Circular RNA is a popular molecule in tumors of the digestive system (Review)

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Abstract. Most tumors of the digestive system, including esophageal, gastric, liver and colorectal cancer, are malignant tumors that are associated with rates of high morbidity and mortality. The lack of effective methods for early diagnosis is an important cause of poor prognosis for these malignancies. Circular RNAs (circRNAs) belong to a family of endogenous, covalently closed non-coding RNAs that are characterized as having no 5' cap structures or 3' poly-A tails. Shortly following discovery, circRNAs were considered to be a product of mis-splicing and have no significant biological function. However, in recent years, accumulating evidence is demonstrating that they serve key roles in tumorigenesis and have the potential to serve as diagnostic markers. The present article summarizes the biogenesis and function of circRNAs and reviews their role in seven common types of tumor of the digestive system whilst exploring their potential as tumor markers and the significant roles they can serve in the digestive system, in addition to providing a referencing point for future studies of digestive system malignancies.

Contents

1. Introduction
2. Biogenesis and function of circRNA
3. circRNA in digestive system malignancies
4. Non-coding RNAs in digestive system malignancies
5. Conclusions and perspectives

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1. Introduction

Circular RNA (circRNA) is a common class of non-coding RNAs produced by back splicing, which is an unconventional splicing event and are characterized as having no 5' end cap structures or 3' end poly-adenylation tails (1). Although Sanger *et al* (2) discovered this special type of RNA molecule in 1976, scientists generally believed that it was a product of incorrect splicing and were generally neglected since. That was not until 2013, when Hansen *et al* (3) and Memczak *et al* (4) reported that circRNA served an endogenous role as a microRNA (miRNA) sponge, that gradually changed the perception of researchers. In recent years, with continuous advancements in sequencing technology, an increasing number of circRNAs have been discovered and subsequently studied. Accumulating evidence have suggested that circRNA serves a significant role in the progression of a number of diseases, including Alzheimer's disease, cardiovascular disease, diabetes and cancer (3-6). Since circRNA is highly conserved and is stably expressed in various tissues and bodily fluids, it can be applied to predict disease and evaluate the effect of diagnosis and treatment (7). However, the emerging role of circRNA as a biomarker in cancer is becoming particularly prominent.

Digestive system malignancies account for a large proportion of all cancer cases. According to the 2018 Global Cancer Statistics Report released by the World Health Organization, colorectal, gastric, hepatocellular and esophageal cancers were ranked amongst the top 10 in terms of morbidity (8), whilst colorectal, gastric, hepatocellular, esophageal and pancreatic cancers were ranked amongst the top 10 in terms of mortality (8). In addition, colorectal and stomach cancer are ranked amongst the top five in terms of both morbidity and mortality (8). These data suggested that digestive system malignancies have become a significant threat to global health. In recent decades, diagnosis and treatment of tumors of the digestive system have been markedly improved, where several novel strategies have been developed. However, since patients are frequently diagnosed at an advanced stage, the survival

rate of patients with digestive system malignancies remain unsatisfactory.

In the present review, the biogenesis, function and role of circRNA in the development of tumors of the digestive system were summarized, where the possibility and emerging role of circRNA as a tumor marker in the digestive system was explored, providing a referencing point for the study of digestive system malignancies.

2. Biogenesis and function of circRNA

Biogenesis of circRNA. CircRNA is a non-coding RNA that is produced by two possible models of loop generation previously proposed by Jeck *et al* (9): i) Intron-pairing-driven circularization; and ii) lariat-driven circularization, both of which are widely accepted. Intron-pairing-driven circularization occurs as a result of complementary base pairing between different introns in the sequence, bringing adjacent exons to close proximity, following which the spliceosome cut away the adjacent exons and paired introns to form the circRNA. Lariat-driven circularization relies on the covalent interaction between the splice acceptor and donor, resulting in a circRNA containing the exon lariat (9). Intron circRNA is another subtype of circRNA discovered in recent years (10). The 11-nucleotide C-rich element and 7-nucleotide G-rich element in the parent gene of the intron circRNA combine to form a circular structure which are then spliced by the spliceosome (10). The spliceosome mechanism serves a significant role in the biogenesis of circRNA, which depends on trans-acting factors and cis-regulatory elements (11). Zhang *et al* (12) used four thiopurines to label newly generated RNA to reveal that low levels of circRNA may be a by-product of incomplete pre-RNA splicing, whilst the transcription of RNA polymerase II (pol II) occurred simultaneously with the formation of circRNA, suggesting that rapid extension of the strand may promote the reverse splicing of complementary paired sequences. In addition, the activity of pol II is strictly controlled by cis-regulatory elements (12). A number of circRNAs can be detected after pre-mRNA transcription is complete, suggesting that the biogenic process of circRNA may be post-transcriptional (13). In addition to pre-RNA and pol II, the biogenesis of circRNA is also regulated by a variety of proteins, enzymes, intron sequences and active elements. A previous study showed that RNA-binding proteins can also serve as regulators of circRNA production, which is a particularly prevalent mechanism observed during epithelial-mesenchymal transition (EMT) in tumors (14). The RNA helicase DExH-box helicase 9 (DHX9) specifically recognizes the reverse repeat Alu element, which is involved in the regulation of RNA post-transcriptional splicing (15). Alu elements are a class of functional sequences that are widely found in primates and are closely associated with the biogenesis of circRNAs (15). The expression levels of DHX9 affects the formation of splicing products, the deletion of which has been found to increase circRNA biogenesis of (15). In addition, exon circularization is dynamic process that is regulated by neighboring introns, where individual and flanking introns compete to regulate the formation of circRNA through base pairing (16). Modifications to the mRNA have been previously demonstrated to regulate transcription, alternative splicing, formation of advanced structures, translation and stability. Tang *et al* (17) found that N^6-methyladenosine (m6A) modification can promote the generation of circRNA carrying open reading frames in mouse male germ cells. In addition, the level of other circRNAs in tissues can also adversely affect the biogenesis of circRNA (18).

Function of circRNA. CircRNA can be classified into exon circRNA, exon-intron circRNA and intron circRNA, according to their origins (19,20). Exon circRNA is generally more commonly observed in eukaryotes (19). Compared with corresponding linear RNA of the same sequence, circRNA is more stable and less susceptible to degradation by RNase R (21), which is one of the main factors for circRNA being considered as a potential biomarker.

CircRNA has a multitude of reported functions (Fig. 1), the most studied of which is its property as an endogenous competitive RNA to sponge miRNA (22). miR-7 is a widely studied miRNA that has been reported to participate in cell proliferation, differentiation, migration, invasion and a number of signaling pathways in various types of malignancies, including lung, breast and thyroid cancer (23-25). Hollensen *et al* (26) previously demonstrated that cerebellar degeneration-related autoantigen 1, antisense can (ciRS7 or CDR1AS) act as an negative upstream regulator of miR-7, downregulating miR-7 expression in cells. In recent years, an increasing number of studies have shown miRNA sponging to be the most common function of circRNA. In addition to sponging miRNA, complex interactions between circRNA and proteins have been observed in regulating biological processes. CircRNA can also act as a protein sponge to directly regulate the expression of functional proteins (27). Du *et al* (28) found that circular RNA-forkhead box O3 blocked cell cycle progression by forming a complex with p21 and cyclin dependent kinase (Cdk)2. By contrast, certain circular RNAs have been demonstrated to act synergistically with specific proteins in response to extracellular stimuli (29). Li *et al* (29) found that the synergy between circRNA and the immune factor interleukin enhancer binding factor 3 promoted cellular responses to viral infections. A small number of circRNAs have also been documented to encode genes that can be translated into proteins directly involved in the regulation of physiological functions (30). Circ-ZNF609 binds ribosomes via an internal ribosome entry site and translates into ZNF609 to regulate the proliferation of myoblasts (31). Yang *et al* (30) reported in 2017 that m6A drives the initiation of circRNA translation in human cells. CircRNA has also been shown to regulate the splicing of pre-RNA and the function of the parental gene (10,16). This is mainly due to the role of some circRNAs located in the nucleus. For example, the circRNA ciankrd52 has been reported to interact with pol II to promote parental ankyrin repeat domain 52 pre-mRNA transcription (10). In summary, circRNA has a variety of biological functions, though this field of research remains incomplete (10).

