

Role of circular RNAs and long non-coding RNAs in the clinical translation of gastric cancer (Review)

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Abstract. Gastric cancer (GC) is a malignancy with high incidence and mortality rates worldwide. It has a severe impact on patients diagnosed and on society. With the rapid development of bioinformatics and detection technologies, non-coding RNAs have been demonstrated to play important roles in gastric carcinogenesis, including circular RNAs (circRNAs) and long non-coding RNAs (lncRNAs). Previous studies have indicated that these two types of RNAs with notable characteristics can serve as promising biomarkers for clinical diagnosis and prognosis. The identification of relevant mechanisms has revealed the immense potential of circRNAs and lncRNAs in the treatment of GC. However, there are still numerous issues that need to be resolved. The present review focuses on the clinical translation of circRNAs and lncRNAs into GC. Important achievements and currently existing limitations in this field of research are summarized from recent studies. The present review also proposes serviceable suggestions for further development.

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1. Introduction

Gastric cancer (GC) is one of the most common malignancies worldwide, and is ranked as the fourth most common type of cancer and the third highest cause of cancer-related mortality. Despite a slight decline in incidence, ~1,000,000 individuals are diagnosed with GC and >700,000 patients succumb to the disease each year (1). Surgery remains the main treatment strategy for GC. In recent years, the wide application of neoadjuvant chemoradiotherapy has improved the survival rates and quality of life of patients, and has reduced the chances of a necessary gastrectomy (2,3). If patients are diagnosed with GC at early stages and receive treatment promptly, then their chances of recovery are optimal. However, the majority of patients are initially diagnosed with GC at an advanced stage due to atypical symptoms and the lack of sensitive examinations (4). Poor prognosis calls for more effective diagnostic methods with improved sensitivity and specificity. There is also a need for developing novel target medicine to enhance the efficacy of cancer treatment and minimize the side-effects of conventional perioperative regimens.

2. Circular RNAs (circRNAs)

In 1976, Kolakofsky (5) reported the existence of circRNAs in viroids. Three years later, Hsu and Coca-Prados (6) found a circular form of RNA in the cytoplasm of eukaryotic cells. circRNAs have long been recognized as the product of error splicing (7,8). This hypothesis has been greatly challenged by accumulating evidence (9,10). circRNAs are a new class of unique RNAs with single-stranded, covalently closed and continuous loop structures (11). The mechanisms through which circRNAs are produced are considered to involve the 'back splicing' or 'head-to-tail splicing' of linear RNAs (12). There are two important biological features of circRNAs, including their notable stability and highly conserved sites. Their high stability may be mostly attributable to their closed 3'-5' links structure, which leads to resistance to exonucleases. Indeed, the half-life period of circRNAs is usually >48 h (8,13). The other feature is the highly conserved sites of eukaryotic genes, which endows them with more potential for target treatment (14). Existing evidence has indicated four functions of circRNAs: i) circRNAs can serve as microRNA (miRNA or miR) sponges to induce miRNA loss-of-function (15,16);

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ii) circRNAs can regulate the expression of protein-coding genes through RNA binding proteins (17); iii) interaction with RNA polymerase can regulate the expression of parental genes (18); and iv) some circRNAs can play the same role of directly encoding proteins as mRNAs (19) (Fig. 1).

circRNAs have been demonstrated to play an indispensable role in physiological and pathological changes (20-22). In recent years, attention has been paid to the association between circRNAs and cancer. Some circRNAs may participate in the carcinogenesis, progression and metastasis of numerous types of cancer (9,23,24), which suggests that they have potential diagnostic and prognostic value for patients with cancer (25,26). Despite the fact that a relatively small number of studies have been conducted on this topic, circRNAs have already demonstrated their optimal function in the clinical translation of tumors.

Diagnostic and prognostic role of circRNAs in GC. A number of circRNAs were identified serendipitously and were largely disregarded as non-specific byproducts when they were found to be expressed at low levels. Nonetheless, circRNAs appear to be abundant in both normal and cancer cells. Some types of circRNAs are present at levels comparable to those of their canonical linear counterparts. Furthermore, Salzman *et al* (27) even reported that the abundance of circular molecules exceeded that of associated linear mRNAs by >10-fold in some cases. These results suggest that circRNA levels are absolutely detectable. Carcinogenesis and progression may lead to the alteration of circRNA profiles, which can serve as a novel indicator of GC.

The first step in exploring the association of circRNAs with GC is to screen the circRNA profiles of patients with GC and normal individuals. The identification of circRNAs at differential expression levels may contribute to a better understanding of the mechanisms of GC, which also suggests their use as potential biomarkers for diagnosis and prognosis. The existing types of specimens that have been studied include tumor tissues, blood and gastric juices. Previous studies have reported GC expression profiles, and some of them have constructed circRNA-miRNA or circRNA-miRNA-mRNA regulatory networks by bioinformatics analysis (28-31). These results provide fundamental evidence for searching potential targets of circRNAs and potential downstream of RNAs. For instance, Gu *et al* (29) found that circ_101504 played a central role in the regulatory network. circ_101504 was predicted to affect some mRNAs by inhibiting miR-454-3p and miR-301a-3p. Future studies should be conducted to verify the signaling pathways. Huang *et al* (30) screened three sets of tissues and found that only circ_0026 was significantly downregulated. Bioinformatics analysis indicated a potential role of circ_0026 in gastric carcinogenesis and its potential use as a diagnostic biomarker. Despite the limited number of GC samples, that study provided a direction of research points (30).

Numerous studies have indicated the potential diagnostic values of circRNAs in GC. The majority of these have focused on altered circRNA expression levels in GC and adjacent tissues. The area under the curve (AUC) of a ROC curve is a comprehensive indicator of diagnostic values. Previous studies have revealed that circ_0001017 has the highest diagnostic accuracy in tissues, with an AUC of 0.871.

The sensitivity and specificity could reach, respectively, 79.4 and 81.1% (32). Li *et al* (33) demonstrated that the down-regulation of circ_002059 had a potential diagnostic value in GC, with its AUC being 0.73. Its sensitivity and specificity were, respectively, 0.81 and 0.62. Samples stored at various temperatures for different periods of time exhibited the same expression levels of circ_002059, which demonstrated its optimal stability as a clinical biomarker (33). circ_0000190 was previously demonstrated to be downregulated in GC tissues, and had a higher AUC (0.75), than that of circ_002059 (34). Tian *et al* (35) found that circ_0003159 could also become a potential GC biomarker. The AUC, sensitivity and specificity were 0.75, 0.852 and 0.565, respectively. As far as circ_0074362 is concerned, despite its low sensitivity and specificity, the levels of circ_0074362 have been shown to be closely associated with lymphatic metastasis, suggesting it may be an auxiliary biomarker for predicting the advancement of GC (36).

