Critical Reviews in Oncology / Hematology 145 (2020) 102854

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Circular RNAs and gastrointestinal cancers: Epigenetic regulators with a prognostic and therapeutic role

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ARTICLE INFO

Keywords:
Circular RNAs
Gastrointestinal cancers
microRNA sponge
Prognostic indicator
Biomarkers
Signaling pathways

ABSTRACT

Both environmental and genetic factors are involved in the initiation and development of gastrointestinal cancer. Covalent closed circular RNAs (circRNAs) are produced by a mechanism called "back-splicing" from mRNAs. They are highly stable and show cell and tissue specific expression patterns. Although some functions such as "microRNA sponge" and "RNA binding protein sponge" have been reported for a small number of circRNAs, the function of thousands of other circRNAs is still unknown. Dysregulation of circRNAs has been reported in many GI cancers and are involved in metastasis and invasion. CircRNAs have been reported to be useful as prognostic markers and targets for developing new treatments. We first describe the properties and biogenesis of circRNAs. We then summarize recent reports about circRNA functions, expression status, and their potential to be used as biomarkers in GI cancers including, gastric cancer, colorectal cancer, esophageal cancer, hepatocellular carcinoma, gallbladder cancer and pancreatic cancer.

1. Introduction

Gastrointestinal (GI) cancers can originate from the stomach, esophagus, pancreas, hepatobiliary system, large intestine (colorectal and anal regions) and together comprise a major cause of cancer-related mortality worldwide (Siegel et al., 2019). Smoking, obesity, *Helicobacter pylori,* hepatitis B virus (HBV) and hepatitis C virus (HCV) are known environmental risk factors for GI cancer development

Abbreviations: GI, gastro-intestinal; circRNAs, covalently closed circular RNAs; GC, gastric cancer; CRC, colorectal cancer; EC, esophageal cancer; ESCC, esophageal squamous cell carcinoma; HCC, hepatocellular carcinoma; GBC, gallbladder cancer; PC, pancreatic cancer; PDAC, pancreatic ductal adenocarcinoma; HBV, Hepatitis B virus; HCV, hepatitis C virus; APC, adenomatous polyposis coli; ORF, open reading frame; DCC, deleted in Colorectal cancer; SRY, sex-determining region Y; rRNA, ribosomal RNA; EIciRNA, exon-intron circRNAs; PHLDA1, pleckstrin homology-like domain family A member 1; EMT, epithelial–mesenchymal transition; BAG4, B-cell lymphoma 2 associated athanogene 4; FMNL2, formin like 2; LASP1, LIM and SH3 domain protein 1; MAPK, mitogen-activated protein kinase; ROCK1, rho-associated protein kinase 1; qRT-PCR, the quantitative reverse transcription polymerase chain reaction

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https://doi.org/10.1016/j.critrevonc.2019.102854
Received 21 August 2019; Received in revised form 28 November 2019; Accepted 29 November 2019

(Pourhoseingholi et al., 2015). Genetic factors such as, *APC* mutation predisposing to familial adenomatous polyposis (Leoz et al., 2015; Nallamilli and Hegde, 2017), and mutations in *E-cadherin* leading to hereditary diffuse-type gastric cancer (Brooks-Wilson et al., 2004; Liu and Chu, 2014) are known risk factors for GI development, but the exact molecular mechanisms underlying the progression and malignancy of other GI cancers remain largely unknown. Despite the success of chemotherapy in the treatment of some GI cancers, many patients continue to have a bad outcome and the 5-year survival rate in gastric cancer is less than 10 % (Orditura et al., 2014; Sitarz et al., 2018). It is important to identify predictive and prognostic biomarkers to improve current treatment strategies and extend the 5-year survival rate.

CircRNAs are a group of single-stranded RNAs molecules that form a covalently closed loop structure as a result of joining the 3′ and 5′ ends. The existence of circRNAs has been known for more than 20 years (Nigro et al., 1991), but they have generally been considered to be artifacts of aberrant splicing (Cocquerelle et al., 1993). The first circRNA was serendipitously identified in a study that aimed to understand how viroids function as plant pathogens (Sanger et al., 1976). It was found by electron microscopy that viroid RNA is a single-stranded circular RNA which does not code for any proteins (Gross et al., 1978). Hepatitis delta was the second virus which was identified as a circular RNA, and in this case the circRNA encoded an open reading frame (ORF) which was translated to a protein (Kos et al., 1986). The first endogenously produced circRNA detected in human cells was a transcript of the *DCC* gene (deleted in colorectal cancer), which was identified in the early 1990s. The authors identified a transcript with the exons not in the expected order (Nigro et al., 1991). In the next two decades shuffled exons in transcripts of other genes such as *SRY* (sex-determining region Y) (Capel et al., 1993) and cytochrome P450 2C24 (*CYPIIC24*) (Zaphiropoulos, 1993, 1996) were also identified. However, recent work has revealed a large number of circRNAs in mammalian cells, and most of them are stable (Guo et al., 2014a; Rybak-Wolf et al., 2015; Salzman et al., 2012). Most circRNAs in humans arise from coding genes (Wilusz, 2017). These transcripts are regulated independently from the linear transcripts of the underlying gene, and their transcription levels vary in a cell-specific manner (Salzman et al., 2013, 2012).

Studies have shown that circRNAs have some common properties. Exonic circRNAs are very stable and most of them have half-lives longer than 48 h inside cells, in comparison to mRNAs that show average half-lives about 10 h (Jeck et al., 2013; Schwanhausser et al., 2011). However, circRNAs are not stable in serum, which could be due to the presence of circulating RNA endonucleases (Haupenthal et al., 2006). Their stability inside cells is because of their resistance to exonucleases. This resistance may explain why some circRNAs are more abundant than the linear RNA products of their respective genes (Salzman et al., 2012). CircRNAs do not contain the 2′-5′ linkage which is present in RNA lariats, and are therefore resistant to RNA debranching enzymes. Using different methods, some studies reported that exonic circRNAs localize in the cytoplasm, and they were susceptible to the siRNA-mediated decay system, which could be useful in clarifying the functional roles of circRNAs (Hansen et al., 2011). The human homologs of the *Drosophila melanogaster* Hel25E (helicase at 25E) similarly regulate circRNA localization, and their export from the nucleus to cytoplasm is size dependent (Azmi, 2018; Huang et al., 2018a). Exonic circRNAs share some sequence-dependent features. The circRNAs that have been described to date all involve a GT-AG pair of canonical splice sites, but this could be unreliable because of the detection methods employed (Jeck et al., 2013). Moreover, some flanking introns are smaller than the average size, but most are usually longer than introns on average (Salzman et al., 2013). Lastly, the length of the exons influences the circularization, and in circRNAs comprising a single exon, the given exon was found to be three fold longer compared to all expressed exons (Jeck and Sharpless, 2014).

The lack of the free 3′ end in the circRNA molecule, which is needed for polyadenylation to take place, prevents researchers from using many molecular techniques that work by adding a poly-A tail to the RNA molecule. This makes it difficult to detect circRNAs and to explore their function. Moreover, because of the backsplicing process, the arrangements of exons are not in the expected order, and circRNAs are usually filtered out in sequencing algorithms. These problems in circRNA detection have been overcome with new bioinformatics tools such as, exonuclease-based enrichment approaches and sequencing of ribosomal RNA (rRNA)-depleted RNA libraries (instead of polyA-enriched libraries) (Jeck and Sharpless, 2014).

Although they have been thought to be a class of non-coding RNAs, some studies have shown that these circRNAs could also act as mRNAs and be translated to produce functional proteins. Moreover this process could be tissue-dependent (Meganck et al., 2018). CircRNAs have been reported to be associated with ribosomes, and it has been reported that circRNAs from the *muscleblind* locus could encode a protein (Pamudurti et al., 2017). More recently, several studies have reported that dysfunction or dysregulation of circRNAs could be associated with the development of human diseases including Alzheimer's (Akhter, 2018) and cancer (He et al., 2017). CircRNAs could act either as tumor suppressor genes or as oncogenes in cancer initiation and development. In this review we focus on new findings concerning circRNA function in gastrointestinal (GI) cancers and their potential as biomarkers and prognostic factors.