3. CircRNA in digestive system malignancies

As an important subtype of non-coding RNA, circRNA has received considerable attention in cancer research in recent decades, where an increasing number of studies have shown that circRNA may serve significant roles in a multiple types of

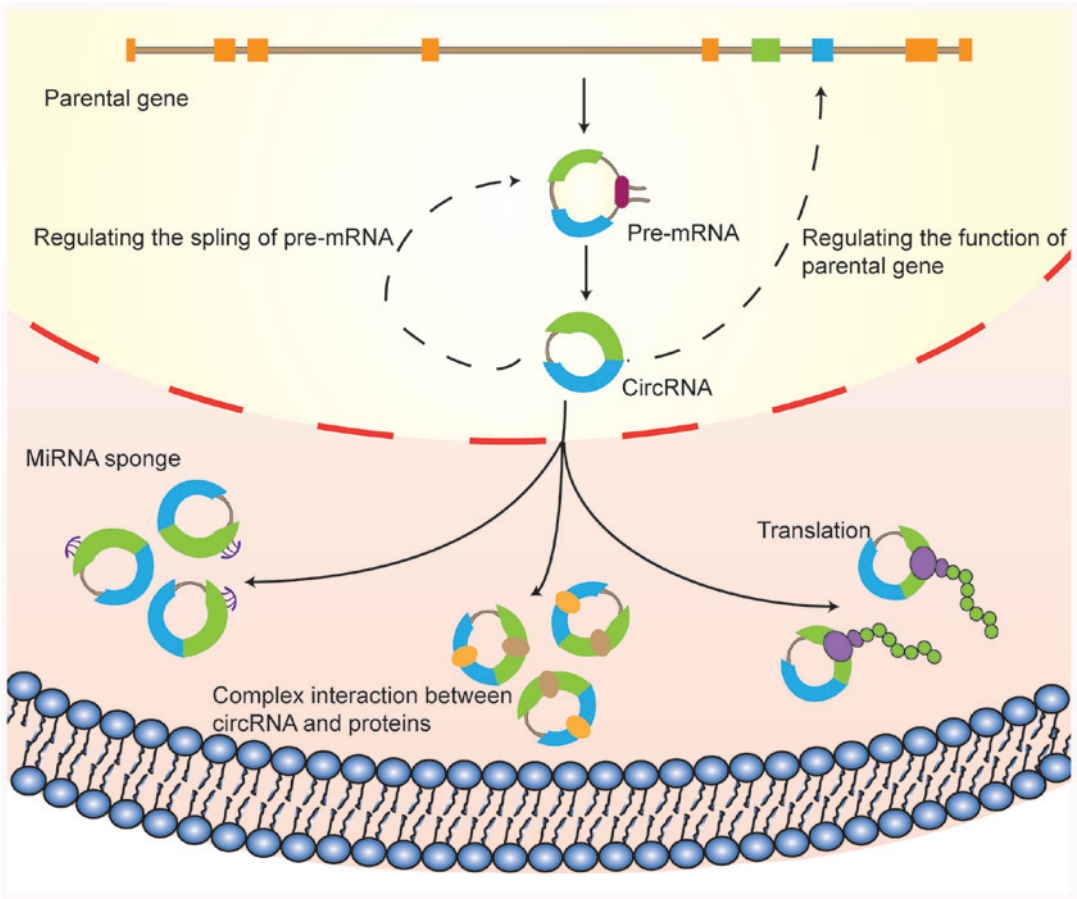

Figure 1. Function of circRNA. CircRNA has a variety of biological functions, including the regulation of pre-mRNA splicing and the function of parent genes, miRNA sponging, interactions with proteins and protein translation. CircRNA, circular RNA; miRNA, microRNA.

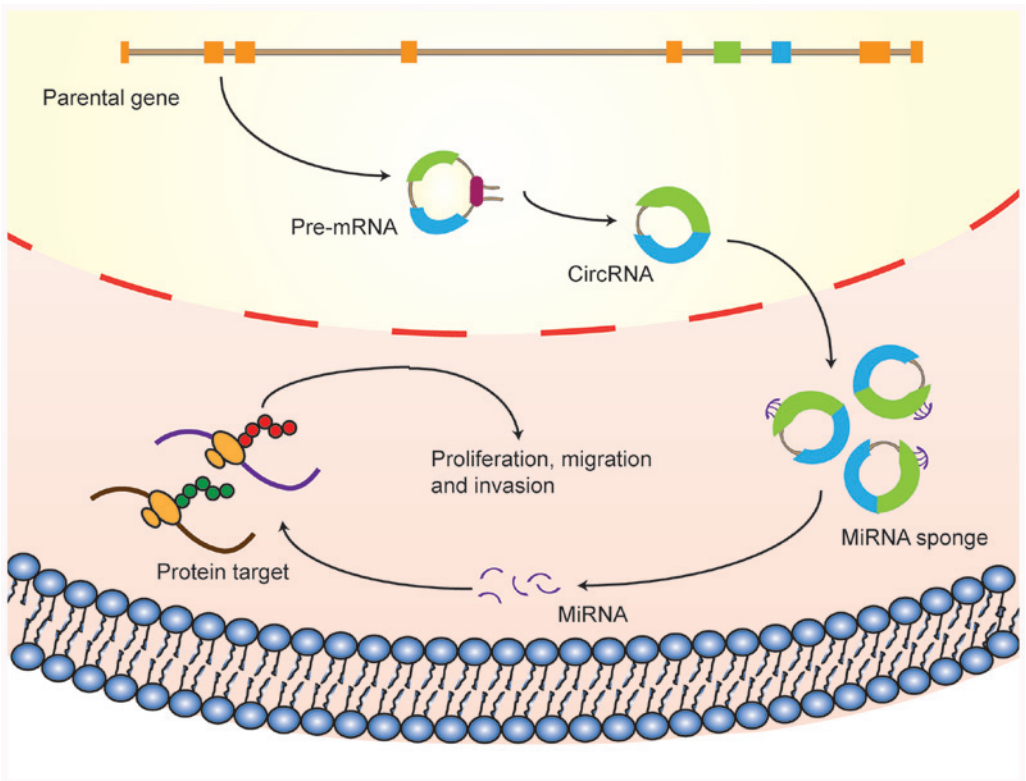

Figure 2. CircRNA serves as a miRNA sponge in tumors of the digestive system. After the parental gene is spliced into a loop through a complex process in the nucleus, the mature circRNA enters the cytoplasm and sequesters miRNAs, reducing their downstream effects, in turn regulating the expression of downstream target proteins and affecting tumor proliferation, invasion and migration. CircRNA, circular RNA; miRNA, microRNA.

digestive system malignancies. By sponging miRNA, circRNA can regulate the expression of target proteins, in turn affecting the pathophysiology of tumors of the digestive system (Fig. 2). This section describes the differential expression profiles and reported functions of circRNA in various types of digestive system malignancies.

Esophageal and gastric cancer. Esophageal cancer is a tumor of the upper digestive tract, which ranks 7th and 6th in terms morbidity and mortality among all cancers, respectively (10). By contrast, gastric cancer ranks 5th and 3rd in terms of morbidity and mortality among all cancers, respectively (8). Although a number of advancements have been made in the diagnosis and treatment of esophageal and gastric cancer in recent years, the etiology of these two malignancies remain to be fully elucidated and the survival rates of patients with advanced disease remain poor. The lack of effective early diagnostic indicators is also an important cause for the high mortality rates observed in patients with these two types of malignancies. Accumulating evidence have shown that circRNA serves a pivotal role in the proliferation, invasion, migration, cell cycle progression and drug resistance of esophageal (Table I) and gastric cancers (Table II).