Some researchers have noted the clinical value of circRNAs in plasma. Previously, the circ_0000745 expression level in plasma was assessed, and its sensitivity reached 0.855. However, the current diagnostic use of circ_0000745 cannot meet clinical standards due to its relatively low specificity (37). The ubiquitous expression of circRNAs can be regarded as the main reason behind this low specificity. The accuracy of circRNAs in tissues is commonly higher than that in plasma partly due to spatial position. Notably, Sun *et al* (38) reported that the diagnostic accuracy of circ_0000520 was much higher than the one in tumor tissues. The AUC, sensitivity and specificity were 0.8967, 0.8235 and 0.8444, respectively. According to the aforementioned studies, the diagnosis of a single circRNA does not meet clinical translation. Li *et al* (32) combined the four biomarkers (circ_0001017 and circ_0061276 both in tissues and in plasma) as a panel. The sensitivity and specificity were 95.5 and 95.7%, respectively. Thus, the circRNA panel is regarded as the most promising for possible and effective translation into clinical application.

The detection of circRNAs in gastric juice is another potential non-invasive type of clinical examination. Shao *et al* (39) recruited 38 healthy volunteers, 30 patients with gastric ulcer, 15 patients with chronic atrophic gastritis and 39 patients with GC in order to evaluate the diagnostic values of circ_0014717. Although no significant differences in circ_0014717 levels were observed amongst the healthy, gastric ulcer and GC groups, a marked reduction was observed in the chronic atrophic gastritis group. Chronic atrophic gastritis is a possible precancerous lesion of GC (40); thus, the aforementioned study suggested that circ_0014717 may be a predictive indicator of GC. This result broadens the horizons that circRNAs can exist in an extreme environment for a long period of time. Their considerable stability suggests that circRNAs are likely to become an excellent non-invasive biomarker for GC.

Accumulating evidence has demonstrated that circRNAs may play a promising role in predicting the prognosis of GC. A common method used for the prognosis of GC is defining the cut-off value of circRNAs. Recruited patients can be divided into positive (high expression) and negative (low expression) groups. Kaplan-Meier survival analysis is then employed to evaluate the association between circRNAs

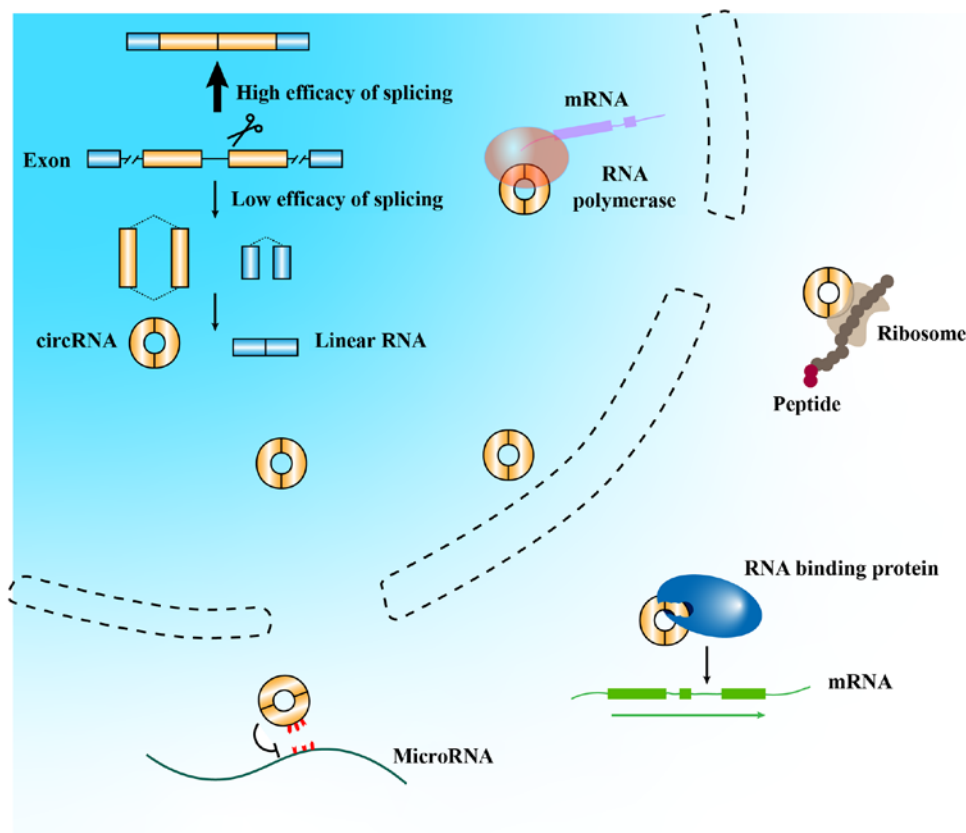


Figure 1. Biological functions of circRNAs. In the nucleus, mRNA precursors can be spliced with high efficiency, producing linear RNAs that contains exons. Comparably, precursors can go through back-splicing and generate circRNAs with low efficiency. The circRNAs can be transferred into the cytoplasm or continue to function in the nucleus. Based on current studies (15-19), the functions of circRNAs can be concluded into four aspects: i) circRNAs can serve as miRNA sponges to induce miRNA loss-of-function; ii) circRNAs can regulate the expression of protein-coding genes through RNA binding proteins; iii) interaction with RNA polymerase can regulate expression of parental genes; iv) some circRNAs can play the same role of directly encoding proteins as mRNA. circRNAs, circular RNAs; miRNAs, microRNAs.

and prognosis. Univariate analysis, further multivariate analysis and the Cox proportional hazard model are also used to assess the prognostic role of circRNAs. circ_100269, circ_0001017 and circ_0061276 have been demonstrated to serve as potential biomarkers for predicting prognosis in GC by these methods (32,41). For instance, Zhang *et al* (42) indicated that circLARP4 (circ_101057) was closely associated with the prognosis of patients with GC at the early stage rather than at the late stage of the disease. Patients at the early stage of the disease with a high expression of circLARP4 had a better overall survival (OS) and a better response to adjuvant chemotherapy with oxaliplatin and 5-fluorouracil. The result revealed that circRNA may have the potential to direct clinical medication to a certain extent. The ability of circRNAs alone to determine the prognosis of GC may not meet clinical needs. Chen *et al* (43) shared a novel approach for this field in 2017. They simultaneously evaluated the predictive values of circPVT1 and PVT1 expression. The combination yielded more accurate results than those obtained by either of the two alone. Future studies are required however, to further concentrate on panels of combined biomarkers to maintain an ideal balance between efficiency and economy.