2. Circular RNA biogenesis

CircRNAs are produced during a unique type of splicing -called back-splicing- which is catalyzed by canonical spliceosomal machinery (Vicens and Westhof, 2014). They are formed whenthe 5' and 3' ends of transcribed exons and/or introns are joined covalently. During this process, down-stream splice site of donor exon/intron joins to the up-stream splice site of acceptor exon/intron in a pre-mRNA molecule (Fig. 1) (Ragan et al., 2019). Several splice variants of circRNA transcripts could be generated from a single gene depending on which exons are selected by alternative back-splice site selection during the back-splicing process (Zhang et al., 2016). There are two types of alternative back-splicing; (a) 5' back-splicing and (b) 3' back-splicing. In the 5' alternative back-splicing, two or more downstream splice sites are alternatively linked to the up-stream 3' splice site. On the other hand, in the 3' alternative back-splicing, two or more up-stream 3' splice sites are alternatively linked to the down-stream 5' splice site (Zhang et al., 2016). The expression level of circRNAs is regulated at three different stages, including transcription, back-splicing regulation, and circRNA turnover (Li et al., 2018f, g).

Regulation of circRNA generation depends on cis-regulatory elements and trans-acting factors (Li et al., 2018f, g). Cis-regulatory elements are the same in all tissues and cells, and the tissue-specific pattern of circRNA expression suggests that trans-factors must be involved in regulation of circRNA expression (Zhang et al., 2016). Splicing machinery, RNA binding proteins, and repeated sequences, such as the Alu transposable element which is inverted (oriented in opposite direction) in the RNA can modulate the biogenesis of circRNA (Zhang et al., 2014). Back-splicing and linear splicing compete with each other in newly-synthesized RNA in a cell-specific manner (Ashwal-Fluss et al., 2014). CircRNAs biogenesis is not yet fully understood, but three main pathways have been identified. Exonic circRNA arise from exons and can be subdivided into two groups: single exon circRNAand multiple exon circRNA. The second group of circRNAs are exon-intron circRNAs (EIciRNA) which contain both intron and exon sequences. Intronic circRNAs originate from the introns of the underlying gene. Analysis of the splice sites in circRNAs has revealed that most exonic circRNAs contain canonical GT/AG splicing sites (Shen et al., 2015b). However the mechanism of splice-site selection in circularization by spliceosomes is poorly understood.

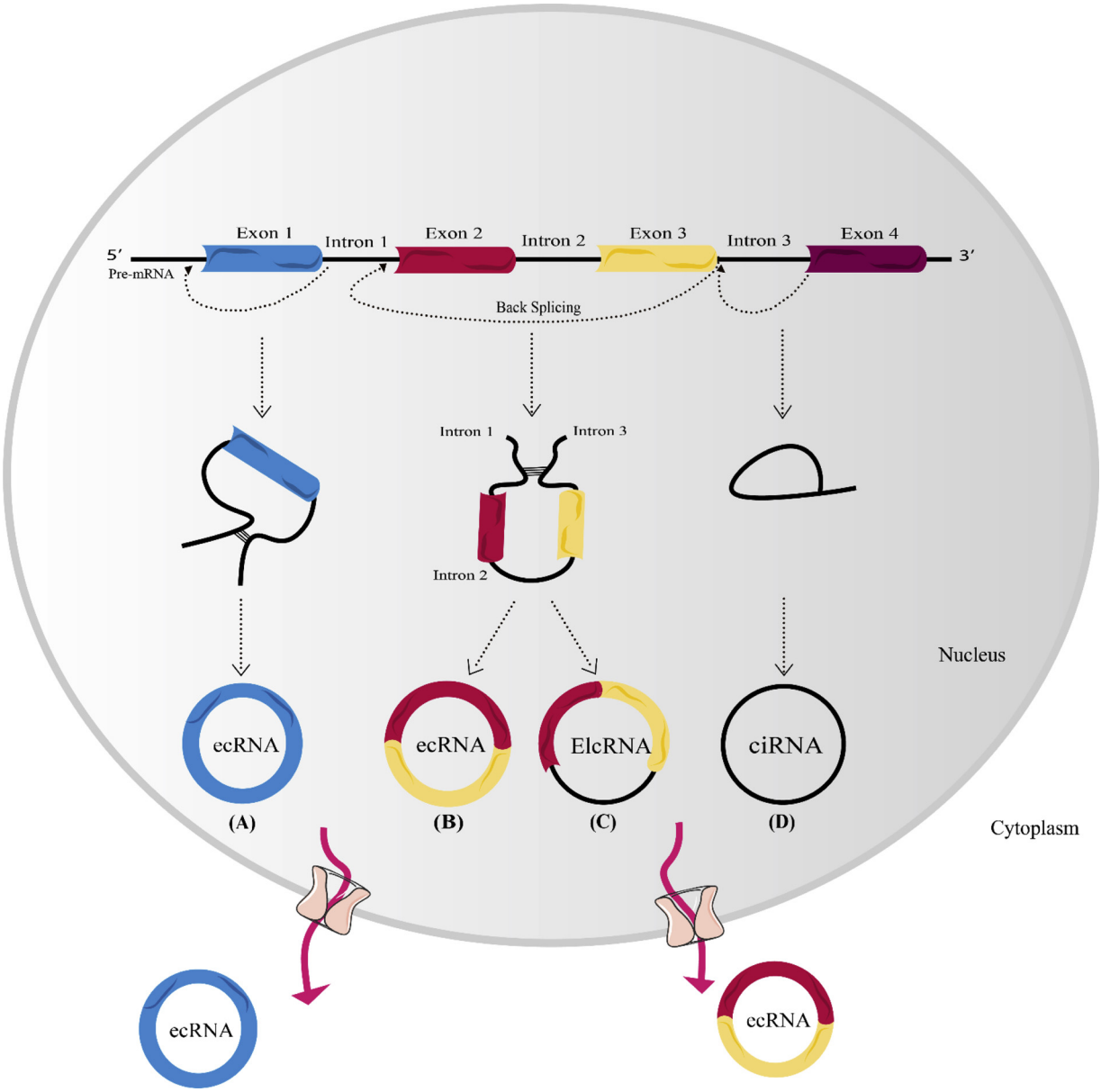

Fig. 1. CircRNAs biogenesis. Exons are shown as rectangles with different colors, and introns are depicted as black lines. Exon-derived circRNA (ecRNA) contains only exons (A and B), while circular intronic RNA (ciRNA) comprises only introns (D). In exon–intron circRNA (EIciRNA), an intron is introduced between two exons (C). The pathway by which mature ecRNAs are exported into the cytoplasm is still unclear. Some circRNAs are assumed to pass through the nuclear membrane *via* a nuclear pore complex.

3. CircRNAs function

All the functions of circRNAs have not been fully elucidated, but some biological functions (especially in gene regulation) have been proposed (Fig. 2). Their diversity, abundance and conservation suggest that they may play key roles in cell physiology (Lasda and Parker, 2014). Several functions such as the microRNA sponge and transcription regulators have been proposed for circRNAs (Holdt et al., 2018)

Based on competitive endogenous RNA (ceRNA) hypothesis, some transcripts with shared microRNA binding site compete for microRNA and post-transcriptional control (Thomson and Dinger, 2016). It was proposed that circRNAs could act as a decoy for binding to microRNAs, hence increasing the level of the microRNA target genes (Figure 3). The first example of a circRNA acting as a microRNA sponge, was circRNACDR1as which could be viewed as an extreme example as itcontained > 70 microRNA binding sites for mir-7. Decreasing the level of CDR1as led to a decreased level of CDR1 mRNA (Hansen et al., 2011). This regulatory pathway was proposed to play a role in tumorigenesis and in the mammalian brain (Kleaveland et al., 2018; Xu et al., 2018). Likewise, the circular SRY contained 16 binding sites for miR-138, and it co-precipitated with Argonaute-2 (Ago-2) which is a key protein in the microRNA regulatory pathway (Hansen et al., 2013). These two are extreme examples of the microRNA sponging activity of circRNAs, and most other circRNAs contain a much smaller number of microRNA binding sites.

