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REVIEW

Current Understanding of Circular RNAs in Gastric Cancer

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Xiaohuan Tang
Jiaming Zhu
Yuanda Liu
Chao Chen
Tianzhou Liu
Jingjing Liu

Department of Gastrointestinal Nutrition and Hernia Surgery, The Second Hospital of Jilin University, Jilin University, Changchun, Jilin, People's Republic of China

Abstract: Gastric cancer (GC) is the third most common cause of cancer-related death worldwide. Advanced diagnosis and high rates of relapse and metastasis are associated with the poor prognosis of this disease. GC has a complex etiopathogenesis of which the underlying mechanisms remain to be explored. Studies on circular RNAs (circRNAs), noncoding RNAs that may be potential targets in GC, have made substantial progress over the past few years. CircRNAs exert important effects on the onset and progression of GC. Hence, this article aims to summarize the findings of recent studies of circRNAs related to GC and to describe the underlying mechanisms and potential applications. The findings indicate that circRNAs participate in GC regulation, proliferation, invasion, and metastasis through regulating microRNAs, proteins, genes, and signaling pathways. In addition, dysregulated circRNAs may be used as novel diagnostic and prognostic biomarkers or therapeutic targets. This review is expected to facilitate a better understanding of GC, and it suggests novel circRNA-based methods to inhibit or prevent GC.

Keywords: gastric cancer, circular RNA, biomarkers, diagnosis, prognosis

Introduction

In 2018, gastric cancer (GC) was the fifth most commonly diagnosed malignancy and the third most common cause of cancer-related death worldwide.[1] Although many mechanisms underlying the onset and progression of GC have been revealed over the past few years, delayed diagnosis and treatment are largely responsible for the high mortality rate among GC patients.[2] Hence, novel biomarkers are crucial to improve early diagnosis and prognosis, and to identify effective therapeutic targets.

Over the past few decades, genetics-based GC studies have mainly concentrated on the exploration of protein-coding genes, as noncoding RNAs (ncRNAs) were largely regarded as the products of transcription errors.[3] However, growing evidence has indicated that ncRNAs are involved in the regulation of cellular proliferation, invasion, migration, and apoptosis, as well as a remarkable variety of biological functions in tumorigenesis.[4,5] Many studies have demonstrated that the expression profiles of some RNAs and proteins vary during cancer onset and progression, thus these RNAs might be useful as biomarkers for the diagnosis, treatment, and prognosis of GC.[6–9] Noncoding RNAs (ncRNAs) are a class of non-protein-coding RNAs that are present in many cell types. Initially, ncRNAs were regarded as byproducts of genetic transcription. However, with the discovery of functional ncRNAs,[10] many unique functional genomic products have been identified.[11,12] In addition, ncRNAs have been reported to play crucial roles in the development of various diseases, including many cancers.[13,14]

Correspondence: Jingjing Liu
Department of Gastrointestinal Nutrition and Hernia Surgery, The Second Hospital of Jilin University, Jilin University, Changchun, Jilin 130041, People's Republic of China
Tel +86-431-81136210
Email jingjingstarone@163.com

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There are three important types of ncRNAs: microRNAs (miRNAs), composed of ≥22 nucleotides; long ncRNAs (lncRNAs), composed of >200 nucleotides;[15,16] and circRNAs, which are normally stable molecules characterized by a covalently closed loop structure of various lengths.[17] In general, the regulatory mechanisms of circRNAs involve the targeting of mRNAs by miRNAs, whereas lncRNAs and circRNAs act as endogenous competitive RNAs or sponges of miRNAs, proteins, and genes, which influence the stability of binding partners.[18] In addition, ncRNAs exert effects on various biological processes through many other mechanisms. For example, miRNAs can encode peptides, interact with non-Argonaute family proteins, activate Toll-like receptors, and upregulate protein expression.[19]

CircRNAs were first described approximately 40 years ago as unique ncRNAs with 3′ and 5′ ends that are covalently joined in a closed loop structure, leaving no free ends. The expression patterns of circRNAs have been described in many tumor types, including GC, but the characteristic loop structure was ignored because of a lack of understanding and was even regarded as a splicing error.[20] With the development of RNA sequencing and bioinformatics technologies, a variety of circRNAs have been confirmed to have various functions in human cells.[21] Many studies have reported the expression profiles of circRNAs in GC. For instance, Sui et al[22] identified 1,285 differentially expressed circRNAs in GC, including 69 that are closely associated with miRNAs, as determined by microarray chip technology. CircRNAs are constitutively expressed in various cells and plasma, are tissue- and disease-specific, and have unique exon sequences, miRNA response elements (MREs), and protein-binding elements.[23] These unique characteristics of circRNAs may have potential in the controlled regulation of cellular functions. CircRNAs play essential roles in the onset and progression of GC.[24,25] For instance, Chen et al[26] reported that circPVT1 can sponge miR-125 and consequently promote the proliferation of cancer cells; therefore, it may serve as a prognostic biomarker of GC. Many studies have provided novel information to improve our understanding of circRNAs in the pathogenesis of GC. However, current information has not yet been summarized in a review. Therefore, the aim of this article is to review the current understanding of the methods for the discovery of circRNAs and to clarify the underlying mechanisms and potential applications of circRNAs in GC.