Since 2016, the number of studies on the relationship between circRNAs and esophageal cancer has increased gradually. The elevated expression levels of several circRNAs in esophageal cancer has been demonstrated to promote the proliferation of esophageal cancer cells, including circ-discs large homolog 1, circRNA_100876 and hsa_circ_0067934 (32-34). In addition to proliferation, aberrant circRNA expression has also been reported to influence the ability of cancer cells to invade and migrate, which is a crucial cause of tumor metastasis and subsequent mortality. Zhong *et al* (35) found that circ-plasmacytoma variant translocation (circ-PVT1) upregulated the expression of paired box proteins and peroxisome proliferator-activated receptors by sponging miR-4663, resulting in the promotion of esophageal cancer cell proliferation and migration. The elevated expression levels of circ-tetratricopeptide repeat domain 17, circ-fibronectin type III domain containing 3B (circFNDC3B) and hsa_circ_0000337 have also been revealed to be involved in the proliferation and migration of esophageal cancer cells (36-38). Hsa_circ_0006168, circ-protein kinase Cι (circ-PRKCI), c-zinc finger protein 292 (cZNF292), circRAD23B, circ-ubiquitin associated protein 2 (circUBAP2) and hsa_circ_0004370 were all found to be upregulated in esophageal cancer cells and tissues, where they have the reported function of promoting proliferation, invasion and migration (39-44). Mechanistically, hsa_circ_0006168, circ-PRKCI, cZNF292, circRAD23B regulate the PI3K/AKT/mTOR signaling pathway by sponging miR-100, miR-3680-3p, miR-206 and miR-5095, respectively; whilst circUBAP2 and hsa_circ_0004370 regulate Rab10 and LIM And SH3 protein 1 by sponging miRNA-422a and miR-1294, respectively (39-44). miR-7 is a widely studied miRNA, the expression of which has been previously found to be reduced as a result of competition from ciRS7 in esophageal cancer, leading to the activation of NF-κB signaling, causing changes to the immune microenvironment to potentiate tumorigenesis (45). In addition to

Table I. Circular RNAs in esophageal cancer.

CircRNA name	Status	Function	Sponge target	Signaling pathway	(Refs.)	Publication date
circUBAP2	Upregulated	Promote proliferation, migration and invasion	miRNA-422a	Rab10	(42)	2020
circPVT1	Upregulated	Proliferative factor, promote migration	miR-4663	Paxs, PPARs	(35)	2019
circ-TTC17	Upregulated	Promote proliferation and migration			(36)	2019
hsa_circ_0000337	Upregulated	Promote growth, migration, and invasion	miR-670-5p		(38)	2019
hsa_circ_0006168	Upregulated	Promote proliferation, migration and invasion	miR-100	mTOR	(39)	2019
circ-PRKCI	Upregulated	Stimulate migration and proliferation	miR-3680-3p	AKT3	(40)	2019
cZNF292	Upregulated	Promote growth, migration, and invasion	miR-206	AMPK, PI3K/AKT	(41)	2020
ciRS-7	Upregulated	Trigger migration and invasion	miR-7	KLF4, NF-κB	(45)	2019
circVRK1	Downregulated	Regulate progression and radio resistance	miR-624-3p	PTEN/PI3K/AKT	(46)	2019
circRAD23B	Upregulated	Facilitates proliferation and invasion	miR-5095	PARP2, AKT2	(43)	2019
hsa_circ_0004370	Upregulated	Regulate proliferation, apoptosis, and migration	miR-1294	LASP1	(44)	2019
circ-DLG1	Upregulated	Promote proliferation			(32)	2018
circRNA_100876	Upregulated	Promote proliferation, migration, invasion			(33)	2018
circFNDC3B	Upregulated	Regulate proliferation, apoptosis, and migration			(37)	2018
hsa_circ_0067934	Upregulated	Promote proliferation			(34)	2016

Table II. Circular RNAs in gastric cancer.

CircRNA name	Dysregulation	Function	Sponge target	Signaling pathway	(Refs.)	Publication date
circHIPK3	Upregulated	Promote Progression And Migration	miR-107	BDNF	(66)	2020
circRBM33	Upregulated	Promote Progression, Migration And Invasion	miR-149	IL-6	(67)	2020
circ_0006282	Upregulated	Promote Progression And Metastasis	miR-155	FBXO22	(68)	2020
circUBA1	Upregulated	Promote Proliferation And Metastasis	miR-375	TEAD4	(69)	2020
hsa_circ_0000467	Upregulated	Promote Progression And Invasion,	miR-326-3p	Cyclin D1	(70)	2020
hsa_circ_0010882	Upregulated	Regulate proliferation, migration and invasion		PI3K/Akt/mTOR	(71)	2020
circSMAD7	Downregulated	Promote Migration, Invasion And Emt			(98)	2020
circ-CEP85L	Downregulated	Suppress Proliferation And Invasion	miR-942-5p	NFKBIA	(83)	2020
circATXN7	Downregulated	Regulate Proliferation, Apoptosis And Invasion	miR-4319	ENTPD4	(84)	2020
circHIAT1	Downregulated	Inhibit Proliferation And Emt	miR-21	p53, p21	(99)	2020
circMAN2B2	Dpregulated	Promote Growth And Migration	miR-145	PI3K/AKT, JNK	(72)	2020
circRHOBTB3	Downregulated	Inhibit Proliferation	miR-654-3p	p21	(85)	2020
circRNA_104433	Upregulated	Regulate Proliferation, Apoptosis And Cell Cycle	miR-497-5p	Cell cycle proteins	(73)	2020
circ-NOTCH1	Upregulated	Promote Progression, Migration And Invasion	miR-449c-5p	MYC/NOTCH1	(74)	2020
circFN1	Upregulated	Enhance Cisplatin Resistance	miR-182-5p		(102)	2020
circMLLT10	Upregulated	Promote Growth And Metastasis	miR-5093-5p	GINS4/Rac1/CDC42	(55)	2019
circNRIP1	Upregulated	Promote Progression	miR-149-5p	AKT1/mTOR	(56)	2019
circCACTIN	Upregulated	Promote Progression	miR-331-3p	TGFBR1	(57)	2019
ciRS-133	Upregulated	Exosome, Promote White Adipose Browning	miR-133		(96)	2019
hsa_circ_0067997	Upregulated	Promote Progression	miR-515-5p	XIAP	(60)	2019
hsa_circ_0081143	Upregulated	Promote Cisplatin Resistance	miR-646	CDK6	(100)	2019
circ-DCAF6	Upregulated	Regulate Invasion, Metastasis And Tnm Stages	miR-1231		(80)	2019
hsa_circ_0000144	Upregulated	Promote Tumor Growth			(61)	2019
circNF1	Upregulated	Promote The Progression	miR-16	MAP7, AKT3	(58)	2019
circRNA_001569	Upregulated	Promote The Progression	miR-145	NR4A2	(59)	2019
circPSMC3	Downregulated	Suppress The Proliferation And Metastasis	miR-296-5p	PTEN	(87)	2019
circPDSS1	Upregulated	Promote The Progression	miR-186-5p	NEK2	(62)	2019
hsa_circ_0006848	Downregulated	Negatively correlated with poor differentiation	hsa_miR-329-5p	RPL6	(75)	2019
hsa_circ_0001368	Downregulated	Suppress The Progression	miR-6506-5p	FOXO3	(76)	2019
circYAP1	Downregulated	Inhibit proliferation and invasion	miR-367-5p	p27 Kip1	(77)	2019
hsa_circ_0000592	Upregulated	Regulate apoptosis, proliferation and metastasis	miR-139-3p		(63)	2019
hsa_circ_006100	Upregulated	Promote Cell Growth And Metastasis	miR-195	GPRC5A	(64)	2019
circSMARCA5	Downregulated	Inhibits gastric cancer progression	miR-346	FBXL2	(78)	2019
circAKT3	Upregulated	Enhance Cisplatin Resistance	miR-198	PIK3R1	(101)	2019
hsa_circ_0008035	Upregulated	Promote Progression	miR-375	YBX1	(65)	2019
circFNDC3B	Upregulated	Promotes Migration And Invasion	IGF2BP3	E-cadherin, CD44	(97)	2019

Table II. Continued.

