Current Understanding of Circular RNAs in Gastric Cancer

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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 Non-coding 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
There are three important types of ncRNAs: microRNAs (miRNAs), composed of ≥22 nucleotides; long ncRNAs (lncRNAs), composed of >200 nucleotides,\textsuperscript{15,16} and circRNAs, which are normally stable molecules characterized by a covalently closed loop structure of various lengths.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{20} With the development of RNA sequencing and bioinformatics technologies, a variety of circRNAs have been confirmed to have various functions in human cells.\textsuperscript{21} Many studies have reported the expression profiles of circRNAs in GC. For instance, Sui et al\textsuperscript{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.\textsuperscript{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.\textsuperscript{24,25} For instance, Chen et al\textsuperscript{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.\textsuperscript{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.\textsuperscript{26,27} Moreover, in a recent study, Josh et al\textsuperscript{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.\textsuperscript{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,\textsuperscript{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.
| CircRNA          | First Author      | Tendency | Binding miRNAs | Binding Proteins                  | Ref.   |
|------------------|-------------------|----------|---------------|-----------------------------------|--------|
| hsa_circ_002059  | Peifei Li         | down     | –             | –                                 | [25]   |
| circPVT1         | Chen Jie          | up       | miR-125       | –                                 | [26]   |
| CircRNA_c100269  | Zhang Yan         | Down     | miR-630       | –                                 | [27]   |
| cirs-7           | Haiyan Pan        | up       | miR-7         | PTEN/P3K/akt                       | [29]   |
| hsa_circ_000745  | Mei Huang          | Down     | –             | –                                 | [30]   |
| Circular RNA_LARP4| Jing Zhang        | Down     | miR-424       | –                                 | [31]   |
| CircPSMC3        | Dawei Rong        | Down     | miR-296-5p    | –                                 | [32]   |
| circNRIP1        | Xing Zhang        | Up       | miR-149-5p    | AKT1/mTOR                         | [33]   |
| circSFMT2        | Handong Sun       | Up       | miR-182-5p    | MAP7/akt                          | [34]   |
| circFATTI(e2)    | Jian Fang         | Down     | miR-548g      | RUNX1/YBX1                        | [35]   |
| circYAP1         | Hui Liu           | Down     | miR-367-5p    | P27                               | [36]   |
| Circ-ZFR         | Tonglei Liu       | Down     | miR-130a      | PTEN/PS3                          | [37]   |
| circRNA_001569   | Fengqian Shen     | Up       | miR-145       | NR4A2                             | [38]   |
| hsa_circ_000993  | Shanzhang Zhong   | Down     | miR-214-5p    | –                                 | [39]   |
| circPDS1         | Yiming Ouyang     | Up       | miR-186-5p    | NEK2                              | [40]   |
| circCOL6a3       | Xiaoli Sun        | Up       | miR-3064-5p   | COL6A3                            | [41]   |
| hsa_circ_008035  | Shifang Huang     | Up       | miR-375       | YBX1                              | [42]   |
| circDLST         | Jing Zhang        | Down     | miR-502-5p    | NRAS                              | [43]   |
| circ-ERBB2       | Xuesong Li        | Up       | miR-503/miR-637| CACUL1/MMP-19                    | [44]   |
| hsa_circ_001368  | Jun Li            | Down     | miR-6506-5p   | FOXO3                             | [45]   |
| circAKT3         | Xiaoxu Huang      | Up       | miR-198       | PIK3R1                            | [46]   |
| circEIF4G3       | Qian Wang         | Up       | miR-335       | –                                 | [47]   |
| circDCAF6        | Ligang Wu         | Up       | miR-1231/miR-1256| –                             | [48]   |
| circRNA0047905   | Zhiyong Lai       | Up       | miR-4516/miR-1227-5p| –                          | [49]   |
| hsa_circ_000096  | Peifei Li         | Down     | –             | cyclin D1/CDK6/MMP-2/MMP-9       | [50]   |
| circDONSON       | Lixian Ding       | Up       | miR-375       | NURF/SOX4                         | [51]   |
| circSERPINE2     | Jianing Liu       | Up       | miR-136-5p    | YWHAZ                             | [52]   |
| circOSBPL10      | Sen Wang          | Up       | miR-125       | WNT2                              | [53]   |
| circHIPK3        | WG Liu            | Up       | –             | WNT11/β-catenin                   | [54]   |
| circHECTD1       | Juan Cai          | Up       | –             | USP5                              | [55]   |
| circPVRL3        | Handong Sun       | Down     | –             | –                                 | [56]   |
| CircFND3B        | Yuling Hong       | Up       | –             | E-cadherin/CD44                   | [57]   |
| CircRNA_0023642  | L-H Zhou          | Up       | –             | EMT                               | [58]   |
| circ-104916      | Jin Li            | Up       | –             | –                                 | [59]   |
| circNHSL1        | Zhonglin Zhu      | Up       | miR-1306-3p   | SIX1                              | [60]   |
| hsa_circ_0014717 | Yongfu Shao       | Down     | –             | –                                 | [61]   |
| hsa_circ_0003159 | Mengqian Tian     | Down     | –             | –                                 | [62]   |
| circ_0066444     | Dawei Rong        | Up       | –             | –                                 | [63]   |
| hsa_circ_001895  | Yongfu Shao       | Down     | –             | –                                 | [64]   |
| hsa_circ_0006633 | Rongdan Lu        | Down     | –             | –                                 | [65]   |
| hsa_circ_0001649 | Wenhan Li         | Down     | –             | –                                 | [66]   |
| hsa_circ_000181  | Qianfu Zhao       | Down     | –             | –                                 | [67]   |
| hsa_circRNA_102958| Juan Wei          | Up       | –             | –                                 | [68]   |
| hsa_circ_0074362 | Yi Xie            | Down     | –             | –                                 | [69]   |
| hsa_circ_0000705 | Yongfu Shao       | Down     | –             | –                                 | [70]   |
| hsa_circ_0001017 | Tianwen Li        | Down     | –             | –                                 | [71]   |
| hsa_circ_0061276 | Tianwen Li        | Down     | –             | –                                 | [72]   |
| hsa_circ_0000190 | Chen Shijun       | Down     | –             | –                                 | [73]   |

