Circular RNAs in gastrointestinal cancer: Current knowledge, biomarkers and targeted therapy (Review)

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Abstract. Circular RNAs (circRNAs) are a type of endogenous non-coding RNAs that are connected at the 3' and 5' ends by exon or intron cyclization, which forms a covalently closed loop. They are stable, well conserved, exhibit specific expression in mammalian cells and can function as microRNA (miRNA or miR) sponges to regulate the target genes of miRNAs, which influences biological processes. Such as tumor proliferation, invasion, metastasis, apoptosis and tumor stage. circRNAs represent promising candidates for clinical diagnosis and treatment. In the present review, the biogenesis, classification and functions of circRNAs in tumors are briefly summarized and discussed. In addition, the participation of circRNAs in signal transduction pathways regulating gastrointestinal cancer cellular functions is highlighted.

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1. Introduction

Circular RNAs (circRNAs), arising from the non-canonical splicing of linear pre-mRNAs, are long non-coding RNAs that lack 5' and 3' ends and a poly(A) tail, and exhibit a circular form (1,2). They were initially identified in RNA viruses as viroids extracted from plants in 1976 (3) and were considered to present a low abundance and to represent errors in splicing (4). With the development of high-throughput RNA sequencing and bioinformatics analysis, >30,000 circRNAs have been discovered to date (5,6). The discovery that the RNA sponge function of circRNAs is involved in carcinogenesis and the malignant behavior of cancers has revealed a novel molecular mechanism involved in cancer and a number of other diseases, such as atherosclerosis and Alzheimer's disease (7).

Gastrointestinal cancer represents a class of cancers affecting the digestive system (8), such as colorectal cancer (CRC), gastric cancer (GC), esophageal cancer, hepatocellular carcinoma (HCC) and gallbladder cancer. These cancers constitute a serious threat to human health worldwide (9). Due to a lack of effective markers for early diagnosis, a number of patients are first diagnosed at an advanced stage of gastrointestinal cancer with the characteristics of regional or distant metastasis, which severely reduces the total 5-year survival rate (10). In recent years, circRNAs have been found to possess clinical potential for regulating the biological behavior and acting as critical biomarkers and treatment targets of gastrointestinal cancer. Therefore, in the present review, the potential significance and latent function of circRNAs in cancer diagnosis, prognosis and therapy in gastrointestinal cancer are briefly discussed, with an aim to provide a better understanding of the regulatory role of circRNAs in the pathogenesis of gastrointestinal cancer and to assist in the identification of effective therapeutic targets.

2. Biogenesis, biology and function of circRNAs

Biogenesis and categories of circRNAs. circRNAs are derived from the exons of coding regions or from 5'- or 3'-untranslated regions, introns, intergenic genomic regions as antisense RNAs (6). Among the identified circRNAs,

>80% originate from a single exon or several exons and can be referred to as exonic circRNAs (ecircRNAs), which result from by back-splicing, a process that differs from canonical linear RNA splicing (11). The generation of circRNAs can be facilitated by reverse complementary sequences, specific protein factors or exon-skipping (12). Currently, there are 4 possible models of circRNA biogenesis, as illustrated in Fig. 1: i) Exon-skipping mechanism or lariat-driven circularization model: The pre-mRNA transcript brings the original non-adjacent exons close to each other, followed by a reverse covalent connection between the 3' donor of the downstream exon and the 5' splice acceptor, which forms a lariat structure containing exon 2 (13). ii) Intron-pairing-driven circularization or back-splicing model: This involves a circulation structure and a linear product can be formed based on the pairing of the complementary motifs in the transcripts (such as Alu elements) when introns are removed or retained (11,14), forming an ecircRNA (circulatory structure containing exons 1 and 2) or an exon-intron circRNA (eiciRNA, a circulatory structure containing exons 1 and 2 and introns). iii) Intron cyclization model: A circular intronic RNA (ciRNA) is produced from intron lariats that escape debranching, and the production of such ciRNAs is highly associated with consensus motifs near splice sites and branchpoint sites (15). iv) RNA-binding protein (RBP)-driven circularization model: In this case, RBPs such as muscleblind-specific motifs within the flanking introns of the pre-mRNA and non-sequential flanking introns can form a bridge between the introns (16).

Functions of circRNAs. Due to the closed loop structures of circRNAs without 5'-3' polarity or a polyadenylated tail, circRNAs are much more stable than linear RNAs and impervious to deregulation by an RNA exonuclease or RNase (6,17). circRNAs with orthologous exons are highly structurally conserved in the third codons compared with intergenic and ciRNAs (18). They are widely expressed in a tissue-specific manner in the body. Although the abundance of circRNAs accounts for approximately 2-4% of all mRNAs, some of them are highly abundant in specific cell types, such as fibroblasts (19). All the characteristics mentioned above suggest that circRNAs are capable of indirectly or directly targeting RNAs and proteins, thereby regulating gene expression at multiple levels. Therefore, the development and progression of non-cancerous and cancerous diseases are affected. The various funcions of circRNAs are discussed below as follows:

i) Indirect regulation of the expression of genes as miRNA sponges. The most vital function of competing endogenous RNAs (ceRNAs) is to function as inhibitors of microRNA (miRNA or miRs) by sponging a specific miRNA at multiple binding sites in the circular sequence. miRNAs are small, endogenous RNAs (22 nucleotides in length) that play critical regulatory roles in animals and plants by targeting 3'UTRs of mRNAs for the cleavage or translational repression of protein-coding genes (20). ceRNAs contain several different miRNA response elements (MREs) within their sequences. ceRNAs act as miRNA sponges to restrain miRNAs, suppressing the expression of their target genes (Fig. 2). It has previously been demonstrated that several abundant ceRNAs can act as miRNA sponges in the cytoplasm, e.g., ciRS-7/CDR1 (21). CiRS-7, as an antisense transcript of the human circRNA cerebellar degeneration-related protein 1 transcript (CDR1), contains over 70 conserved binding sites for miRNA-7. The relatively high expression of CiRS-7 in a number of human tissues increases the expression of miR-7 target genes by suppressing miR-7 activity. The sponging of miR-7 by ciRS-7 affects the proliferation, migration and invasion of cancer cells by regulating oncogenes in cancer-related signaling pathways (16,22,23).

ii) Interacting with RNA-binding proteins. In addition to acting as miRNA sponges, circRNAs are also able to interact with, sequester and transport RBPs and subsequently influence target protein activities (24) (Fig. 2). Examples include circ-Foxo3, circ-MBL (muscleblind) and circCcnb1, etc (25). circ-Foxo3 is highly expressed in non-cancer cells and can bind cyclin-dependent kinase (CDK)2 and CDK inhibitor 1 (p21). The circ-Foxo3-p21-CDK2 complex can suppress the formation of the cyclin E/CDK2 complex, which results in the arrest of the cell cycle from the G1 to the S phase (26). In p53 mutant cells, circ-Ccnb1 can form a complex by interacting with H2AX and Bclaf1, which induces the death of breast cancer cells, whereas circ-Ccnb1 can prevent the cancer-suppressing effects by binding H2AX and wild-type p53 (25).

iii) Regulation of parental gene transcription and splicing. Some subclasses of circRNAs are enriched in the nucleus. They can function as post-transcriptional regulators of genes with various mechanisms. ciRNAs and eiciRNAs can participate in parental gene transcription and splicing under different regulatory models. ci-ankrd52 and ci-sirt7 positively promote parental gene transcription in *cis* regulatory elements by interacting with the RNA polymerase II (Pol II) complexes at the transcription sites of their host genes (16). In HeLa and 293 cells, eiciRNAs, such as circEIF3J and circPAIP can promote the transcription of parental genes in a *cis*-acting manner by interacting with U1 small nuclear ribonucleoproteins (snRNPs) and further combining with RNA polymerase II (Pol II) complexes (14) (Fig. 2).