Therapeutic role of circRNAs in GC. Considerable progress has been made in the identification of the mechanisms

through which circRNAs participate in gastric carcinogenesis. Numerous studies have focused on identifying circRNAs that may play potential roles in the treatment of GC (Table I). Multiple circRNAs were selected, and the majority of these were demonstrated to be involved in GC by acting as miRNA sponges. Binding to target miRNAs can downregulate miRNA expression and subsequently affect the functions of downstream molecules. A number of circRNAs have been reported to be upregulated in GC, such as circPVT1, circ_0047905, circ_0138960, circ_7690-15, circHIPK3 (circ_0000284), circ_0023642 and circ_001569. They may participate in cancer proliferation, migration or invasion. Their downregulation can inhibit malignant behaviors (43-47). However, other circRNAs, such as circLARP4 and circ_100269 have been demonstrated to be expressed at lower levels in GC cancer tissues. They have both been demonstrated to be involved in cancer growth, and may function as suppressors of GC through sponging miR-424-5p and miR-630. The upregulation of these two circRNAs significantly reverses carcinogenesis and proliferation (41,42).

The aforementioned circRNAs naturally exist in cancer or normal cells. Their regulation can interrupt or reverse the development of tumors. However, previous studies on GC have focused on basic research, which is far from clinical translation due to complex mechanisms *in vivo*. Liu *et al* (54) provided a novel approach of the clinical translation of circRNAs. Since

Table I. Summary of circRNA mechanisms in GC.

circRNA	Expression	Pathway	Effects	(Refs.)
circ_0001368	Down	circ_0001368/miR-6506e5p/FOXO3	Knockdown of hsa_circ_0001368 promoted proliferation and invasion <i>in vitro</i> and accelerated growth <i>in vivo</i> .	(48)
circNRIP1	Up	circNRIP1/miR-149-5p/AKT1	Knockdown of circNRIP1 inhibited proliferation, migration, invasion whereas it could promote EMT and metastasis <i>in vivo</i> .	(49)
circPSMC3	Down	circPSMC3/miR-296-5p/PTEN	Overexpression of circPSMC3 inhibited cell proliferation, invasion <i>in vitro</i> and growth, metastasis <i>in vivo</i> .	(50)
circ_0023642	Up	UK	Knockdown of circ_0023642 inhibited migration, invasion and EMT process.	(47)
circ_0027599	Down	circ_0027599/miR-101-3p.1/PHDLA1	Overexpression of circ_0027599 inhibited cell proliferation and metastasis.	(51)
circPVT1	Up	circPVT1/miR-125 family	UK	(43)
circAGO2	Up	circAGO2/HuR/AGO2-miRNA complexes	CircAGO2 promotes the growth, invasion, and metastasis of cancer cells <i>in vitro</i> and <i>in vivo</i> .	(52)
circFAT1	Down	circFAT1/miR-548g/RUNX1 and circFAT1/YBX1	Overexpression of circFAT1 inhibited proliferation, migration and invasion	(53)
synthetic scRNA21	-	scRNA21/miR-21/DAXX	ScRNA21 inhibited proliferation and induced apoptosis.	(54)
circPDSS1	Up	circPDSS1/miR-186-5p/NEK2	CircPDSS1 promoted GC cell cycle, proliferation and inhibited apoptosis.	(55)
circPVRL3	Down	circPVRL3/9 miRNAs	Knockdown of circPVRL3 promoted the proliferation and migration.	(56)
circ-sFMBT2	Up	circ-sFMBT2/miR-182-5p/CREB1	Knockdown of inhibited the cell proliferation.	(57)
circ-SFMBT2	Down	Unknown	Knockdown of circ_0001649 promoted proliferation, migration, invasion and attenuated apoptosis.	(58)
circLARP4	Down	circLARP4/miR-424/LATS1	Knockdown of circLARP4 promoted proliferation and invasion.	(42)
circ_100269	Down	circ_100269/miR-630	Overexpression of circRNA_100269 inhibited cell proliferation.	(41)
ciRS-133	Up	ciRS-133/miR-133/PRDM16	Knockdown of ciRS-133 inhibited cancer cachexia, decreasing oxygen consumption and heat production <i>in vivo</i> .	(59)
circDONSON	Up	Recruitment of NURF	Silencing of circ-complex to SOX4 promoter significantly suppressed the proliferation, migration and invasion while promoting apoptosis.	(60)
DONSON				
circDLST	Up	miR-502-5p/NRAS	Knockdown of circDLST inhibited proliferation, invasion and metastasis.	(61)
circNHSL1	Up	miR-13063p/SIX1/vimentin	Upregulation of circNHSL1 promoted cell proliferation, migration, invasion.	(62)
circCACTIN	Up	miR-331-3p/TGFBR1	Knockdown of circCACTIN inhibited GC cells proliferation, migration, invasion and EMT.	(63)
circOSBPL10	Up	miR-136-5p/WNT2	circOSBPL10 significantly inhibited cell growth, migration, and invasion in multiple experiments.	(64)

GC, gastric cancer; circRNA, circular RNA; UK, unknown.

miRNA sponges rely on the antisense sequences, synthetic molecules with these sequences are likely to exhibit similar effects on miRNA inhibition. The researcher can decide the circRNA levels and quantity of binding sites in each circRNA. Controllable modulation ability should provide an optimal balance between efficiency and safety. Liu *et al* designed a synthetic circRNA functioning as a miR-21 sponge. The administration of this circRNA led to the inhibition of proliferation and induction of apoptosis (54). Downstream proteomic screening revealed that proteins which should have been downregulated by miR-21 were effectively restored (54). Moreover, the reduction of the cancer burden may not be the sole direction of research. The inhibition of ciRS-133 has been shown to alleviate GC-associated cachexia by repressing miR-133 (59). The elucidation of the mechanisms responsible for complications associated with GC is also expected to be meaningful, helping to prolong the lifetime and comfort of patients with late-stage GC. In addition to miRNA sponges, circRNAs in the nucleus can initiate the expression of transcriptional factors to promote cancer growth (60). Future studies are required to pay greater attention to this field and explore additional approaches with which to improve the prognosis and quality of life of patients.

