



# CircRNA: a rising star in gastric cancer

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## Abstract

In recent years, a large number of circRNAs have been identified in mammalian cells with high-throughput sequencing technologies and bioinformatics. The aberrant expression of circRNAs has been reported in many human diseases including gastric cancer (GC). The number of GC-related circRNAs with validated biological functions and mechanisms of action is growing. CircRNAs are critically involved in GC cell proliferation, apoptosis, migration, and invasion. CircRNAs have been shown to function as regulators of parental gene transcription and alternative splicing and miRNA sponges. Moreover, circRNAs have been suggested to interact with proteins to regulate their expression level and activities. Several circRNAs have been identified to encode functional proteins. Due to their great abundance, high stability, tissue- and developmental-stage-specific expression patterns, and wide distribution in various body fluids and exosomes, circRNAs exhibit a great potential to be utilized as biomarkers for GC. Herein, we briefly summarize their biogenesis, properties and biological functions and discuss about the current research progress of circRNAs in GC with a focus on the potential application for GC diagnosis and therapy.

**Keywords** CircRNA · Gastric cancer · miRNA sponge · Biomarker · Therapeutic target

## Abbreviations

GC	Gastric cancer	BHB	Bulge–helix–bulge
EcircRNAs	Exonic circRNAs	HCC	Hepatocellular carcinoma
CiRNAs	Intronic circRNAs	ESCC	Esophageal squamous cell carcinoma
EiRNAs	Exon–intron circular RNAs	IRES	Internal ribosome entry sites
TricRNAs	TRNA intronic circRNAs	CDK2	Cyclin-dependent kinase 2
MBL	Muscleblind	M6A	N6-methyladenosine
A-to-I	Adenosine-to-Inosine	PES1	Pescadillo homologue 1
QKI	Quaking	AGO2	Argonauto 2
EMT	Epithelial-mesenchymal transition	AUC	Area under the ROC curve
RBPs	RNA-binding proteins	Ex-circRNAs	Exosomes-derived circRNAs
TSEN	TRNA splicing endonuclease complex	CAFs	Cancer-associated fibroblasts
		SiRNAs	Small interfering RNAs

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## Introduction

Gastric cancer (GC) is one of the most common malignant tumors with high morbidity and mortality worldwide. In 2018, there are estimated 1,033,701 new cases of GC and 782,685 cases of GC-related death, which ranks the fifth and third in cancer incidence rates and mortality rates, respectively [1]. Gastric tumorigenesis is a multifactorial, multicellular and multistep process [2]. Environmental factors (diet, exogenous chemicals), intragastric formation of carcinogens and *Helicobacter pylori* can induce the occurrence of GC

[3]. The communication of GC cells and cancer microenvironment cells determines the development and progression of GC [4–6]. The detailed pathological mechanisms for GC remain not well understood. Currently, the diagnosis of GC is mainly dependent on imaging examination, serum tumor marker examination, endoscopy, and tissue biopsy [7]. However, as gold standard method, tissue biopsy can induce obvious surgical trauma and hysteresis. Besides, due to the fact that early GC lacks specific symptoms, most GC patients are diagnosed in the intermediate or terminal stage with poor prognosis [8]. Moreover, the main available treatments like radiotherapy and chemotherapy have strong side effects on GC patients and sometimes, the curative effect of chemotherapy is obvious but could not last for a long period due to drug resistance. Therefore, it is urgent to explore more specific and effective method for GC diagnosis and treatment.

CircRNAs, a novel type of RNAs with covalently closed loop structure, are becoming a new hotspot in the field of ncRNAs lately. Since they were first discovered in viruses as early as the 1970s [9], a handful of such RNAs were found and considered to be the rare errors in canonical and non-canonical RNA splicing. However, with recent advances in RNA deep sequencing technology and bioinformatics, a large amount of circRNAs have been revealed to be abundant in mammalian cells. Salzman et al. have confirmed that circRNAs are predominant transcripts of diverse human cell types [10]. Jeck et al. have identified over 25,000 circRNAs in human fibroblasts and considered them as stable, conserved and nonrandom products of RNA splicing which could be associated with complementary ALU repeats in bordering introns [11]. Afterwards, Memczak et al. and Hansen et al. both made breakthrough in circRNA biological functions researches and first proposed that circRNAs could act as miRNA sponge in gene expression and regulation and could function in posttranscriptional process [12, 13]. Since then, circRNAs have begun to attract wide attention of the public and relevant studies on their biogenesis, characteristics, functional mechanisms as well as potential application in clinical diagnosis and treatment have been carried out. Nowadays, an increasing number of circRNAs have been found to regulate gene expression at transcriptional, posttranscriptional and translational levels. They participate in many pathological processes such as Alzheimer's disease, diabetes, atherosclerosis and glioma through regulating alternative splicing, sponging miRNAs, sequestering functional proteins or even encoding proteins [14–17]. Particularly, circRNAs play an important role in cancer growth, metastasis, recurrence and therapy resistance [18]. A variety of circRNAs have been reported to be aberrantly expressed in GC tissues or cell lines. Biological experiments proved that many of them harbor miRNA-binding sites and could act as miRNA sponges to suppress

or promote GC progression. Given that circRNAs are of high abundance and stability, evolutionary species conservation as well as tissue specificity, and are widespread in various body fluids, exploring GC-related circRNAs as biomarkers or targets would create new possibilities for GC early diagnosis, prognosis and effective treatment.

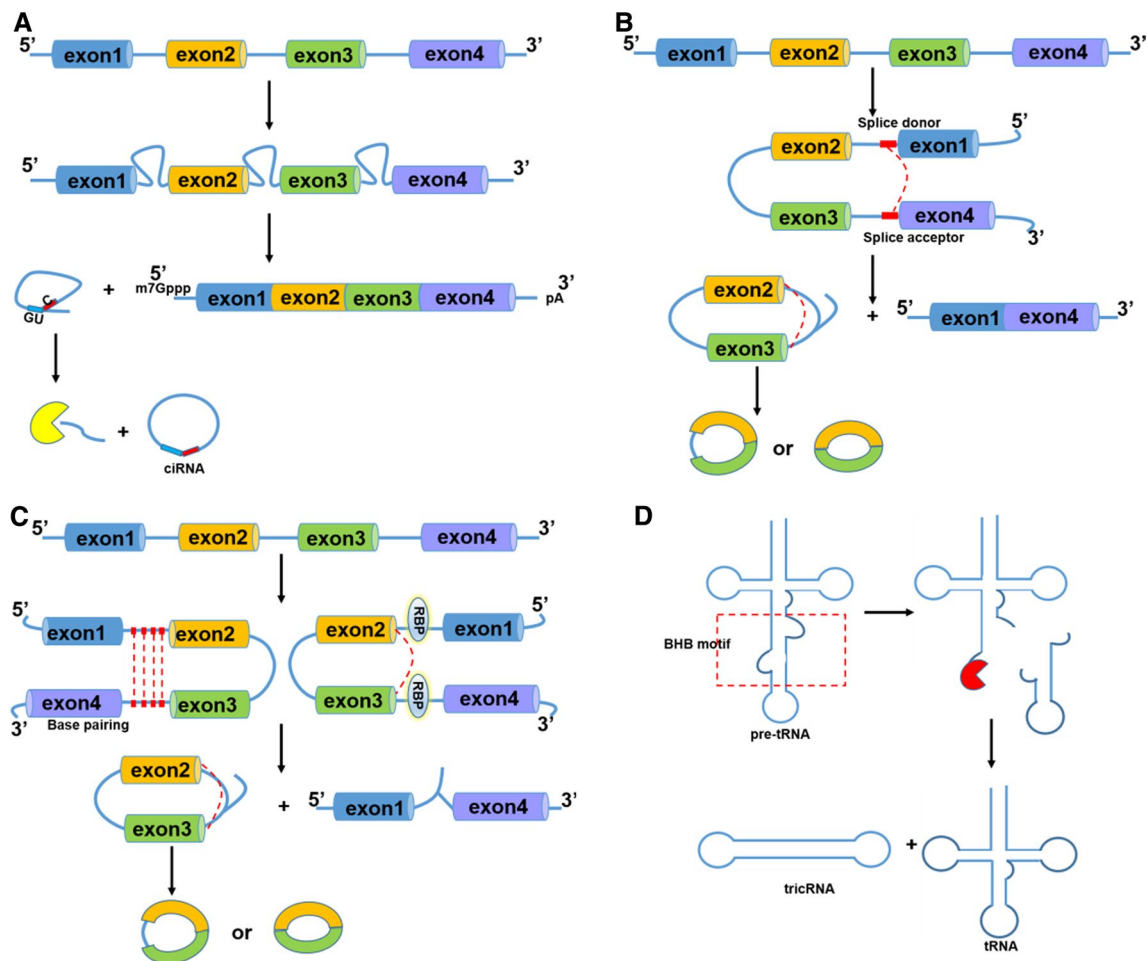
In this review, we summarize the biogenesis, characteristics, biological functions and mechanisms of circRNAs. Then, we review GC-related circRNAs, and finally discuss their potential applications as biomarkers, therapeutic targets or tools.