iv) Translation and the modulation of translation. circRNAs have long been considered to be a type of endogenous non-coding RNA, which largely do not encode proteins (27). However, some researchers have demonstrated that a few circRNAs have the potential to be translated into proteins *in vitro* and *in vivo* when they possess internal ribosome entry sites (IRESs) upstream of start codons (28) (Fig. 2). Circular zinc-finger protein 609 (Circ-ZNF609) contains an open reading frame (ORF) and can be translated into a protein in murine myoblasts when driven by an IRES (29). The ORFs of circ-SHPRH and circ-FBXW7 are driven by IRESs and can be translated into functional proteins in a similar pattern to circ-ZNF609 (30,31). In addition, the most abundant base modification of RNAs, the N^6-methy-ladenosine (m6A) residues found in circRNAs, have been suggested to accelerate the cap-independent translation of circRNAs (32). Furthermore, the translation of certain linear mRNAs can be modulated by their cognate circRNAs. In HeLa cells, circPABPN1 can bind HuR, an RNA-binding protein that promotes translation, and the complex that is formed inhibits HuR binding to PABPN1 mRNA. Finally, the translation of PABRN1 is reduced (33).

v) Biomarkers. Due to their conservation, specificity and stability, circRNAs can be used as potential biomarkers for various diseases, particularly cancers (34). Growing evidence

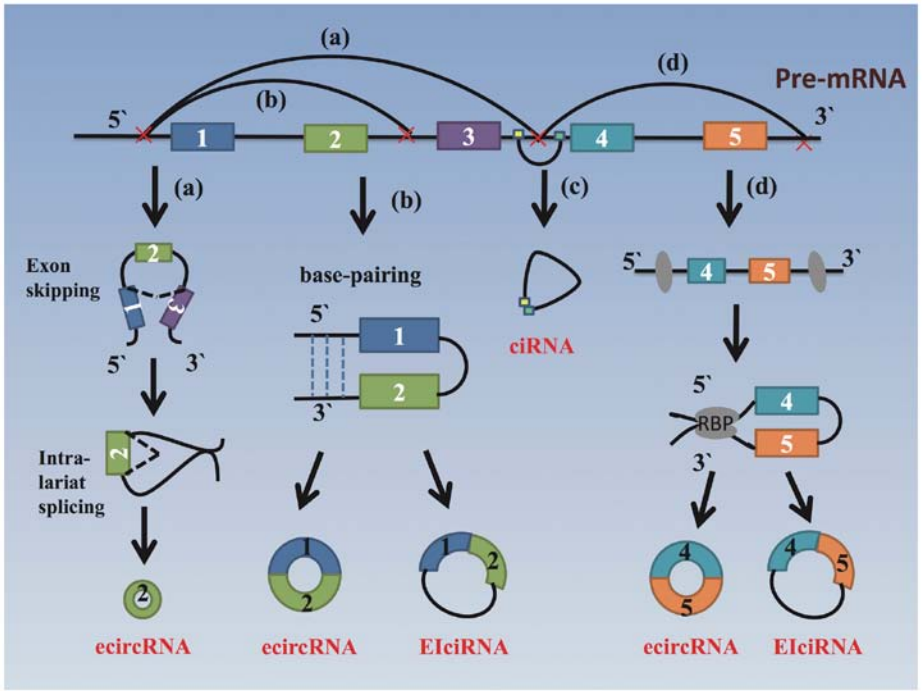

Figure 1. Models of circRNA biogenesis. Exons are indicated by rectangles and introns by thin lines, while dotted lines indicate base pairing. (a) Exon skipping or lariat-driven circularization. In this model, an exon-skipping event creates a lariat containing exon 2. This lariat is spliced internally, removing the intronic sequence and producing a circular RNA. (b) Direct back-splicing or intron-pairing-driven circularization. The flanking introns of exons 1 and 2 contain inverted repeats or complementary sequences, which form a circular structure through direct base pairing. The introns are removed or retained to form ecirRNA or eiciRNA. (c) Intron cyclization model. Some conserved motifs at both ends of the intron can promote the formation of a circular structure by an intron by preventing intron debranching through the debranching enzyme after splicing, which produces stable ciRNAs. (d) RBP-driven circularization. In this case, RBPs bind to introns upstream and downstream of exons 4 and 5. The RBPs are then attracted to each other and form a bridge between the introns. The 2'-hydroxyl group of the upstream intron then reacts with the 5'-phosphate of the downstream intron, which is followed by the 3'-hydroxyl of the 3'-exon reacting with the 5'-phosphate of the 5'-exon. The introns are removed or retained to form ecirRNA or eiciRNA. circRNA, circular RNA; ecirRNA, exonic circRNA; eiciRNA, exon-intron circRNA; RBP, RNA-binding protein.

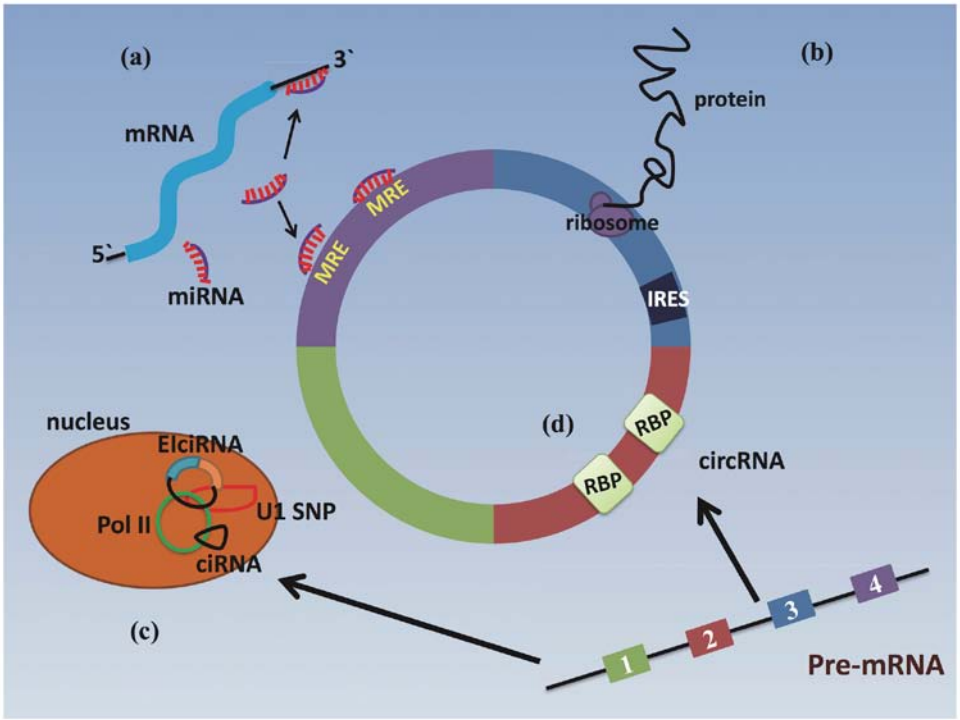

Figure 2. Regulatory mechanisms of circRNAs. (a) circRNAs function as miRNA sponges to protect their target mRNAs from miRNA attack, promoting the more efficient translation of target mRNAs. (b) circRNAs containing an IRES upstream of the start codon can be translated to produce proteins. (c) Model of circRNAs regulating the expression of a parental gene: ciRNAs can bind to RNA pol II and function in the promoter regions of genes. eiciRNA can interact with the U1 snRNP and then bind to RNA Pol II in the promoter to stimulate host gene expression. (d) circRNAs can function as RBP sponges that interact with RBPs. circRNA, circular RNA; IRES, internal ribosome entry site; ciRNA, circular intronic RNA; RNA Pol II, RNA polymerase II; snRNP, small nuclear ribonucleoprotein.

has indicated that a single circRNA possesses moderate diagnostic value, whereas combined circRNAs improve the diagnostic efficacy (35). circLPAR1 exhibits a low expression level in muscle-invasive bladder cancer (MIBC) and predicts a poor prognosis. It may regulate the invasion and metastasis of MIBC by targeting miR-762 and has the potential to serve as a stable biomarker for the prognosis of MIBC (36). In HCC, circSMARCA5 can stimulate apoptosis and suppress proliferation, invasion and metastasis. It exhibits a high accuracy for the diagnosis of HCC and may function as a potential biomarker for monitoring HCC (37). circ_0068871 can promote bladder cancer progression by modulating the miR-181a-5p/FGFR3 axis and activating STAT3 (38). Therefore, it may function as a potential biomarker.