3. Long non-coding RNAs (lncRNAs)

lncRNAs belong to a characterized group of RNAs without the capacity of transcription, which are >200 nt in length. In the 1990s, lncRNAs were identified without optimal origins and functions (65). lncRNAs were initially regarded as transcriptional noises (66). However, accumulating evidence suggested that lncRNAs may play a crucial role in physiological activities and various diseases (67-69). Compared with their small-length counterparts, miRNAs, the main functional mechanism of which is binding to 3' untranslated regions and activating the degradation of target mRNAs (70), lncRNAs have richer regulatory methods, including levels of transcription, post-transcription, alternative splicing and translation (71). For instance, lncRNA h5S-OT modulates retrotransposons jump into alternative-splicing by virtue of the Alu element. Alternative splicing produces variants of proteins responsible for distinct physiological or pathological processes (72,73). lncRNA RoR has been reported to interact with c-Myc mRNA and increase its stability, leading to cell proliferation and tumorigenesis (74). lncRNA-protein regulatory mechanisms can be generally summarized by four aspects: i) Signal, lncRNAs reflect on the spatiotemporal expression level of genes via alterations of transcription factors or signaling pathways; ii) decoy, lncRNAs titrate specific proteins in the cell nucleus and perform concrete functions; iii) guide, lncRNAs direct ribonucleoprotein complex to locate on specific regions; and iv) scaffold, the lncRNA scaffold is structural and stabilizes nuclear structures or signaling complexes (75) (Fig. 2).

The association between lncRNAs and GC has been gradually revealed. Numerous lncRNAs have been found to participate in carcinogenesis and progression. Diverse biological functions and wide distribution determines the complexity of lncRNA networks in GC. One lncRNA can regulate multiple cancer behaviors through different pathways (76,77). One cancer behavior can be under the control of several

lncRNAs and their respective downstream molecules (78,79). Additionally, intersectional lncRNA profiles and regulatory mechanisms vary in different cancer types (80,81). Their theoretical links with GC provide substantial biomarkers and targets with potential clinical values. Therefore, lncRNAs are one of the most promising approaches for GC diagnosis and treatment.

Diagnostic role of lncRNAs in GC. The biological characteristics of lncRNAs facilitate the speed of translation into the clinical diagnosis of GC. Optimal diagnostic biomarkers require remarkable stability of molecular structures and expression levels. Given the existing number of studies, lncRNAs are suitable candidates for this purpose. lncRNAs have been found to stably exist in extreme environments, such as gastric juice, urine and hair follicles (82-84). lncRNAs have distinct half-life periods, which range from <2 to >16 h (85). A long half-life period would lead to the accumulation and would impair the accuracy of the biomarker. On the other hand, an excessively short detectable time exerts more pressure on the limitation of technology to form a reliable clinical diagnosis. In a previous study, the median half-life period of lncRNAs was ~3.5 h shorter than that of protein-coding RNAs (85). The appropriate half-life period indicates their potential to function as diagnostic biomarkers due to the prompt reactions of lncRNAs consistent with the degrees of primary focus. The characteristics and severity of diseases can be reflected by these reliable indicators.

The majority of studies concerning lncRNA diagnosis have focused on the detection of cancerous tissues. Alterations in lncRNA expression are significantly associated with numerous clinicopathological features. For instance, Sun *et al* (86) found that lncRNA AC096655.1-002 expression was associated with TNM stage, differentiation, lymph node metastasis and depth of invasion. lncRNA ABHD11-AS1 has also been proven to be associated with differentiation, Lauren histological classification and carbohydrate antigen 19-9 (CA19-9) (87). Testing the expression levels of some lncRNAs may provide a reference for the evaluation of disease severities and the selection of treatment regimens. However, the association between lncRNAs and clinicopathological features is not stable. Baratieh *et al* (88) analyzed data from patients with GC in The Cancer Genome Atlas (TCGA) database. Their results revealed limited features associated with FAM83H-AS1 expression; however, FAM83H-AS1 mean and median gene expression data in the TCGA cohort exhibited a significant association with M-classification, tumor stage, grade and different Lauren's classes. Thus, further investigations into more reliable associations of lncRNAs with clinical characteristics are required using larger sample numbers and standardizing experimental procedures.

Non-invasive and pain-free detection methods of lncRNAs are also pursued, such as in the case of circRNAs. lncRNA performance in GC diagnosis is commonly better than that of classical biomarkers, as highlighted from current methods, such as CEA and CA19-9 (89). A meta-analysis (90) indicated that the clinical values of lncRNAs are limited to screening tools rather than diagnosis with high accuracy. This conclusion may not be convincing enough, partly due to the inclusion of relatively old studies and the ignorance of the respective