## Biogenesis, classification and properties of circRNAs

As a novel type of RNAs, circRNAs have circular structure which is generated from unique back-splicing biogenesis process with different molecular mechanisms. This circular structure and biogenesis mechanisms also confer many unique characteristics to them such as high abundance and stability, evolutionary species conservation, and tissues-specific expression patterns.

### Biogenesis and classification

Alternative splicing of RNA is a basic gene expression event in eukaryotic cells. Pre-mRNA is catalyzed by spliceosomal machinery to remove introns and then exons with protein-encoding information are sequentially connected to form mature mRNA (Fig. 1a). With alternative splicing such as exon skipping, a gene generates several different mRNAs and proteins, which increases the diversity of cell transcriptome. Unlike canonical splicing of mRNA, circRNAs are generated by back-splicing process that ligates a downstream 5' splice donor site with an upstream 3' splice acceptor site to form a single-strand covalently closed loop. Then, the spliceosome removes all or part of introns and the rest of sequences are connected. Afterwards, three types of circRNAs are generated, including exonic circRNAs (ecircRNAs) which contain exon sequence only [10], intronic circRNAs (ciRNAs) which synthesized from introns, and exon–intron circular RNAs (EIciRNAs) which contain both exon and intron sequences [19, 20]. The detailed mechanisms for circRNA biogenesis have not been completely elucidated. Jeck et al. proposed two models of ecircRNA formation [11]. One is termed “lariat-driven circularization” and the other one is “intron-pairing-driven circularization” (Fig. 1b, c). In addition, Zhang et al. suggested that exon circularization is dependent on flanking intronic complementary sequences [21]. Liang et al. demonstrated that the miniature introns containing splice sites and short (30–40 nt) inverted repeats are sufficient for circRNA formation [22].



**Fig. 1** Biogenesis of circRNA. **a** Canonical splicing. Pre-mRNA is spliced by spliceosome to remove intervening introns and leave only exons sequentially connected to form mature mRNA. The rest lariat intron can escape debranching and degradation with 7 nt GU-rich sequences near the 5' splice site and 11 nt C-rich sequence near branch site and instead the 3' "tail" downstream sequence is trimmed to form stable ciRNA. **b** Lariat-driven circularization. A downstream 5' splice site of exon 4 is joined to an upstream 3' splice site of exon 1 forming lariat structure. And then, the lariat containing skipped exons undergoes internal splicing of one intron to form EIciRNA or splicing

of two introns to form ecircRNA. **c** Intron-pairing-driven circularization. Intronic motifs flanking circularized exon 2 and 3 have considerably complementary sequences which bring splicing sites close to form EIciRNA or ecircRNA. RNA binding proteins (RBPs) driven circularization. RBPs with binding sites on flanking introns of exons 2 and 3 could bring two splicing sites close together to facilitate circularization. **d** The tRNA splicing endonuclease complex (TSEN) recognizes bulge-helix-bulge (BHB) motif and carries out intron excision of pre-tRNA and then release and ligate the end to form tRNA and tricRNA

Both studies provide evidence to the models proposed above. It is generally believed that introns removed by spliceosome are unstable and can be degraded by exonucleases. While, ciRNAs generated from introns that form lariat structure by joining with both ends are resistant to exonuclease degradation (Fig. 1a) [19]. In addition, tRNA intronic circRNAs (tricRNAs) are another type of circRNAs which are generated during the splicing of pre-tRNA (Fig. 1d) [23].

The recent studies have indicated that some proteins are involved in circRNA biogenesis (Fig. 1c). MBL (muscleblind) is shown to have binding sites on flanking introns of its pre-mRNA, which bring two splicing sites close together to facilitate circularization [24]. Besides, ADAR1 can inhibit

circRNA expression by Adenosine-to-Inosine (A-to-I) editing to diminish RNA pairing structure of flanking introns and decrease back-splicing efficiency [25]. RNA-binding protein QKI (quaking) is also demonstrated as a regulator of circRNA biogenesis during human epithelial-mesenchymal transition (EMT) where it binds to sites flanking circRNA-forming exons to induce exon circularization [26].

## Properties

CircRNAs are usually widespread and many of them exist with high abundance. More than 25,000 different circRNAs have been identified in human fibroblasts and 14.4%

of actively transcribed genes can generate ecircRNAs [11]. Most of them contain less than 5 exons and their size can range from under 100 nt to over 4000 nt [27]. Because of alternative circularization resulting from competition between different flanking complementary introns (ALU sequence), a gene can give rise to a single or many circRNA isoforms, which increases the number of circRNAs [21]. Moreover, the amount of some circRNAs is more abundant than its linear RNAs. In some cases, the abundance of circRNAs is more than tenfold of that of linear mRNAs [11]. Also, circRNAs have been discovered in several species including human, mouse, plants, *Archaea*, *C. elegans* and so on [11, 28, 29]. Additionally, circRNAs are located in different subcellular portions. EcircRNAs are mainly located in the cytoplasm while both ciRNAs and EiciRNAs are present in the nucleus of eukaryotic cells [10, 12, 19, 23]. However, the detailed mechanisms for the import/export of circRNAs are not clear. Huang et al. recently reported that the key modulators UAP56 or URH49 could control the nuclear export efficiency of long and short circRNAs, respectively [30].

CircRNAs are expressed across the tree of eukaryotic life, and thus presented to be evolutionarily conserved among distinct species [31]. Up to date, 69 circRNAs containing precisely conserved backsplice junctions have been identified between human and mouse [11]. Studies focusing on the sequence conservation within 3 subtypes of circRNAs suggested that ecircRNAs composed of coding sequence are overall conservative, while a few ciRNAs or intergenic circRNAs show a mild but abundant conserved nucleotides [12]. The conservation of splicing regulatory elements might be responsible for this phenomenon. Besides, complementary flanking introns such as ALU sequences facilitating circRNAs biogenesis are relatively conserved in animals or plants. Also, the miRNA target sites of circRNA sponges display few polymorphisms [32], which also ensure the conservation of circRNAs.

Typically, circRNAs have high stability and are more stable than the linear transcripts. They are covalently closed with neither 5'–3' polarity nor polyadenylated tail; thus, they could resist degradation by RNase R, debranching enzyme or RNA exonuclease and are more stable than the linear transcripts [33, 34]. Their average half-life in cells is over 48 h, which is much longer than that of mRNA (< 10 h) [35]. Although it is still unclear how circRNAs are degraded and cleared, circRNAs are able to be targeted by siRNA [11]. Furthermore, circRNAs are also targets of microRNAs. For instance, CDR1as is targeted by miR-7 and subjected to the silencing activity of Ago2 and cleaved in a miR-671-dependent manner [36].

Most circRNAs present tissue/developmental-stage-specific expression pattern. Their expression levels are significantly diverse in various cell types and are dynamically

changed across the development of embryonic tissues. For example, ciRS-7 is highly expressed in brain tissues but lowly expressed or absent in non-neuronal tissues [12]. The repertoire of genes expressing circRNAs, the relative levels between circRNAs and linear transcripts, and even pattern of splice isoforms of circRNAs from each gene are cell-type specific [37]. Moreover, a recent study showed that circRNAs are highly abundant and dynamically expressed in a spatio-temporal manner in porcine fetal brain [38]. During human fetal development, fetal brain, such as frontal cortex with marked enrichment for genes, is the region where circRNA isoforms are predominant among various tissues [39]. All the researches above suggest that the distribution of circRNAs is regulated by an uncharacterized pathway which needs to be further explored.