Some studies have reported that circRNAs can regulate gene transcription. Nuclear localized circRNAs can interact with the complex between RNA polymerase II and U1 snRNP (small nuclear ribonucleoprotein) that acts as a regulator of transcription and splicing machinery (Maiti et al., 2017). Some circRNAs regulate splicing and promote circularization thereby decreasing linear mRNA levels (Bose and Ain, 2018). CircRNAs could also regulate gene expression (and even its own expression) at a post-transcriptional level by acting as a RNA binding protein sponge. CircRNAs have some properties, which suggest they

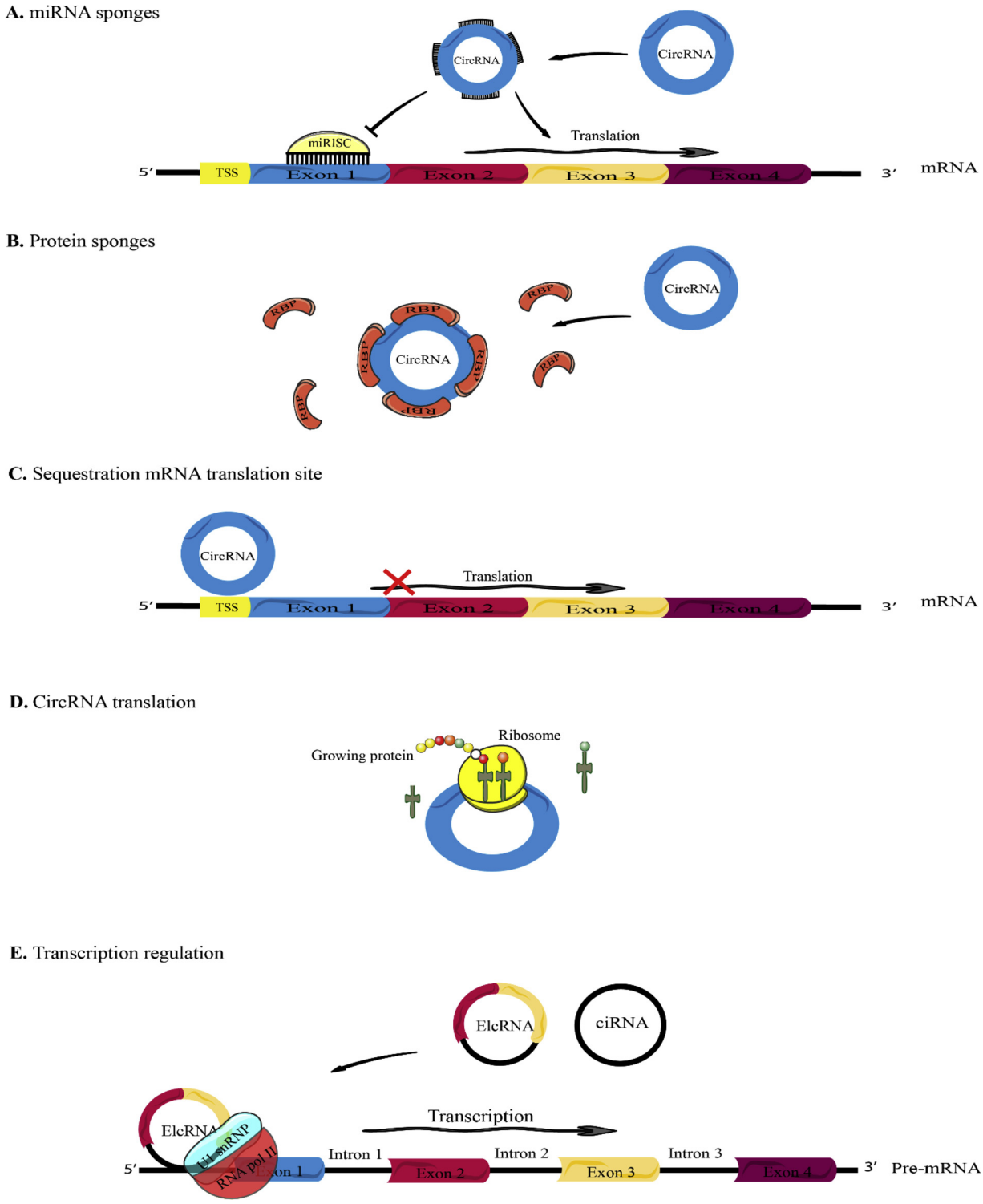

Fig. 2. Schematic illustration of circRNA functions. (A) CircRNAs might function as miRNA sponges by competing for binding of miRNA sequences, lessening the impact of miRNA-mediated regulationon gene expression. (B) CircRNAs might function as protein sponges, by binding to other RNA-binding proteins (RBPs). (C) Some circRNAs might control the expression of proteins by sequestering mRNA translation start sites. (D) CircRNAs might be translated to create functional proteins. (E) CircRNAs (*e.g.*, EIciRNAs and ciRNAs) might interact with transcription complexes and increase the expression of their parental genes.

might act as scaffolds for RNA binding proteins (Dudekula et al., 2016; Zang et al., 2018). They may have roles as sequence targeting elements, which could simultaneously bind to RNA binding proteins and also to complementary sequences in target RNA or DNA molecules. However, the function of thousands of other circRNAs has not yet been elucidated and awaits further study.

4. Circular RNAs as biomarkers

Hulka et al. have defined biomarkers as “cellular, biochemical or molecular alterations, which can be measured in biological media, including human tissues, cells, or fluids". However, recently researchers have extended the above definition to cover biological processes, which may be objectively measured and assessed as indices of normal or

Table 1
CircRNAs which act as microRNA sponges in gastric cancer.

CircRNA	Target	Model (*In vitro*, *in vivo*, Human)	Type of cell line	Ref
Hsa_circ_0000993	miR-214-5p	Human	–	(Chen et al., 2018b)
Has_circ_0001461	miR-548 g, RUNX1 in the cytoplasm; YBX1 in the nucleus	Human, *In vitro*	GSE-1, SGC-7901, BGC-823, MKN-28, AGS, MGC-803, MKN-45	(Fang et al., 2019)
Hsa_circ_0027599	miR-101, PHLDA1	Human, *In vitro*	SGC-7901, MGC-803, HGC-27, MKN-45, MKN-28	(Wang et al., 2018c)
CircRNA_001569	miR-145, NR4A2	Human, *In vitro*	…	(Shen et al., 2019)
CiRS-7	miR-7, PTEN/PI3K/AKT pathway	*In vitro*	MGC-803, HGC-27, GES-1	(Pan et al., 2018)
CircRNA_101057	miR-424, LATS1	Human, *In vitro*	SGC-7901, MKN-45, MKN-28, HGC-27, MGC-803, AGS, BGC-823, GES-1	(Zhang et al., 2017a)
CircRNA_100269	miR-630	*In vitro*	AGS, MKN28, MKN45, BGC823, MGC803, SGC7901, GES1	(Zhang et al., 2017e)
CircZFR	miR-130a/miR-107, PTEN	*In vitro*	AGS, AZ521, HGC-27, GES-1	(Liu et al., 2018b)
Has_circ_0002320	miR-367-5p, p27	*In vitro*	HGC-27, GES-1, MKN-45,	(Liu et al., 2018a)
Hsa_circ_0017639	miR-182-5p, CREB1	*In vitro*	MKN-45, BGC-823, MGC-803, SGC-7901 AGS	(Sun et al., 2018b)
CircPDSS1	miR-186-5p, NEK2	Human, *In vitro*	MGC-803, HGC-27, BGC-823, GES-1	(Ouyang et al., 2019)
CircRNA_0000284	miR-124 and miR-29b, COL1A1, COL4A1 and CDK6	*In vitro*	XGC-1, XGC-2, MGC-803, BGC-823	(Cheng et al., 2018)
CircNF1	miR-16, MAP7 and AKT3		…	(Wang et al., 2018d)
Hsa_circ_0058092	PODXL	Human	–	(Bu et al., 2019)
circ_0001546	miR-421, ATM/checkpoint kinase 2 (Chk2)/p53-dependent signaling pathway	*In vitro*	HGC-27, L-OPH	(Wu et al., 2019b)
RNA circNHSL1	miR-1306-3p/SIX1/vimentin axis	Human, *In vitro*	MKN-28, AGS, MKN-45, BGC-823, MGC-803, HGC-27, SGC-7901, GES-1	(Zhu et al., 2019b)
Hsa_circ_101882	EMT signaling pathway	Human, *In vitro*	MGC-803, HGC-27, SGC-7901, MNK-45, GES	(Yin et al., 2019)
circHECTD1	miR-1256 and activating β-catenin/c-Myc signaling	*In vivo*	BGC823, MKN45, HGC27, AGS, MGC803, SGC7901, GES-1	(Cai et al., 2019a, b)
Circ_SPECC1	miR-526b on downstream KDM4A/YAP1 pathway	*In vitro*	AGS, BGC-823, HGC-27, MGC-803, MKN-45, SGC-7901, GES-1	(Chen et al., 2019a)
hsa_circ_0067582, hsa_circ_0005758	CEA level and stages	Human	–	(Lu et al., 2019c)
miRNA-340	tumorigenesis and invasion	Human, *In vitro*	HFE145, BGC-823	(Wang et al., 2019c)
circ-NOTCH1	sponge of miR-637, expression of Apelin	Human, *In vitro*	GC	(Guan et al., 2019)
circ-DCAF6	sponging miR-1231 and miR-1256	Human	–	(Wu et al., 2019a)

pathogenic biological parameters, or responses to therapeutic interventions (Mayeux, 2004; Naylor, 2003).