CircRNAs in GC

CircRNAs are generally localized in the cytoplasm with lower abundances in the nucleus.[23] Through various mechanisms, circRNAs can influence gene expression and transcription in many diseases, including GC. Substantial progress has been made in the application of circRNAs, especially as diagnostic and prognostic biomarkers, as well as therapeutic targets. The general attributes of circRNAs are summarized in Table 1.

Resources for Research on Target circRNAs

The discovery of novel circRNAs associated with GC has been the focus of many studies. Second-generation sequencing and bioinformatics technologies, the most common methods used in such studies, are crucial for the screening of circRNAs, as demonstrated by the recent characterizations of circPVT1 and circRNA_100269.[26,27] Moreover, in a recent study, Josh et al[28] detected the expression response of circRNAs in >2000 cancer samples through an exome capture RNA sequencing detection method that is more effective than previous methods. The authors established the most comprehensive multi-tumor circRNA database, MiOncoCirc, which provides circRNA expression data and enables the analysis of circRNA expression in different cancers, including 17 cancer cohorts. Of note, the prostate cancer data have been extensively studied, and some circRNAs in urine have been suggested to have potential as diagnostic or prognostic biomarkers. Numerous genes that are aberrantly expressed in many cancers have been identified by referencing studies of other diseases. For example, Pan et al validated the presence of circRNA ciRS-7 in GC by referring to a previous study of the brain.[29] More recently, many databases have been created that are useful to predict the roles of various circRNAs. In fact, 15 of 47 relevant studies have reported referencing target circRNAs from databases (Table 2). The primary convenience of circRNA databases, such as CircBase and circ2Traits,[30] is that they provide circRNA expression results. However, the identification and quantification of circRNAs can be complicated in some databases, such as that developed by the University of California, Santa Cruz. In mechanistic research, databases are indispensable to the discovery of potential miRNAs and protein targets in a timely and cost-effective manner. Some researchers have also used complementary sequences, as determined with sequencing technology, to predict potential miRNAs and protein targets.

Table 1 Current Research on circRNAs Associated with Gastric Cancer

CircRNA	First Author	Tendency	Binding	Binding Proteins	Ref.
			miRNAs		
hsa_circ_002059	Peifei Li	down	–	–	[25]
circPVT1	Chen Jie	up	miR-125	–	[26]
CircRNAc100269	Zhang Yan	Down	miR-630	–	[27]
ciRS-7	Haiyan Pan	Up	miR-7	PTEN/PI3K/AKT	[29]
hsa_circ_0000745	Mei Huang	Down	–	–	[30]
Circular RNA_LARP4	Jing Zhang	Down	miR-424	LATS1	[36]
CircPSMC3	Dawei Rong	Down	miR-296-5p	PTEN	[37]
circNRIP1	Xing Zhang	Up	miR-149-5p	AKT1/mTOR	[38]
circNF1	Zhe Wang	Up	miR-16	MAP7/AKT3	[39]
circ-SFMBT2	Handong Sun	Up	miR-182-5p	CREB1	[40]
circFAT1(e2)	Jian Fang	Down	miR-548g	RUNX1/YBX1	[41]
circYAP1	Hui Liu	Down	miR-367-5p	P27	[42]
Circ-ZFR	Tonglei Liu	Down	miR-130a miR-107	PTEN/P53	[43]
circRNA_001569	Fengqian Shen	Up	miR-145	NR4A2	[44]
hsa_circ_0000993	Shanliang Zhong	Down	miR-214-5p	–	[45]
circPDSS1	Yiming Ouyang	Up	miR-186-5p	NEK2	[46]
circCOL6A3	Xiaoli Sun	Up	miR-3064-5p	COL6A3	[47]
hsa_circ_0008035	Shifang Huang	Up	miR-375	YBX1	[48]
circDLST	Jing Zhang	Up	miR-502-5p	NRAS	[49]
circ-ERBB2	Xuesong Li	Up	miR-503/miR-637	CACUL1/MMP-19	[50]
hsa_circ_0001368	Jun Li	Down	miR-6506-5p	FOXO3	[51]
circAKT3	Xiaoxu Huang	Up	miR-198	PIK3R1	[52]
circEIF4G3	Qian Wang	Up	miR-335	–	[53]
circDCAF6	Ligang Wu	Up	miR-1231/miR-1256	–	[54]
circRNA0047905	Zhiyong Lai	Up	miR-4516/miR-1227-5p	–	[55]
hsa_circ_0000096	Peifei Li	Down	–	cyclin D1/CDK6/MMP-2/MMP-9	[56]
circ-DONSON	Lixian Ding	Up		NURF/SOX4	[58]
circ-SERPINE2	Jianing Liu	Up	miR-375	YWHAZ	[59]
circOSBPL10	Sen Wang	Up	miR-136-5p	WNT2	[63]
circHIPK3	W.G Liu	Up	–	WNT1/β-catenin	[64]
circHECTD1	Juan Cai	Up	miR-1256	USP5	[65]
circPVRL3	Handong Sun	Down	–	–	[67]
CircFNDC3B	Yuling Hong	Up		E-cadherin/CD44	[68]
CircRNA_0023642	L-H Zhou	Up	–	EMT	[71]
circ-104916	Jin Li	Up	–	EMT	[72]
circNHSL1	Zhonglin Zhu	Up	miR-1306-3p	SIX1	[73]
hsa_circ_0014717	Yongfu Shao	Down	–	–	[75]
hsa_circ_0003159	Mengqian Tian	Down	–	–	[76]
circ_0066444	Dawei Rong	Up	–	–	[77]
hsa_circ_0001895	Yongfu Shao	Down	–	–	[78]
hsa_circ_0006633	Rongdan Lu	Down	–	–	[79]
hsa_circ_00001649	Wenhan Li	Down	–	–	[80]
hsa_circ_0000181	Qianfu Zhao	Down	–	–	[82]
hsa_circRNA_102958	Juan Wei	Up	–	–	[82]
hsa_circ_0074362	Yi Xie	Down	–	–	[83]
hsa_circ_0000705	Yongfu Shao	Down	–	–	[84]
hsa_circ_0001017	Tianwen Li	Down	–	–	[85]
hsa_circ_0061276	Tianwen Li	Down	–	–	[85]
hsa_circ_0000190	Chen Shijun	Down	–	–	[86]