CircRNA name	Dysregulation	Function	Sponge target	Signaling pathway	(Refs.)	Publication date
circLMTK2	Downregulated	Suppress viability and mobility			(82)	2019
circFAT1(e2)	Downregulated	Inhibit progression	miR-548g	YBX1	(79)	2019
circ-DONSON	Upregulated	Facilitates growth and invasion	NURF	SOX4	(81)	2019
circHECTD1	Upregulated	Facilitates glutaminolysis, promote progression	miR-1256	β-catenin/c-Myc	(86)	2019
circRNA_0023642	Upregulated	Promotes migration and invasion	EMT		(88)	2018
hsa_circ_0074362	Downregulated	Associate with lymphatic metastasis			(89)	2018
circ_0027599	Downregulated	Suppress progression	miR-101-3p	PHLDA1	(90)	2018
hsa_circ_0003159	Downregulated	Inhibit metastasis			(91)	2018
circPVRL3	Downregulated	Suppress the proliferation and migration	9 miRNAs	PTB, EIF4A3	(92)	2018
circ-SFMBT2	Upregulated	Promotes the proliferation	miR-182-5p	CREB1	(93)	2018
circ_0066444	Upregulated	Promote proliferation, invasion and migration			(94)	2018
circ_0009910	Upregulated	Regulate proliferation, migration and invasion			(95)	2018
circRNA_100269	Downregulated	Suppress growth	miR-630		(47)	2017
circLARP4	Downregulated	Inhibit proliferation and invasion	miR-424-5p	LATS1	(48)	2017
hsa_circ_0000705	Downregulated	Borrmann type, pathologic diagnosis			(49)	2017
hsa_circ_0001895	Downregulated	Regulate cell differentiation, Borrmann type			(50)	2017
hsa_circ_00001649	Downregulated	Regulate cell differentiation, Borrmann type			(51)	2017
hsa_circ_0000745	Downregulated	Regulate tumor differentiation			(52)	2017
hsa_circ_0000190	Downregulated	Regulate metastasis, TNM stage			(53)	2017
circPVT1	Upregulated	Proliferative factor	miR-125		(54)	2017

proliferation, invasion and migration, evidence also exists demonstrating the role of circRNA in tumor sensitivity to radiotherapy. He *et al* (46) previously found that the downregulation of circ-vaccinia-related kinase 1 (circVRK1) in patients with esophageal cancer was associated with a lower survival rates, whilst the overexpression of circVRK1 could effectively inhibit EMT and resistance to radiotherapy in esophageal cancer cells.

Similar to esophageal cancer, research on the association between circRNA and gastric cancer has been gradually increasing since 2017. In 2017, studies discovered that circRNA_100269, circRNA_La ribonucleoprotein 4, hsa_circ_0000705, hsa_circ_0001895, hsa_circ_00001649, hsa_circ_0000745 and hsa_circ_0000190 are all significantly downregulated in gastric cancer, which were found to be closely associated with the increased cell proliferation, differentiation, subcellular localization, stage, Borrmann type and invasion (47-53). By contrast, circ-PVT1 was demonstrated to serve as a proliferative factor regulating downstream gene expression by sponging miR-125 in gastric cancer (54). miRNA sponging remains to be the predominant mechanism through which circRNA promotes the proliferation, invasion and migration of gastric cancer cells. By sponging miR-509-3-5p, circ-myeloid/lymphoid or mixed-lineage leukemia has been found to be regulated by the expression of GINS4, which binds to and activates Rac1/cell division cycle to promote cell growth and metastasis *in vivo* and *in vitro*, whilst inhibiting apoptosis (55). Circ-nuclear receptor interacting protein 1, circ-cactin, circ-neurofibromatosis type 1 along with 37 other circRNAs have been previously revealed to regulate the expression of downstream target genes in gastric cancer through miRNA sponging to promote the proliferation and invasion of gastric cancer (Table II) (56-95). Disorder in fat metabolism is the main cause of cachexia in patients with advanced gastric cancer and systemic inflammation (96). CiRS-133 is a plasma exosomal circRNA that has been found to be significantly upregulated in gastric cancer (96). Zhang *et al* (96) found that it can activate PR/SET domain 16 by inhibiting miR-133, causing the browning of white adipose tissues in patients with gastric cancer. Other circRNAs can also affect the invasion and metastasis of gastric cancer by regulating EMT. The increased expression of circFNDC3B and the reduced expression of circSMAD7 and circ-hippocampus abundant transcript 1 (circHIAT1) in gastric cancer has been found to promote EMT in gastric cancer and induce distant metastasis, which is the primary cause of poor prognosis in patients with advanced gastric cancer (97-99). Hsa_circ_0081143 is another circRNA that is highly expressed in gastric cancer, which is positively associated with lymph node metastasis and TNM staging in advanced gastric cancer (100), the silencing of which can inhibit the development of gastric cancer and enhance the sensitivity of gastric cancer cells to chemotherapeutic agents such as cisplatin (100). Similarly, circAKT3 and circ-fibronectin 1 were found to enhance cisplatin resistance by sponging miR-198 and miR-182-5p, respectively (101,102).

Pancreatic cancer. Pancreatic cancer is a common tumor of the digestive system. Although the rates of morbidity associated with pancreatic cancer is not as high as other types of digestive system malignancies, including gastric, esophageal, colorectal and hepatocellular cancers, its mortality rate ranks among the highest (8). Pancreatic cancer is mainly divided into two subtypes: Pancreatic ductal adenocarcinoma and pancreatic squamous cell carcinoma, both of which have a poor prognosis, with a 5-year survival rate of <10% (103). Identifying specific biomarkers and therapeutic targets is important for improving the survival rates of patients with pancreatic cancer.

Interestingly, the majority of circRNAs associated with pancreatic cancer that have been discovered are found to be upregulated (Table III). CircRNAs, including hsa_circRNA_0007334, circ-Ras homolog family member T1, hsa_circ_0006215, circ-zinc finger MYM-type containing 2, circ-disintegrin and metalloproteinase domain-containing protein (ADAM) 9 and ciRS-7, compete with miRNAs to promote pancreatic cancer proliferation and inhibit apoptosis (104-109). Other circRNAs can regulate endothelial monolayer permeability, thereby promoting the invasion and migration of pancreatic cancer cells. Circ-low density lipoprotein receptor class a domain containing 3 promotes lymphatic and venous metastasis by sponging miR-137-3p, whilst circ-isoleucyl-tRNA synthetase enhances endothelial monolayer permeability by sponging miR-122 (110,111). Abnormalities in the immune microenvironment are common changes observed in advanced pancreatic cancer. Circ_0000977 has been previously found to increase the expression of hypoxia-inducible factor 1 and ADAM10 by competitively binding to miR-153, where circ_0000977 silencing can significantly enhance the cytotoxic effects of natural killer cells on pancreatic cancer (112). Drug resistance is another important underlying cause of poor prognosis in patients with advanced pancreatic cancer. Liu *et al* (113) previously found that knocking down circ-homeodomain interacting protein kinase 3 expression can effectively improve the sensitivity of pancreatic cancer to gemcitabine. In general, there have been a number of studies on the relationship between pancreatic cancer and circRNA, where the role of circRNA in the development of pancreatic cancer require further exploration.