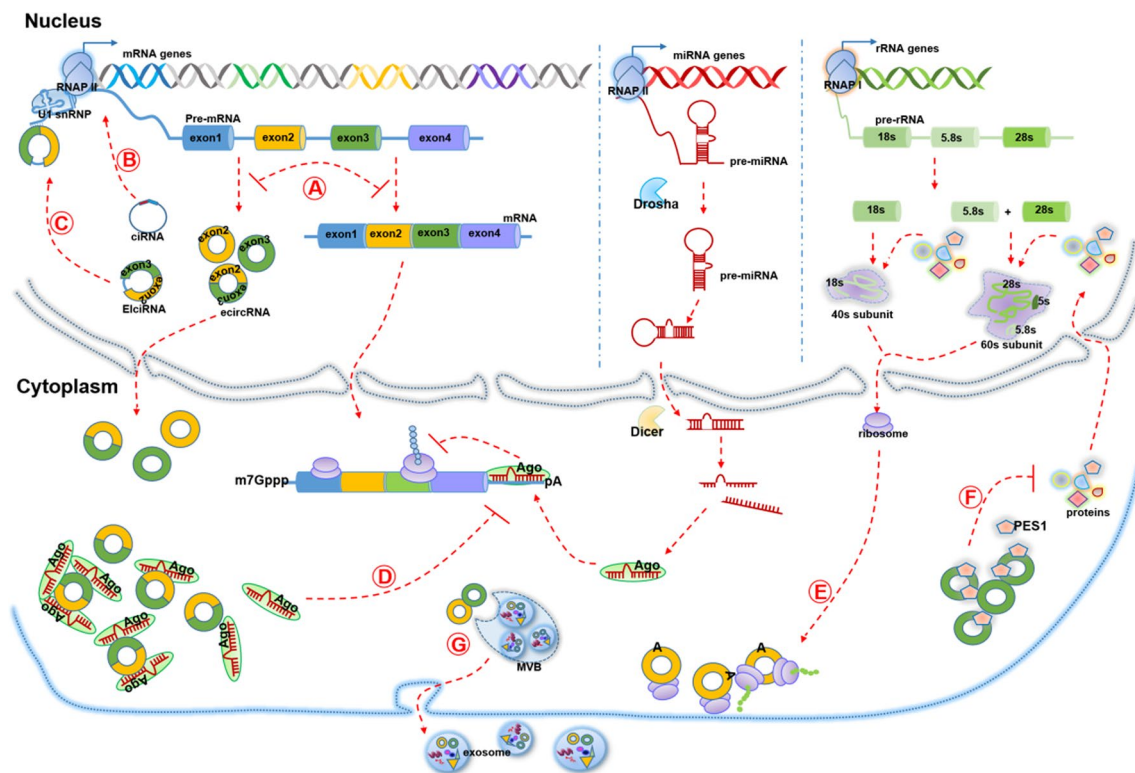
## Functions and mechanisms of circRNAs

Apart from its unique properties, the manners by which circRNAs participate in the regulation of biological processes further broaden our understanding of ncRNAs. So far, circRNAs have been demonstrated to serve as miRNA sponges, regulate alternative splicing, bind to RNA binding proteins (RBPs) as well as encode proteins.

### MiRNA sponge

MiRNAs are able to directly bind to target mRNA in a base-pairing manner and trigger cleavage of mRNAs or repress mRNA translation [40]. CircRNAs located in cytoplasm also contain complementary miRNA binding sites, and thus serve as competitive inhibitors for miRNAs (Fig. 2d). CiRS-7 was first demonstrated to harbor 63 conserved binding sites for miR-7 and suppress its biological activity and functions [13]. Later, increasing studies have shown the existence and importance of ciRS-7 serving as miR-7 sponges in many pathophysiology process such as insulin secretion, myocardial infarction, hepatocellular carcinoma (HCC) and GC progression [15, 41–43]. In addition, several new cancer-related circRNA sponges have been discovered. CircITCH sponges miR-7, miR-17, and miR-214 in esophageal squamous cell carcinoma (ESCC) and exerts suppressive effects [42]. Hsa\_circ\_001569 targets miR-145 and promotes the proliferation and invasion of colorectal cancer [44]. CircMOT1 binds with miR-9 to inhibit HCC progression, while circTCF25 interacts with miR-103a and miR-107 to enhance the proliferation and migration of bladder carcinoma cells [45, 46]. These results collectively indicate that miRNA sponges may be a common function for circRNAs.

Although some researches still doubt the sponge function of circRNAs as most of circRNAs contain less than 10 miRNA binding sites [11], the other studies are in support



**Fig. 2** Functions and mechanisms of circRNA. **a** circRNAs' back-splicing process forms three types of circRNAs and competes with linear RNAs' canonical splicing to maintain the transcripts dynamic balance. Mature mRNA could be translated into proteins or inhibited by miRNAs which bound with Argonauto 2 (AGO2) protein. **b** CiRNAs accumulate to transcription sites and promote transcription by regulating elongation Pol II machinery. **c** EICIcRNAs located in nucleus bind to U1 snRNA and form EICIcRNA–U1 snRNP complexes to enhance gene transcription by interacting with Pol II transcription complex at the promoters of parental genes. **d** EcircRNAs exported

into cytoplasm share some miRNA binding sites and sponge miRNAs to inhibit their effects on mRNA. **e** CircRNAs containing extensive m6A modification are sufficient to drive translation of circRNAs in a cap-independent fashion. **f** CircRNA (circANRIL) binds to PES1 which is essential to 36S and 32S pre-rRNA processing to mature 5.8S and 28S rRNA and thus impair exonuclease-mediated pre-rRNA processing and ribosome biogenesis. **g** CircRNAs could be packaged into exosomes and exported to extracellular space or circulating system

of this notion. Many circRNAs harbor binding sites for multiple miRNAs and regulate them simultaneously and these evolutionarily conserved binding sites ensure the efficiency of targets [32]. Moreover, circRNAs are able to accumulate in cells and maintain its role for a relatively longer time due to high stability [47].

### Regulation of alternative splicing

The backsplicing of circRNAs could compete with linear splicing of pre-mRNA for splicing sites (Fig. 2a). For example, circMbl, generated by second exon of MBL, has MBL binding sites in flanking introns [24]. MBL levels thus significantly influence circMbl biogenesis. The increase of canonical splicing efficiency results in the decrease of relevant circRNAs expression level, which indicates that circRNAs are involved in alternative splicing regulation. In addition, it is proposed that circRNAs also act as an “mRNA trap”. During the back-splicing process, circRNAs might

sequester the translation start site and prevent the existence of certain normal linear transcripts that could be translated, which thereby reduce the expression level of certain proteins. For example, ecircRNAs produced from *Fmn* gene and *DMD* gene result in inactive mRNA transcripts with certain deletion mutations and lower levels of normal functional proteins [48, 49].

### Regulation of parental gene transcription

EICIcRNAs and ciRNAs harbor few binding sites for miRNAs and have distinct functions. EICIcRNAs hold U1 snRNP through interaction with U1 snRNA, and then the EICIcRNA–U1 snRNP complexes further interact with Pol II transcription complex at the promoters of parental genes to enhance gene transcription and expression (Fig. 2c) [20]. CiRNAs also positively regulate Pol II transcription. For example, ci-ankrd52, generated from gene *ANKRD52*, is capable of accumulating to its transcription sites and

regulates elongation Pol II machinery acting as a positive regulator for transcription (Fig. 2b) [19].

### Protein production

CircRNAs were initially recognized as non-coding RNAs [10, 11]. Only the engineered circRNAs inserted an internal ribosome entry sites (IRES) in upstream of the start codons of a protein could be translated in vitro and in vivo [50, 51]. While, extensive *N*6-methyladenosine (m6A) modification is sufficient to drive translation of circRNAs in a cap-independent fashion along with m6A reader YTHDF3 and translation initiation factors eIF4G2 and eIF3A (Fig. 2e) [52]. Further analyses showed that translatable circRNAs might be common in human transcriptome and a subset of circRNAs is found to be translated in vivo by performing ribosome footprinting and mass spectrometry [53]. Furthermore, circ-SHPRH was revealed to encode a new protein SHPRH-146aa which protects full-length SHPRH from degradation by the ubiquitin proteasome and suppresses glioma tumorigenesis [54].

However, the translational ability of circRNA remains controversial. Compared to linear transcripts, a circular structure may help ribosome recycling once translation is initiated and facilitate protein synthesis. While, some studies argue that this translation may be inefficient because a circular structure makes the beginning and the end of same ORF close to each other and thus, initiation and termination of translational process occur in the same place simultaneously [55]. Thus, new approaches should be developed to further study the coding potential of circRNAs.