(*Continued*)

Table 1 (Continued).

CircRNA	First Author	Tendency	Binding	Binding Proteins	Ref.
			miRNAs		
hsa_circ_0000467	Jun Lu	Up	–	–	[87]
hsa_circ_0005654	Yezhao Wang	Down	–	–	[88]
hsa_circ_0001821	Shan Kong	Down	–	–	[89]
hsa_circ_0006848	Jun Lu	Down	–	–	[90]
circ-KIAA1244	Weiwei Tang	Down	–	–	[96]
circLMTK2	Jian He	Down	–	–	[97]
circ-ARHGAP26	Wangxia Lv	Down	–	–	[98]
hsa_circ_0000520	Handong Sun	Down	–	–	[99]
hsa_circ_0047905	Zhiyong Lai	Up	–	–	[100]
hsa_circ_0138960	Zhiyong Lai	Up	–	–	[100]
hascircRNA7690-15	Zhiyong Lai	Up	–	–	[100]
cir_ITCH	Sara Ghasemi	Down	–	–	[101]
circHIPK3	Sara Ghasemi	Down	–	–	[101]

Hence, these methods are indispensable to the study of circRNAs.

The Underlying Mechanisms of circRNAs in GC

Accumulating evidence suggests that circRNAs play various functional roles in GC, although the underlying mechanisms remain unclear. Overall, the mechanisms of many direct binding targets have been identified, while many other potential mechanisms remain unknown. The targets of circRNAs include DNA, miRNAs, proteins, and ribosomes. CircRNAs can also affect GC progression by the epigenetic regulation of DNA-templated processes. Although some functional circRNAs have been implicated in the pathogenesis of GC, the underlying mechanisms remain to be explored. According to these findings, the mechanisms of circRNAs can be divided into two general groups: those with and those without known direct targets.

Direct Regulation of Specific Targets

By directly targeting miRNAs, circRNAs can influence the traits of GC, the expression profiles of protein-coding miRNAs, and the regulation of related signaling pathways (Figure 1). In fact, the direct binding of circRNAs and

Table 2 Associated circRNA Databases

Content	Data	Website	Ref.
CircRNAs chose	CircBase	(http://circbase.org/)	[25,30,37,44] [79,84,87]
	Circ2Traits	(http://gyanxetbeta.com/circdb/)	[25,30]
	MiOncoCirc	(https://nguyenjoshvo.github.io/)	[28]
	GEO database	(https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE89143)	[40,41,67,75,79]
Identification and quantification of circRNAs	UCSC genome database	(http://genome.ucsc.edu/)	[26]
MiRNA traget	TargetScan	(http://www.targetscan.org)	[27,41,87]
	circinteractome database	(https://circinteractome.nia.nih.gov/)	[37,40,67]
	StarBase v2.0	(http://starbase.sysu.edu.cn)	[27,87]
	TCGA sequencing database	(http://xena.ucsc.edu/getting-started/)	[36]
Protein target	TCGA sequencing database	(http://xena.ucsc.edu/getting-started/)	[36]
	miRanda database	(http://mirdb.org/)	[37,40]
	MiOncoCirc	(https://nguyenjoshvo.github.io/)	[28]