3. circRNAs and gastrointestinal cancer

circRNAs are involved in the regulation of tumor progression. The deregulation of circRNAs affects cell proliferation, epithelial-mesenchymal transition, apoptosis, angiogenesis and the cell cycle (39). Thus, circRNAs have the potential to serve as tumor-targeted sites in tumor metastasis therapy. In this section, the diagnostic and prognostic significance of circRNAs in the development of tumor metastasis in gastrointestinal cancer is emphasized.

circRNAs in CRC. Colorectal cancer is a common type of malignant tumor with the third highest occurrence rate; however, it represents the second leading cause of cancer-related mortality worldwide. Over 1.8 million new cases and 881,000 deaths were attributed to CRC in 2018 (40). The majority of patients have already developed metastasis at the initial diagnosis. The development of CRC is a multistep process involving various factors, such as the BRAF gene, the APC gene and the KRAS oncogene mutations, abnormal chromosome segregation, abnormal hypermethy lation of gene promoter region, loss of function of the p53 gene (41,42). The more in depth understanding of the underlying molecular mechanisms of the development and progression of CRC is of utmost importance in order to identify and develop novel therapeutic markers and strategies. During CRC progression, some circRNAs play a positive regulatory role in the disease, while others do not. circRNAs play critical roles in the biological behavior of tumors.

circ-1569, located on the plus strand of chromosome 16q13.1, is upregulated in CRC tissues and is associated with aggressive characteristics in CRC. It directly inhibits miR-145 transcription by acting as a sponge. The miR-145 functional targets (E2F5, BAG4 and FMNL2) are then upregulated, which carry out a tumor-promoting function in CRC cells (43). This finding reveals a novel mechanistic connection between miR-145 and circ-1569 in regulating the progression of CRC, which may provide new insight into CRC progression and may lead to the development of therapeutic strategies for CRC prevention and treatment.

CDR1as (ciRS-7) harbors ~70 conserved binding sites. It exhibits a higher expression in CRC tissues than in the adjacent normal mucosa. CDR1as may influence tumor biological behavior as an miRNA sponge. The tumor inhibitory effect of miR-7 can be reversed by the overexpression of ciR-7 in HCT116 and HT29 cells. The target gene EGFR is then activated, which results in the increased proliferation, invasion and migration of CRC cells. This finding reveals that aberrant CDR1as/miR-7/EGFR may serve as a promising molecular target for the development of novel therapies to control CRC progression (44).

Several studies have demonstrated that miR-21 and miR-31 act as oncogenic molecules in various types of cancer. miR-21 can increase the proliferation and migration of colon cancer cells, such as SW480 and HCT116 cells (45). miR-31 can promote the resistance of CRC cells to 5-fluorouracil (46). circ-0026344, which is downregulated >5-fold in CRC tissues compared to normal tissues (47), acts as an miRNA sponge for miRNA-21 and miRNA-31. The low expression of circ-0026344 increases the expression of miR-21 and miR-31, which promotes the growth and invasion, but suppresses the apoptosis of CRC cells. The circ_0026344/miR-21/miR-31 regulatory axis plays an important role in the progression of CRC, and circ-0026344 can be used as a reliable prognostic biomarker in patients with CRC (41).

circRNA_103809 expression in colorectal cancer cell lines is lower than that in normal colorectal epithelial cells and can promote the proliferation and migration of CRC cells. As circRNA-103809 has a binding site within miR-532-3p, the deregulation of miR-532-3p can increase the expression of circRNA-103809 and Foxo4 in SW620 cells. This indicates that circRNA-103809 competitively binds to miR-532-3p as a ceRNA, which in turn regulates FOXO4 expression and thereby restrains the proliferation and migration of colorectal cancer cells (48).

Overall, almost 30 circRNAs participate in the progression of the cell cycle, proliferation, invasion, metastasis and apoptosis by functioning as oncogenes or antioncogenes in CRC. Further information on this matter is presented in Table I.

circRNAs in GC. GC is the most common type of tumor in the digestive system and was responsible for over 1,000,000 new cases in 2018, resulting in an estimated 783,000 deaths (110). These statistics render GC the fifth most frequently diagnosed type of cancer and the third leading cause of cancer-related mortality (40). Due to the high pateint mortality due to GC, the identification of appropriate molecular biomarkers for its early diagnosis and potential targets for GC therapy re urgently required.

circHIPK3 can sponge miR-124 and miR-29. The upregulation of circHIPK3 decreases the expression of miR-124 and miR-29b, which promotes GC cell proliferation. During this process, the mRNA transcriptional levels of 3 target genes (COL1A1, COL4A1 and CDK6) of the circHIPK3-miRNA-124/miRNA-29b axes are upregulated in GC cells. The survival status of GC can be predicted by detecting the expression levels of COL1A1 and COL4A1. These findings indicate that not only circHIPK3, but also COL1A1 and COL4A1 can serve as prognostic biomarkers of the survival of patients with GC, which expands our understanding of the transcriptional mechanisms in GC (111).

miR-206 has been reported to function as an inhibitory miRNA in GC, and its overexpression can inhibit the expression of CXCR4. circ_0056618, which is upregulated in GC, can sponge miR-206 in GC, and suppress cell

Table I. Summary of the expression of circRNAs and the circRNA/miRNA axis in signaling pathways related to colorectal cancer.

circRNA	Expression	miRNA sponge	Intersection molecules and/or pathway	Function	(Refs.)
hsa_circ_001569	↑	miR-145	E2F5, BAG4, FMNL2↑	Proliferation (+) Invasion (+)	(43)
hsa_circ_0071589	↑	miR-600	EZH2↑	Viability (+) Proliferation (+) Invasion (+) Migration (+)	(49)
ciRS-7	↑	miR-7	EGFR/RAF1/MPK pathway	Invasion (+) Metastasis (+)	(50)
hsa_circ_0020397	↑	miR-138	TERT, PD-L1↓	Viability (+) Apoptosis (-)	(42)
Circular RNA ZNF609	↓	miR-150-5p	AKT3↑	Proliferation (-) Migration (-)	(51)
hsa_circ_0000284	↑	miR-7	FAK, IGF1R, EGFR, YY1↑	Proliferation (+) Migration (+) Invasion (+) Apoptosis (-)	(52)
hsa_circ_000984	↑	miR-106b	CDK6↑	Proliferation (+) Migration (+) Invasion (+) Cell Cycle (+)	(53)
hsa_circ_0026344	↓	miR-21 miR-31 miR-183	PTEN↓ SATB2, FIH-1α↓	Proliferation (-) Invasion (-) Apoptosis (+)	(40,54)
circRNA_100290	↑	miR-516b	FEDZ4-Wnt/β-catenin signal pathway↑	Proliferation (+) Migration (+) Invasion (+) Apoptosis (-)	(55)
hsa_circRNA_103809	↓	miR-532-3p	FOXO4↓	Proliferation (+) Migration (+)	(48)
circRNA-ACAP2	↓	miR-21-5p	Tiam1↑	Proliferation (+) Clonogenicity (+) Migration (+) Invasion (+)	(56)
circITGA7	↓	miR-370-3p	NF1↓-Ras signaling pathway↑	Proliferation (-) Migration (-)	(57)
cir-ITCH	↓	miR-7/20a	Wnt/β-catenin; ITCH, TCF, c-myc, cyclinD1	-	(58)
circ-BANP	↑	-	PI3K/Akt pathway↑	Proliferation (+)	(59)
hsa_circ_104700	↓	miR-141/500a/509-5p miR-619-3p/578	-	-	(24)
hsa_circ_0007031	↑	miR-885-3p	-	-	(60)
hsa_circ_0007006	↑	-	AKT3	-	(24)
hsa_circ_0048234	↓	miR-671-5p	EGFR↓	Crr (-)	(60)
hsa_circ_105055	↑	miR-7	PRKCB, EPHA3, BRCA1, ABCC1	Proliferation (+) Apoptosis (-)	(61)
hsa_circ_0000504	↑	miR-485-5p	STAT3↓	5-FU resistance	(60)
circCCDC66	↑	miRNA-33b miR-93	MYC↑	Proliferation (+) Migration (+)	(62)
hsa_circ_0005075	↑	-	Wnt/β-catenin pathways↑	Metastasis (+) Invasion (+) Growth (+)	(63,64)
circPIP5K1A	↑	miR-1273a	-	Migration (+) Invasion (+)	(65)
circ_0000218	↑	miR-139-3p	RAB1A↑	Proliferation (+) Metastasis (+)	(66)
circ_0079993	↑	miR-203a-3p.1	CREB1↑	Proliferation (+)	(67)
circ_0021977	↓	miR-10b-5p	P21↓/P53↓	Proliferation (-) Migration (-) Invasion (-)	(68)
circ_0055625	↑	miR-106b-5p (miR-106b)	ITGB8↑	Proliferation (+) Metastasis (+)	(69)