### Protein decoy

Several circRNAs were reported to bound and sequester proteins to suppress their function. For example, circMbl harbors several MBL binding sites and can sponge out the excessive MBL proteins to maintain its balance [24]. CircANRIL is able to bind to pescadillo homologue 1 (PES1), an essential 60S-preribosomal assembly factor, and then impair exonuclease-mediated pre-rRNA processing and ribosome biogenesis (Fig. 2f) [16]. Circ-Foxo3 binds to cyclin-dependent kinase 2 (CDK2) and cyclin-dependent kinase inhibitor 1 (p21) to form a ternary complex, which arrests the function of CDK2 and blocks cell cycle progression [56]. Circ-Foxo3 also has high binding affinity to anti-senescent ID-1, transcription factor E2F1, as well as anti-stress proteins FAK and HIF1a, and makes them retain in the cytoplasm and leads to increased cellular senescence [56]. Similarly, nuclear circRNA cia-cGAS is able to bound DNA sensor cGAS to block its enzymatic activity and prevent cGAS from recognizing self-DNA to maintain homeostasis [57]. CircPABPN1 binds to HuR and, thus, prevents

HuR from binding to PABPN1 mRNA to lower PABPN1 translation [58]. However, not all of circRNAs interacting with proteins inhibit proteins functions. Ectopic circ-Amotl1 interacts with and stabilizes nuclear oncogene c-myc to upregulate c-myc targets and promote tumorigenesis [59].

### Public database for circRNAs studies

Nowadays, many circRNAs-associated public databases have been developed. Many of them provide prediction on circRNAs' possible biological functions or regulatory network in human diseases. For example, Circ2Traits provides information about human diseases-associated circRNAs [60]. StarBasev2.0 and circInteractome predict circRNA-miRNA-mRNA network and interaction between circRNA and RBPs [61, 62]. The protein-encoding ability could be predicted in CircRNADb and CSCD [63, 64]. Additionally, TRCirc starts to provide the regulatory information of circRNAs transcription [65]. Other databases and their available services are listed (Table 1), which are beneficial to data sharing and further study of circRNAs' biological functions and applications. Despite this, the lack of standardized nomenclature still makes it difficult to search the same circRNA in all different databases and compare different studies. Also, curated database is still limited.

### CircRNAs profiles in gastric cancer

Through high-throughput sequencing technologies and bioinformatic analyses, lots of novel circRNAs have been identified in GC cells. Some of them are differentially expressed between GC tissues and adjacent normal tissues, which implies the important roles of circRNAs in GC development and progression.

So far, several circRNA sequencing data have shown that circRNAs are abundant in GC tissues and many of them have aberrant expression levels which could be GC-related circRNAs. According to the circRNAs microarray data in 8 GC tissues and adjacent tissue samples, Sui et al. identified 467 differentially expressed circRNAs between GC tissues and adjacent normal tissues, of which 214 were significantly upregulated and 253 were downregulated in GC tissues [71]. Huang et al. found over 2000 circRNAs expressed in 3 paired GC and adjacent normal tissues, of which 100 circRNAs had over twofold change and were predicted to function in circRNA-miRNA-mRNA/gene network [72]. Fang et al. identified 306 differently expressed circRNAs (141 upregulated and 165 downregulated) between advanced GC and adjacent normal tissues, among which 273 were predicted to regulate target miRNAs [73]. Other circRNA sequencing data are listed (Table 2). Many factors affect the final

**Table 1** Public database for circRNAs

Name	URL	Number of human circRNAs	Associated diseases	Resources available	Refs.
Circ2Traits	<a href="http://gyanxet-beta.com/circdb/">http://gyanxet-beta.com/circdb/</a>	1953	105 diseases	Predicted disease-associated circRNAs and miRNA–circRNA–mRNA–lncRNA interactions	[60]
CircBase	<a href="http://circrna.org/">http://circrna.org/</a>	Over 90000	–	CircRNAs annotation	[66]
StarBase V2.0	<a href="http://starbase.sysu.edu.cn/">http://starbase.sysu.edu.cn/</a>	Over 120000	–	Predicted lncRNAs, circRNAs, miRNAs, mRNAs interaction networks	[61]
CircNet	<a href="http://circnet.mbc.nctu.edu.tw/">http://circnet.mbc.nctu.edu.tw/</a> ; <a href="http://syslab5.nchu.edu.tw/CircNet/">http://syslab5.nchu.edu.tw/CircNet/</a>	212950	–	CircRNAs annotation and predicted circRNA–miRNA–mRNA interaction networks	[67]
DeepBase v2.0	<a href="http://rna.sysu.edu.cn/deepBase/">http://rna.sysu.edu.cn/deepBase/</a>	14867	–	Small ncRNAs, lncRNAs and circRNAs annotation	[68]
CircInteractome	<a href="http://circinteractome.nia.nih.gov/">http://circinteractome.nia.nih.gov/</a>	Over 120000	–	Predicted circRNA–miRNA interactions and RNA-binding proteins	[62]
CircRNADb	<a href="http://reprod.njmu.edu.cn/circrnadb">http://reprod.njmu.edu.cn/circrnadb</a>	32914	–	CircRNAs annotation and protein-encoding ability	[63]
CSCD	<a href="http://gb.whu.edu.cn/CSCD">http://gb.whu.edu.cn/CSCD</a>	1394023	19 cancers	Cancer-specific circRNAs annotation, cellular localization, protein-encoding ability, predicted circRNA–miRNA interactions and RNA-binding proteins	[64]
ExoRBase	<a href="http://www.exoRBase.org">http://www.exoRBase.org</a>	58330	5 diseases	Human blood exosome-derived circRNAs, lncRNAs and mRNAs annotation	[57]
CircRNADisease	<a href="http://cgga.org.cn:9091/circRNADisease/">http://cgga.org.cn:9091/circRNADisease/</a>	330	48 diseases	Published disease-associated circRNAs annotation	[69]
CIRCpedia v2	<a href="http://www.picb.ac.cn/rnomics/circpedia">http://www.picb.ac.cn/rnomics/circpedia</a>	183943	–	CircRNAs annotation including conservation and enrichment analysis	[70]
TRCirc	<a href="http://www.licpathway.net/TRCirc">http://www.licpathway.net/TRCirc</a>	92375	–	Regulatory information of circRNAs transcription	[65]

**Table 2** Overview of circRNAs identified by RNA sequencing and microarrays in GC

Sample	Special treatment	Detection method	Number of circRNAs	Number of circRNA differently expressed ( $\geq$ twofold change)	Refs.
3 paired GC and GCN tissues	RNase R	CircRNA microarray	About 2000	100(16 upregulated, 84 down-regulated)	[72]
8 paired GC and GCN tissues	RNase R	CircRNA microarray	4458	467(214 upregulated, 253 down-regulated)	[71]
3 paired GC and GCN tissues	–	CircRNA microarray	5396	308(107 upregulated, 201 down-regulated)	[74]
3 paired III stage GC and GCN tissues	–	CircRNA microarray	–	306(141 upregulated, 165 down-regulated)	[73]
3 paired GC and GCN tissues	Ribosome-depleted	RNA-seq	About 3000	180(82 upregulated, 98 down-regulated)	[75]
3 groups of gastric tissues (gastric tissue without cancer, GC tissue, GCN tissue)	Ribosome-depleted	RNA-seq	736	–	[76]
5 paired GC and GCN tissues	RNase R	Microarray chip assay	62998	713(191 upregulated, 522 down-regulated)	[77]
3 paired plasma of patients and healthy persons	–	CircRNA microarray	5396	343(171 upregulated, 172 down-regulated)	[78]
6 paired GC and GCN tissues	–	CircRNA microarray	2070	400(176 upregulated, 264 down-regulated)	[79]

results of sequencing data including clinical reasons (clinical sample resources), pre-analytical reasons (sample processing and preparing), analytical reasons (detection methods), and postanalytical reasons (methods or tools for circRNA validation). Although these data may have discrepancies due to factors above, most of them indicate that the down-regulated circRNAs are more than up-regulated ones in GC tissues. Moreover, function prediction results suggest that most of the circRNAs are able to act as miRNAs regulators in GC, which needs to be further confirmed in future studies.

## CircRNAs in GC and molecular mechanisms

Recently, several oncogenic and antioncogenic circRNAs have been discovered to regulate the proliferation, migration, invasion and apoptosis of GC cells (Fig. 3). Most of them could regulate GC-related signaling pathways through miRNA sponges. Also, the circRNA interacting with RBPs in GC starts to be identified.