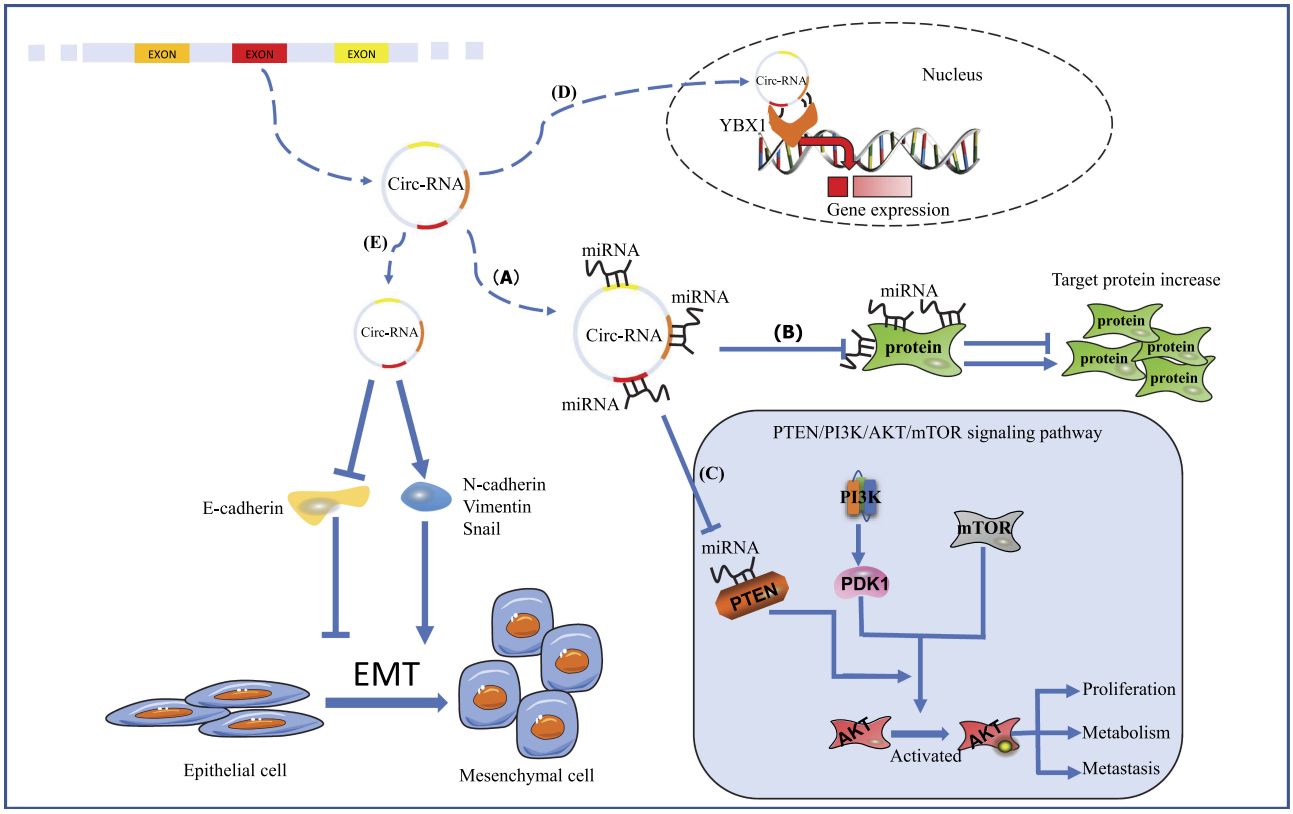

Figure 1 The diverse regulatory mechanisms of circRNAs in GC. (**A**) CircRNAs act as sponges of miRNAs and subsequently exert functions. (**B**) CircRNAs regulate the expression of proteins through miRNAs. (**C**) CircRNAs affect the PTEN/PI3K/AKT/mTOR signaling pathway indirectly. (**D**) CircFAT1 directly binds YBX1 and influences gene expression. (**E**) By regulating the EMT process, circRNAs affect invasion and metastasis in GC.**Abbreviations:** Akt, protein kinase B; EMT, epithelial-mesenchymal transition; GC, gastric cancer; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homolog; YBX-1, Y-box binding protein-1.

proteins is known to affect the expression of target genes. Moreover, a recent report demonstrated that circRNAs can encode proteins by binding to the ribosome.

Modulation of miRNAs

Increasing evidence suggests that the most common mechanism of circRNAs in GC involves miRNA sponges. The sequences of circRNAs contain MREs that facilitate binding to miRNAs. Normally, the number of MREs, which are thought to be located within exon sequences, is closely related to circRNA length.[31] Many studies have demonstrated that miRNAs can negatively regulate gene expression at the post-transcriptional level, mainly through mRNAs.[32,33] For example, CircRNA_100269 inhibits the proliferation of GC cells by sponging miR-630.[27] To our knowledge, an antisense sequence to the cerebellar degeneration-related protein 1 transcript (CDR1as) was the first circRNA reported to act as a miRNA sponge. CDR1as/ciRS-7 is the genome antisense strand to the human CDR1 locus (hence the name CDR1as), which targets miR-7 (hence the name ciRS-7–circular RNA sponge for miR-7). MiR-7 is a well-known tumor suppressor with 63 binding sites.[21,34,35] Recently, ciRS-7 was reported to promote the development of GC by inhibiting miR-7-related functions.[29] In addition, circPVT1,[26] circular RNA_LARP4,[36] circPSMC3,[37] circNRIP1,[38] circNF1,[39] circ-SFMBT2,[40] circFAT1(e2),[41] circYAP1,[42] circ-ZFR,[43] circRNA_001569,[44] hsa_circ_0000993,[45] circPDSS1,[46] circCOL6A3,[47] hsa_circ_0008035,[48] circDLST,[49] circ-ERBB2,[50] hsa_circ_0001368,[51] circAKT3,[52] circEIF4G3,[53] circ-DCAF6[54] and circRNA0047905[55] also exert effects in GC by binding to miRNAs (Table 1). In general, upregulation of circRNAs in GC tissues exerts cancer-promoting effects, whereas downregulation inhibits the onset and development of GC. Notably, downregulated expression of hsa_circ_0000096 promotes tumorigenesis in GC.[56] Although the underlying cause remains unclear, this anomalous finding indicates that other mechanisms are activated along with the sponge-like activities of miRNAs.