Based on the National Cancer Institute, a biomarker is "a biological molecule found in blood, other body fluids, or tissues, which could be a marker of a normal or abnormal process, or of a condition or disease" such as cancer (Henry and Hayes, 2012). In general, biomarkers could differentiate an affected individual from a healthy individual (Henry and Hayes, 2012). Studies have identified a diverse range of biomarkers, such as proteins (enzymes or receptors) (Álvarez-Chaver et al., 2007; Watabe-Rudolph et al., 2012), nucleic acids (microRNAs or other non-coding RNAs) (Witwer, 2015; Zhou et al., 2015), antibodies (Schwarz et al., 2006), and peptides (Belogurov et al., 2008). Moreover, a biomarker may also consist of a set of modifications, including metabolomic and proteomic signatures, and gene expression profiles. It should be noted that many biomarkers are capable of being detected in the circulation: (serum, plasma, or whole blood); or in excretions or secretions (urine, stool, nipple discharge, or sputum). For this reason, they can be readily evaluated in a non-invasive serial manner. Other biomarkers may be only detectable in whole tissue, in which case, they would need special imaging or biopsies to be evaluated (Henry and Hayes, 2012).

Contemporary studies have shown that many features of circRNAs enable them to serve as biomarkers for some human diseases (Conn et al., 2015). One of these features is their stability. As a result of the covalently closed-loop structure with no free 5′ and 3′ ends, circRNA molecules show high resistance to the exonuclease RNase R compared to linear RNAs (Enuka et al., 2015; Memczak et al., 2013). Other studies have found that the average half-life of circRNAs in plasma exceeds 48 h, which is much longer than the average half life of mRNAs (10 h) (Jeck and Sharpless, 2014; Zhong et al., 2018c). Another feature is universality. According to some researchers, circRNAs are among the most universal molecules found in human cells (Salzman et al., 2012). circRNAs can be more abundant than their linear isoforms under some conditions (Glažar et al., 2014). Moreover, circRNA is more abundant in the brain compared to other organs (Rybak-Wolf et al., 2015). The relatively high concentration of circRNAs in the blood could be ascribed to their high stability (Li et al., 2018c; Memczak et al., 2015). Another advantageous feature is specificity; that is, the circRNAs are expressed in a tissue-specific and developmental stage-specific manner. This characteristic makes circRNAs useful bio-markers for particular diseases. Several studies have found that circRNAs are differentially expressed between cancerous and noncancerous tissues (Memczak et al., 2013) and that there identity and abundance are also distinctive of cancer cells (Floris et al., 2017; Salzman et al., 2013). Finally, circRNAs are strongly conserved across various species, meaning that a number of circRNA biomarkers that have been detected in murine models are also candidates for translation to clinical applications in humans (Jeck et al., 2013).

5. GI cancers and circRNAs

The aberrant expression of circRNAs has been linked to many human diseases including cancer (He et al., 2017). CircRNAs are becoming an interesting subject in cancer research due to their abundance, stability and regulatory function. To date some circRNAs have been implicated with several hallmarks of cancer, such as cell death and survival, invasion, metastasis and angiogenesis (Kristensen et al., 2018). These circRNAs can be detected in body fluids such as saliva and blood, and also in exosomes, suggesting that they could be used as non-invasive biomarkers in cancer detection (Bahn et al., 2015; Memczak et al., 2015; Qian et al., 2018; Wang et al., 2016). The role of circRNAs in GI cancers remains unknown, but some studies have shown that they are differentially expressed, and could be linked with prognosis, stage determination, and 5-year survival. The results have similarities and differences between studies, which could be due to different sample size, expression analysis methods, and subject status or race. Here we briefly review the current knowledge of circRNAs in different GI cancers.

5.1. Role of circRNAs in gastric cancer

Gastric cancer (GC) is an aggressive disease and despite declining in prevalence in recent decades, due to improved nutrition, better food preservation, reduction of *H. pylori* infection, and earlier diagnosis, it still remains the fourth most frequent malignancy worldwide, with a poor prognosis (Ferro et al., 2014). GC is the result of a combination of environmental factors and an accumulation of genetic alterations (Carcas, 2014; Sitarz et al., 2018). This cancer is usually diagnosed at advanced stages, and unfortunately the treatment of advanced and metastatic cancers has made little progress with a median survival only around 1 year (Cervantes et al., 2013).

CircRNAs have been proposed to have a key role in GC carcinogenesis through functioning as a sponge for microRNA and interacting with RNA binding proteins. To date there have been 13 reported circRNAs which can act as microRNA sponges in gastric cancer, some of them can act as tumor suppressors, while others could act as oncogenes in GC progression (Table 1) (Wang and Dong, 2019). The microarray expression level analysis of circRNAs in 5 samples of GC in comparison with adjacent non-tumor tissues showed different expression patterns of 713 circRNAs in GC. In GC tissues, 522 circRNAs were down-regulated whereas 191 were up-regulated, and among them,hsa_circ_0076305, hsa_circ_0035431, and hsa_circ_0076304showed the greatest alteration levels. Pathway analysis of differentially expressed circRNAs revealed that they were mostly related to carcinogenesis (Dang et al., 2017). Shen et al. showed 603 down-regulated and 347 up-regulated circRNAs in GC tissue in comparison to healthy gastric tissue. Further analysis showed that these circRNAs expression levels did not relate to their host gene linear mRNA levels, suggesting a different mechanism of regulation in the circularization process (Shen et al., 2018). CircRNA expression analysis using a circRNA chip on 8 GC and normal paired tissue samples identified 1285 differentially expressed circRNAs, 594 were down-regulated and 691 were up-regulated. Functional analysis of these circRNAs showed that 69 circRNAs could potentially sponge microRNAs and therefore regulate the target mRNAs. They also suggested that cancer-related genes such as *CD44, CXXC5, MYH9* and *MALAT1* could be regulated in GC development through the interaction of circRNA-miRNA-mRNA pathways (Sui et al., 2017). Another study revealed 16 up-regulated and 84 down-regulated circRNAs in GC. Prediction of interactions between circRNAs and miRNAs targeting specific genes revealed that hsa-circ-0026 probably regulates gene silencing, gene expression, RNA metabolism, RNA transcription and other biological activities relevant to GC. They also suggested that hsa_circ-0026 could be a potential biomarker for diagnosing GC as well as for its targeted therapy (Chen et al., 2017b). In this report, uni-variate and multi-variate Cox proportional hazard models were used to assess whether circPVT1 levels were able to predict survival independently from other pathological and clinical parameters in GC patients. In addition, if the expression levels of circPVT1 and TNM phase were combined, they could provide a better prognostic indicator compared to the TNM phase alone. This study also examined the clinical importance of linear PVT1 expression. Differently from circPVT1, patients showing lower levels of PVT1 exhibited better DFS and OS in comparison to the patients having higher levels of PVT1. When the combined levels of circPVT1 and PVT1 were examined, patients with lower levels of circPVT1 and higher levels of PVT1 showed a considerably shorter DFS and OS compared to patients having higher levels of circPVT1 and lower levels of PVT1 (Chen et al., 2017b).

736 unique annotated circRNAs were detected by RNA sequencing in several types of gastric tissues. Further analysis found that five microRNAs could be regulated by 5 differentially expressed circRNAs out of the 736 totals (Vidal et al., 2017). All of these circRNAs were previously shown to play roles in GC (Chen et al., 2017b; Shao et al.,

2017; Tian et al., 2018).