Table I. Continued.

circRNA	Expression	miRNA sponge	Intersection molecules and/or pathway	Function	(Refs.)
Circular RNA CBL.11	↑	miR-6778-5p	YWHAE↑	Proliferation (-)	(70)
circDDX17	↓	miR-31-5p	KANK1↓	Metastasis (-) Invasion (-) 5-Fu resistance (-) Apoptosis (+)	(71)
circDENND4C	↑	miR-760	GLUT1↑	Proliferation (+) Migration (+) Glycolysis (+)	(72)
hsa_circ_0007534	↑	miR-613	SLC25A22↑	Proliferation (+) Migration (+) Invasion (+) Glycolysis (+) Colony formation (+)	(73)
circ_0056618	↑	miR-206	CXCR4, VEGF-A↑	Proliferation (+) Migration (+) Angiogenesis (+)	(74)
circ_0001313	↑	miR-510-5p	AKT2↑	Proliferation (+) Apoptosis (-)	(75)
circAPLP2	↑	miR-101-3p miR-485-5p	NOTCH↑ FOXK1↑	Proliferation (+) Migration (+) Invasion (+) Apoptosis (-)	(76)
circ_001971	↑	miR-29c-3p	VEGFA↑	Proliferation (+) Invasion (+) Angiogenesis (+)	(77)
circPRKDC	↑	miR-375	FOXMI↑	5-Fu resistance (+)	(78)
circHUWE1	↑	miR-486	-	Proliferation (+) Migration (+) Invasion (+)	(79)
circSAMRCC1	↑	miR-140-3p	MMPs↑	Proliferation (+) Migration (+) Invasion (+) Metastasis (+)	(80)
circCTNNA1	↑	miR-149-5p	FOXM1↑	Proliferation (+) Migration (+) Invasion (+)	(81)
circRUNX1	↑	miR-145-5P	IGF1↑	Proliferation (+) Migration (+) Metastasis (+) Apoptosis (-)	(82)
circ_0001946	↑	miR-135a-5p	EMT pathway↑	Proliferation (+) Migration (+) Invasion (+)	(83)
hsa_circ_0038646	↑	miR-331-3p	GPIK3↑	Proliferation (+) Migration (+)	(84)
circIFT80	↑	miR-1236-3p	HOXB7↑	Proliferation (+) Migration (+) Invasion (+)	(85)
circFAT1	↑	miR-520b miR-302c-3p	UHRF1↑	Proliferation (+) Glycolysis (+) Apoptosis (-)	(86)
hsa_circ_001680	↑	miR-340	BMI1↑	Proliferation (+) Migration (+)	(87)
hsa_circ_102209	↑	miR-761	RIN1↑	Proliferation (+) Metastasis (+) Invasion (+) Apoptosis (-)	(88)
circCBL.11	↓	miR-6778-5p	YWHAE↓p53↓	Proliferation (+)	(70)
circCCT3	↑	miR-613	WNT3↑VEGFA↑	Metastasis (+) Invasion (+) Apoptosis (-)	(89)
circFARSA	↑	miR-330-5p	LASP1↑	Proliferation (+) Migration (+) Invasion (+)	(90)
hsa_circ_0079993	↑	miR-203a-3p	CREB1↑	Proliferation (+)	(67)
hsa_circ_0005615	↑	miR-149-5p	TNKS↑	Proliferation (+)	(91)
circ_0000218	↑	miR-139-3p	RAB1A↑	Proliferation (+) Metastasis (+)	(66)
hsa_circ_0001178	↑	miR-382/587/616	ZEB1↑	Metastasis (+) Invasion (+)	(92)
circPACRGL	↑	miR-142-3p miR-506-3p	TGF-β1↑	Proliferation (+) Migration (+) Invasion (+)	(93)
hsa_circ_0001806	↑	miR-193-5p	COL1A1↑	Metastasis (+) Invasion (+)	(94)
hsa_circ_0008285	↓	miR-382-5p	PTEN↓	Proliferation (-) Migration (-)	(95)
hsa_circ_0128846	↑	miR-1184	AJUBA↑	Proliferation (+) Migration (+) Invasion (+)	(96)
hsa_circ_0060745	↑	miR-4736	CSE1L↑	Proliferation (+) Metastasis (+)	(97)

Table I. Continued.

circRNA	Expression	miRNA sponge	Intersection molecules and/or pathway	Function	(Refs.)
hsa_circ_0005963	↑	miR-122	PKM2↑	Chemoresistance (+)	(98)
hsa_circ_0053277	↑	miR-2467-3p	MMP14↑	Proliferation (+) Migration (+) EMT (+)	(99)
circHIPK3	↑	miR-1207-5p	FMNL2↑	Proliferation (+) Metastasis (+) Invasion (+)	(100)
circPRMT5	↑	miR-377	E2F3↑	Proliferation (+) Migration (+)	(101)
circ_0004277	↑	miR-512-5p	PTMA↑	Proliferation (+) Apoptosis (-)	(102)
hsa_circ_0137008	↓	miR-338-5p	-	Proliferation (-) Migration (-) Invasion (-)	(103)
circ_0007142	↑	miR-122-5p	CDC25A↑	Proliferation (+) Migration (+) Invasion (+)	(104)
circ_100876	↑	miR-5166	-	Proliferation (+) Metastasis (+) Apoptosis (-)	(105)
circAGFG1	↑	miR-4262 miR-185-5p	YY1↑CTNNB1↑	Proliferation (+) Migration (+) Invasion (+) Apoptosis (-)	(106)
circPIP5K1A	↑	miR-1273a	-	Migration (+) Invasion (+)	(65)
circVAPA	↑	miR-125a	CREB5↑	Migration (+) Invasion (+) Glycolysis (+)	(107)
circNOL10	↓	miR-135a/b-5p	KLF9↓	Proliferation (-) Migration (-) Invasion (-)	(108)
circCAMSAP1	↑	miR-328-5p	E2f1↑	Proliferation (+)	(109)

circRNA, circular RNA; ↓, downregulation; ↑, upregulation; -, no finding; (+), promotion; (-), inhibition.

proliferation and invasion by upregulating CXCR4. Therefore, circ_0056618/miR-206/CXCR4 is able to improve the survival rates of patients with GC by inhibiting GC cell proliferation and metastasis (112).

circRNAs also function as anti-oncogenes. circLARP4, derived from exons 9 and 10 of the LARP4 gene, is overexpressed in GC. It can inhibit DNA synthesis, cell proliferation and invasion by sponging miR-424 and subsequently upregulates the expression of the LATS1 and YAP genes in GC. Thus, circLARP4 may function as a tumor-suppressive factor in GC by regulating the miR-424/LATS1/YAP signaling pathway. circLARP4 can also serve as an independent prognostic marker for the 5-year overall survival rate of patients with GC and patients undergoing chemotherapy (113).