### Oncogenic circRNAs in GC

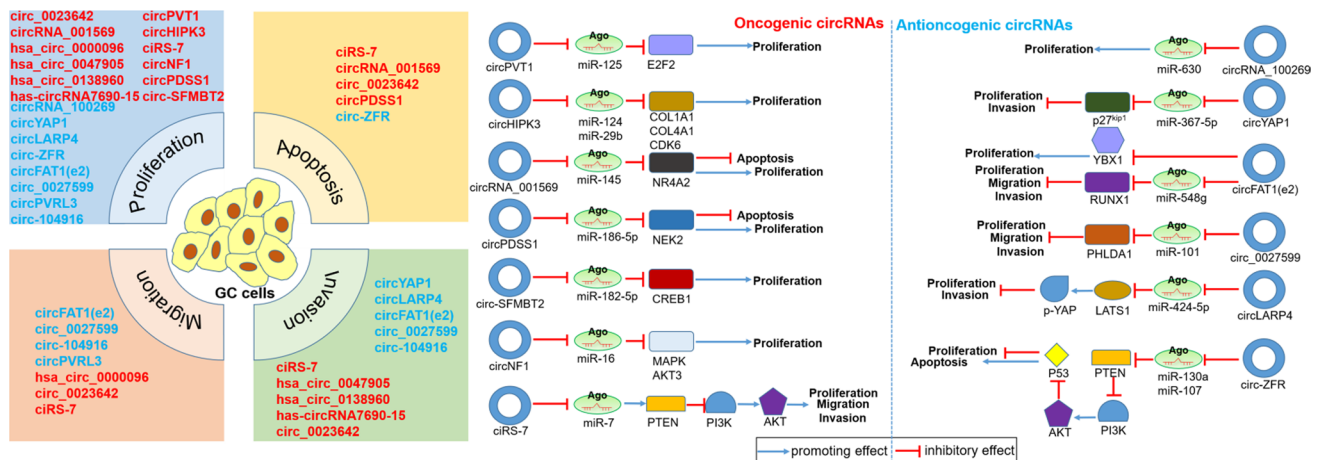
CiRS-7, one of the most studied circRNAs is miR-7 sponge. While, ciRS-7 was recently found to act as oncogenic circRNA by antagonizing miR-7-mediated PTEN/PI3K/AKT pathway in GC [80]. Overexpression of ciRS-7 could neutralize the suppressive effects of miR-7 on GC cells migration ability and reduce apoptotic cells induced by miR-7. Xenograft mice model experiment also showed that ciRS-7 is able to abrogate miR-7-mediated suppressive effects on tumor growth. Further studies suggested that ciRS-7 weakens miR-7 effects on upregulating expression of PTEN and downregulating the levels of PI3K and AKT phosphorylation

of PTEN/PI3K/AKT pathway in vitro. As PTEN/PI3K/AKT pathway is involved in multiple tumors such as lung cancer, breast cancer and colorectal cancer [81–83]. PTEN acting as antioncogene negatively regulates PI3K/AKT signal pathway to affect cell proliferation, apoptosis, migration of tumor. Here, ciRS-7-miR-7-PTEN/PI3K/AKT regulatory axis in GC progression is firstly found.

CircPVT1, derived from a cancer susceptibility locus PVT1, was initially confirmed to be frequently upregulated in GC tissues partly due to DNA amplification [75]. Further studies indicated that circPVT1 might serve as a proliferative factor through sponging miR-125 in GC. Silencing circPVT1 selectively impairs proliferation of GC cells and decreases the expression of miR-125b target E2F2. Co-expression of circPVT1 and miR-125b attenuates the anti-proliferative effects of miR-125b. In addition, circPVT1 expression level is related to T4 stage tumor numbers and neural invasion. CircPVT1 level, along with TNM stage and tumor size, was verified as independent prognostic factors for GC patients.

CircHIPK3 might be involved in GC progression through circHIPK3-miR-124/miR-29b axis [84]. As known sponge for miR-124 and miR-29b, circHIPK3 are upregulated in GC tissues and related to T stage and Ming's classification, and negatively correlated with miR-124/miR-29b in GC tissues and cell lines. Moreover, circHIPK3-miR-124/miR-29b axes were predicted and most of the target genes are closely related to cell proliferation. Gain and loss of function studies also verified that circHIPK3 promotes GC cell proliferation. Meanwhile, the axes target genes COL1A1, COL4A1 and CDK6, upregulated in GC tissues, could be potential biomarker for diagnosis and prognosis.

CircRNA\_001569 was revealed as miR-145 sponge and could regulate cell proliferation and apoptosis through oncogene NR4A2 in GC [85]. CircRNA\_001569 were



**Fig. 3** The role and regulatory pathway of GC-related circRNAs. The schematic diagram depicts the known role of circRNAs in GC progression and the way that circRNAs involved in miRNA-associated gene regulatory pathway



found to be upregulated in GC tissues and cells and positively correlated with NR4A2, while negatively correlated with miR-145. Overexpression and knock-down experiment suggested that circRNA\_001569 significantly promotes GC cell proliferation and suppresses cell apoptosis through decreasing miR-145 expression and increasing expression of miR-145 target NR4A2. Although circRNA\_001569-miR-145 regulatory axis was previously reported in colorectal cancer [86], here, its promotive effects were also verified in GC progression.

CircPDSS1 promotes GC progression as miR-186-5p sponge [87]. CircPDSS1 is significantly upregulated in GC tissues and cells, and related with poor prognosis in GC patients. Gain and loss of function experiments indicated that circPDSS1 promotes GC cell proliferation and suppresses cell apoptosis. Moreover, bioinformatic prediction showed that circPDSS1 binds with miR-186-5p, while NEK2 could be miR-186-5p target. Functional assays demonstrated that circPDSS1 acts as oncogene through sponging miR-186-5p and increasing NEK2 expression level. As NEK2 is abnormally expressed in a wide variety of cancer and involved in tumorigenesis and metastasis [88], circPDSS1-miR-186-5p-NEK2 axis seems to be important in GC progression.

Circ-SFMBT2, derived from exons 5–8 of gene SFMBT2, was found to be upregulated in GC tissues, cell lines and plasma from GC patients, and positively associated with TNM stage [89]. Silencing circ-SFMBT2 in the cytoplasm markedly inhibits GC cell proliferation. Furthermore, circ-SFMBT2 was predicted and validated to target miR-182-5p and competitively share it with oncogene CREB1. Overexpression of miR-182-5p decreases CREB1 expression and suppresses cell proliferation. While, circ-SFMBT2 knockdown simultaneously enhances these effects as more functional miR-182-5p are released. Here, circ-SFMBT2 was revealed to regulate CREB1 expression through competing for miR-182-5p in GC.

CircNF1 (hsa\_circ\_0042881), derived from exons 2–8 of tumor-suppressive gene NF1, serves as a novel oncogenic circRNA through functioning as miR-16 sponge in GC [90]. CircNF1 was found to be markedly upregulated in GC tissues and cell lines and promote cell proliferation. Luciferase reporter assays showed that circNF1 binds to miR-16 and then derepresses its downstream target mRNA, MAP7 and AKT3. Additionally, the expressions of circNF1 and linear NF1 are not significantly correlated, suggesting that they might have independent roles in GC development. Here, novel circNF1 was demonstrated to promote GC progression through absorbing miR-16.

## Antioncogenic circRNAs in GC

CircRNA\_100269, transcribed from gene LPHN2, may serve as tumor suppressor in GC through sponge for miR-630. CircRNA\_100269 was found to be significantly down-regulated in recurrent cancer tumors compared with non-recurrent cancer tissues and could be an independent predictor of early recurrence of stage III GC [91]. Later, further studies showed that miR-630 might be a direct target of circRNA\_100269 [92]. Overexpression of circRNA\_100269 suppresses GC cell growth, while co-expression of miR-630 and circRNA\_100269 evidently increases the growth rates of GC cells as miR-630 could bind to circRNA\_100269 and block its suppressive effects on GC cells. Although accumulating evidence indicated that miR-630 is overexpressed in various tumors and related to cell proliferation and invasion [93–95], here, a novel circRNA\_100269-miR-630 regulatory axis were found to be involved in GC cell growth.

CircYAP1 might serve as potential suppressive factor for GC [96]. CircYAP1 (hsa\_circ\_0002320), selected from CircNet database, was found to be decreased in GC tissues. Patients with lower circYAP1 expression might have shorter survival time, suggesting that circYAP1 could serve as prognostic factors. Overexpression and knockdown experiments indicated that circYAP1 is able to inhibit GC proliferation and invasion *in vitro* and *in vivo*. Moreover, circYAP1-miR-367-5p-p27<sup>kip1</sup> regulatory axes were predicted and validated in GC cells. CircYAP1 overexpression or silence could upregulate or downregulate target gene p27<sup>kip1</sup>, respectively, which could be reversed by miR-367-5p mimics or inhibitor. Although circYAP1 is derived from oncogene YAP1 [97], it could act as an anti-oncogene in GC.