In GC cells, hsa_circ_0000993 inhibits invasion as well as proliferation through sponging miR-214-5p (Zhong et al., 2018b). Hsa_circ_000146 is negatively associated with survival in GC patients, and could sponge miR-548 g, which is a tumor suppressor microRNA (Hu et al., 2014). miR-548 directly targets mRNA, and could reverse the effects of hsa_circ_000146 overexpression, such as invasion, migration, and proliferation of GC cells.miR-548 directly targets runt-related transcription factor 1 (RUNX1),which controls genes expression implicated in the regulation ofcell cycle, the p53 and transforming growth factor β (TGF- β)signaling pathways (Cai et al., 2015; Chuang et al., 2013; Sood et al., 2017). Therefore, hsa_circ_000146 was revealed to act as a tumor suppressor *via*modulatingthemiR-548/RUNX1 axis in GC cells (Fang et al., 2019). It has been also demonstrated that hsa_circ_0027599could sponge miR-101-3p, and its overexpression inhibited proliferation and metastasis in GC cells. Pleckstrin homology-like domain family A member 1 (*PHLDA1*) overexpression, a direct target of miR-101, decreased the growth and migration of GC cells (Wang et al., 2018c). Some studies reported pro-apoptotic and anti-proliferative roles ofPHLDA1, which is involved in drug resistance in cancer (Fearon et al., 2018; Nagai, 2016). The result of another study was in contradiction with the above results, since it reported that miR-101 overexpression inhibited invasion and proliferation in the AGS gastric cancer cell line (Wu et al., 2017). It seems that clarification of the role of miR-101 in GC needs more investigation, and it is worth distinguishing between the modulatory and regulatory functions of circRNAs. Knockdown of hsa-circ_001569, which sponges miR-145(a known tumor suppressor gene in human cancer) decreased cell viability and promoted apoptosis, while it led to increased miR-145 levels(Shen et al., 2019).

CircRNAs could sponge RNA binding proteins and decrease their availability within the cell. A down-regulated circRNAin GC cells called hsa_circ_104916 could suppress proliferation, invasion and migration by decreasing the expression of Slug, a transcription factor suppressing the expression of E-cadherin, and hence modulates the epithelial–mesenchymal transition (EMT) (Li et al., 2017a). Hsa_circ_104916 overexpression up-regulated E-cadherin, which could be due to down-reglation of Slug (Li et al., 2017a).

Recent work has revealed the different expression of circRNAs in GC, and some studies have suggested specific circRNAs which could be used as biomarkers in GC diagnosis (Table 2). Hsa_circ_0000190 expression level was evaluated in 104 GC and adjacent non-tumor samples, and also in plasma samples from 104GC patients and normal subjects. The results showed down-regulation of this circRNA in GC, which could differentiate patients from normal samples and subjects with specificity and sensitivity values of 0.750 and 0.712 respectively (Chen et al., 2017c). Hsa_circ_002059 expression level was proposed as a biomarker for GC progression, and it was down-regulated in plasma samples from 36 post-operative patients in comparison to pre-operative plasma samples. According to the findings, Hsa_circ_002059 was down-regulated in gastric cancer tissues in comparison to the adjacent non-cancerous tissue. Moreover, it was found that the levels of hsa_circ_002059 in plasma collected from post-operative gastric cancer patients were significantly different from the levels obtained from pre-operative gastric cancer patients. Lower levels of expression showed a significant correlation with distant metastasis, TNM stage, and patient age (Li et al., 2015b). Hsa_circ_0003159 expression was evaluated in 108 paired GC samples, and it was suggested that its down regulation could be a biomarker in GC (Tian et al., 2018). Hsa_circ_0000467 was reported to promote cancer progression and was upregulated in GC cell lines, tissues, and plasma samples from GC patients. It was proposed as a promising non-invasive marker for GC prognosis as well as diagnosis. Findings also showed significant upregulation of Hsa_circ_0000467 in GC tissues in comparison to adjacent non-tumor tissues. The same results were observed in the MGC-803, HGC-27, NUGC-3, AGS, and GES-1 cell lines and in samples of plasma from GC patients. Results showed that the area under the ROC curve of hsa_circ_0000467 was 0.790, which was higher than widely utilized biomarkers such as CA-724 and CEA. In addition, the levels of hsa_circ_0000467 expression were significantly reduced after surgical operation. Furthermore, a close relationship was found between the expression levels of hsa_circ_0000467 and the TNM phase. Cox multivariate analysis also suggested hsa_circ_0000467 could be a new independent prognostic marker. In-vitro experiments showed that proliferation, migration, and invasion of GC cells were considerably suppressed by knockdown of hsa_circ_0000467. In addition, hsa_circ_0000467 silencing resulted in increased tumor cell apoptosis in-vitro. Therefore, it was suggested that Hsa_circ_0000467 could function as a novel non-invasive biomarker in GC, and could also be a therapeutic target for GC (Lu et al., 2019a, b). Hsa_circ_KIAA1244 was down-regulated in GC patient plasma, tissues and exosomes, and was proposed as a diagnostic marker for GC. Its expression status was related to TNM stage, metastasis and shorter survival rates (Tang et al., 2018).

5.2. Role of circRNAs in colorectal cancer

Colorectal cancer (CRC) accounts for 10 % of cancer-related deaths, and is the second and third most frequent malignancy among women and men, respectively (Marley and Nan, 2016). CRC prevalence has been increasing in recent decades mainly because of changes in life style, obesity, low physical activity, smoking, and dietary habits (Kuipers et al., 2015; Marmol et al., 2017). Most of the hereditary forms of CRC are caused by mutations in genes, including *EPCAM*,*PMS2*, *MSH6, MSH2*or *MLH* involved in DNA mismatch-repair system(Tiwari et al., 2016), and the adenomatous polyposis coli *(APC)* gene which handles the Wnt signaling pathway) (Vasen et al., 2015). Of note, polyposis is related to mutations in the mutY DNA glycosylase (*MUTYH)* gene (Kashfi et al., 2013; Markkanen et al., 2013).

The association between CRC and circRNAs was reported for the first time, with the identification of a circular transcript of the Deleted in CRC (*DCC)*gene (Nigro et al., 1991). As its name suggests the deletion of the *DCC* gene in CRC had been known for more than two decades (Fearon and Pierceall, 1995). Bachmayr-Heyda and colleagues (Bachmayr-Heyda et al., 2015) indicated the global decrease of the expression of circRNAs in tumor tissues and CRC cell lines in comparison with normal colonic mucosa. They found 39 circRNAs differentially expressed between CRC samples and normal mucosa. Of these, 28 circRNAs were down-regulatedand11 circRNAs were up-regulated. Interestingly, this data agreed with a recent study that also reported the global decrease of circRNAs in CRC tissues and cell lines (Taborda et al., 2017). It was hypothesized that circularization is less functional in tumors than in normal tissues, and this could be due to onco-micoRNAs which are up-regulated in CRC (Ragusa et al., 2015). CircRNA sequencing data in two CRC cell lines,SW620(a metastasis-derived cell line)and SW480 (a primary tumor cell line), and abnormal colorectal cell, NCM460,showed an overall circRNA abundance decreasein CRC cell lines in comparison to normal colonic epithelial cells. 2919 circRNAs that were differentially expressed between CRC cells and normal cells were identified, and it was also found that circRNAs in CRC cells were usually shorter than those in normal cells (Jiang et al., 2018a).

The circRNAs expression profile from three paired CRC samples and adjacent non-tumor tissues revealed 136 significantly over-expressed circRNAs and 243 down-regulated circRNAs in CRC tissues. Circ-BANP was up-regulated in 35 CRC samples and its knockdown attenuated the proliferation of CRC cells (Zhu et al., 2017). CircRNA-seq analysis in 40 samples of CRC and CRC with liver metastasis (CRC-m) revealed 113 differentially expressed circRNAs, of which 92 circRNAs were up-regulated and 21 circRNAs were down-regulated.Hsa_circRNA_0001178 and hsa_circRNA_0000826wereconsiderably up-regulated in CRC-m tissues. In order to assess the utility of circRNAs as diagnostic biomarkers, the ROC curves of circRNA_0000826 and circRNA_0001178 were analyzed in CRC-m patients with liver metastasis. The results

Table 2
CircRNAs as biomarkers in gastric cancer.