(Continued)
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 miRNAs can be crucial in understanding the complex regulatory networks involved in GC progression.

Table 1 (Continued).

| CircRNA          | First Author | Tendency | Binding miRNAs | Binding Proteins | Ref.   |
|------------------|--------------|----------|----------------|------------------|--------|
| 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    | Weimei Tang  | Down     | –              | –                | [96]   |
| circLMTK2        | Jian He      | Down     | –              | –                | [97]   |
| circ-ARHGAP26    | Wangxia Lv   | Down     | –              | –                | [98]   |
| hsa_circ_0000920 | Handong Sun  | Down     | –              | –                | [99]   |
| hsa_circ_0047905 | Zhiyong Lai  | Up       | –              | –                | [100]  |
| hsa_circ_0138960 | Zhiyong Lai  | Up       | –              | –                | [100]  |
| hascircRNA7690-15| Zhiyong Lai  | Up       | –              | –                | [100]  |
| cirITCH          | Sara Ghasemi | Down     | –              | –                | [101]  |
| circHIPK3        | Sara Ghasemi | Down     | –              | –                | [101]  |

Table 2 Associated circRNA Databases

| Content                        | Data                                | Website                                                                 | Ref.       |
|--------------------------------|-------------------------------------|------------------------------------------------------------------------|------------|
| CircRNAs chose                 | CircBase                            | (http://circbase.org/)                                                 | [25,30,37,44]|  
|                                | Circ2Traits                         | (http://gyanxetbeta.com/circdb/)                                     | [79,84,87] |
|                                | 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 target                   | 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]       |
proteins is known to affect the expression of target genes. Moreover, a recent report demonstrated that circRNA 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. Many studies have demonstrated that miRNAs can negatively regulate gene expression at the post-transcriptional level, mainly through miRNAs. For example, CircRNA_100269 inhibits the proliferation of GC cells by sponging miR-630. 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. Recently, ciRS-7 was reported to promote the development of GC by inhibiting miR-7-related functions. In addition, circPVT1, circular RNA_LARP4, circPSMC3, circNRP1, circNFR1, circ-SFMBT2, circFAT1(e2), circYAP1, circZFR, circRNA_001569, hsa_circ_0000993, hsa_circ_0000996, circPDSS1, circCOL6A3, hsa_circ_0008035, circDLST, circERBB2, hsa_circ_0001368, circAKT3, circEIF4G3, circDCAF6, and circRNA0047905 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_000096 promotes tumorigenesis in GC. 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 circERBB2,50 hsa_circ_0001368,51 circAKT3,52 circDONSON,58 and circ-SERPINE259 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 circZFR 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. 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. Overexpressed circFND3C3B decreases the expression of E-cadherin and increases CD44 expression, thus regulating the migration and invasion of GC cells. 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. 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. 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 circFND3C3B, circRNA_0023642 and circ-104916 induce EMT and consequently promote invasion and metastasis in GC. 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.

**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. 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. Moreover, Shao et al. have found that circRNAs exist in gastric juice. 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.

