids, including blood, saliva and gastric fluid (9-12). In addition, RNA sequencing and reverse transcription-quantitative PCR have made the detection of circRNAs more convenient and accurate than proteins as detection time is shorter, smaller amount of sample is required and the sensitivity is higher. Numerous circRNAs are highly enriched in the blood compared with the corresponding linear RNAs. Moreover, the expression of circRNAs in cancer tissue is higher than in precancerous tissue derived exosomes (85), which is consistent with another study showing that the levels of circ-KIAA1244 in plasma

and plasma exosomes are similar (76). Therefore, circRNAs in extracellular exosomes represent the ideal candidates as reliable biomarkers for prognosis and diagnosis in gastric cancer. However, at present, circRNAs can only be used in combination with other biomarkers for cancer diagnosis, and the clinical application of circRNAs still requires further investigation and optimization. Although there are many studies about circRNAs, there no current standardized methodology for detecting circRNAs. Also, to the best of our knowledge there is no detailed study about the application of circRNAs as biomarkers for malignant cells, particularly regarding cost and the specificity and sensitivity for detecting cancer cells.

The biological functions of several circRNAs may be utilized to explore the underlying mechanism of circRNAs during the development of gastric cancer. Despite many specific circRNAs reportedly expressed in gastric cancer, the features of circRNAs, including their biogenesis, degradation, location and function, remain to be explored. Therefore, comprehensive studies are required to determine the function and molecular mechanisms of circRNAs in gastric cancer. Moreover, further understanding of the relationship between circRNAs and gastric cancer may reveal the complex regulatory networks of carcinogenesis and accelerate the clinical application of circRNAs in prognosis, diagnosis and therapy of gastric cancer.

## 6. Conclusions

In the present review, the biological functions and molecular mechanisms of circRNAs were examined, and the clinical values of circRNAs with an emphasis on gastric cancer were summarized. Although numerous circRNAs have been identified, only a small amount of functional circRNAs has been elucidated, and most studies on circRNAs have focused on their regulation of cancer development through interactions with miRNAs and RBPs. In the future, the mechanistic study of its roles in genomic and mRNA transcription needs to be further explored. As circRNAs are known to be stable in different body fluids, including blood, circRNAs may act as ideal biomarkers and therapeutic targets for gastric cancer.

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## Availability of data and materials

Not applicable.

## Authors' contributions

CY and GQ conceived the study and wrote the manuscript. LS generated the tables and diagrams. LM and SB revised the manuscript for important intellectual content. All authors have read and approved the manuscript.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

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## Competing interests

The authors declare that they have no competing interests.

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