CircRNA	Expression status	Target	Model (*In vitro*, *in vivo*, Human)	Type of cell line	Ref
Hsa_circ_0003159	Down	–	Human	–	(Tian et al., 2018)
Hsa_circ_0001895	Down	t-CEA	Human, *In vitro*	SGC-7901, AGS, HGC-27, MGC-803,, BGC-823,	(Shao et al., 2017)
Hsa-circ-104916	Down	EMT	Human, *In vitro*	AGS, MKN-28, NCI-N87, MKN-45, GES-1	(Li et al., 2017a)
Hsa_circ_0000190	Down	–	Human	–	(Zhang et al., 2017a)
Hsa_circ_002059	Down	–	Human	–	(Li et al., 2015b)
Hsa_circ_0000467	Up	TNM stage	Human, *In vitro*	HGC-27, MGC-803, AGS, NUGC-3, GES-1	(Lu et al., 2019a, b)
CircSMARCA5	Down		Human, *In vitro*	MGC803, MKN45, MKN74, AGS, BGC823, SGC7901, GES-1	(Cai et al., 2019a, b)
Hsa_circ_0000181	Down	Carbohydrate antigen, CEA	Human	–	(Zhao et al., 2018)
Hsa_circ_0000520	Down		Human, *In vitro*	MKN-45, BGC-823, MGC-803, AGS	(Sun et al., 2018a)
Hsa_circ_0000745	Down	CEA	Human	–	(Huang et al., 2017a)
Hsa_circ_00001649	Down-regulated	PCHNTs	Human	–	(Li et al., 2017c)
Hsa_circ_0006633	Down	CEA	Human, *In vitro*	HGC-27, SGC-7901, MGC-803, AGS, GES-1	(Lu et al., 2017)
Hsa_circ_0066444	Up	–	Human, *In vitro*	MKN-45, BGC-823, MGC-803, AGS, GES-1	(Rong et al., 2018)
Hsa_circ_0074362	Down	–	Human, *In vitro*	GES-1, AGS, BGC-823, HGC-27, MGC-803, SGC-7901	(Xie et al., 2018)
Hsa_circ_0001017, Hsa_circ_0061276	Down	–	Human, *In vitro*	BGC-823, MGC-803, SGC7901, GES-1	(Li et al., 2018e)
Hsa-circ_0000096	Down	CDK6, MMP-2, MMP-9, Ki67, VEGF	Human, *In vitro, In vivo*	AGS, BGC-823, HGC-27, SGC-7901, MGC-803 GES-1, And mouse model	(Li et al., 2017b)
circPVRL3	Down		Human, *In vitro*	MKN-45, MGC-803, SGC-7901, AGS, GES-1	(Sun et al., 2018c)
hsa_circ_0103398, hsa_circ_0127859 hsa_circ_0103398, hsa_circ_0127859	Up	–	Human	–	(Wang et al., 2019a)
hsa_circ_0005654	Down	–	Human	–	(Wang et al., 2019e)
hsa_circ_0000144	Up	ErbB	Human, *In vitro*	MGC-803, line GES-1	(Wei et al., 2019)
hsa_circ_0006848	Down	CEA	Human	–	(Lu et al., 2019a, b)
Hsa_circ_0065149	Down		Human	–	(Shao et al., 2019)
hsa_circ_006100	Up	miR-195/GPRC5A signaling	*In vivo*	KN-45, MGC-803, AGS and SGC-7901, GES-1-T	(Liang et al., 2019)
hsa_circ_0001821	Down		Human, *In vitro*	SGC-7901, HGC-27, BGC-823, AGS, MKN-1, GES-1	(Kong et al., 2019)

showed increased expression levels of circRNA_0000826 and circRNA_0001178 in patients with CRC-m. The ROC curves were analyzed for assessing the diagnostic value of both circRNAs in CRC-m patients. The analysis showed that AUC was 0.816 for circRNA_0000826 and 0.945 for circRNA_0001178. The mentioned circRNAs could be promising markers for the diagnosis of liver metastasis from CRC (Xu et al., 2019a).

Expression pattern analysis has shown significantly higher hsa_circ_001569 expression in CRC, which was related to aggressive features such as metastasis (Taborda et al., 2017). Over-expression of hsa_circ_001569 increased invasion as well as proliferation in the CRC cell lines, while its suppression showed a remarkable decrease in invasiveness and proliferation rate. It has also been shown that hsa_circ_001569 sponges miR-145 leading to increased protein levels of formin like 2 (FMNL2), "B-cell lymphoma 2 associated athanogene 4" (BAG4), and E2F5 (Taborda et al., 2017). E2F5 is a transcription factor regulating the expression of genes implicated in the cell cycle (Jiang et al., 2011). BAG4 and FMNL2 are implicated in invasion and growth as well as metastasis (Annunziata et al., 2007; Li et al., 2010; Liang et al., 2013). MiR-145 has been reported to be correlated with survival in patients with CRC (Li et al., 2012), and also inhibits invasion and migration in CRC cell lines (Sheng et al., 2017). Hsa_circ_001988 down-regulation was reported in CRC tissues compared with adjacent normal mucosa in 62 patients, and its expression level was related to differentiation and invasion (Wang et al., 2015). Hsa_circ_0000069 was significantly up-regulated in 30 paired CRC samples and non-tumor adjacent tissues (Guo et al., 2016). The knockdown of hsa_circ_0000069 can inhibit invasion, migration, and proliferation of tumor cells. CircCCDC66 expression was elevated in CRC and was associated with poor prognosis. CircCCDC66 could function as an oncogene and its knockdown significantly reduced cell migration and metastasis (Hsiao et al., 2017). Evaluation of ciRS-7-A in 44 matched healthy mucosal samples and 153 primary CRC tissues revealed that this biomarker was remarkably up-regulated in cancer tissues (Weng et al., 2017). CiRS-7 over-expression led to miR-7 suppression, and the RAF1 and EGFR oncogene activation, and was also correlated with poor patient survival. Cir-ITCH was found to be down-regulated in 45 CRC tissues in comparison to adjacent non-tumor tissues (Huang et al., 2015). Functional analysis showed that cir-ITCH increases ITCH levels implicated in the Wnt/β-catenin pathway suppression. Therefore, cir-ITCH may play a key role in CRC through modulating the Wnt/β-catenin pathway.

A summary of the circRNAs that have been reported to be involved with CRC is shown in Tables 3 and 4.

5.3. Role of circRNAs in esophageal cancer

Esophageal cancer (EC) has an overall five-year survival ranging from 15 % to 20 %, and is the eighth most frequent malignancy in the world, and the sixth most prevalent cause of cancer-related mortality. The two histological subtypes of EC are squamous cell carcinoma and adenocarcinoma, that each has varying geographical and racial distribution (Abbas and Krasna, 2017; Sohda and Kuwano, 2017). The risk factors for EC are abuse of tobacco and alcohol, obesity, diet, race and gender (Domper Arnal et al., 2015). EC continues to be a generally fatal disease with only a modest improvement in survival, and surgery still plays the main role in EC treatment (D'Journo and Thomas, 2014). The poor prognosis in EC is mainly because of late diagnosis, and more than 50 % of patients already had metastatic tumor at the time of diagnosis (D'Journo and Thomas, 2014). Identifying a biomarker for the detection of EC at an early stage is crucial to improve disease management.

Accumulating evidence suggests that circRNAs have a crucial role in EC (Table 5). Microarray analysis of circRNAs in esophageal squamous cell carcinoma (ESCC) and adjacent-cancer tissues in three patients revealed 3288 differentially expressed circRNAs of which 2139 were up-regulated, and 1149 were down-regulated. Further network analysis of circRNAs-mRNA-microRNA interactions showed that 32 differentially expressed circRNAs and 98 differentially expressed mRNAs were linked to 64 miRNAs in ESCC (Jiang et al., 2019b). The expression pattern of the circRNAs revealed that 1045 were up-regulated and 1032 were down-regulated in 3 pairs of frozen tumor and non-tumor ESCC tissues. Three circRNAs including hsa_circ_0043603, hsa_circ_0001946, andhsa_circ_0062459 were detected in plasma, and the combination of hsa_circ_0043603 and hsa_circ_0001946 could be utilized as a diagnostic biomarker with sensitivity of 0.928 and specificity of 98 %.The findingsdemonstratethat these two circRNAs could be utilized as diagnostic biomarkers.