By regulating corresponding miRNAs, circRNAs can regulate the expression levels of downstream proteins. For example, Liu et al reported that circYAP1

upregulates p27 by sponging miR-367-5p.[42] P27, also named KIP1, inhibits cyclin-dependent kinase (CDK), which influences cellular proliferation and apoptosis.[57] The binding of miR-367-5p and p27 contributes to the inactivation of p27. When miR-367-5p is sponged by circYAP1, p27 is activated and subsequently promotes tumorigenesis in GC. In this case, circYAP1 acts as an endogenous competitive RNA that regulates the activation of p27. Huang et al found that circAKT3 inhibits the apoptosis of GC cells and promotes DNA damage repair in vivo and in vitro.[52] CircAKT3 exerts its function by sponging miR-198 and upregulating its targeting PIK3R1 gene.[52] ciRS-7,[29] circPSMC3,[37] circNRIP1,[38] circNF1,[39] circ-SFMBT2,[40] circFAT1 (e2),[41] circ-ZFR,[43] circRNA_001569,[44] circPDSS1,[46] circCOL6A3,[47] hsa_circ_0008035,[48] circDLST,[49] circ-ERBB2,[50] hsa_circ_0001368,[51] circAKT3,[52] circ-DONSON,[58] and circ-SERPINE2[59] are also known to regulate the effects of various proteins after sponging corresponding miRNAs.

In addition, circRNAs can also influence the expression of proteins at the pre-transcriptional level. For example, circular RNA_LARP4 binds to miR-424, and the LATS1 gene is the target of miR-424, a miRNA that decreases the expression of LATS1 at the protein level. Regardless of the mechanism, circRNAs have important roles in the regulation of the expression profiles and activities of proteins.

Another important mechanism of circRNAs in cancer-related signaling occurs via the circRNA-miRNA-protein pathway. Researchers have identified many miRNA targets of known signaling pathways that are associated with circRNAs in GC. Proteins are key molecules for the regulation of various signaling pathways involved in the onset and progression of cancer, including GC,[60,61] such as the phosphatase and tensin homolog (PTEN)/phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) signaling pathway. After stimulation, PI3K activates Akt, which in turn is translocated to the nucleus, where it induces proliferation, metastasis, and metabolism in GC. mTOR complex 2 signaling activates other sites of Akt. PTEN negatively regulates the activation and recruitment of activated Akt.[62] PTEN/PI3K/Akt/mTOR signaling is the most commonly studied pathway between circRNAs and GC. CircPSMC3 and circ-ZFR indirectly upregulate PTEN by sponging miRNAs.[37,43] In the same way, circNRIP1 can increase the expression of Akt. However, miR-7, the target miRNA of ciRS-7, increases the expression of PTEN, while decreasing that of Akt and mTOR. CiRS-7 downregulates PTEN expression and upregulates that of Akt and mTOR.[29] Liu et al reported that circ-ZFR inhibits tumor growth in GC via the p53 cascade, and p53 is a well-known tumor suppressor.[43] CircOSBPL10 plays an oncogenic role in GC by activating Wnt/β-catenin signaling pathway.[63] Given that the binding sites between miR-136-5p and WNT2, the expression level of WNT2 is upregulated because of overexpressed circOSBPL10, the molecular sponge of miR-136-5p. Thereby, WNT2 activates Wnt/β-catenin signaling pathway and promotes GC development.[63] Besides that, circHIPK3 and circHECTD1 also promote GC development through upregulating Wnt/β-catenin pathway.[64,65] Although associations among various signaling pathways and GC have been demonstrated, the involvement of other signaling cascades, such as the Notch signaling pathway, remains unclear.