CircLARP4 may act as a novel suppressive factor and a potential GC biomarker [98]. CircLARP4 derived from exon 9 and 10 regions of LARP4 is preferentially located in the cytoplasm and presents high stability (half-life exceeds 24 h). Moreover, ectopic upregulated miR-424-5p could promote GC cell growth and invasion through targeting LATS1 gene, while circLARP4 might serve as miR-424-5p sponge. Overexpression of circLARP4 would inhibit the ability of proliferation and invasion through counteracting miR-424-5p effects and revive expression of LATS1 and its downstream p-YAP *in vitro*. Hippo-Yap pathway is known to play a pivotal role in the regulation of tumor proliferation and metastasis [99]. By phosphorylating YAP, LATS1 could prevent YAP from transporting to nucleus to suppress oncogene transcription which has been confirmed in GC [100]. While, circLARP4 is a newly discovered molecular involved in modulating Hippo-Yap pathway as miR-424-5p sponge.

Circ-ZFR are markedly down-regulated in GC tissues and cells and acts as antioncogene [101]. Functional experiments showed that circ-ZFR promotes cell apoptosis and suppresses cell proliferation by arresting cell cycle and cell

propagation. Meanwhile, circ-ZFR-miR-130a/miR-107-PTEN network was predicted and confirmed to regulate GC. Overexpression of circ-ZFR would weaken miR-130a/miR-107 effects on GC cell cycle, cell propagation and apoptosis. Transfection of miR-130a/miR-107 mimics promotes GC cell propagation and impedes apoptosis by targeting PTEN. Moreover, in vivo experiment approved that circ-ZFR is able to curb GC tumor growth and increase expression of PTEN and p53 through sponging miR-130a/miR-107. Here, circ-ZFR was verified as novel antioncogenic circRNA regulating GC proliferation and apoptosis through miR-130a/miR-107-PTEN regulatory network.

CircFAT1(e2), derived from exon 2 of gene FAT1, inhibits GC progression through sponging miR-548g in the cytoplasm and binding to protein YBX1 in nucleus [102]. CircFAT1(e2) was confirmed to be downregulated in GC tissues and cell lines and correlated with clinical stage. Overexpression of circFAT1(e2) significantly suppresses GC cell proliferation, invasion and migration in vitro and tumor growth in vivo. Subcellular location results showed circFAT1(e2) is localized in both cytoplasm and nucleus of GC cells. In cytoplasm, circFAT1(e2) was predicted and validated to directly bind to miR-548g and negatively regulate miR-548g expression which promotes GC progression through RUNX1. In nucleus, circFAT1(e2) interacts with protein YBX1 and then downregulates its target genes, EGFP, c-Met, CDC25A. As oncoprotein YBX1 belongs to DNA- and RNA-binding family of transcription factors and is involved in many cellular processes including transcription, translation and DNA damage repair [103], here, circFAT1(e2) could bind to YXB1 and block its activities in GC.

Circ\_0027599 suppresses GC cell proliferation and metastasis through circ\_0027599-miR-101-PHLDA1 axis [104]. PHLDA1, as tumor suppressor, is downregulated in GC cell lines and inhibits cell proliferation, migration and invasion. While, circ\_0027599 was found to reduce miR-101 expression and increase its target PHLDA1 levels. Overexpression circ\_0027599 could suppress GC cell proliferation and metastasis through regulating miR-101 and derepressing its target tumor-suppressive gene PHLDA1.

### Other circRNAs with unknown mechanisms

Hsa\_circ\_0000096, derived from gene HIAT1, presents oncogenic activity [105]. It is downregulated in GC tissues and cells and associated with gender, tumor invasion and TNM stage. Knockdown of hsa\_circ\_0000096 arrests cells at G0/G1 phase, and inhibits cell proliferation and migration. Xenograft nude mouse model experiment also confirmed these effects. Here, downregulated hsa\_circ\_0000096 acting as an oncogene is interesting as it is not consistent with that

low expression of non-coding RNA in cancers generally acts as a suppressor gene.

Circ-104916, derived from gene NEK6, seems to be a novel tumor-suppressive circRNA. It is downregulated in GC tissues and associated with tumor stage, lymphatic metastasis, nerve invasion and invasion depth [93]. Overexpression of circ-104916 inhibits cell proliferation, migration and invasion capability. Meanwhile, circ-104916 might suppress EMT process to affect GC cell migration and invasion as the level of E-cadherin was upregulated, while N-cadherin, Vimentin and Slug were downregulated.

circRNA\_0023642 (hsa\_circ\_0023642), one of the top 5 upregulated circRNAs in previous sequencing data, seems to have tumor-promotive function in GC [72, 106]. Knockdown of it inhibits cell proliferation, migration, invasion and induces cell apoptosis. Also, circRNA\_0023642 might affect EMT signaling pathway in GC as downregulation of circRNA\_0023642 could decrease the EMT-related gene.

CircPVRL3, derived from exons 4, 5, 6 and 7 of gene PVRL3, are involved in proliferation and migration of GC [107]. It is downregulated in GC tissues and cell lines and associated with TNM stage and prognosis. Knockdown of circPVRL3 would promote proliferation and migration. Moreover, bioinformatics prediction revealed its several potential functions. CircPVRL3 has a high degree of AGO occupancy and might serve as miRNA sponge. Meanwhile, circPVRL3 might function through RBPs complexes with FUS, LIN28A, PTB, and EIF4A3. Additionally, CircPVRL3 contains internal ribosome entry sites, ORF and m<sup>6</sup>A modification structure and might encode functional proteins. However, such potential functions have not been verified.

Through circRNA and mRNA co-expression network, hsa\_circ\_0047905, hsa\_circ\_0138960 and has-circRNA7690-15 were focused as these circRNAs interacting with more mRNAs might play more significant roles in GC [108]. They are upregulated in GC tissues and stable in the cytoplasm. Depletion of them downregulate their parent gene expression and suppress GC cells proliferation and invasion. In addition, these three circRNAs present good diagnostic value.

### CircRNAs as diagnostic and prognostic biomarkers for GC

The high incidence and mortality of GC make new requirements for early diagnosis and the prognosis. CircRNAs show great potential to be used as cancer biomarkers. Firstly, they can be easily detected due to their high stability, abundance and conservation in human cells. Secondly, they often display tissue- and developmental-stage-specific expression. Thirdly, circRNAs are also present in human serum, plasma and other body fluids [109, 110], especially in microvesicles

and exosomes [111], which can be easily detected by non-invasive method. Also, qRT-PCR with high sensitivity could facilitate detection of circRNAs in drops of fluids.

Furthermore, the clinical value of circRNAs as biomarkers has been explored in many studies. According to large clinical sample test including tissues and serum from GC patients and healthy controls, followed with clinicopathologic factors correlation analysis as well as prognostic and survival analysis, a group of potential circRNAs biomarkers are emerged for GC early diagnosis and prediction of recurrence and metastasis. Hsa\_circ\_0000096 and hsa\_circ\_0047905 present good diagnostic value as their area under the ROC curve (AUC) in GC tissues is up to 0.82 and 0.85, respectively [105, 108]. Plasma hsa\_circ\_0000520 presents a better diagnostic value than that in tissues as its AUC, sensitivity and specificity in plasma are 0.897, 82.4% and 84.4%, respectively, which are higher than that in tissues (0.613, 53.6%, 85.7%) [112]. While, hsa\_circ\_0000190 is opposite. Its expression is downregulated in GC tissues and plasma and associated with tumor diameter, lymphatic and distal metastasis, TNM stage as well as CA19-9 level [113]. The AUC of hsa\_circ\_0000190 in tissues is 0.75 much higher than 0.60 in plasma, suggesting a modest diagnostic value. Besides, the combination of hsa\_circ\_0001017 and hsa\_circ\_0061276 in tissues and plasma exhibits the best diagnostic value and its AUC reaches to 0.996, with 95.5% sensitivity and 95.7% specificity. Additionally, hsa\_circ\_0058246 was upregulated in GC patients with metastasis and recurrence [73], while patients with lower levels of circPVT1 had a significantly shorter OS and DFS (disease-free survival) [75]. Both of them could be used as a prognostic biomarker. Other circRNAs with potential diagnostic and prognostic value are listed (Table 3).