A circular RNA micro-array was employed to analyze three pairs of ESCC frozen tumor and non-tumor tissue in order to detect ESCC-associated circRNAs. A total of 1045 up-regulated and 1032 down-regulated circRNAs were observed, among which six circRNAs (hsa_circ_0062459, hsa_circ_0076535, hsa_circ_0072215, hsa_circ_0042261, hsa_circ_0001946, and hsa_circ_0043603) were confirmed by qRT-PCR analysis. Because blood is the most widely utilized sample in the laboratory, these six circRNAs were also investigated in blood as diagnostic biomarkers. The results indicated there were no detectable levels of hsa_circ_0042261, hsa_circ_0072215, or hsa_circ_0076535 in the plasma or serum of either patients or healthy individuals. ROC curve analysis was used to assess the specificity and sensitivity of the other three circRNAs. The AUCs of hsa_circ_0001946 and hsa_circ_0062459 respectively were 0.894 (sensitivity = 92 %, specificity = 80 %) and 0.836 (sensitivity = 64 %, specificity = 92 %) respectively. A logistic regression analysis was run to establish the whether a combination of the expression levels of both circRNAs in plasma was useful. The formula was established as 3.272-(0.465*level of hsa_circ_0001946) – (1.706* level of hsa_circ_0062459). Logistic regression analysis showed better diagnostic precision with the combination AUC, specificity of 98 % and sensitivity of 0.928. Moreover, hsa_circ_0001946 over-expression decreased invasion, migration, and proliferation in cell lines (Fan et al., 2019).

Another study reported that 267 circRNAs revealed considerably different levels of expression in ESCC tissues from five patients and adjacent non-tumor tissues (Jiang et al., 2019b). Of these circRNAs, 92 were up-regulated and 175 were down-regulated. Hsa_circRNA_406826and hsa_circRNA_101125 were proposed as novel potential markers for ESCC treatment and diagnosis. Another study identified 813 significantly up-regulated and 445 down-regulated circRNAs in normal epithelial and malignant esophageal cell lines (Sun et al., 2017). The five most up-regulated circRNAs were ciRNA11, circRNA904, circRNA3594, ciRNA101, circRNA1241, and the top five most down-regulated circRNAs were circRNA9864, circRNA9650, circRNA9865, circRNA9671 and circRNA9930. Pathway analysis showed that differentially expressed circRNAs were linked to cancer-related pathways including metabolism, cell apoptosis, proliferation and migration.

Evaluation of circRNA expression in ESCC using microarray technology revealed that 469 circRNAs were up-regulated, and 275 were down-regulated in ESCC in comparison with non-tumor adjacent tissue. Of these, the most up-regulated (increased 20.3-fold) circRNA was hsa_circRNA_103670, while the most down-regulated (decreased 12.1-fold) was hsa_circRNA_030162 (Shi et al., 2018).

In addition to profiling circRNAs in EC, there have been some reports, which have explored the expression of specific circRNAs in EC, and clarified their roles *in vitro*. Hsa_circ_0067934 was significantly up-regulated in 51 paired ESCC samples in comparison to the adjacent normal tissues. SiRNA inhibition of hsa_circ_0067934 blocked migration and proliferation, and suppressed the progression of cell cycle in ESCC cells (Xia et al., 2016). Cir-ITCH expression status was analyzed in a total of 684 ESCC and paired adjacent non-tumor tissue samples and its overall down-regulation was established in ESCC samples (Li et al., 2015a). Cir-ITCH sponges miR-7, -17, and -214. In addition, Cir-ITCH probably exerts its suppressive effects on ESCC through modulating the Wnt/β-catenin signaling pathway. The circ-TTC17 expression levels

Table 3
CircRNAs related to colorectal cancer.

Circular RNA	Expression in CRC	Target	miRNA sponge	Model/Source	Type of cell line	Ref
has_circ_103809	Down	FOXO4	miR-532-3P	*In vitro*, Human/CRC tissues (n = 30)	SW620, HCT116, COCA-2, HT29	(Bian et al., 2018)
circITCH	Down	Wnt/β-catenin signaling pathway	miR-214	*In vitro*, Human/CRC tissues (n = 45)	HCT116, SW480	(Huang et al., 2015)
hsa_circ_0000523	Down	Dkk1	miR-31	*In vitro*	COLO205, COLO320HSR, DLD-1, HCT-15, HCT-8, SW480, SW620, SW1116, HT-29, LoVo, NCM460, FHC, LS 174 T, Caco-2	(Jin et al., 2018)
circDDX17 (hsa_circ_0002211)	Down	–	–	Human/CRC tissues (n = 60)	–	(Li et al., 2018h)
hsa_circ_0001649	Down	–	–	*In vitro*,Human/CRC tissues (n = 64), Serum (n = 18)	HCT116	(Ji et al., 2018)
hsa_circ_0000711	Down	–	–	*In vitro*,Human/CRC tissues (n = 101)	HCT116, H-T29, COLO205	(Li et al., 2018a, b)
hsa_circ_0000567	Down	–	–	Human/ *In vitro*/CRC tissues (n = 102)	SW480, SW620, RKO, HCT116, CACO2	(Wang et al., 2018b)
hsa_circ_0026344	Down	–	miR-31, miR-21	*In vitro*,Human/CRC tissues (n = 32)	SW620, HCT116, HT29, SW480	(Yuan et al., 2018)
hsa_circ_104700	Down	–	–	Human/CRC tissues (n = 170)	–	(Zhang et al., 2017b)
circITGA7	Down	NF1	miR-370-3p	Human/CRC tissues (n = 69)	–	(Li et al., 2018f, g)
hsa_circ_0014717	Down	p16	–	*In vitro*,Human/CRC tissues (n = 46)	HCT116, SW480, HT29	(Wang et al., 2018a)
hsa_circ_001988	Down	–	–	Human/CRC tissues (n = 62)	–	(Wang et al., 2015)
hsa_circ_0003906	Down	–	–	*In vitro*,Human/CRC tissues (n = 122)	HCT8, SW480, LoVo, HCT116, HT29, SW620	(Zhuo et al., 2017)
circACAP2	Up	Tiam1	miR-21-5p	*In vitro*,Human/CRC tissues (n = 21)	SW480	(He et al., 2018)
hsa_circ_001569	Up	E2F5, FMNL2, BAG4	miR-145	*In vitro*,Human/CRC tissues (n = 30)	SW480, HCT116	(Shen et al., 2015a)
hsa_circ_0020397	Up	TERT PD-L1	miR-138	*In vitro*	SW480, LoVo, SW620, HCT116	(Zhang et al., 2017d)
hsa_circ_0071589	Up	EZH2	miR-600	*In vitro*,Human/CRC tissues (n = 40)	HCT116	(Yong et al., 2018)
hsa_circ_0000069	Up	–	–	*In vitro*,Human/CRC tissues (n = 30)	HCT-116, HT-29, SW480, LoVo	(Guo et al., 2016)
hsa_circ_0007534	Up	–	–	Human/CRC tissues (n = 33)	–	(Zhang et al., 2018c)
hsa_circ_000984	Up	CDK6	miR-106b	*In vitro*, Human/CRC tissues (n = 32)	HT29, W480, SW620	(Xu et al., 2017b)
hsa_circ_0055625	Up	ITGB8	miR-106b-5p	Human/CRC tissues	–	(Zhang et al., 2019d)
circBANP	Up	p-Akt	–	*In vitro*, Human/CRC tissues (n = 35)	HT29, HCT116	(Zhu et al., 2017)
ciRS-7	Up	EGFR/RAF1/MAPK pathway	miR-7	*In vitro*, Human/CRC tissues (n = 44)	HT29, HCT116	(Tang et al., 2017)
circRNA_100290	Up	FZD4	miR-516b	*In vitro*,Human/CRC tissues (n = 24)	HT29, HCT116, SW620, SW480	(Fang et al., 2018)
hsa_circ_0136666	Up	SH2B1	miR-136	*In vitro*	Cell line	(Jin et al., 2019)
circHIPK3	Up	FAK, YY1, EGFR, IGF1R	miR-7	*In vitro*,Human/CRC tissues (n = 178)	HCT116, SW620, HT29, DLD1, SW480	(Zeng et al., 2018)
circCCDC66	Up	–	–	*In vitro*,Human/CRC tissues (n = 48)	HCT116, HT-29	(Hsiao et al., 2017)

Table 4
CircRNAs as biomarkers in colorectal cancer.