Targeting Proteins

Regardless of the physiological or pathological conditions, proteins play unique roles in cells and organs. CircRNAs directly bind proteins and exert effects. For example, Y-box binding protein-1 (YBX1) can bind both DNA and RNA and consequently influence gene expression. In fact, studies have reported that YBX1 exerts an oncogenic function in GC. In the nucleus, circFAT1(e2) inhibits cell proliferation in GC by directly binding to YBX1.[41] SOX4, a member of the SOX family, normally regulates cell biological processes through the high-mobility group domain, thereby mediating DNA binding. The deregulation of SOX expression plays an essential role in the onset and progression of cancer, and SOX4 usually exerts a carcinogenic effect.[66] Circ-DONSON promotes the expression of SOX4 by recruiting the NURF complex to the promoter region of the SOX4 gene in the nucleus. The upregulated SOX4 then contributes to GC progression.[58] Moreover, a database search revealed that EIF4A3 has potential binding sites for differentially expressed circRNAs in GC.

The Protein-Coding Ability of circRNAs Through Direct Binding to the Ribosome

CircPVRL3 has been reported to possess protein-coding abilities via protein-coding structures, open reading frames, internal ribosome entry sites, and m6A modification.[67] CircPVRL3 is thought to directly bind the ribosome via internal ribosome entry sites and to subsequently inhibit translation. In addition, other mechanisms may exist that

open the loop structure, thereby facilitating the conversion of circRNAs back to pre-mRNAs.[23] Therefore, circRNAs appear to encode proteins after conversion to mRNAs. However, no study has reported an association between mRNAs and circRNAs. Because of the limited research results, further studies are needed to investigate such mechanisms, given that relationships are anticipated.

Indirect Regulation Without Accurate Targets

CircRNAs have also been reported to influence the expression of genes involved in epithelial-mesenchymal transition (EMT), although no direct binding target has been identified to date, as discussed in the following two sections.

Regulating Gene Transcription

Some studies have found that circRNAs regulate gene expression, but without known targets. For example, cyclin D1 and CDK6 are cycle-related proteins, and matrix metalloproteinase (MMP)-2 and MMP-9 are associated with migration. Hsa_circ_0000096 has been reported to positively regulate the protein levels of cyclin D1, CDK6, MMP-2, and MMP-9 in a dose-dependent manner.[56] Overexpressed circFNDC3B decreases the expression of E-cadherin and increases CD44 expression, thus regulating the migration and invasion of GC cells.[68] However, there is a lack of accurate information regarding the targets of many miRNAs and protein-coding genes.

EMT Related Mechanisms

The EMT process has increasingly been shown to have essential roles in various physiological and pathological processes in cancer.[69] After adopting the traits of mesenchymal cells, epithelial cells become more flexible to migration and proliferation. The key proteins involved in the EMT process include E-cadherin, N-cadherin, vimentin, and snail. Of these, E-cadherin is a key molecule that ensures cell-cell contact, and decreased expression of E-cadherin is thought to be a key event in EMT.[70] In GC, EMT is closely associated with invasion and metastasis. CircRNAs regulate the expression of these key proteins, thereby influencing the EMT process in GC (Figure 1). Through the upregulation of N-cadherin, vimentin, and snail, and the downregulation of E-cadherin, the circRNAs circFNDC3B, circRNA_0023642 and circ-104916 induce EMT and consequently promote invasion and metastasis in GC.[68,71,72] Because no exact targets in the regulation of EMT have been identified, further studies are needed to clarify the underlying mechanisms. Besides that, circNHSL1 upregulates SIX1 expression level by targeting miR-1306-3p, and then SIX1 can increase Vimentin expression by binding to its promoter, thereby promote EMT process in GC cells.[73]

The Applications of circRNAs in GC

Because many circRNAs have crucial roles in GC, the exploitation of these molecules is promising in three main applications: diagnostic biomarkers, prognostic biomarkers, and therapeutic targets.

Promising Biomarkers for the Diagnosis of GC

According to cancer statistics, GC is fifth among cancers regarding incidence but third regarding mortality.[1] Although substantial progress has been made in therapeutic strategies, the early stage diagnosis rate is too low to achieve timely treatment for some patients with advanced GC, thus resulting in the relatively low survival rate. Hence, the identification of promising biomarkers for early-stage diagnosis is a necessary strategy to improve survival of GC patients. Over the past few years, circRNAs have received extensive attention. The closed loop structure stabilizes circRNAs in tissues and plasma because of resistance to the enzymatic activities of exonucleases.[74] Moreover, Shao et al have found that circRNAs exist in gastric juice.[75] In addition, some circRNAs have been found to have better diagnostic power than carcinoembryonic antigen and carbohydrate antigen 19–9, which are currently used for the diagnosis of GC.[30,75] As shown in Table 3, many circRNAs may be suitable as diagnostic biomarkers in GC.[25,30,36,37,56,67,75–90] Among these circRNAs, hsa_circ_0001017 in the plasma and circPSMC3 in tissues have relatively better diagnostic values, with areas under the receiver operating characteristic curves of > 0.90. Combining two or more circRNAs may be a good method to improve diagnostic power. For instance, combining hsa_circ_0001017 and hsa_circ_0061276 in both plasma and tissues has resulted in a diagnostic power as high as an AUC of 0.966, a sensitivity of 0.955 and a specificity of 0.957.[85] Related meta-analyses have indicated that circRNAs might be a good choice as a diagnostic biomarker for tumors, including GC.[91,92] Although much progress has been made, further studies are needed, as current data are limited to tissues, even though collecting plasma samples for the diagnosis of early-stage GC would be easier.