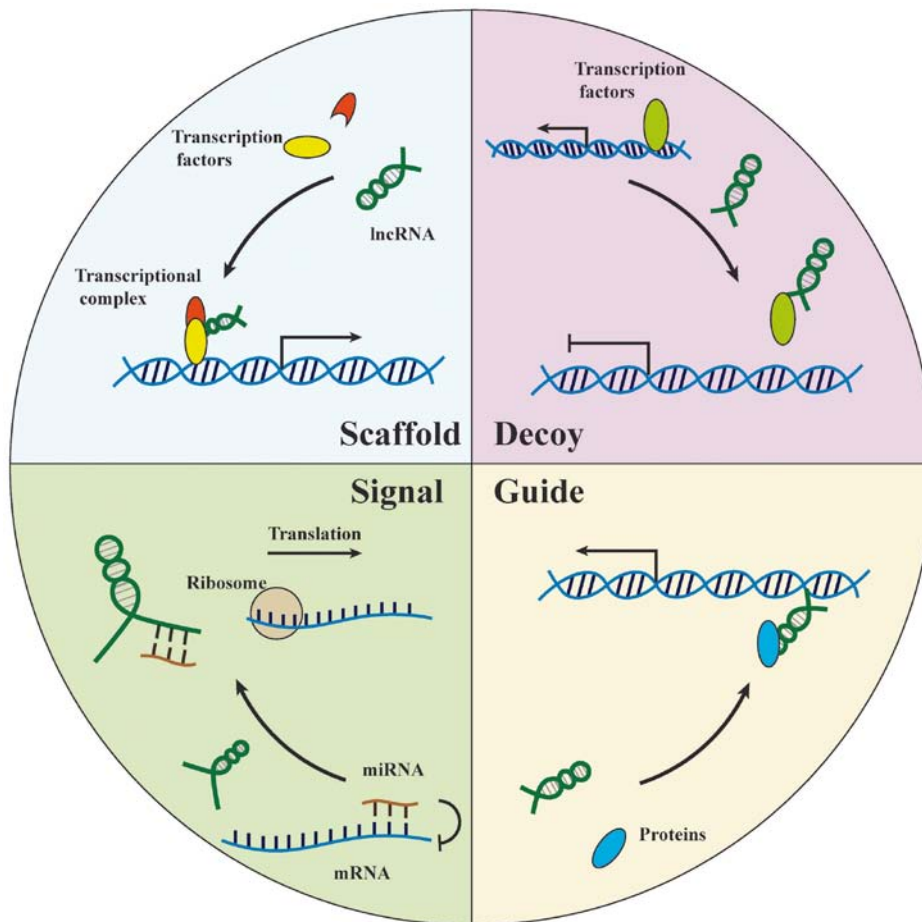


Figure 2. Biological functions of lncRNAs. The biological functions of lncRNAs can be classified into four aspects: i) Scaffold, lncRNA scaffold is structural and stabilizes nuclear structures or signaling complexes; b) decoy, lncRNAs titrate specific proteins in the cell nucleus and perform concrete functions; c) signal, lncRNAs can participate in the regulation of signaling pathways and reflect on spatiotemporal expression level of relative genes; iv) guide, lncRNAs direct ribonucleoprotein complex to locate on specific regions. lncRNAs, long non-coding RNAs.

discussions of each lncRNA. Some lncRNAs have exhibited great potential for clinical translation. lncRNA H19 and HOTAIR were demonstrated to be effective biomarkers with high AUC. Their combination with CEA significantly enhanced their diagnostic capacity (91-93). Furthermore, a multi-lncRNA diagnostic panel in plasma is a feasible approach to compensate for the comparably low sensitivity of a single lncRNA. Dong *et al* (89) created a panel with three plasma lncRNAs (CUDR, LSINCT-5 and PTENP1) in 2015, which was sensitive and specific to the discrimination of healthy controls from patients with GC, patients with peptic ulcers from patients with GC, and patients with stage I and II-IV disease from healthy controls. Zhang *et al* (94) employed the genome-wide profiling identifies TINCR, CCAT2, AOC4P, BANC1 and LINC00857 in plasma. The diagnostic panel was estimated to be an excellent method for the discrimination of patients with GC from both precancerous individuals and gastrointestinal stromal tumors. Another advantage of this research is that these data were translated into Fagan's nomogram, a tool used to calculate the probability that an individual has GC based on this panel. A convenient evaluation method is a developing direction of GC diagnosis. In addition, Li *et al* (95) found that the levels of LINC00152 in plasma and exosomes were consistent, which suggested that lncRNAs detected in exosomes may also have optimal clinical values as plasma biomarkers.

Some studies have focused on lncRNAs in gastric juice (Table II). These stomach-specific, single-source biomarkers can be easily obtained with non-invasive methods, and multiple lncRNA targets have been selected. lncRNA ABHD11-AS1 and UCA1 were found in gastric juice with an AUC of 0.653 and 0.721, respectively. These data do not seem satisfactory. However, the specificities of ABHD11-AS1 and UCA1 were 0.934 and 0.803, respectively (84,96). lncRNAs can serve as outstanding indicators of excluded diagnosis. As sensitive indicators at fluctuating levels are influenced by numerous factors; thus, accurate detection needs another reliable biomarker for revision. Shao *et al* (97) found that GAPDH was a satisfactory reference for lncRNAs in plasma and gastric juice. Their combination with GAPDH may elevate the clinical confidence level of diagnostic biomarkers.

Current treatment methods cannot reach curative goals for patients at advanced stages of the disease. A basic method with which to resolve GC-associated mortality and the poor prognosis of affected patient is to search for efficient diagnostic biomarkers for the early stages of the disease. *H. pylori* is an important carcinogenic factor, estimated to be prevalent in developing countries (102,103). NR_026827 has been demonstrated to be downregulated in gastric epithelial cells infected with *H. pylori* (104). Despite the wide application of C¹³ or C¹⁴ examinations, NR_026827

Table II. Summary of lncRNAs in gastric juice.

lncRNA	Locus	AUC of tissues	AUC of plasma	AUC of gastric juice	Conclusion	(Refs.)
UCA1	19p13.12	0.721	0.838	UK	UCA1 in gastric juice is significantly higher than normal individuals.	(96)
ABHD11-AS1	7q11.23	UK	UK	0.653	Combinative use of ABHD11-AS1 and CEA promotes the positive rates of advanced GC.	(84)
RMRP	9p13.3	UK	0.639	0.699	RMRP in gastric juice has higher diagnostic value, particularly for specificity compared with those in plasma.	(98)
AA174084	chr 13	0.676	UK	0.848	AA174084 in gastric juice levels has great potential as a screening biomarker of early GC.	(97)
LINC00152	2p11.2	0.645	UK	UK	LINC00152 in gastric juice levels from patients with gastric cancer were significantly higher than those from normal subjects.	(99)
LINC00982	1p36.32	0.742	UK	UK	LINC00982 in gastric juice levels from patients with gastric cancer were significantly higher than those from normal subjects.	(100)
H19	11p15.5	0.697	0.838	UK	H19 levels in gastric juice from patients with GC were significantly higher than those from normal subjects.	(93,101)

GC, gastric cancer; lncRNA, long non-coding RNA; UK, unknown.

may be a predictive role of GC risks. H19 in plasma enabled the discrimination of early-stage GC from controls with an AUC of 0.877 (93). Lu *et al* (105) also developed a panel of five lncRNAs in tumor tissues with high values of early diagnosis, which helps to identify indistinguishable focus in endoscopy. The single nucleotide polymorphism (SNP) rs4759314, which contributes to a genotype-specific effect on the expression of the host gene HOTAIR, has been shown to be closely associated with the risk of developing GC in Chinese populations (106).