Phosphatase and tensin homolog (PTEN) is a tumor suppressor that is mutated in various types of cancers at a high frequency (114). It can be targeted and regulated by miR-130a and miR-107, thereby affecting the activity of cancer cells (115,116). circ-ZFR can regulate the expression of miR-130a and miR-107 by sponging these miRNAs, thereby regulating the expression of PTEN. This indicates that circ-ZFR can suppress GC cell propagation and the cell cycle, and can promote apoptosis by sponging miR-107/miR-130a and modulating PTEN, which provides comprehensive insight into the regulatory role of the circ-ZFR/miR-130a/miR-107/PTEN axis in GC and facilitates the discovery of novel therapeutic targets for the treatment of GC (117).

Although there are many circular RNAs that serve as biomarkers for GC, further clinical and basic research is required to improve the survival time of patients with GC. Over 15 circRNAs participate in the cell cycle, proliferation, invasion, metastasis and apoptosis by functioning as oncogenes or anti-oncogenes in GC. For further information on circRNAs in GC, please refer to Table II.

circRNAs in esophageal cancer. Esophageal cancer is one of the most common gastrointestinal malignancies and was ranked 7th in terms of its incidence and 6th overall in 2018. Patients with esophageal cancer present various symptoms, such as difficulty swallowing, a hoarse voice and weight loss (40,183). However, the clinical diagnosis of esophageal cancer is mainly dependent on biopsy using an endoscope, and the most common treatments are surgery, chemotherapy and radiation, depending on the cancer stage and location (184). circRNAs mainly function as oncogenes in esophageal cancer. These circRNAs influence the expression of specific genes or their associated signaling pathways. In the present review, the findings of recent investigations into the role of circRNAs in the development and progression of esophageal cancer are discussed and summarized.

The most well-known circRNA, ciRS-7, has been reported to contain >70 binding sites for miR-7. It can suppress miR-7 activity by acting as an miR-7 sponge (185,186). In addition, it also harbors 19 miR-876-5p-binding sites and functions

Table II. Summary of the expression of circRNAs and the circRNA-miRNA axis in signaling pathways related to gastric cancer.

circRNA	Expression	miRNA sponge	Intersection molecules and/or pathway	Function	(Refs.)
circRNA-100269	↓	miR-630	-	Proliferation (+)	(118)
circLARP4	↓	miR-424	LATS1↓	Proliferation (-) Invasion (-)	(113)
circPVT1	↑	miR-125b	E2F2↑	Proliferation (+)	(119)
hsa_circ_0005075	↓	miR-23b-5p	Wnt/β-catenin signal pathway	-	(120)
hsa_circ_000425	-	miR-17/ miR-106b	p21/BIM↑	Cell growth (-)	(121)
circRBMS3	↑	miR-153	SNAI1↑	Proliferation (+) Invasion (+)	(122)
hsa_circ_0000673	↓	miR-532-5p	RUNX3↑	Proliferation (+) Invasion (+)	(123)
circ_0056618	↑	miR-206	CXCR4↑	Proliferation (+) Metastasis (+)	(112)
circHIPK3	↑	miR-124/ miR-29b	-	Proliferation (+)	(111)
hsa_circ_0000993	↓	miR-214-5p	-	Migration (+) Invasion (+) Proliferation (+)	(124)
hsa_circ_0000096	↓	miR-224/200a	cyclinD1, CDK6, MMP2/9, Ki67, VEGF↓	Proliferation (-) Migration (-) Cell Cycle (-)	(125)
hsa_circ_0000026	↓	miR-23a/23b/ 581/146a/450a	-	Regulates transcription, RNA metabolism, gene expression and gene silencing	(126)
hsa_circ_104916	↓	-	E-cadherin↓; N-cadherin↑	Proliferation (+) Migration (+)	(127)
hsa_circ_0000520	↓	miR-556-5p/ 521/1204/ 512-5p/663b/ 1258/1233/ 1296/146b-3p	-	TNM stage of gastric cancer (-)	(128)
circ-ZFR	↓	miR-130a/107	PTEN, p53↓	Proliferation (-) Apoptosis (+)	(117)
circ-ERBB2	↑	miR-503/ miR-637	CACUL1↑/ MMP-19↑	Proliferation (+) Invasion (+)	(129)
hsa_circ_0001368	↓	miR-6506-5p	FOXO3↓	Proliferation (-) Invasion (-)	(130)
hsa_circ_0001821	↓	miR-197	MTDH/PTEN/ AKT↓	Proliferation (-) Metastasis (-)	(131)
circ-ZNF609	↑	miR-145-5p	-	Proliferation (+) Invasion (+)	(132)
circ-GRAMD1B	↓	miR-130a-3p	PTEN/P21↓	Proliferation (-) Migration (-) Invasion (-)	(133)
circ-NOTCH1	↑	miR-637	Apelin↑	Proliferation (+) Invasion (+) Apoptosis (-)	(134)
hsa_circ_0000291	↑	miR-183	ITGB1↑	Proliferation (+) Migration (+)	(135)
circ_SPECC1	↓	miR-526b	KDM4A/ YAP1 pathway (+)	Proliferation (-) Invasion (-) Apoptosis (+)	(136)
hsa_circ_0092306	↑	miR-197-3p	PRKCB↑	Proliferation (+) Migration (+) Invasion (+)	(137)
circ_PRMT5	↑	miR-145/1304	MYC↑	Proliferation (+) Invasion (+) Apoptosis (-)	(138)
hsa_circ_006100	↑	miR-195	GPRC5A↑	Proliferation (+) Metastasis (+) Invasion (+) Apoptosis (-)	(139)
circ_EIF4G3	↑	miR-335	-	Proliferation (+) Metastasis (+) Invasion (+)	(140)

Table II. Continued.

circRNA	Expression	miRNA sponge	Intersection molecules and/or pathway	Function	(Refs.)
circ_LMTK2	↑	miR-150-5p	c-Myc↑	Proliferation (+) Metastasis (+)	(141)
circ_DCAF6	↑	miR-1231/1256	-	Proliferation (+) Metastasis (+) Invasion (+)	(142)
hsa_circ_0067997	↑	miR-515-5p	XIAP↑	Proliferation (+) Metastasis (+) Invasion (+)	(143)
circ_NHSL1	↑	miR-1306-3p	SIX1↑	Proliferation (+) Metastasis (+) Invasion (+)	(144)
circ_0000267	↑	miR-503-5p	HMGA2↑	Proliferation (+) Migration (+) Invasion (+)	(145)
circRHOBTB3	↓	miR-654-3p	p21↓	Proliferation (-)	(146)
circREPS2	↓	miR-558	RUNX3↓ β-catenin signaling pathway (+)	Proliferation (-) Migration (-) Invasion (-)	(147)
circ_0006282	↑	miR-155	FBXO22↑	Proliferation (+) Migration (+)	(148)
circMTO1	↓	miR-3200-5p	PEBP1↓	Proliferation (-) Migration (-) Invasion (-)	(149)
hsa-circ-0017639	↑	miR-224-5p	USP3↑	Proliferation (+) Metastasis (+)	(150)
circ_0008035	↑	miR-599	EIF4A1↑	Proliferation (+) Apoptosis (-)	(151)
hsa_circ_0001017	↓	miR-197	RHOB↓	Proliferation (-) Migration (-) Invasion (-)	(152)
circ_PRL15	↑	miR-502-3p	OLFM4↑ STAT3 pathway (+)	Proliferation (+) Migration (+) Invasion (+) Apoptosis (-)	(153)
circNRIP1	↑	miR-182	ROCK1↑	Migration (+) Invasion (+) Apoptosis (-)	(154)
circCYFIP2	↑	miR-1205	E2F1↑	Proliferation (+) Metastasis (+) Invasion (+)	(155)
hsa_circ_000684	↑	miR-186	ZEB1↑	Proliferation (+) Migration (+) Invasion (+)	(156)
circ_OXCT1	↓	miR-136	SMAD4↓	Metastasis (-)	(157)
circ_MAT2B	↑	miR-515-5p	HIF-1α↑	Metastasis (+)	(158)
hsa_circ_0000670	↑	miR-384	SIX4↑	Proliferation (+) Migration (+) Invasion (+)	(159)
circ_CEP85L	↓	miR-942-5p	NFKBIA↓	Proliferation (-) Invasion (-)	(160)
circ_RanGAP1	↑	miR-877-3p	VEGFA↑	Proliferation (+) Metastasis (+)	(161)
circCCDC9	↓	miR-6792-3p	CAV1↓	Proliferation (-) Migration (-) Invasion (-)	(162)
circPIP5K1A	↑	miR-376c-3p miR-671-5p	ZNF146↑ KRT80↑	Proliferation (+) Migration (+) Invasion (+)	(163,164)
hsa_circ_0000467	↑	miR-326-3p	-	Proliferation (+) Invasion (+)	(165)
circHIAT1	↓	miR-21	-	Proliferation (-)	(166)
circMAN2B2	↑	miR-145	JNK↑ PI3K/AKT pathway (-)	Proliferation (+) Migration (+)	(167)
circ_0000190	↓	miR-1252	PAK3↓	Proliferation (-) Migration (-)	(168)
hsa_circ_0003159	↓	miR-223-3p	NDRG1↓	Proliferation (-) Migration (-) Invasion (-) Apoptosis (+)	(169)
circRBM33	↑	miR-149	IL-6↑	Proliferation (+) Migration (+) Invasion (+) Apoptosis (-)	(170)
circ_0001023	↑	miR-409-3p	PHF10↑	Proliferation (+) Metastasis (+) Apoptosis (-)	(171)
circ_104433	↑	miR-497-5p	CDC25A↑	Proliferation (+) Apoptosis (-)	(172)