Biomarkers for Prognosis

The incidence of GC has been consistent over the past several years, but the overall prognosis is poorer and

Table 3 CircRNAs Associated with GC Diagnosis

CircRNA	Expression	Sample Size		Diagnostic Power				Ref
		Tumor	Normal	Sensitivity	Specificity	AUC	Cut off	
tissue								
hsa_circ_002059	Down	101	101	0.81	0.62	0.73	12.9	[25]
hsa_circ_0000745	Down	20	20	0.86	0.45	0.68	–	[30]
circLARP4	Down	387	41	0.67	0.68	0.64	20.8	[36]
hsa_circ_0000096	Down	96	96	0.88	0.56	0.82	12.9	[56]
hsa_circ_0000096 &hsa_circ_002059	Down	96	96	0.90	0.81	0.91	–	[56]
circPVRL3	Down	62	62	0.90	0.56	0.76	–	[67]
hsa_circ_0014717	Down	96	96	0.59	0.81	0.69	12.14	[75]
hsa_circ_0003159	Down	108	108	0.85	0.57	0.75	12.31	[76]
circ_0066444	Up	106	106	0.71	0.69	0.73	–	[77]
hsa_circ_0001895	Down	65	96	0.68	0.86	0.79	9.53	[78]
hsa_circ_0006633	Down	96	96	0.60	0.81	0.74	8.17	[79]
Hsa_circ_00001649	Down	76	76	0.71	0.82	0.83	0.23	[80]
hsa_circ_0000181	Down	115	115	0.54	0.85	0.76	9.40.	[82]
hsa_circRNA_102958	Up	30	30	0.61	0.86	0.74	–	[82]
hsa circ 0074362	Down	127	127	0.36	0.84	0.63	12.17	[83]
hsa_circ_0000705	Down	96	96	0.65	0.70	0.71	9.13	[84]
hsa_circ_0000190	Down	104	104	0.72	0.68	0.75	6.83	[86]
plasmas								
circPSMC3	Down	106	106	0.86	0.95	0.93	−9.97	[37]
hsa_circ_0000181	Down	105	102	0.99	0.20	0.58	7.27	[82]
hsa_circ_0001017	Down	121	121	0.76	0.96	0.85	–	[85]
hsa_circ_0061276	Down	121	121	0.67	0.90	0.85	–	[85]
hsa_circ_0000190	Down	104	104	0.41	0.88	0.60	3.07	[86]
hsa_circ_0000467	Up	20	20	0.71	0.65	0.79	–	[87]
circ-KIAA1244	Down	28	25	0.77	0.68	0.75	1.43	[96]
Tissues&plasmas								
hsa_circ_0001017 &hsa_circ_0061276	Down	112	112	0.97	0.96	0.97	-	[85]

survival times are shorter than those for other cancers.[1] Surgical resection is the most effective treatment for GC, but relapse and metastasis severely affect postoperative prognosis. Recent studies have reported that circRNAs are closely associated with the clinicopathological features of GC and can serve as prognostic biomarkers. As shown in Table 4, many clinicopathological factors are related to circRNAs, especially the tumor-node-metastasis stage, which normally dominates the prognosis of GC patients. CircRNA_100269[27] is associated with early relapse, whereas circPVT1,[26] circLARP4,[36] and circYAP1[42] have been recommended as prognostic biomarkers of survival in GC. Moreover, hsa_circ_0001895, hsa_circ_0000467, circNRIP1, circFAT1(e2), hsa_circ_0000993, circPDSS1, and ciRS-7 are associated with the prognosis of GC. Nonetheless, further information is needed to determine the prognostic usefulness of circRNAs for the treatment of GC.

Therapeutic Targets

Many patients with advanced and unresectable GC receive chemotherapy. Targeted therapy is an important treatment option for chemotherapy-resistant GC. In recent years, given the improved understanding of the pathogenesis of GC, many molecules and signaling pathways may be suitable for targeted therapies. Trastuzumab, which inhibits the activation of human epidermal growth factor receptor 2, was the first targeted therapy for GC shown to improve survival.[93] In contrast, several other targeted therapies for GC have shown little benefit. At present,

Table 4 Altered Expression of circRNAs Associated with the Clinicopathological Features of GC Patients