Hepatocellular carcinoma. As of 2018, liver cancer ranks 6th in terms of prevalence and 4th in terms of mortality rates among other cancers (8). Liver cancer can be divided into three main subtypes: Hepatocellular carcinoma, bile duct carcinoma and mixed carcinoma by cell type, of which hepatocellular carcinoma is the most frequently observed. Viral hepatitis B (HBV) is one of the main causes of liver cancer in China whereas alcoholic fatty liver disease is the main cause in the Western world (114). Hepatocellular carcinoma as a result of both HBV infection and excessive alcohol consumption are associated with high rates of morbidity and mortality (8). Due to the lack of symptoms in the early developmental stage of hepatocellular carcinoma, many are not diagnosed until advanced stages of the disease (115). Studying the molecular mechanism of circRNA in hepatocellular carcinoma is of great importance for the early diagnosis and treatment of this disease.

In 2016, Yu *et al* (116) found that circ-cerebellar degeneration related protein 1; antisense served as a cancer promotor by binding to miR-7 and upregulating the expression of cyclin E1 and phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit d, promoting the proliferation and metastasis of hepatocellular carcinoma. Studies into the role of circRNA in hepatocellular carcinoma has since increased annually. A total of four studies

Table III. Circular RNAs in pancreatic cancer.

CircRNA name	Dysregulation	Function	Sponge target	Signaling pathway	(Refs.)	Publication date
circHIPK3	Upregulated	Promote gemcitabine resistance	miR-330-5p	RASSF1	(113)	2020
hsa_circ_0007334	Upregulated	Promote proliferation and invasion	miR-144-3p, miR-577	MMP7, COL1A1	(104)	2019
circRHOT1	Upregulated	Promote proliferation and invasion	miR-26b, miR-125a		(105)	2019
circADAM9	Upregulated	Promote proliferation, migration and invasion	miR-217	PRSS3/ERK/VEGF	(108)	2019
ciRS-7	Upregulated	Promote the proliferation and metastasis	miR-7	EGFR/STAT3	(109)	2019
circ_0000977	Upregulated	Regulate NK cell immune activity	miR-153	HIF1, ADAM10	(112)	2019
hsa_circ_0006215	Upregulated	Regulate proliferation and apoptotic	miR-378a-3p	SERPINA4	(106)	2018
circZMYM2	Upregulated	Regulate proliferation, invasion, and apoptosis	miR-335-5p	JMJD2C	(107)	2018
circ-IARS	Upregulated	Regulate endothelial monolayer permeability	miR-122	F-actin	(111)	2018
circ-LDLRAD3	Upregulated	Promote invasion, invasion, and metastasis			(110)	2017

were published the following year, which reported that circRNA serves as an endogenous competitor by regulating the expression of downstream target genes by sponging miRNA to promote hepatocellular carcinoma proliferation, invasion, migration and differentiation, whilst inhibiting apoptosis. This suggests that circRNA can be applied as a biomarker for hepatocellular carcinoma (Table IV) (117-120). The number of studies on circRNA in relation to hepatocellular carcinoma increased to 16 in 2018, where it was revealed that in addition to sponging miRNA, circRNA can also participate in the progression of hepatocellular carcinoma by directly binding to proteins to regulate their function (Table IV) (121-136). For example, circ-cullin 2 was previously demonstrated to promote epithelial-mesenchymal transition by combining vimentin under the regulation of Twist1 in hepatocellular carcinoma (130).

The association between circRNA and cancer, especially that of hepatocellular carcinoma, has become a popular topic of research over the last 2 years. In early 2020, a total of 56 related research articles reporting the relationship between circRNA and hepatocellular carcinoma have been published, which is higher than the number recorded in previous years (Table IV) (137-192). The expression of several circRNAs has been reported to be dysregulated in hepatocellular carcinoma, which compete with miRNAs to regulate the expression of downstream target proteins and affect the proliferation, invasion and migration of hepatocellular carcinoma. Some of these circRNAs include hsa_circ_0101432, circ-PVT1, circ-tripartite motif containing 33-12, circRNA-104718, circ-SET domain containing 3, actin histidine methyltransferase, has_circ_0078710, hsa_circ_0064428, circHIAT1, circ-adducin3, hsa_circ_0001649, circ-ADAM metallopeptidase with thrombospondin type 1 motif 14, circ_0008450, hsa_circRNA_103809, circ-homer scaffold protein 1, hsa_circ_0003645, circ-SMG1.72, hsa_circ_0091581, hsa_circ_0000092, hsa_circ_0056836, circ-TCF4.85, circ-protein arginine methyltransferase 5 (circPRMT5), circ_0001955, circ-pecanex 1, circRNA-5692, circ-ATP binding cassette subfamily B member 10 and circ-ArfGAP with SH3 domain, ankyrin repeat and PH Domain 1 (137,138,140,145,147-150, 155-157,163,166,176-180,183-185,187,189-192). Previous studies have demonstrated that circRNA in exosomes can regulate the development of hepatocellular carcinoma by deubiquitylation. Circ-leptin receptor, circ-matrix metallopeptidase 2 and hsa_circ_0051443 are common exosomal circRNAs found in hepatocellular carcinoma (142,181,186). Hypoxia is a principal characteristic of the tumor microenvironment that is considered to be an important factor affecting sensitivity to radiotherapy and chemotherapy (146). Yang *et al* (146) previously found that knocking down cZNF292 expression can inhibit angiogenesis, cell proliferation and resistance to radiotherapy in hepatocellular carcinoma, which may be due to the hypoxic environment induced by cZNF292. Similar to cZNF292, the dysregulation of circRNA_101505, circRNA_104797 and circ_0003418 expression in hepatocellular carcinoma has been demonstrated to increase the resistance of hepatocytes to sorafenib and cisplatin, which is considered to be one of the main underlying causes of poor prognosis in patients with advanced hepatocellular carcinoma (162,168,174). CircRNA can also directly bind to protein components of important signaling pathways, thereby affecting the physiological behavior of hepatocellular carcinoma. The

Table IV. Circular RNAs in hepatocellular carcinoma.

CircRNA name	Dysregulation	Function	Sponge target	Signaling pathway	(Refs.)	Publication date
circBACH1	Upregulated	Promote growth, regulate cell cycle		HuR/p27	(182)	2020
circ-HOMER1	Upregulated	Regulate the growth and invasion	miR-1322	CXCL6	(176)	2020
hsa_circ_0056836	Upregulated	Promote migration, proliferation and invasion	miR-766-3p	FOSL2	(183)	2020
hsa_circ_0051443	Downregulated	Exosome, regulate apoptosis and cell cycle			(186)	2020
hsa_circ_0000092	Upregulated	Promote proliferation, migration and invasion	miR-338-3p	HN1	(180)	2020
hsa_circ_0003645	Upregulated	Regulate proliferation, apoptosis and invasion	miR-1299	PI3K/mTOR	(177)	2020
hsa_circ_0091581	Upregulated	Promote cell proliferation	miR-526b	c-MYC	(179)	2020
circ-PRMT5	Upregulated	Promote proliferation, migration and glycolysis	miR-188-5p	HK2	(185)	2020
circ-TCF4.85	Upregulated	Regulate proliferation, apoptosis and invasion	miR-486-5p	ABCF2	(184)	2020
circ_MMP2	Upregulated	Exosome, Promote metastasis	miR-136-5p	MMP2	(181)	2020
circ-SMG1.72	Upregulated	Promote invasion	miR-141-3p	Gelsolin	(178)	2020
hsa_circ_0101432	Upregulated	Promote growth	miR-1258	MAPK1	(137)	2019
circPVT1	Upregulated	Promote progression	miR-203	HOXD3	(138)	2019
hsa_circ_0079929	Downregulated	Inhibit growth		PI3K/AKT/mTOR	(139)	2019
circTRIM33-12	Downregulated	Suppress progression	miR-191	TET1	(140)	2019
circ_0008450	Upregulated	Regulate proliferation, apoptosis and invasion	miR-548p		(141)	2019
exo-circ-DB	Upregulated	Promote growth and reduces DNA damage	miR-34a	USP7/Cyclin A2	(142)	2019
circRNA_103809	Upregulated	Promote proliferation and migration	miR-377-3p	FGFR1/ERK	(143)	2019
hsa-circ-0046600	Upregulated	Regulate tumor size, TNM stage and invasion	miR-640	HIF-1 alpha	(144)	2019
circRNA-104718	Upregulated	Promote progression	miR-218-5p	TXNDC5	(145)	2019
cZNF292	Upregulated	Regulate proliferation and radio resistance			(146)	2019
circSETD3	Downregulated	Inhibiting growth	miR-421	MAPK14	(147)	2019
has_circ_0078710	Unregulated	Promoted proliferation, migration and invasion	miR-31	Cyclin protein	(148)	2019
hsa_circ_0064428	Downregulated	Regulate tumor size and metastasis			(149)	2019
circHIAT1	Downregulated	Inhibits cell growth	miR-3171	PTEN	(150)	2019
hsa_circ_0000517	Upregulation	Associated with adverse prognosis		MAPK, Ras	(151)	2019
circRHOT1	Upregulation	Promote progression		NR2F6	(152)	2019
circPTGR1	Upregulation	In exosomal, Promote metastasis	miR449a	MET	(153)	2019
circZFR	Upregulation	Promote progression	miR-3619-5p	CTNNB1, Wnt	(154)	2019
circ-ADD3	Downregulated	Inhibit metastasis+		CDK1/EZH2	(155)	2019
hsa_circ_0001649	Downregulated	Inhibit progression	miR-127-5p,		(156)	2019
circADAMTS14	Downregulated	Suppress progression	micR-572	Calcineurin1	(157)	2019
circADAMTS13	Downregulated	Suppress proliferation	miR-484		(158)	2019
circ_0000267	Upregulation	Promote progression	miR-646		(159)	2019
circRNA-10720	Upregulation	Metastasis		Twist1	(160)	2019
circARSP91	Downregulated	Increase cell cytotoxicity		ULBP1	(161)	2019