Table II. Continued.

circRNA	Expression	miRNA sponge	Intersection molecules and/or pathway	Function	(Refs.)
circ_0005075	↑	miR-431	p52/EMT↑	Proliferation (+) Migration (+)	(173)
hsa_circ_0001546	↓	miR-421	ATM↓ Chk2/ p52 pathway (-)	Proliferation (-) Chemoresistance (-)	(174)
circSMC3	↑	miR-4720-3p	TJP1↑	Proliferation (+) Migration (+)	(175)
circSHKBP1	↑	miR-582-3p	HUR/VEGF↑	Proliferation (+) Migration (+) Invasion (+) Angiogenesis (+)	(176)
hsa_circ_0007766	↑	miR-1233-3p	GDF15↑	Proliferation (+) Migration (+) Invasion (+)	(177)
circ_100876	↑	miR-136	MIEN1↑	Proliferation (+) Metastasis (+) Invasion (+)	(178)
circ_ATAD1	↑	miR-140-3p	YY1↑/ PCIF1 signaling pathway (+)	Proliferation (+)	(179)
hsa_circ_0023642	↑	miR-223	-	Proliferation (+) Migration (+) Invasion (+)	(180)
circ_DUSP16	↑	miR-145-5p	-	Proliferation (+) Invasion (+)	(181)
circATXN7	↑	miR-4319	ENTPD4↑	Proliferation (+) Invasion (+) Apoptosis (-)	(182)

circRNA, circular RNA; ↓, downregulation; ↑, upregulation; -, no finding; (+), promotion; (-), inhibition.

as a sponge of miR-876-5p, which directly targets the tumor antigen MAGE-A family and suppresses the migration and invasion of esophageal squamous cell carcinoma (ESCC) cells. The discovery of ciRS7 provides a novel potential therapeutic target for the treatment of ESCC (187).

cir-ITCH is expressed in low levels in esophageal carcinoma. As a potential tumor suppressor, it upregulates the expression of the miRNA target gene, ITCH, by sponging miRNAs, such as miR-7, miR-17 and miR-214, which results in the suppression of the canonical Wnt pathway by inhibiting phosphorylated Dvl2, preventing oncogenesis. This indicates that the low expression of cir-ITCH increases cell viability and promotes proliferation via the cir-ITCH/miR-7/miR-17/miR-214/ITCH/Dvl2/Wnt/β-catenin signaling pathway in ESCC cells (188). For further information regarding the regulation of signaling by other circRNAs in esophageal cancer, please refer to Table III.

circRNAs in HCC. HCC is the 4th most common cause of cancer-related mortality and the 6th most diagnosed type of cancer worldwide, accounting for approximately 841,000 new cases and 782,000 deaths annually (40). However, due to the high frequency of disease metastasis, recurrence and poor diagnoses, HCC remains one of the most lethal forms of cancer worldwide, and liver resection and transplantation are the main therapies applied (202). Therefore, it is necessary to identify potential biomarkers for the early detection of HCC and to explore new strategies for HCC treatment. A large amount of evidence related to cancer diagnostics and therapeutics indicates that circRNAs are involved in HCC progression, and may therefore serve as sensitive biomarkers and miRNA sponges for the detection of carcinogenesis, as well as for the monitoring of therapies for HCC (203,204). However, the expression profiles, functions and deregulation of circRNAs in HCC remain to be determined.

Hsa_circ_0005057 was first found to be expressed at significantly higher levels in HCC tissues than in adjacent liver tissues. Hsa_circ_0005057 inhibits the expression and function of miR-23b-5p, and miR-23b-5p is subsequently downregulated. In addition, a potential interaction between miR-23b-5p and the Wnt/β-catenin signaling pathway has been identified. The ultimate effect of hsa_circ_0005057 is to promote the growth of tumors (120).

It has been demonstrated that Cdr1as expression is upregulated in HCC tissues compared with adjacent non-tumor tissues. The knockdown of Cdr1as inhibits HCC cell proliferation and invasion by targeting miR-7 and CCNE1 and PIK3CD, and Cdr1as functions as an oncogene partly by targeting miR-7 in HCC (202,205,206). Hsa_circ_0001649, which is significantly downregulated in HCC tissues, exhibits miRNA-binding sites for miR-1283, miR-4310 and miR-182-3p and is positively associated with the metastasis and invasion of HCC (207). circRNA mitochondrial translation optimization 1 homologue (circMTO1; hsa_circRNA_0007874/hsa_circRNA_104135) is downregulated in HCC tissues, and miR-9 is overexpressed in HCC, which results in the HCC cell proliferation and invasion. The finding that circMTO1 co-localizes with miR-9 in the cytoplasm and that this co-localization is decreased in tumors compared to adjacent non-tumor tissues, has indicated that circMTO1 can inhibit the progression of HCC by serving as a

Table III. Summary of the expression of circRNAs and the circRNA-miRNA axis in signaling pathways related to esophageal cancer.

circRNA	Expression	miRNA sponge	Intersection molecules and/or pathway	Function	(Refs.)
cir_ITCH	↓	miR-7/17 miR-214	ITCH↑-Dvl2↑-Wnt/β-catenin signaling pathway (-)	Viability (-) Proliferation (-)	(188)
ciRS_7	↑	miR-876-5p	MAGE-A↑	Metastasis (+)	(187)
		miR-7	HOXB13-mediated NF-κB/p65 pathway(+)	Proliferation (+) Invasion (+)	(183)
hsa_circ_001059	↑	miR-30c-1*/30c-2*/122*/139-3p/339-5p/1912	-	Influence Radiotherapy Resistance	(189)
hsa_circRNA_100873	↑	miR-663a	-	Metastasis (+)	(190)
hsa_circ_0006948	↑	miR-490-3p	HMGA2↑	Proliferation (+) Migration (+) Invasion (+)	(191)
circ_100367	↑	miR-217	Wnt3 pathway↑	Proliferation (+) Migration (+) Radioresistance (+)	(192)
hsa_circ_0004771	↑	miR-339-5p	CDC25A↑	Proliferation (+) Migration (+) Invasion (+)	(193)
circ_0003340	↑	miR-564	TPX2↑	Proliferation (+) Invasion (+) Apoptosis (-)	(194)
circRAD23B	↑	miR-5095	PARP2↑ AKT2↑	Proliferation (+) Invasion (+)	(195)
circZNF292	↑	miR-206	AMPK/PI3K/AKT signaling pathway (-)	Proliferation (+) Migration (+) Invasion (+) Apoptosis (-)	(196)
circPRKCI	↑	miR-186-5p	PARP9↑	Proliferation (+) Radiosensitivity (-)	(197)
hsa_circ_0006168	↑	miR-100	mTOR↑	Proliferation (+) Migration (+) Invasion (+)	(198)
circUBAP2	↑	miR-422a	Rab10↑	Proliferation (+) Migration (+) Invasion (+)	(199)
hsa_circ_0000654	↑	miR-149-5p	IL-6↑/STAT3 signaling pathway (+)	Proliferation (+) Migration (+) Invasion (+) Apoptosis (-)	(200)
circLARP4	↓	miR-1323	PTEN↓	Proliferation (-) Migration (-) Apoptosis (+)	(201)

circRNA, circular RNA; ↓, downregulation; ↑, upregulation; -, no finding; (+), promotion; (-), inhibition.