In addition, the combination of several circRNAs or a single circRNA with traditional diagnostic indicators could increase the sensitivity, specificity and accuracy of GC diagnosis and prognosis. The AUC of downregulated hsa\_circ\_0000096 and hsa\_circ\_002059 in GC tissues is 0.82 and 0.73, respectively, while increased to 0.91 when combined [105], indicating that the diagnostic value of a combination of circRNAs is higher than that of individual circRNA. Besides, Zhang et al. constructed a four-circRNA-based classifier and a new formula combined circRNA classifier with TNM stages to evaluate the risk of early recurrence of stage III GC after radical surgery and distinguish patients with a high risk from those with a low risk. The AUC of two classifiers was 0.763 and 0.711 as well as 0.866 and 0.818, respectively, in the two cohorts [91], suggesting that the prognostic value of circRNAs combined with traditional factors is much higher. Similarly, the AUC of downregulated hsa\_circ\_0000745 in plasma is 0.683, while increased to 0.775 in combination with CEA [114]. Although the potential of circRNAs to be promising GC biomarkers is

emerging, their real value still needs to be further tested in a larger cohort of clinical samples. Furthermore, due to the lack of adequate biomarkers with high specificity and sensitivity simultaneously, the novel diagnostic pattern combining circRNAs with other traditional biomarkers like CEA and CA19-9 might be one of the solutions. Additionally, circRNAs are enriched and stable in exosomes [111]. The presence of circRNAs in exosomes provides a new mechanism for the communication between cancer cells and the other cells [115]. Therefore, exosomes-derived circRNAs (ex-circRNAs) may be associated with cancer progression and could be a novel diagnostic and prognostic marker.

### CircRNAs as potential therapeutic targets for GC

As their regulatory roles in cancer are gradually being unveiled, circRNAs might be developed as effective therapeutic targets. Several strategies based on the functions of circRNAs have been proposed to treat GC. Firstly, exogenous upregulation or downregulation of relevant circRNAs to regulate miRNA molecules might be a useful method. Several methods have been applied. For example, siRNA or shRNA targeting the specific backspliced sequence of circRNA is used to inhibit its expression [42]. CRISPR/Cas9 system could achieve knockout of circRNAs [116]. While, plasmid and lentiviral vector are used to increase circRNAs levels [75, 86, 117]. Liang et al. introduced how to construct effective overexpression vectors of circRNAs with short intronic repeat sequences [22]. However, how to control the process of endogenous circularization remains unknown. Additionally, synthetic circRNAs sponges might be a simple, effective and convenient strategy. Recently, synthetic circular RNA containing miR-21 binding sites was proved to achieve targeted loss of miRNA function and suppress GC cell proliferation in vitro, suggesting that synthetic circRNAs sponges could be potential therapeutic application in human patients [118]. Also, artificially controlled endogenous circularization may be another choice. Using an “mRNA trap” to sequester translation start site of dysfunctional mRNAs, the biogenesis of diseases-related proteins might be reduced [48]. Furthermore, applying circRNAs functioning as protein decoys to regulate disease-related proteins release and biological activity, or targeting encoding circRNAs involving in tumorigenesis or progression like circ-SHPRH might be potential treatment methods. Although such circRNAs have not been found and disclosed in GC recently, it will be promising application for future tumor treatment with further studies.

Using circRNAs as novel therapeutic targets broadens the universe of potential “druggable” targets. Nevertheless, the real clinical application of circRNAs as drugs or targets

**Table 3** CircRNAs as diagnostic and prognostic biomarkers for GC

CircRNA	CircBase ID	Sample	Dysregulation in GC	Clinicopathological association	Potential function	AUC	Sensitivity and specificity	Refs.
Hsa_circ_0003159	Hsa_circ_0003159	Paired GC and GCN tissues ( <i>n</i> = 108)	↓	Gender, stage, distal metastasis, tumor node metastasis	Diagnosis	0.75	85.2%, 56.5%	[121]
CircFAT1(e2)	Hsa_circ_0001461	Paired GC and GCN tissues ( <i>n</i> = 38) GC cell lines	↓	Metastasis, TNM stage	–	–	–	[102]
Circ-104916	Hsa_circ_0008383	Paired GC and GCN tissues ( <i>n</i> = 70) GC cell lines	↓	Invasion depth, tumor stage, lymphatic metastasis	–	–	–	[93]
Hsa_circ_0000096	Hsa_circ_0000096	Paired GC and GCN tissues ( <i>n</i> = 101) GC cell lines	↓	Gender, invasion, TNM stage	Diagnosis	0.82	–	[105]
CircRNA_100269	Hsa_circ_0013048	Paired GC and GCN tissues ( <i>n</i> = 112) GC cell lines	↓	Histological subtype, node invasion number	Prognosis	–	–	[91]
CircLARP4	Hsa_circ_0003222	GC and GCN tissues ( <i>n</i> = 80) GC cell lines	↓	Tumor size, lymphatic metastasis	Prognosis	–	–	[117]
CircYAP1	Hsa_circ_0002320	Paired GC and GCN tissues ( <i>n</i> = 97)	↓	Tumor size, TNM stage	Prognosis	–	–	[96]
CircPVRL3	Hsa_circ_0066779	Paired GC and GCN tissues ( <i>n</i> = 62) GC cell lines	↓	TNM stage	Diagnosis	0.763	90.3%, 56.4%	[107]
Hsa_circ_0074362	Hsa_circ_007436	GC and GCN tissues ( <i>n</i> = 127) Gastritis tissues ( <i>n</i> = 83) GC cell lines	↓	CA19-9, lymphatic metastasis	Diagnosis	0.63	36.2%, 84.3%	[122]
Hsa_circ_0001895	Hsa_circ_0001895	GC and GCN ( <i>n</i> = 96) Gastric mucosa tissues ( <i>n</i> = 35) Gastric dysplasia tissues ( <i>n</i> = 30) GC cell lines	↓	Cell differentiation, Borrmann type, CEA	Diagnosis	0.792	67.8%, 85.7%	[123]
Hsa_circ_0014717	Hsa_circ_0014717	Paired GC and GCN tissues ( <i>n</i> = 96) Gastric juice ( <i>n</i> = 38) Gastric ulcer ( <i>n</i> = 30) Chronic atrophic gastritis ( <i>n</i> = 15) GC tissues ( <i>n</i> = 39)	↓	Tumor stage, distal metastasis, tissue CEA and CA19-9	Diagnosis	0.696	59.4%, 81.3%	[74]

Table 3 (continued)

CircRNA	CircBase ID	Sample	Dysregulation in GC	Clinicopathological association	Potential function	AUC	Sensitivity and specificity	Refs.
Hsa_circ_0000705	Hsa_circ_0000705	Paired GC and GCN tissues (n = 96) Gastric mucosa tissues (n = 35) Gastric ulcer tissues (n = 16) Erosive gastritis tissues (n = 18) Gastric dysplasia tissues (n = 25)	↓	Tumor location, stage, Borrmann type, pathologic diagnosis, CA19-9	Diagnosis	0.719	64.6%, 69.8%	[124]
CircPDSS1	Hsa_circ_0093398	Paired GC and GCN tissues (n = 20) GC cell lines	↑	-	Prognosis	-	-	[87]
Hsa_circ_0058246	Hsa_circ_0058246	Paired GC and GCN tissues (n = 43)	↑	Lymph node invasion (>=16), recurrence	Prognosis	-	-	[73]
Hsa_circ_0047905, Hsa_circ_0138960, Hsa-circ-cRNA7690-15	Hsa_circ_0047905, Hsa_circ_0138960, -	GC and GCN tissues (n = 31) GC cell lines	↑	-	Diagnosis	0.85, 0.647, 0.681	-	[108]
CircPVT1	Hsa_circ_0001821	Paired GC and GCN tissues (n = 187)	↑	T4 stage tumors, neural invasion	Prognosis	-	-	[75]
CIRS-7	Hsa_circ_0001946	Paired GC and GCN tissues (n = 102)	↑	TNM stage, lymph node involvement, distant metastasis	Prognosis	-	-	[80]
CircHIPK3	Hsa_circ_0000284	Paired GC and GCN tissues (n = 63)	↑	T stage, Ming's classification	-	-	-	[84]
CircRNA_001569	Hsa_circ_001569	Paired GC and GCN tissues (n = 30) GC cell lines	↑	Tumor size, clinical stage, invasion	-	-	-	[85]
Circ-SFMBT2	Hsa_circ_0017639	Paired GC and GCN tissues (n = 36) Plasma samples from 26 GC patients and 18 healthy controls GC cell lines	↑(GC tissues) ↑(GC plasma)	Tissues: TNM stage	Diagnosis	0.759 (Tissues)	80.6%, 63.9%	[89]

Table 3 (continued)