Table IV. Continued.

CircRNA name	Dysregulation	Function	Sponge target	Signaling pathway	(Refs.)	Publication date
circRNA_101505	Downregulated	Sensitizes to cisplatin	miR-103	NOR1	(162)	2019
hsa_circ_0008450	Upregulated	Promote proliferation, invasion and migration	miR-214-3p	EZH2	(163)	2019
circ-catenin	Upregulated	Promote growth		Wnt	(164)	2019
circMYLK	Upregulated	Promote progression	miR-362-3p	Rab23	(165)	2019
hsa_circ_103809	Downregulated	Suppress proliferation and invasion	miR-620		(166)	2019
hsa_circ_0078602	Downregulated	Suppress proliferation			(167)	2019
circRNA_104797	Upregulated	Sorafenib resistance		UBQLN1	(168)	2019
hsa_circ_0016788	Upregulated	Regulate tumorigenesis	miR-486	CDK4	(169)	2019
circ-IGF1R	Upregulated	Pro-proliferative and anti-apoptotic		PI3K/AKT	(170)	2019
hsa_circ_0002124	Upregulated	Promote proliferation		MAPK	(171)	2019
circLARP4	Downregulated	Regulate proliferation, cell cycle and senescence	miR-761	RUNX3/p53/p21	(172)	2019
circRNAs_100395	Downregulated	Regulate differentiation, microvascular invasion	miR-1228		(173)	2019
circ_0003418	Downregulated	Inhibit genesis and cisplatin chemoresistance		Wnt/β-Catenin	(174)	2019
hsa_circ_101280	Upregulated	Promote proliferation	miR-375	JAK2	(175)	2019
circ_0001955	Upregulated	Promote proliferation	miR-516a-5p	TRAF6, MAPK11	(187)	2019
circ-MALAT1	Upregulated	Promote cancer stem cell self-renewal	miR-6887-3p	PAX5	(188)	2019
circPCNX	Upregulated	Promote proliferation	miR-506		(189)	2019
circRNA-5692	Downregulated	Inhibit proliferation and invasion	miR-328-5p	DAB2IP	(190)	2019
circABCB10	Upregulated	Promote proliferation and invasion	miR-670-3p	HMG20A	(191)	2019
circASAP1	Upregulated	Promote proliferation, migration and invasion	miR-326	MAPK1, CSF-1	(192)	2019
circ_0067934	Upregulated	Promote growth and metastasis	miR-1324	FZD5/Wnt	(121)	2018
circC3P1	Downregulated	Suppress growth and metastasis	miR-4641	PCK1	(122)	2018
hsa_circ_0001445	Upregulated	Regulate proliferation and migration			(123)	2018
circRNA_104075	Upregulated	Promote progression	miR-582-3p	HNF4a, YAP	(124)	2018
circSMAD2	Downregulated	Inhibit the epithelial-mesenchymal transition	miR-629		(125)	2018
circSLC3A2	Upregulated	Promote growth and invasion	miR-490-3p	PPM1F/AKT	(126)	2018
hsa_Circ_0091579	Upregulated	Associated with a worse overall survival			(127)	2018
cSMARCA5	Downregulated	Inhibit growth and metastasis	miR-181b-5p	TIMP3	(128)	2018
hsa_circRBM23	Upregulated	Increase cell viability and also migration	miR-138	Vimentin, CCND3	(129)	2018
circCul2	Upregulated	Promote EMT		Twist1, Vimentin	(130)	2018
circPTPRM	Upregulated	Promote proliferation and migration			(131)	2018
circ_101368	Upregulated	Correlated with poorer prognosis	miR-200a	HMGB1/RAGE	(132)	2018
hsa_circ_0005075	Upregulated	Increase proliferative, migrate and invasive	miR-431		(133)	2018
circ-ZEB1.33	Upregulated	Promote the proliferation	miR-200a-3p	CDK6	(134)	2018
hsa_circ_0128298	Upregulated	A diagnostic factor			(135)	2018
hsa_circ_0103809	Upregulated	Promote and inhibits apoptosis	miR-490-5p	SOX2	(136)	2018

Table IV. Continued.

CircRNA name	Dysregulation	Function	Sponge target	Signaling pathway	(Refs.)	Publication date
circZKSCAN1	Downregulated	Inhibit growth, migration and invasion			(117)	2017
circRNA_000839	Upregulated	Promote the invasion and migration	miR-200b	RhoA	(118)	2017
circRNA-100338	Upregulated	Regulate metastatic progression	miR-141-3p		(119)	2017
circ_ 0004018	Downregulated	Regulate tumor diameters, differentiation			(120)	2017
circCdr1as	Upregulated	Promote proliferation and invasion	miR-7	CCNE1, PIK3CD	(116)	2016

Table V. Circular RNAs in gallbladder cancer.

CircRNA name	Dysregulation	Function	Sponge target	Signaling pathway	(Refs.)	Publication date
circFOXP1	Upregulated	Promote progression and Warburg effect	miR-370	PKLR	(194)	2019
circERBB2	Upregulated	Regulate proliferation, ribosomal DNA transcription			(196)	2019
circHIPK3	Upregulated	Promote growth	miR-124	ROCK1-CDK6	(195)	2018

expression of hsa_circ_0079929 and circ-insulin-like growth factor 1 receptor in hepatocellular carcinoma was demonstrated to be significantly reduced, which induced cell cycle arrest and inhibited apoptosis through the PI3K/AKT/mTOR signal transduction pathway (139,170). Circ-BTB domain and CNC homolog 1 was found to be highly expressed in hepatocellular carcinoma, which binds to the embryonic lethal, abnormal vision, drosophila, homolog-like 1 protein and p27 to regulate cell cycle progression and promotes the growth of tumor cells (182). Ma *et al* (161) previously found that circARSP91 enhance innate immune monitoring by enhancing NK cell cytotoxicity and its downregulation in hepatocellular carcinoma promotes immune escape of hepatocellular cancer cells.

In conclusion, circRNA serves a significant role in proliferation, invasion, migration, differentiation, apoptosis, cell cycle and sensitivity to chemotherapy in hepatocellular carcinoma. Future research should focus on identifying specific and sensitive circRNAs that can serve as biomarkers for the early diagnosis and effective treatment of hepatocellular carcinoma, to improve the survival rate of patients with hepatocellular carcinoma.