Prognostic role of lncRNAs in GC. The number of lncRNAs for the prediction of prognosis remains smaller than that for GC diagnosis. A substantial number of lncRNAs have been screened out, which have remarkable predicting performance, theoretically. The majority of previous studies suggest the potential values of tissue lncRNAs in evaluating the survival of patients with GC. Liu and Shangguan (107) employed the Kaplan-Meier curve to prove that high level of lncRNA

CARLo-5 was associated with overall survival (OS) and recurrence-free survival (RFS). Further univariate and multivariate analyses indicated that CARLo-5 could serve as an independent predictor of OS and RFS. Feng *et al* (108) reported that patients with a high expression of lncRNA AFAP1-AS1 had a significantly poorer OS. Some other biomarkers for the prediction of prognosis have been identified in recent years, such as CASC15, UPF1, ZEB1-AS1 and PANDAR (109-112). They were all found to be independent prognostic factors of survival time.

The degree of metastasis is an important factor for patient prognosis, and there is a close association between lncRNAs and GC metastasis. Xia *et al* (113) found that MALAT1 both in tissue and plasma could serve as a prognostic biomarker of distant metastasis. CARLo-5 has also been reported to be associated with lymph node involvement and distant metastasis (107).

Nevertheless, the selected predictors are considerable, while the pace of clinical translation has stagnated for a long

time. None of these lncRNAs can reach the criterion of wide application. A previous study even demonstrated that a combination of 24 lncRNAs had the clinical value of predicting prognosis (114). Superfluous lncRNAs in a panel may decrease the prognostic values and increase the economic burden of patients. Overall, the value of lncRNAs is not regarded as a preferable indicator for the prediction of prognosis based on current studies.

Therapeutic role of lncRNAs in GC. The identification of the elusive mechanisms of carcinogenesis and progression remains at a preliminary stage. Both explored and unexplored pathological processes contain multiple molecules with clinical values. Unlike diagnostic and prognostic biomarkers, a therapeutic candidate requires the marked involvement of important mechanisms; thus, there is a great difficulty. Numerous studies have paid attention to lncRNAs in the view of the established regulatory network of GC. Large quantities of targets have been successfully selected to act as potential targets of clinical treatment. For instance, Chen *et al* (115) measured the expression of lncRNA-ATB in a pathological specimen in GC cell lines by RT-qPCR. lncRNA-ATB was found to be significantly upregulated in cancer tissues and cell lines. Its knockdown led to the alteration of clinicopathological features, including proliferation, invasion and migration (115).

Long intergenic non-coding RNAs (lincRNAs) are one of the four defined categories of lncRNAs (116). lincRNAs and lncRNAs share similar features. However, the difference between the two types of molecules should be emphasized, owing to frequent errors made by numerous studies, including gene expression analyses, evolutionary conservation patterns and targeted gene disruptions that did not alter adjacent protein-coding genes or genic RNAs (117). Previous studies have suggested that lincRNAs may be potential targets of treatment. HOTAIR is recognized as a key lincRNA in GC, which can modulate cancer development and fate determination through multiple molecules and pathways. HOTAIR, as a type of non-coding RNA sponge, can competitively inhibit several miRNAs and affect downstream functioning molecules, such as miR-217, miR-152, miR-454-3p and miR-17-5p (118-121). The interaction of HOTAIR with crucial proteins also plays an indispensable role in various biological functions of GC. Runx3 endows gastric cells with the capacity of excessive proliferation and invasion (122). The combination of HOTAIR and Mex3b, a type of E3 ligase possessing RNA binding domains, can attenuate the degradation of Runx3, thus regulating cancer migration and invasion (123). Zeng *et al* (124) found that LINC00675 could enhance the phosphorylation of vimentin on Ser8 and the p53 signaling pathway. The downregulation of LINC00675 facilitated cancer proliferation, migration and invasion *in vitro* and *in vivo* (124). Previous studies have validated that LINC00052, Linc00152, Linc00483 and H19 are attributable to the genesis and development of GC (125-128). The intervention of their expression may lead to the reversion of cancer progression and an improvement in patient prognosis.

Drug resistance can limit the efficacy and effectiveness of GC treatments. The prognosis and quality of life of numerous patients deteriorate at the late stages of the disease due to

the failure of existing chemotherapeutics or targeted medicine (129). Previous studies have indicated that lncRNAs may be capable of preventing and reversing drug resistance. A high expression of GHET1 and ANRIL was detected in GC tissues. Further experiments demonstrated that these two lncRNAs were associated with multi-drug resistance (MDR)-related genes. The attenuation of these sensitized the reactions of GC cells (130,131). CASC2 overexpression has also been shown to overcome cisplatin resistance by binding to miR-19a, whereas MALAT1 potentiates cisplatin resistance through sponging miR-30b (132,133).

An increase in the apoptotic protein, cleaved caspase-3, has been shown to restore the sensitivity to multiple drugs, including doxorubicin, cisplatin and 5-fluorouracil (134,135). Autophagy is a complex and highly regulated process that delivers cellular material to lysosomes for degrading, recycling, and generating molecules that fuel cellular metabolism (136). Recent research has revealed that there is a close association between autophagy and MDR (137). Two studies separately explained the mechanisms of MALAT1-induced autophagy concerning the formation of GC resistance. MALAT1 served as a miRNA sponge to target miR-23-3p and miR-30b, and related proteins downstream of autophagy functioned subsequently (132,138). The inhibition of MALAT1 was considered as a promising approach to alleviating MDR at late stages.

The regulatory mechanisms of lncRNAs are not simply considered as a 'one-to-many' mode. Previous evidence suggests that lncRNAs share the same regulated targets. These common targets cannot only help delineate sophisticated networks of non-coding RNAs and GC, but also serve as intervention sites with great values. YB-1 is a multifunctional protein that regulates apoptosis, cell proliferation, differentiation and stress response (139). lncRNAs GAS5 and HOXC-AS3 can directly bind to YBX1 proteins, promoting the conversion of YBX1 configuration. The inhibition of these two lncRNAs in GC cells has been shown to abolish G1 phase cell cycle arrest, and the cell proliferative capacity has been shown to be considerably enhanced (140,141). Moreover, EZH2, which is associated with genetic abnormalities, has been found to participate in the regulation of epigenetics and transcription. HOTAIR, MALAT1, UCA1 and LINC00673 can interact with EZH2 and suppress downstream E-cadherin, PCDH10, AKT and KLF4, respectively (142-145). The inhibition of the intersection of the mechanism means partially refraining functions of upstream lncRNAs. Therapeutic efficacy may be enlarged manifold.