CircRNA	CircBase ID	Sample	Dysregulation in GC	Clinicopathological association	Potential function	AUC	Sensitivity and specificity	Refs.
Hsa_circ_0006633	Hsa_circ_0006633	Paired GC and GCN tissues ( $n=96$ ) Healthy gastric mucosa ( $n=35$ ) Gastritis mucosa ( $n=51$ ) Gastric dysplasia tissues ( $n=20$ ) Paired plasma samples from GC patients and healthy controls ( $n=20$ ) GC cell lines	↓(GC, gastritis and dysplasia tissues and GC cells) ↑(GC plasma)	Tissues: Distal metastasis, CEA	Diagnosis	0.741 (Tissues)	60%, 81%	[125]
Hsa_circ_002059	Hsa_circ_002059	Paired GC and GCN tissues ( $n=101$ ) Paired pre- and post-operative plasma sample ( $n=36$ )	↓(GC tissues) ↑(pre-operative plasma)	Tissues: TNM stage, distal metastasis, gender, age	Diagnosis	0.73	81%, 62%	[126]
Hsa_circ_0001649	Hsa_circ_0001649	Paired GC and GCN tissues ( $n=76$ ) Paired preoperative and postoperative blood samples ( $n=20$ )	↓(GC tissues) ↓(pre-operative plasma)	Tissues: Pathological differentiation	Diagnosis	0.834 (Tissues)	71.1%, 81.6%	[127]
Circ_0027599	Hsa_circ_0027599	Paired GC and GCN tissues ( $n=78$ ) Blood samples from GC patients and healthy controls	↓(GC tissues) ↓(GC blood)	Tissues: Tumor size, invasion, lymph node distant metastasis, distant metastasis, TNM stage	–	–	–	[104]
Circ-KIAA1244	Hsa_circ_0130810	Paired GC and GCN tissues ( $n=28$ ) Plasma samples from 62 GC patients and matched 25 healthy controls GC cell lines	↓(GC tissues and cell lines) ↓(GC serum)	Plasma: TNM stage, lymphatic metastasis	Diagnosis Prognosis	0.748 (Plasma)	77.4%, 68.0%	[128]

Table 3 (continued)

CircRNA	CircBase ID	Sample	Dysregulation in GC	Clinicopathological association	Potential function	AUC	Sensitivity and specificity	Refs.
Hsa_circ_0000190	Hsa_circ_0000190	Paired GC and GCN tissues ( $n=104$ ) Paired plasma samples from GC patients and healthy controls ( $n=104$ )	↓(GC tissues) ↓(GC plasma)	Tissues: Tumor diameter, lymphatic metastasis, distal stage, CA19-9 Plasma: CEA	Diagnosis	0.75 (Tissues) 0.60 (Plasma)	72.1%, 68.3% (Tissues) 41.4%, 87.5% (Plasma)	[113]
Hsa_circ_0000745	Hsa_circ_0000745	GC and GCN tissues ( $n=80$ ) Paired plasma samples from GC patients and healthy controls ( $n=60$ )	↓(GC tissues) ↓(GC plasma)	Tissues: Tumor differentiation Plasma: Tumor node metastasis, stage	Diagnosis	0.683 (Plasma)	85.5%, 45%	[114]
Hsa_circ_0000181	Hsa_circ_0000181	Paired GC and GCN tissues ( $n=115$ ) Paired plasma samples from GC patients and healthy controls ( $n=102$ )	↓(GC tissues) ↓(GC plasma)	Tissues: Tumor diameter, lymphatic metastasis, distal metastasis, CA19-9 Plasma: Differentiation, CA19-9	Diagnosis	0.756 (Tissues) 0.582 (Plasma)	53.9%, 85.2% (Tissues) 99.0%, 20.6% (Plasma)	[129]
Hsa_circ_0001017, Hsa_circ_0061276	Hsa_circ_0001017, Hsa_circ_0061276	Paired GC and GCN tissues ( $n=121$ ) Paired plasma samples from GC patients and healthy controls ( $n=121$ )	↓(GC tissues) ↓(GC plasma)	Tissues: Age, tumor size, TNM stage, distal metastasis, CEA Plasma: Gender, tumor size, differentiation, poor prognosis	Prognosis Diagnosis	0.966 (Combinative AUC)	95.5%, 95.7%	[78]
Hsa_circ_0000520	Hsa_circ_0000520	Paired GC and GCN tissues ( $n=56$ ) Plasma samples from 45 GC patients and matched 17 healthy controls	↓(GC tissues) ↓(GC plasma)	Tissues: TNM stage Plasma: CEA	Diagnosis	0.613 (Tissues) 0.897 (Plasma)	53.6%, 85.7% (Tissues) 82.4%, 84.4% (Plasma)	[112]

needs more detailed and complete experimental data such as safety and efficacy. Additionally, how to deliver engineered circRNAs in vivo safely is another question. Using modified exosomes which contain engineered circRNAs or siRNAs targeting circRNA might be an effective approach because a large amount of researches have proved that exosome-mediated delivery of RNA could be used for therapy purposes [119, 120]. The lipid bilayer structure of exosomes prevents RNAs from degradation and ensures the effective concentration of circRNAs. Moreover, the small size of exosome and its membrane structure are helpful for their absorption and fusion by cancer cells. Therefore, researches on circRNAs as therapeutic targets or tools will be one of the most noticeable areas in the field of circRNAs.

## Challenges and perspectives

Nowadays, circRNAs are becoming new research frontier in tumor biology and therapy. Up to date, at least hundreds of circRNAs have been discovered to be aberrantly expressed in GC tissues. Many of them have been proved to modulate GC cell proliferation, migration, invasion and apoptosis and could be potential biomarker or effective therapeutic targets for GC. Although some new perspectives on the clinical application of circRNAs are generated rapidly, the experimental and clinical researches in GC still lag behind. Firstly, circRNAs mechanisms of circularization, degradation and cellular localization remain poorly understood. Besides, the number of circRNAs in GC with clear biological functions and mechanisms is limited. Novel functions or mechanisms except miRNA sponge need to be disclosed. Moreover, circRNAs effects on GC microenvironmental cells such as cancer-associated fibroblasts (CAFs) and macrophages are still not very clear as tumor microenvironment could affect tumor progression [130, 131]. Since exosomes have been verified to contain stable and enriched circRNAs, whether ex-circRNAs are critical to GC progression and can be developed as a novel biomarker, therapeutic targets for GC need further exploration. In addition, current studies on exploring circRNAs as GC biomarkers and therapeutic tools or targets are simple and limited. Standardized methodology for clinical circRNAs detecting is lacked. Systematical assessment including costs, accuracy, reproductivity, specificity and sensitivity of circRNAs biomarkers in larger samples and comparison with traditional tumor markers are insufficient. Synthetic circular RNA molecules seem to be effective as gene therapy methods, while the efficacy, safety and potential side effects are unknown. Moreover, clinical trials on circRNAs as biomarkers and therapeutic targets or tools remain to be carried out.

Exosome might extremely extend circRNAs' studies and applications. Exosome, as nano-sized vesicles released by

many cells especially tumor cells, could transfer signaling molecules including circRNAs to recipient cells and regulate cancer progression. For example, exosomal ciRS-133 derived from GC cells could be delivered into pre-adipocytes and promote white adipose browning through targeting miR-133/PRDM16 pathway [132]. Some researchers proposed that the concentration of circulating non-coding RNAs is too low to induce biological responses [133]. Nonetheless, several non-coding RNAs including circRNAs could regulate the same gene and multiple genes in same signaling pathway. Thus, exosomal circRNAs would be potential therapeutic targets. Also, membrane of exosome could protect inner signaling contents from nuclease and other environmental factors and make it easier to be detected in many biological fluids like blood, urine, saliva and breast milk [134]. Recent RNA sequencing data revealed that many circRNAs are stable and enriched in exosome and could be a promising biomarker for cancer diagnosis (Fig. 2g) [111]. Exosomal circ-PDE8A could be detected in blood circulation and are associated with progression and prognosis in pancreatic ductal adenocarcinoma patients [135]. Moreover, as natural intracellular communication mediators, exosomes have been proved to be good targeted drug delivery tool. Exosomes could even act as natural and effective carriers for small interfering RNAs (siRNAs) delivery of gene therapy [120]. Therefore, detection and modification of exosome contents provide a new direction to disease diagnosis and treatment. Also, exosomal circRNAs are expected to become remarkable biomarkers and therapy tools for GC.

## Conclusion

With biological methods and informatics technologies along with further studies, more and more GC-related circRNAs along with the physiological and pathological functions have been identified. Moreover, circRNAs present great potential to be biomarker for GC diagnosis and prognosis as well as novel therapeutic targets or tools. Although the knowledge of precise mechanisms of circularization, degradation, cellular localization and functions in GC is still limited, the mystery of circRNAs will finally be solved, and novel diagnostic and therapeutic strategies based on circRNAs will serve clinical practice effectively in future.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no competing interests.

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