Gallbladder cancer. Compared with hepatocellular carcinoma, although the rates of morbidity associated with gallbladder cancer is not as high, the rates of mortality are high where its prognosis poor, due to the highly invasive properties which is frequently diagnosed during the advanced stages of the disease (193). Studies have found that circRNA promotes the proliferation of gallbladder cancer cells through miRNA sponging and direct binding to proteins. As a miRNA sponge, circ-forkhead box protein P1 regulates the expression of pyruvate kinase L/R by sponging miR-370, enhancing the Warburg effect and promoting the proliferation and invasion of gallbladder cancer cells (194). In addition, circ-homeodomain interacting protein kinase 3 has been previously found to increase the expression of Rho-associated coiled-coil containing protein kinase 1-CDK6 by sponging miR-124, promoting the proliferation of gallbladder cancer cells (195). Circ-Erb-B2 binds to the circErb-B2 receptor tyrosine kinase 2 located in the nucleus, which regulates proliferation-associated 2G4-dependent ribosomal DNA transcription and promotes the proliferation of gallbladder cancer (196). In conclusion, research on the mechanism of circRNA involvement in the occurrence and development of gallbladder cancer remains limited (Table V) and several important issues have yet to be explained. Therefore, there remains room for exploration in this particular field.

Colorectal cancer. Colorectal cancer ranks 3rd and 2nd worldwide in terms of morbidity and mortality, respectively, among other types of cancers. (8). Advancements in colonoscopy have facilitated the detection and treatment of precancerous colorectal polyps. However, the mortality and risk associated with colorectal cancer have changed little since 1997 (197). At present, there is an urgent need in identifying novel tumor biomarkers and targeted treatment strategies to improve the early diagnosis and survival rate of patients with colorectal cancer.

Studies into the relationship between colorectal cancer and circRNA preceded those of other digestive system malignancies. In 2015, a study on 31 clinical samples of colorectal cancer found that the elevated expression of hsa_circ_001988 in colorectal cancer is closely associated with the differentiation and infiltration of tumor cells (198). In 2016, circRNA_001569 and hsa_circ_0000069 were found to be highly expressed in patients with colorectal cancer (199,200). CircRNA_001569 was demonstrated to regulate the expression of Bcl-2-associated athanogene 4, transcription factor E2F5 and formin like 2 by adsorbing miR-145, though the mechanism mediated by hsa_circ_0000069 remain unknown (199,200). In 2017, it was found that the expression of circRNA0003906, circ-BTG3-associated nuclear protein and hsa_circ_0020397 were dysregulated in colorectal cancer (201-203). A total of 10 studies reporting that circRNA regulated the development of colorectal cancer were published in 2018 (Table VI) (204-213), which rose to 17 in 2019 and 9 related articles have already been published in the first 2 months of 2020 (Table VI) (214-239). Over the last 5 years, the number of studies into the role of circRNA in colorectal cancer has been increasing annually. Most aberrantly expressed circRNAs in colorectal cancer exert their function by adsorbing miRNAs, regulating proteins associated with proliferation, invasion and metastasis, thereby promoting the progression of colorectal cancer. Particular circRNAs of interest include hsa_circ_0136666, circCBL.11, hsa_circRNA_102958, circ-vesicle-associated membrane protein-associated protein A, circ-formin 2, circ_0021977, circ_0026344, circ-integrin subunit-α7, has_circ_0055625, circ-calmodulin regulated spectrin associated protein 1, hsa_circ_0007142, circ-HECT, UBA and WWE domain containing E3 ubiquitin protein ligase 1, circ-chaperonin containing TCP1 subunit 3, circ_0000218, hsa_circ_0001178, circPRMT5 and hsa_circ_0004277 (215-220,223,226,227,229-234,236,238). CircRNAs have been reported to serve either a synergistic or antagonistic role by directly binding to downstream target proteins to regulate various aspects of colorectal cancer pathophysiology. Circ-catenin b1 (circ-CTNNB1) mainly exists in the nucleus and directly binds to DEAD-box helicase 3/yin and yang 1, resulting in b-catenin activation and promoting the growth and metastasis of colorectal cancer (225). CircRNA_104916, circ-zinc finger protein 609 and circ-protein tyrosine kinase 2 have been previously demonstrated to function in a similar manner to circ-CTNNB1 (221,228,237). Exosome circRNA has been a topic of particular research interest in recent years, as it is believed that circRNA may regulate tumor development. Using nanoparticle tracking analysis and transmission electron microscopy, Pan *et al* (222) verified the exosomes in the peripheral blood of patients with colorectal cancer. Hsa_circ_0004771, ciRS-122 and circ-ATP binding cassette subfamily C Member 1 were found to be significantly increased in these exosomes, suggesting their possible application as a suitable biomarker for this disease (222,235,239).

Gastrointestinal stromal tumor. A gastrointestinal stromal tumor is a non-epithelial type of tumor that can occur in the esophagus, stomach, small intestine, colorectum and abdominal cavity that can cause a variety of symptoms, including pain, bleeding and abdominal discomfort (240). Surgical resection is currently the most common treatment method (240). In a recent study, Jia *et al* (241) used a selective binding complementary competitive endogenous RNA array to analyze gastrointestinal stromal tumors, which found circ_0084097, circ_0069765 and circ_0079471 to be aberrantly expressed in gastrointestinal

Table VI. Circular RNAs in colorectal cancer.

CircRNA name	Dysregulation	Function	Sponge target	Signaling pathway	(Refs.)	Publication date
circ-ABCC1	Upregulated	Exosome, Promote metastasis		Wnt/β-catenin pathway	(239)	2020
circPTK2	Upregulated	Promote tumor growth, EMT, metastasis		Vimentin protein	(237)	2020
circPRMT5	Upregulated	Promote proliferation	miR-377	E2F3	(236)	2020
ciRS-122	Upregulated	Exosome, Promote oxaliplatin resistance	miR-122	PKM2	(235)	2020
hsa_circ_0004277	Upregulated	Regulate proliferation and apoptosis	miR-512-5p	PTMA	(238)	2020
hsa_circ_0001178	Upregulated	Promote invasion and metastasis	miR-382	ZEB1	(234)	2020
circ_0000218	Upregulated	Enhance the proliferation and metastasis	miR-139-3p	RAB1A	(233)	2020
circCCT3	Upregulated	Enhance metastasis	miR-613	VEGFA, Wnt	(232)	2020
circHUWE1	Upregulated	Promote proliferation, migration and invasion	miR-486		(231)	2020
hsa_circ_0007142	Upregulated	Regulate differentiation and metastasis	miR-103a-2-5p		(230)	2019
circZNF609	Downregulated	Promote apoptosis		PCNA, c-Myc, Bax,	(228)	2019
has_circ_0055625	Upregulated	Increases colon cancer cell growth	miR-106b-5p	ITGB8	(227)	2019
circ-ITGA7	Downregulated	Suppress proliferation	miR-3187-3p	ASXL1	(226)	2019
circ-CTNNB1	Upregulated	Promote progression		DDX3/YY1/β-Catenin	(225)	2019
hsa_circ_0004585	Upregulated	Regulate tumor size and metastasis			(224)	2019
circ_0026344	Downregulated	Restrain metastasis and EMT	miR-183	CCL20, CXCL8	(223)	2019
hsa-circ-0004771	Upregulated	Exosome, as a biomarker			(222)	2019
circRNA_104916	Downregulated	Regulate migration, apoptosis and EMT		LoVo, Caco-2	(221)	2019
circ_0021977	Downregulated	Suppress growth, migration and invasion	miR-10b-5p	P21, P53	(220)	2019
circVAPA	Upregulated	Promote proliferation, migration, invasion	miR-101		(218)	2019
circRNA_102958	Upregulated	Promote tumorigenesis	miR-585	CDC25B	(217)	2019
circCBL.11	Downregulated	Suppress proliferation	miR-6778-5p	YWHAE	(216)	2019
hsa_circ_0136666	Upregulated	Promote the proliferation and invasion	miR-136	SH2B1	(215)	2019
hsa_circ_0009361	Downregulated	Suppress progression	miR-582	APC2	(214)	2019
circCAMSAP1	Upregulated	Promote growth	miR-328-5p	E2F1	(229)	2019
circFMN2	Upregulated	Promote proliferation	miR-1182	hTERT	(219)	2019
hsa_circ_0007534	Upregulated	Promote progression, Suppress apoptosis			(204)	2018
circHIPK3	Upregulated	Promote growth and metastasis	miR-7	FAK, IGF1R, EGFR	(205)	2018
circ_0026344	Downregulated	Suppress progression	miRNA-31		(206)	2018
circ-ZNF609	Upregulated	Promote migration	miR-150	Gli1	(207)	2018
circDDX17	Downregulated	Suppress proliferation, invasion and apoptosis			(208)	2018
circITGA7	Downregulated	Inhibit growth and metastasis	miR-370-3p	Ras, ITGA7	(209)	2018
hsa_circ_0000523	Downregulated	Suppress proliferation and induce apoptosis	miR-31	Wnt/β-catenin	(210)	2018
circRNA-ACAP2	Downregulated	Suppress growth, migration and invasion	miR-21-5p	Tiam1	(211)	2018
circRNA_100290	Upregulated	Promote progression	miR-516b	FZD4, Wnt/β-catenin	(212)	2018
circRNA_103809	Downregulated	Suppress proliferation and migration	miR-532-3p	FOXO4	(213)	2018