Despite progress being made in determining the role of lncRNAs in the treatment of GC, none of these lncRNAs have reached the standard of clinical translation to date. A few key lncRNAs, including HOTAIR, UCA1 and MALAT1, have been reported to regulate various downstream molecules and suppress tumors *in vitro* and *in vivo*. Relevant agents for clinical use were kept at a slow pace due to the distinction between human physiological processes and simulation environment of cells and animals. Furthermore, the existing mechanisms were scattered and unable to constitute an integral network. The inability to recognize the overall perspective of may set obstacles for finding regimens of curing GC thoroughly. Additional in-depth investigations are warranted to mine more effective therapeutic targets.

Table III. Summary of lncRNAs and circRNAs in exosomes in GC.

RNA	Diagnostic potentials	Prognostic potentials	Therapeutic potentials	Conclusion	(Refs.)
lncRNA ZAFS1	+	+	+	lncRNA ZASF1 can enhance cell proliferation and migration, which also serves as a potential diagnostic and prognostic biomarker.	(149)
ciRS-133	-	-	+	Intervention of ciRS-133 can alleviate cachexia caused by GC.	(59)
lncRNA UEGC1	+	-	-	lncRNA UEGC1 may serve as a reliable diagnostic biomarker of early GC.	(150)
LINC00152	+	-	-	LINC00152 can be a potential biomarker of GC diagnosis with high specificity but low sensitivity.	(95)
lncRNA HOTTIP	+	+	-	lncRNA HOTTIP was reported to act as an excellent diagnostic and prognostic biomarker.	(151)
circ-KIAA1244	+	-	-	Circ-KIAA1244 can serve a novel circulating biomarker for detection of GC.	(152)
circ_0065149	+	+	-	Circ_0065149 in exosomes is an indicator for early GC screening and prognosis prediction.	(153)

GC, gastric cancer; lncRNA, long non-coding RNA; circRNA, circular RNA; +, reported; -, unknown.

4. lncRNAs and circRNAs in exosomes

Exosomes are nm-sized vesicles in the extracellular fluid, which span 40-150 nm and contain numerous functional molecules such as proteins, miRNAs, lncRNAs and circRNAs. The exploration of exosome-relevant surface markers and transmission electron microscope contribute to the development of detection and further research. The processes of formation, content selection, loading, trafficking and release of exosomes are strictly under physical control (146-148).

Disorders of exosomes in GC have been revealed in recent years (Table III). Exosomes and inclusion compounds may play an important role in the deterioration and metastasis of GC. Pan *et al* (149) found that lncRNA ZFAS1 in exosomes enhanced GC cell proliferation and migration, while ciRS-133 in exosomes has been shown to participate in lipid metabolism and to be associated with cancer cachexia (59).

On the other hand, alteration in the levels and modified states of lncRNAs and circRNAs have potential for use in the diagnosis and prognosis of GC. Exosomes encapsulate biomarkers and protect them from RNase degradation, which endow them with extraordinary stability and capability of representativeness. For example, Lin *et al* found

that lncUEGC1 was early GC-specific, and could discriminate patients with early GC from healthy individuals and those with premalignant chronic atrophic gastritis (150). Moreover, LINC00152, lncRNA HOTTIP, circ-KIAA1244 and circ_0065149 were identified as biomarkers for GC diagnosis and prognosis (95,151-153).

5. Comparison of achievements regarding circRNAs and lncRNAs

circRNAs and lncRNAs both belong to the family of non-coding RNAs. Similar constructions determine consistent characteristics: i) Relative incapacity of expressing proteins; ii) some highly conserved sequences; iii) stable existence in extreme environments for a relatively long period of time; iv) wide varieties and distribution; v) diversity and complexity of the involved regulatory mechanisms; and vi) association with multiple diseases. The isoforms derived from the same genes have been demonstrated to play important roles in cancer. For instance, lncRNA PVT1 and circPVT1 both play oncogenic roles in GC progression, and have great diagnostic and therapeutic potential (43,154). The biological functions also overlap. circRNAs and lncRNAs can bind to miRNAs through complementation, which serves as a negative regulatory method for

target miRNAs. During the past decade, numerous studies concerning miRNAs have been published (20,21,44,52). The network of miRNAs in tumorigenesis has begun to take shape. The association of miRNAs with lncRNAs and circRNAs suggests a vast number of uncovered regulatory pathways. The classical view indicates that circRNAs and lncRNAs lack the capacity of coding proteins. However, recent evidence supports coding competence for these (155), which universally overturns traditional impression. Additionally, although limited studies have been published regarding the crosstalk of circRNAs and lncRNAs, the shared features indicated an abundance of underlying interactions in carcinogenesis and development. Further basic and translational studies are required on this topic.

Researchers strive to identify a novel method of clinical translation. As aforementioned, circRNAs and lncRNAs have great potential for use in the diagnosis and treatment of GC. Extensive focus has been placed on lncRNAs over the past decade, with multiple studies suggesting effective clinical performance for GC. Although circRNAs have been discovered for a long time, they have only increased in popularity in recent years. However, unique translational methods of circRNAs provide a new direction for clinical use and research. Both ncRNAs have their own strengths and shortcomings.

According to previous studies (86-88,91-93,106-114), the diagnostic and prognostic values of lncRNAs are ideal. Initially, researchers tested single lncRNA values in GC; however, the result could not reach clinical standards. Next, panels of lncRNAs or lncRNA combined with other types of biomarkers were developed, which exhibited good sensitivity and specificity, particularly compared with those of classical cancer biomarkers. The Fagan's nomogram created by Zhang *et al* (94) accelerated the pace of lncRNA diagnosis. Nevertheless, practical usage requires not only theoretical effects, but also a cost-benefit balance. If a large number of lncRNAs is involved, this can hinder making definite conclusions and can increase medical costs, thus adding pressure for both doctors and patients. In terms of circRNAs, previous studies have focused on single molecules or on their combination with other biomarkers (30,32-42). The results were relatively satisfactory. However, similar to lncRNAs, the future role of circRNAs in GC diagnosis and prognosis requires more systematically designed studies and long-term clinical trials. Another developmental direction is to combine panels with several types of ncRNAs. The RNAs with optimal clinical performance and robust endurance in extreme environments should be collected and compensate for the shortcomings of single biomarkers. The exploration of associated biomarkers is necessary in order to promote their clinical application.

The location association of lncRNAs and circRNAs is important for the exploration of their potential clinical translation. Distinct location endows these molecules with different biological functions. lncRNAs were estimated to be mostly located in the nucleus, while circRNAs are mostly located in the cytoplasm, acting as the miRNA sponges to regulate downstream signaling pathways. This location association determines their potential for use in clinical research or practice. Researchers should not only verify their experimental capability of interfering GC progression, but also ascertain the natural location of these molecules in cancer cells.