Clinicopathological Factors	Altered Expression of circRNAs		P value		Ref
	Up	Down	Up	Down	
Age		hsa_circ_002059		0.022	[25]
Gender		hsa_circ_002059		0.002	[25]
		circ-104916		0.045	[72]
		hsa_circ_0003159		0.003	[76]
Diameter	circNRIP1	hsa_circ_0000190	0.043	0.034	[38,86]
		hsa_circ_0000181		0.027	[82]
Borrmann type		hsa_circ_0001895		0.047	[78]
		Hsa_circ_0000705		0.005	[84]
Differentiation		hsa_circ_0000745		0.012	[30]
		hsa_circ_0001895		0.042	[78]
		csa_circ_00001649		0.039	[80]
Lymphatic metastasis		circPSMC3 (plasmas)		0.021	[37]
		circFAT1 (e2)		0.046	[41]
		circ-104916		0.019	[72]
		hsa_circ_0000181		0.044	[82]
		circ-KIAA1244		0.049	[96]
		circLMTK2		0.01	[97]
	circNRIP1	circRNA_100269	0.018	0.03	[27,38]
	circ_0066444	hsa_circ_0074362	0.023	0.039	[77,83]
	hsa_circ_0000467	hsa_circ_0000190	0.001	0.026	[86,87]
Distal metastasis		hsa_circ_002059		0.036	[25]
		circFAT1 (e2)		0.034	[41]
		Hsa_circ_0014717		0.048	[75]
		hsa_circ_0003159		0.02	[76]
		hsa_circ_0006633		0.037	[79]
		hsa_circ_0000181		0.023	[82]
		hsa_circ_0000190		0.001	[86]
Invasion	circPVT1	circ-104916	0.02	0.001	[26,72]
	hsa_circ_0000467		0.001		[87]
TNM stage		circPSMC3 (plasmas)		0.001	[37]
		circFAT1 (e2)		0.042	[41]
		circ-104916		0.015	[72]
		hsa_circ_0014717		0.037	[75]
		circ-KIAA1244		0.011	[96]
	circ-SFMBT2	hsa_circ_002059	0.002	0.042	[25,40]
	hsa_circ_0000467	hsa_circ_0003159	0.001	0.018	[76,87]
	hsa_circRNA_102958	circPVRL3	0.032	0.012	[67,82]
CEA		hsa_circ_0001895		0.001	[78]
		hsa_circ_0006633		0.041	[79]
		hsa_circ_0000190 (plasmas)		0.001	[86]
CA19-9		hsa_circ_0014717		0.021	[75]
		hsa_circ_0000181		0.031	[82]
		hsa circ 0074362		0.027	[83]
		hsa_circ_0000705		0.01	[84]
		hsa_circ_0000190		0.019	[86]
Nervous invasion	circPVT1	circ-104916	0.03	0.019	[26,72]
		circLMTK2		0.071	[97]

exploring the applications and indications of novel molecules is crucial for the continued development of targeted therapies for GC.[94] Some circRNAs target important GC-related molecules and signaling pathways, and consequently regulate the expression patterns of corresponding genes. In addition, circRNAs also influence some important clinicopathological features and are closely associated with prognosis. The overexpression or knockdown of circRNAs not only allows for better understanding of the mechanisms underlying the onset and progression of GC, but also provides useful information for the design of targeted therapies to regulate important GC-related molecules, signaling pathways, and genes. For example, circPSMC3 inhibits the growth of GC cells in vivo, whereas circNRIP1 has the opposite effect. Overexpression of circPSMC3 or knockdown of circNRIP1 has been predicted to inhibit the progression of GC.[37,38] Cisplatin-resistant GC tissues show elevated expression of circAKT3, and the level of circAKT3 is negatively associated with disease-free survival. The role of circAKT3 in cisplatin resistance of GC also emphasizes its potential as a therapeutic target to reverse drug resistance.[52] Overexpression results in translocation of circFAT1(e2) to the nucleus, where it binds YBX1, a tumor promoter. In addition, circSFMBT2,[40] circRNA_001569,[44] circ-ZFR,[43] circPDSS1,[46] and ciRS-7[29] have been investigated for use in targeted therapies, thus indicating promising clinical applications for circRNAs in the treatment of GC. In addition, the expression of PVT1 RNA is positively associated with regulation of *c-myc*, a key oncogene.[95] CircPVT1 is encoded by exon 3 of the *PVT1* gene, and overexpression of circPVT1 upregulates the level of *c-myc*.[26] However, some circRNAs respond to the level of the therapeutic target and thereby may potentially serve as prognostic indicators of targeted therapy.

In addition, some circRNAs, such as circ-KIAA1244,[96] circLMTK2,[97] circ-ARHGAP26,[98] hsa_circ_0000520,[99] hsa_circ_0047905,[100] hsa_circ_0138960,[100] hascircRNA 7690-15,[100] cir_ITCH,[101] and circHIPK3[101] are differentially expressed in GC, although little is known about the underlying mechanisms and potential applications.

Conclusion

The onset and progression of GC involves many steps and factors, but the mechanisms underlying the etiopathogenesis must be further explored. Databases have played essential roles in bioinformatics research on circRNAs and have resulted in substantial progress in the field. CircRNAs have been found to act as miRNA sponges regulating the expression of proteins that directly affect signaling pathways and induce the EMT process, thereby influencing proliferation, invasion, and metastasis in GC. Various corresponding applications are also emerging, such as diagnostic biomarkers, prognostic biomarkers, and therapeutic targets. Although circRNA research is still in its infancy, circRNAs offer promising applications in the diagnosis, treatment, and prognosis of cancers, including GC.

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Disclosure

The authors report no conflicts of interest in this work.

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