Table VI. Continued.

CircRNA name	Dysregulation	Function	Sponge target	Signaling pathway	(Refs.)	Publication date
circRNA0003906	Downregulated	Regulate metastasis and poor differentiation			(201)	2017
circular BANP	Upregulated	Promote cell proliferation			(202)	2017
hsa_circ_0020397	Upregulated	Promote invasion, inhibit apoptosis	miR-138	TERT, PD-L1	(203)	2017
circRNA_001569	Upregulated	Regulate proliferation and invasion	miR-145	E2F5, BAG4, FMNL2. I	(199)	2016
hsa_circ_0000069	Upregulated	Promote growth, migration and invasion			(200)	2016
hsa_circ_001988	Upregulated	Regulate differentiation and invasion			(198)	2015

stromal tumors. Although further study suggested these circRNAs to serve a regulatory role by sponging mir-144-3p, mir-142-5-p and mir-485-3p (241), there is no experimental data on the mechanism of circRNA involved in the development of gastrointestinal stromal tumors. It remains unclear if circRNA can be applied as a biomarker and therapeutic target for the diagnosis of gastrointestinal stromal tumors at present.

4. Non-coding RNAs in digestive system malignancies

Non-coding RNA is comprised of a large family of different subtypes of RNA molecules. In addition to circRNA, it also includes miRNA, long non-coding RNA (lncRNA), piwi-interacting RNA, transfer RNA, ribosomal RNA and small interfering RNA. Over the past decade, numerous studies have demonstrated that non-coding RNAs can exert regulatory effects. They serve an irreplaceable role in transcription, post-transcriptional modification, protein remodeling and cell signal transduction (242). Supporting this, non-coding RNA dysfunction has been documented to be associated with the occurrence and progression of various chronic diseases and tumors (242).

miRNA is a family of single-stranded, non-coding RNA that are typically 21-25 nucleotides in length and negatively regulates >60% of coding genes (243). Most miRNAs contain a 2-7 nucleotide seed sequence at the 3'untranslated region (3'-UTR) end, which can conservatively bind to a variety of target protein-coding genes to inhibit target mRNA translation (243). The function of miRNA itself is under negative regulation by circRNA- or lncRNA-mediated sponging (243). In a previous study, miR-7 was found to inhibit osteosarcoma cell proliferation and migration, but circRNA-CDR1as promotes osteosarcoma growth by sponging miR-7 (244) Similar cancer-promoting effects as a result of reduced miR-7 expression have also been reported in gastric cancer, colorectal cancer, pancreatic cancer and hepatocellular carcinoma (109,206,245,246). However, it should be noted that not all miRNAs have a seed sequence at the 3'UTR end. In addition to directly inhibiting mRNA translation, a number of miRNAs can also participate in pre-transcriptional regulation by binding to the argonaute-2 protein in the nucleus (247). However, this phenomenon is yet to be observed in tumors of digestive system.

LncRNA is a type of non-coding RNA that are >200 nucleotides in length, which has been previously shown to serve a significant role in maintaining the tumor microenvironment and the progression of various digestive system malignancies (248). Similar to circRNA, many lncRNAs also have the ability to sponge miRNAs. Yuan *et al* (248) found that the lncRNA SWI/SNF related, matrix associated, actin dependent regulator of chromatin subfamily C member 2 upregulates transmembrane serine protease 2 by binding to miR-551b-3p, promoting the proliferation and invasion of gastric cancer. LncRNA can also directly interact with double-stranded RNA to regulate the activity of some proteins (249). A previous study has found that LINC00665 can activate and enhance the expression of protein kinase R by protecting it from ubiquitin-dependent degradation, in turn upregulating the NF-κB signaling pathway and the widespread expression of inflammatory factors, resulting in changes to the microenvironment and the occurrence of hepatocellular carcinoma (249).

In short, non-coding RNA forms a complex network of interactions in the body. where dysfunctions in any one of the nodes will significantly impact the entire non-coding RNA network, resulting in the development of diseases. The occurrence and procession of digestive system malignancies are closely associated with the aberrant expression of these non-coding RNAs. CircRNA is an important part of the non-coding RNA family, where its function in tumors has garnered attention in recent years. The present study reviewed the research status of circRNA in seven types of tumors in the digestive system, where the potential mechanism underlying circRNA function in their respective malignancies were discussed in detail and the possibility of using circRNA as a diagnostic and prognostic marker for tumors in the digestive system was demonstrated. However, this article is associated with limitations, since it did not discuss in detail the role of circRNAs in cellular and signal transduction pathways. CircRNA has a complex intracellular mechanism of action, which is regulated by a variety of transcriptional regulatory factors and can also affect downstream biological functions by direct interaction with miRNAs and proteins. In addition, circRNA can exert biological functions in the nucleus, cytoplasm or through exosomes secreted into bodily fluids. The associated in-depth mechanism in digestive system malignancies remain to be fully elucidated and require further investigation in future studies.

5. Conclusions and perspectives

The present review briefly explored the biogenesis and function of circRNA and reviewed in detail the current status of circRNA research in various types of digestive system malignancies. CircRNA is a class of endogenous non-coding RNA that is evolutionarily conserved, the expression of which was found to be dysregulated in a variety of digestive system tumors. In digestive system malignancies, the majority of circRNAs serve an endogenous competitive role through miRNA sponging, whilst a selective number of circRNAs can directly bind to proteins either as sponges or synergistic factors to regulate tumor growth, invasion and migration, in turn influencing patient prognosis. Compared with traditional linear RNA and other families of RNA molecules, including long-chain non-coding RNA and miRNA, circRNA is widely expressed in various tissues, cells and bodily fluids, where its expression is stable, increasing their potential as biomarkers and targets for therapy. With continuous advancements in experimental technology and continuing research, it is hoped that novel functions and modes of action mediated by circRNA will be discovered and clarified in the future. With the joint efforts of researchers and clinicians, the pathogenesis of various malignant tumors of the digestive system will be elucidated, so that patients will have an increased chance of survival.

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Availability of data and materials

All data analyzed during this review are included in this published article.

Authors' Contributions

HW, YW, and XZ consulted and analyzed the literature, produced the figures and wrote the manuscript. YZ and QG were responsible for reviewing and correcting the manuscript. RJ and YZ proposed and built the theoretical framework of the article. All authors read and approved the final version of this 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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