sponge of oncogenic miR-9 to promote p21 expression (208). For further information on circRNAs in HCC, please refer to Table IV.

circRNAs in gallbladder cancer. Gallbladder cancer is the most common malignant neoplasm of the biliary tract, with a low 5-year overall survival rate of 5-10% (275,276). Gallbladder cancers are detected either incidentally or by clinical manifestation (277). However, patients with gallbladder cancer who present symptoms are usually at the advanced disease stage. Therefore, 90% of gallbladder cancers are diagnosed at regional or metastatic stages. It is widely acknowledged that surgical resection is the only curative method for gallbladder cancer, and other treatment modalities, such as chemoradiotherapy, are not effective in most cases without surgical resection (278). Due to the high recurrence, morbidity and mortality of gallbladder cancer, further research is warranted to discover potential biomarkers for the early detection and prognosis predication of this type of cancer.

Recent studies have demonstrated that circHIPK3 plays a critical role, not only in CRC, but also in gallbladder cancer. It is upregulated in human gallbladder cancer tissues and can modulate miR-124 downregulation and ROCK1-CDK6 upregulation as an miRNA sponge, thereby promoting gallbladder cancer cell growth (279). circFOXP1 (hsa_circ_0008234), derived from the exon region of the

Table IV. Summary of the expression of circRNAs and the circRNA-miRNA axis in signaling pathways related to hepatocellular carcinoma.

circRNA	Expression	miRNA sponge	Intersection molecules and/or pathway	Function	(Refs.)
circRNA_10720	↑	miRNA	Vimentin↓	EMT (+)	(209)
hsa_circ_103809	↓	miR-620	-	Proliferation (-) Migration (-) Invasion (-)	(210)
circRNA_CDYL	↑	miR-328-3p miR-892a	HIF1N↑ NOTCH2↓ SURVIVIN↓ HDGF↑ NC↑ PI3K/Akt pathway	Proliferation (+) Self-renewal (+) Chemoresistance (+)	(211)
hsa_circ_0005986	↓	miR-129-5p	NOTCH1↓	Cell cycle (-) Proliferation (-)	(212)
Hsa_circ_0004018	↓	miR-30e-5p miR-626	MYC pathway	-	(213)
hsa_circ_0001649	↓	miR-127-5p miR-4688 miR-612	SHPRH↓	Proliferation (-) Migration (-) Invasion (-)	(214)
hsa_circ_101280	↑	miR-375	JAK2↑	Proliferation (+) Apoptosis (-)	(215)
hsa_circ_0016788	↑	miR-486	CDK4 pathway	Proliferation (+) Invasion (+) Apoptosis (-)	(216)
circRNA-ZNF652	↑	miR-203 miR-502-5p	Snail↑	Metastasis (+) Poor Prognosis	(217)
hsa_circ_0000673	↑	miR-767-3p	SET↑	Proliferation (+) Invasion (+)	(218)
hsa_circ_0005075	↑	miR-431	-	Proliferation (+) Migration (+) Invasion (+)	(219)
circ_001569	↑	miR-411-5p miR-432-5p	-	Proliferation (+) Metastasis (+) Poor prognosis	(220)
circ_0021093	↑	miR-766-3p	MTA3 pathway	Proliferation (+) Metastasis (+) Invasion (+) Poor prognosis Apoptosis (-)	(221)
circ_0000267	↑	miR-646	-	Proliferation (+) Metastasis (+) Invasion (+) Apoptosis (-)	(222)
circ_PRKC1	↑	miR-545	AKT3↓	Invasion (+) Apoptosis (+)	(223)
hsa_circ_0091570	↓	miR-1307	ISM1↓	Proliferation (-) Migration (-) Apoptosis (+)	(224)
hsa_circ_0078710	↑	miR-31	HDAC2 CDK2↑	Proliferation (+) Migration (+) Invasion (+)	
circ_SETD3	↓	miR-421	MAPK14↓	Proliferation (-)	(225)
circ_0008450	↑	miR-548p	-	Proliferation (+) Migration (+) Invasion (+) Apoptosis (-)	(226)
hsa_circ_0079929	↓	-	PI3K/Akt/ mTOR pathway	Proliferation (-) Cycle (-)	(227)
cdr1as	↑	miR-7	CCNE1, PIK3CD↑	Proliferation (+) Invasion (+)	(206)
circ_ADAMTS14	↓	miR-572	RCAN1↓	Proliferation (+) Invasion (+) Apoptosis (-)	(228)
circ_TRIM33-12	↓	miR-191	TET1↑ 5hmC↓	Proliferation (-) Migration (-) Invasion (-) Immune evasion (-)	(229)
circ_MTO1	↓	miR-9-p21	-	Proliferation (-) Invasion (-)	(208)
hsa_circ_0000594	↑	miR-217	SIRT1↑	Proliferation (+) Invasion (+) Apoptosis (-)	(230)
circ_0067934	↑	miR-1324	FZD5↑-β-catenin↓	Proliferation (+) Migration (+) Invasion (+)	(231,232)

Table IV. Continued.

circRNA	Expression	miRNA sponge	Intersection molecules and/or pathway	Function	(Refs.)
circVAPA	↑	miR-377-3p	PSAP↑	Proliferation (+)	(233)
circSETD3	↓	miR-421	MAPK14↓	Proliferation (-)	(225)
circ_ZFR	↑	miR-3619-5p	CTNNB1↑	Proliferation (+)	(234)
circ_SMAD2	↓	miR-629	-	Migration (-) Invasion (-)	(235)
circABCB10	↓	miR-340-5p miR-452-5p	NRP1/ABL2↓	Proliferation (-) Migration (-) Invasion (-)	(236)
hsa_circ_0056836	↑	miR-766-3p	FOSL2↑	Proliferation (+) Migration (+) Invasion (+)	(237)
hsa_circ_0003141	↑	miR-1827	UBAP2↑	Proliferation (+) Invasion (+) Apoptosis (-)	(238)
hsa_circ_0101145	↑	miR-548c-3p	LAMC2↑	Proliferation (+) Migration (+) Invasion (+)	(239)
circMYLK	↑	miR-362-3p	Rab23↑	Proliferation (+) Migration (+) Invasion (+)	(240)
hsa_circ_0008450	↑	miR-214-3p	EZH2↑	Proliferation (+) Migration (+) Invasion (+)	(241)
circ_0015756	↑	miR-7	FAK↑	Proliferation (+) Migration (+) Invasion (+) Apoptosis (-)	(242)
circ_5692	↓	miR-328-5p	DAB2IP↓	Proliferation (-)	(243)
hsa_circ_0070269	↓	miR-182	NPTX1↓	Proliferation (-) Invasion (-)	(246)
hsa_circ_0000204	↓	miR-191	KLF6↓	Proliferation (-)	(244)
circZFR	↑	miR-511	AKT1↑	Proliferation (+) Migration (+) Invasion (+) Apoptosis (-)	(245)
circ_0005075	↑	miR-335	MAPK1↑	Proliferation (+)	(246)
circ_0001955	↑	miR-515a-5p	TRAF6/MAPK1↑	Proliferation (+)	(247)
circPVT1	↑	miR-203	HOXD3↑	Proliferation (+) Migration (+)	(248)
hsa_circ_0101432	↑	miR-1258 miR-622	MAPK1↑	Proliferation (+) Invasion (+) Apoptosis (-)	(249)
hsa_circ_103809	↑	miR-1270 miR-377-3p	PLAG1↑ FGFR1↑	Proliferation (+) Migration (+) Invasion (+) ETM (+)	(250)
circ_PRMT5	↑	miR-188-5p	HK2↑	Proliferation (+) Migration (+) Glycolysis (+)	(251)
circ_MAN2B2	↑	miR-217	MAPK1↑	Proliferation (+)	(252)
circ_TCF4.85	↑	miR-486-5p	ABCF2↑	Proliferation (+) Migration (+) Invasion (+)	(253)
circ_0001178	↑	miR-382	VEGFA↑	Proliferation (+) Migration (+) Invasion (+) Apoptosis (-)	(254)
circ_ZNF609	↑	miR-15a/b-5p	GLI2↑ Hedgehog pathway (+)	Proliferation (+) Metastasis (+) Apoptosis (-)	(255)
circMET	↑	miR-30-5p	Snail↑ DPP4↑	Invasion (+) Metastasis (+) EMT (+)	(256)
circ_PTN	↑	miR-326	-	Proliferation (+)	(257)
circNFATC3	↓	miR-5481	NFATC3↓	Proliferation (-) Migration (-) Invasion (-) Apoptosis (+)	(258)
circFBXO11	↑	miR-605	FOXO3/ABCB1↑	Proliferation (+) OXA Resistance (+)	(259)
circZNF566	↑	miR-4738-33p	TDO2↑	Proliferation (+) Migration (+) Invasion (+)	(260)
circPVT1	↑	miR-3666	SIRT7↑	Proliferation (+) Apoptosis (-)	(261)
circGprc5a	↑	miR-1283	YAPI↑/TEADI signaling pathway (+)	Proliferation (+) Apoptosis (-)	(262)