A novel therapeutic method for GC relies on the elucidation of the mechanisms responsible for the development of GC. Previous studies have screened out numerous circRNAs and lncRNAs with therapeutic potential (41-43,47-64,115,118-121,123-128,132,133,138,140-145), mainly by small interference *in vitro* and by inhibition of tumor burden *in vivo*. Various new signaling pathways were identified, which were connected with established cancer promoters or suppressors. The reported efficacy of regulating circRNAs and lncRNAs was demonstrated to be effective. It is worth mentioning that the application of synthetic circRNAs offers a brand-new perspective for researchers, which is considered as a more direct and controllable method for GC treatment. The limitations of these studies are evident. Basic studies cannot replace clinical trials. Unknown efficacy, administration method and dosage of human agents hinder the further use of these RNAs. The therapeutic regimens should also refer to the cost-benefit principle. No studies available to date have reported the side-effects associated with the interference, at least to the best of our knowledge. In short, detailed information on therapeutic applications requires more in-depth investigations.

6. Prospects

The following are some suggestions for the development of circRNAs and lncRNAs. Firstly, sample sizes should be enlarged. The majority of studies collected tissue and plasma samples from <200 GC patients with GC. The limited number of sources definitely increases the contingency of false results. Despite the lack of evidence, circRNA and lncRNA profiles may vary in different groups of age, ethnicity, and living conditions. Therefore, additional large-scale, multi-center studies conducted under strict supervision are required, which will draw more convincing and compelling conclusions. More reliable information is also required for individual diagnosis.

Secondly, clinical trials concerning optimal biomarkers should be implemented as early as possible. Despite findings of therapeutic targets at the preliminary stages, the diagnostic and prognostic biomarkers have been demonstrated to be more convenient and efficient than compared to classical use. Plasma detection is a promising future due to non-invasive examination, a high acceptance by patients and better sensitivity. With the development of detection technologies, circRNAs and lncRNAs can be measured in gastric juice, which has exhibited great efficacy in the diagnosis of GC. Their high stability endows these biomarkers with the ability to endure extreme environments. Furthermore, despite the limited number of studies available concerning lncRNAs and circRNAs in exosomes of GC, exosomes can serve as shields to protect non-coding RNAs from RNases and extreme environments. The potential diagnostic values of lncRNAs and circRNAs in exosomes need to be more deeply investigated. Exosomes may also be effective transporters of RNA interference drugs. Additional detection media for GC diagnosis and prognosis, such as feces, warrant further exploration in the future. These gastrointestinal-specific, alteration-immediate biomarkers will be more promising for future applications.

Thirdly, the distinction of cancer locations in GC should be recognized. Previous research has suggested that carcinogenesis in different sites of GC, such as the cardia and antral stomach, involves different mechanisms (156). However, to the best of our knowledge, to date, there are no studies available differentiating the location discrepancy. Studies have explored circRNA and lncRNA profiles, and the regulatory pathways in the whole stomach, which may be an important factor leading to partially contradictory results, attenuating the development of clinical translation, and promoting the unbalance of clinical accuracy and practicability.

Fourthly, the disturbance of non-cancer factors should be emphasized. circRNAs and lncRNAs exist in both normal and pathological tissues, and are secreted into the extracellular environment. Previous studies showed that the expression of these two kinds of RNAs can be influenced by numerous non-cancer factors, including inflammation, neurodegenerative diseases, drugs and circadian rhythms (157-161). The fluctuation of circRNA and lncRNA levels leads to inaccurate results. It is advisable to remove background disturbances by mathematical modulation or molecular biology techniques. On the other hand, diagnostic and prognostic translation of circRNA and lncRNA levels requires normative criterion of sampling time, methods and criteria of patients' inclusion and exclusion.

Fifthly, the specificity of circRNAs and lncRNAs can be poor, which decreases down the accuracy and safety of non-coding RNA interference in patients. This may be an important reason for the slow pace of relevant therapeutic drugs. An efficient approach is to administer drugs *in situ*, since this can reduce the effects on non-targets and optimize the sufficient dose of drugs for tumor focus. The efficacy and accompanying side-effects can be easily observed in animal models. However, administration *in situ* definitely would lead to more difficulties in clinical practice and patient compliance. Biomaterial serves as a robust star for modern biomedicine. A large number of novel transporter systems have been established, and have been demonstrated to be effective for maximizing the specificity and minimizing side effects of interference drugs, such as nanoparticles and nanotube sponges. More efficient and reliable mediators should be constructed to improve the specificity and reduce the side-effects of lncRNA and circRNA treatment.

7. Conclusion

The advantages and disadvantages of these two types of RNA have been compared in the present review based on their similar biological features and research achievements. Accumulating evidence has revealed their essential role in the diagnosis, prognosis and treatment of GC. Certain circRNAs and lncRNAs have been reported to exhibit optimal effects and act as convenient detection methods. Panels of combined biomarkers serve as a novel trend in early diagnosis and prognostic prediction. Furthermore, the identification of the mechanisms responsible for GC can promote the development of GC therapeutic targets. Previous studies have identified numerous circRNA and lncRNA molecules (28-31,82,85,94,114), as well as relevant signaling pathways. The interference of target expression significantly affects GC cell behavior and tumor burden.

However, there are still several limitations concerning circRNAs and lncRNAs. The number of previous studies on these molecules is relatively small, and numerous unknown molecules require further exploration. Publication bias may partly cover the potential targets. The small number of collected samples and the different GC locations impair the reliability of the results. A number of translational questions remain to be answered, such as: i) the clinical position compared with that of classical biomarkers and therapeutic regimens; ii) the development of strategies with which to combine biomarkers to reach the cost-benefit balance; and iii) the development of strategies with which to administer circRNA and lncRNA disruptors into the human body with minimal side-effects and optimal efficacy. It is too early to assert definite values in clinical application.

In conclusion, the present review summarized the current achievements of circRNAs and lncRNAs in GC. Numerous biomarkers and targets were selected with theoretically optimal performance. However, several issues remain to be resolved. The translational procedures will encounter setbacks and difficulties. Nevertheless, it is expected that circRNAs and lncRNAs will play crucial roles in the diagnosis and treatment of GC in the future.

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Authors' contributions

BC and GL were mainly responsible for collecting relevant information and completing this review. WZ and YS were mainly responsible for consulting literature materials and revising the manuscript. BW was responsible for the conception of this review and the assignment of tasks. There was no additional assistance with manuscript preparation. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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