As shown in Table 3, many circRNAs may be suitable as diagnostic biomarkers in GC, 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. Related meta-analyses have indicated that circRNAs might be a good choice as a diagnostic biomarker for tumors, including GC. 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
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\(\text{e}(2)\), hsa_circ_0000993, circPDS51, 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,
| Clinicopathological Factors | Altered Expression of circRNAs | P value | Ref |
|-----------------------------|--------------------------------|---------|-----|
| Age                         |                                | Up      | Down |
|                             | hasa_circ_002059               | 0.022   | [25]|
| Gender                      |                                | Up      | Down |
|                             | hasa_circ_002059               | 0.002   | [25]|
|                             | circ-104916                    | 0.045   | [72]|
|                             | hasa_circ_0003159              | 0.003   | [76]|
| Diameter                    |                                | Up      | Down |
|                             | circNRIP1                      | 0.043   | 0.034 | [38,86]|
|                             | hasa_circ_0000190              |         | 0.027 | [82]|
|                             |                                |         |       | |
| Borrmann type               |                                | Up      | Down |
|                             | hasa_circ_0001895              | 0.047   | [78]|
|                             | Hsa_circ_0000705               | 0.005   | [84]|
| Differentiation             |                                | Up      | Down |
|                             | hasa_circ_0000745              | 0.012   | [30]|
|                             | hasa_circ_0001895              | 0.042   | [78]|
|                             | csa_circ_00001649              | 0.039   | [80]|
| Lymphatic metastasis        |                                | Up      | Down |
|                             | circPSMC3 (plasmas)            | 0.021   | [37]|
|                             | circFAT1 (e2)                  | 0.046   | [41]|
|                             | circ-104916                    | 0.019   | [72]|
|                             | hasa_circ_0000181              | 0.044   | [82]|
|                             | circ-KIAA1244                  | 0.049   | [96]|
|                             | circLMTK2                      | 0.01    | [97]|
|                             | circRNA_100269                 | 0.018   | 0.03  | [27,38]|
|                             |                                |         |       | |
|                             |                                | 0.023   | 0.039 | [77,83]|
|                             |                                |         |       | |
|                             |                                | 0.001   | 0.026 | [86,87]|
| Distal metastasis           |                                | Up      | Down |
|                             | hasa_circ_002059               | 0.036   | [35]|
|                             | circFAT1 (e2)                  | 0.034   | [41]|
|                             | Hsa_circ_0014717               | 0.048   | [75]|
|                             | hasa_circ_0003159              | 0.02    | [76]|
|                             | hasa_circ_0006633              | 0.037   | [79]|
|                             | hasa_circ_0000181              | 0.023   | [82]|
|                             | hasa_circ_0000190              | 0.001   | [86]|
| Invasion                    |                                | Up      | Down |
|                             | circPVT1                       | 0.02    | 0.001 | [26,72]|
|                             | hasa_circ_0000467              | 0.001   | [87]|
| TNM stage                   |                                | Up      | Down |
|                             | circPSMC3 (plasmas)            | 0.001   | [17]|
|                             | circFAT1 (e2)                  | 0.042   | [41]|
|                             | circ-104916                    | 0.015   | [72]|
|                             | hasa_circ_0014717              | 0.037   | [75]|
|                             | circ-KIAA1244                  | 0.011   | [96]|
|                             | hasa_circ_002059               | 0.002   | 0.042 | [25,40]|
|                             | hasa_circ_0003159              | 0.001   | 0.018 | [76,87]|
|                             | circPVR3L3                     | 0.032   | 0.012 | [67,82]|
| CEA                         |                                | Up      | Down |
|                             | hasa_circ_0001895              | 0.001   | [78]|
|                             | hasa_circ_0006633              | 0.041   | [79]|
|                             | hasa_circ_0000190 (plasmas)    | 0.001   | [86]|
| CA19-9                      |                                | Up      | Down |
|                             | hasa_circ_0014717              | 0.021   | [75]|
|                             | hasa_circ_0000181              | 0.031   | [82]|
|                             | hasa_circ_0074362              | 0.027   | [83]|
|                             | hasa_circ_0000705              | 0.01    | [84]|
|                             | hasa_circ_0000190              | 0.019   | [86]|
| Nervous invasion            |                                | Up      | Down |
|                             | circPVT1                       | 0.03    | 0.019 | [26,72]|
|                             | circLMTK2                      | 0.071   | [97]|

Table 4: Altered Expression of circRNAs Associated with the Clinicopathological Features of GC Patients
exploring the applications and indications of novel molecules is crucial for the continued development of targeted therapies for GC. 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. 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. Overexpression results in translocation of circFAT1(e2) to the nucleus, where it binds YBX1, a tumor promoter. In addition, circSFMBT2, circRNA_001569, circ-ZFR, circPDSS1, and ciRS-7 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. CircPVT1 is encoded by exon 3 of the PVT1 gene, and overexpression of circPVT1 upregulates the level of c-myc. 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, circLMTK2, circ-ARHGAP26, hsa_circ_000520, hsa_circ_0047905, hsa_circ_0138960, hascircRNA 7690-15, cirITCH, and circHIPK3 are differentially expressed in GC, although little is known about the underlying mechanisms and potential applications.

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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