Table IV. Continued.

circRNA	Expression	miRNA sponge	Intersection molecules and/or pathway	Function	(Refs.)
circ_0091579	↑	miR-490-5p	CASC3↑	Proliferation (+) Migration (+) Invasion (+) Glycolysis (+)	(263)
circ_DENND4C	↑	miR-195-5p	TCF4↑	Proliferation (+) Invasion (+) Apoptosis (-)	(264)
hsa_circ_0000092	↑	miR-338-3p	HN1↑	Proliferation (+) Migration (+) Invasion (+) Angiogenesis (+)	(265)
hsa_circ_0003998	↑	miR-143-3p	FOSL2↑	Invasion (+) EMT (+)	(266)
circ_CSPP1	↑	miR-577	CCNE2↑	Proliferation (+)	(267)
circ_FOXP1	↑	miR-875-3p miR-421	SOX9↑	Proliferation (+) Invasion (+) Apoptosis (-)	(268)
hsa_circ_0091581	↑	miR-5266	c-MYC↑	Proliferation (+)	(269)
circ_100084	↑	miR-23a-5p	IGF2↑	Proliferation (+) Migration (+) Invasion (+)	(270)
circMAST1	↑	miR-1299	CTNND1↑	Proliferation (+) Migration (+) Invasion (+)	(271)
circ_0000517	↑	miR-1296-5p	TXNDC5↑	Apoptosis (-)	(272)
hsa_circ_0026134	↑	miR-127-5p	TRIM25/IGF2BP3↑	Proliferation (+) Migration (+)	(273)
circ_HOMER1	↑	miR-1322	CXCL6↑	Proliferation (+) Migration (+) Invasion (+) Apoptosis (-)	(274)

circRNA, circular RNA; ↓, downregulation; ↑, upregulation; -, no finding; (+), promotion; (-), inhibition.

FOXP1 gene, is upregulated in GBC tissues and cells. It can promote PKLR expression by sponging miR-370 in GBC cells, resulting in the promotion of the Warburg effect in GBC progression. The effects include the promotion of cell proliferation, migration and invasion, and the inhibition of cell apoptosis in GBC (280). circERBB2, derived from the ERBB2 gene locus, differs from general circRNAs that are located in the cytoplasm and function as miRNA sponges. circERBB2 is enriched in nucleoli. It regulates the nucleolar localization of proliferation-associated protein 2G4 (PA2G4), thereby forming a circERBB2/PA2G4/TIFIA regulatory axis to upregulate Pol I activity and rDNA transcription. Finally, it promotes GBC proliferation and progression (281). Generally, only 3 circRNAs to date have been found to participate in GBC progression by functioning as oncogenes or anti-oncogenes.

4. Detection and therapeutic applications of circRNAs in gastrointestinal cancer

An ideal biomarker should be non-invasive, accurate, inexpensive, specific, sensitive and reliable, and reproducible body fluids are ideal material for use in the diagnosis of human cancer (282). circRNAs are usually stable both inside cells and in extracellular plasma, including blood and saliva (22). In addition, they are involved in the pathogenesis of a variety of diseases, such as diabetes, Alzheimer's disease and cancer. Therefore, the stability of circRNAs in bodily fluids and the specificity of circRNAs in diseases have made them promising non-invasive alternatives for use as diagnostic biomarkers for diseases, such as for the real-time monitoring of tumor progression and therapeutic responses, cancer screening, and susceptibility evaluation, particularly in gastrointestinal cancer (2). Currently, a few available clinical biomarkers, such as CEA and CA19-9, have been reported to exhibit low sensitivity and specificity for the early detection of CRC (283,284). circ_0014717 exists stably in human gastric juices and can potentially be used as a biomarker for the screening of high-risk GC (285). It has been discovered that the hsa_circ_0001017 and hsa_circ_0061276 levels are tightly associated with the main clinicopathological features of patients with GC, which indicates that they can serve as valuable blood-based biomarkers (282).

Some circRNAs function as oncogenes, and several therapeutic strategies have been proposed to target these. An exogenously delivered siRNA can accurately target unique back-splice junctions of circRNAs. The expression of circRNAs can then be suppressed (119,286,287). Another approach is the use of artificial miRNA sponges, such as TuD, with the aim of deceasing the level of oncomiRs (288).

The early diagnosis of gastrointestinal cancer is a main strategy to decrease the mortality rate associated with gastrointestinal cancer, and the regulation of circRNA expression will be the next therapeutic method tested for patients with gastrointestinal cancer. It is considered that more accurate disease detection will be achieved via the combined analysis of body fluid circRNAs and specific biological biomarkers.

5. Conclusion and future perspectives

In summary, circRNAs have been discovered as novel molecules in recent years and are no longer recognized as products of transcription errors. Some circRNAs present unique advantages, such as high abundance, stability and widespread expression. These unique characteristics of circRNAs indicate that they are potentially valuable biomarkers for assessing the prognosis and diagnosis of gastrointestinal cancers. Some circRNAs function as miRNA sponges and regulators of parental gene transcription and possess the ability to bind with RBPs. The functions and regulatory roles of circRNAs in tumors indicate that they are a potential target for the treatment of cancer. These findings provide new insight and potential therapeutic strategies for cancer prevention and treatment in the future.

However, the underlying molecular mechanisms of circRNAs are more complex than discussed in the present review. They may exhibit multiple interactions in cancers, that are not yet clearly understood. A number of studies have focused on the 'sponge' function of certain circRNAs. In fact, not all circRNAs possess a sponge function, as only a small number of circRNAs exhibit rich binding sites for certain target miRNAs (289). It is necessary to pay attention to other roles and uncover additional functions of circRNAs, such as the binding of RBPs and the mechanisms through which they affect gene translation. Furthermore, as the current methods for the detection and characterization of circRNAs are still limited and challenging, circRNAs are far from being implicated into clinical practice. These fundamental problems require further investigation.

Therefore, due to the numerous amounts of unanswered questions, circRNAs warrant further investigation. The regulatory networks of circRNAs/miRNAs/mRNAs and circRNAs/RBPs and other roles of circRNAs in gastrointestinal cancers need to be clarified in the future. The full elucidation of all the ceRNA and RNA/protein crosstalk that occurs under pathophysiological conditions in gastrointestinal cancers will certainly have exciting applications for the development of promising therapeutic approaches related to circRNAs.

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Authors' contributions

XZ, YW, PY, QZ and XY collected the related literature and drafted the manuscript. QY and DG participated in the design of the review and drafted the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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