circRNAs	Dysregulation	miRNA sponge	Related molecules or pathways	Model	Type of cell line	Ref
hsa_circRNA_104700	Down	–	–	Human	–	(Zhang et al., 2017b)
circRNA0003906	Down	–	–	Human *In vitro*	SW480, HCT8, SW620, LoVo, HT29, HCT116	(Zhuo et al., 2017)
circ_0026344	Down	miR-31, miR-21	–	Human	–	(Yuan et al., 2018)
hsa_circ_001988	Down	–	–	Human	–	(Wang et al., 2015)
hsa_circ_0000567	Down	–	–	Human *In vitro*	SW480, SW620, RKO, HCT116, CACO2	(Wang et al., 2018b)
Hsa_circ_0014717	Down	–	p16	Human *In vitro*	HCT116, SW480, HT29	(Wang et al., 2018a)
hsa_circ_0000711	Down	–	–	Human *In vitro*	HCT116, HT29, COLO205	(Li et al., 2018a, 2018b)
circITGA7	Down	miR-307-3p	ITGA7	Human *In vitro*	SW480, Caco-2, RKO, SW620, HCT116, LoVo, DLD1	(Li et al., 2018f, g)
hsa_circ_0001649	Down	–	–	Human *In vitro*	H116	(Ji et al., 2018)
hsa_circ_0136666	Up	miR-136	SH2B1	Human *In vitro*	LoVo, DLD1, SW480, SW620, HCT116, HCT8, HT29	(Jin et al., 2019)
circCCDC66	Up	–	–	Human *In vitro*	–	(Hsiao et al., 2017)
circRNA_100290	Up	miR-516b	FZD4	Human *In vitro*	HCT116, HT29, SW480, SW620	(Fang et al., 2018)
circHIPK3	Up	miR-7	FAK, YY1, IGF1R, EGFR	Human *In vitro*	HT29, HCT116	(Zeng et al., 2018)
ciRS-7	Up	miR-7	EGFR/RAF1	Human *In vitro*	HCT116, HT29	(Weng et al., 2017)

were observed to be greater in ESCC plasma and tissue from ESCC patients in comparison to healthy subjects. The ROC curves were utilized for investigating the diagnostic value of circ-TTC17 in differentiating ESCC samples from normal plasma. As shown by the analysis, the cutoff value of circ-TTC17 was –2.548, and the area under the ROC curve (AUC) was 0.8200. Moreover, this showed a sensitivity of 73.33 % and a specificity of 88.00 %. In addition, a positive relationship was observed between the expression of circ-TTC17 and the TNM phase and the presence of lymphatic metastasis. Kaplan–Meier survival analysis and log-rank statistics were used to compare patient postoperative survival and the expression levels of circ-TTC17 for the prognosis of ESCC patients. The ESCC patients with higher levels of circ-TTC17 expression demonstrated a considerably shorter survival time in comparison to patients with lower levels of circ-TTC17 expression. Univariate analysis revealed that the TNM phase, relative circ-TTC17 expression level, and lymphatic metastasis were all prognostic indices for OS rates of ESCC patients. Nevertheless, multi-variate analyses of the variance showed that only the size of the tumor was an independent marker to assess the prognosis of the ESCC patients. Hence, circ-TTC17 has potential to be utilized as a prognostic and diagnostic marker for ESCC. Circ-TTC17 can act as an oncogene, and promote ESCC cell proliferation and migration. Bioinformatics analysis suggested that circ-TTC17 could play a role in ESCC by sponging microRNAs such as miR-153, -217, -224, and -370 (Wang et al., 2019d).

It was observed that hsa_circ_0004370 was up-regulated in both EC tissues and cell lines. Interestingly, loss of hsa_circ_0004370 function suppressed invasion as well as proliferation of EC cell lines and increased their apoptosis rate. Hsa_circ_0004370 can sponge miR-1294 and indirectly increase the level of “LIM and SH3 domain protein 1” (LASP1) suggesting that hsa_circ_0004370 can function as an oncogene affecting proliferation, apoptosis, and invasion *via* the miR-1294/LASP1 axis (Zhang et al., 2019c). LASP1 enhances tumor invasion as well as proliferation in various cancers and could act as an essential EMT mediator by mediating the mitogen-activated protein kinase (MAPK) phosphorylation, triggering Smad and PI3K/AKT pathways (Wang et al., 2014; Zhang et al., 2017c). Circ-SMAD7 derived from the gene SMAD7 intron, is remarkably downmodulated in plasma samples from ESCC patients in comparison with healthy subjects, and showed a negative correlation with the TNM stage. *in vitro* circ-SMAD7 overexpression could suppress migration and proliferation in ESCC cells, while circ-SMAD7 knockdown showed the opposite effects. Taken together these finding suggested a tumor suppressor role for circ-SMAD7 in ESCC (Zhang et al., 2019b). Functional analysis of circ0043898 shown to be downmodulated in ESCC tissue samples, indicating its inhibitory effects on invasion, migration, and proliferation of tumor cells, and could induce apoptosis in ECA-109 and Kyse-520 ESCC cells. *in vivo* experiments showed that circ0043898 was associated with inhibition of oncogenesis (Guo et al., 2018). Besides playing a role in carcinogenesis, circRNAs could be involved in other aspects of cancer, such as the development of drug and radiation resistance. Evaluation of circRNAs found significant up-regulation of 57 circRNAs and down-regulation of 17 circRNAs in KYSE-150R, a radioresistant EC cell line, compared with the radiosensitive KYSE-150 (Su et al., 2016).

5.4. Role of circRNAs in hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is increasing in incidence worldwide with an average survival rate between 6–20 months (Waller et al., 2015). HCC is more common among males, with a male: female ratio of 2.4 worldwide, and the most common age at presentation is between the third and fifth decades of life (Kulik and El-Serag, 2019). Chronic liver diseases caused by hepatitis B and C viruses, and excessive consumption of alcohol contributes most to the HCC subjects (Ghouri et al., 2017). HCC pathogenesis involves different genetic aberrations, and alterations in several signaling pathways, which lead to a heterogeneity in the disease at a molecular level (Bertino et al., 2014). An improved knowledge of the molecular mechanisms of hepatocarcinogenesis could help to improve diagnostic methods, and enable possible therapeutic strategies to inhibit cancer-driving signaling pathways.

Mounting data suggests that circRNAs are related to HCC development (Tables 6 and 7), but their mechanism of action in the development of HCC remains unclear. Shang et al. analyzed circRNA expression in 3 paired HCC and non-tumor tissues, and identified 61 differentially expressed circRNAs. Among them, 26 circRNAs were up-regulated and 35 were down-regulated in tumor cells. Additionally, they reported that hsa_circ_0005075 levels were considerably up-regulated in HCC, was associated with HCC tumor size, and could be used as potential biomarker with sensitivity of 83.3 %and specificity of 90.0 %. Bioinformatics analysis of the circRNA-miRNA-mRNA interaction network predicted that a total of 4 miRNAs and 121 mRNAs could interact with hsa_circ_0005075 (Shang et al., 2016). Micro-array analysis detected twenty specific circRNAs with differential expression levels between tumor and non-tumor tissues. qRT-PCR was employed to verify the expression levels of the above 20 circRNAs. Moreover, the micro-array test results showed that hsa_circ_0091579 mRNA and hsa_circ_16245-1 expression was consistent with the respective levels. However, because the levels of hsa_circ_16245-1 and hsa_circ_0091579 were significantly enhanced in the HCC tissues, it was decided to evaluate their potential diagnostic value. ROC curves were obtained for hsa_circ_0091579 and hsa_circ_16245-1 levels in HCC. The areas under the ROC curve were

Table 5
circRNAs and esophageal cancer.

CircRNAs	Dysregulation	Target	Model (*In vitro*, *in vivo*, Human)	Type of cell line	Ref
circPVT1	Up	Paxs, PPARs	Human, *In vitro*	EC109, CaES-17, TE-1, TE-10,HEEC, HepG2, MKN45, SW60, A549	(Zhong et al., 2019)
hsa_circ_0006168, miR-100	Down		Human, *In vitro*	TE13, ECA109, Kyse150, Kyse450, Kyse510, Het-1A	(Shi et al., 2019)
Hsa_circ_0004370	Up	miR-1294/LASP1 pathway	Human, *In vitro*	Eca-109,TE-1, KYSE-150, Het-1A	(Zhang et al., 2019c)
CircRNA_000543	Up	miR-9	Human, *In vitro*	NPC, CNE1, 5e8F	(Chen et al., 2019b)
has_circ_0067934	Up		Human, *In vitro*	TE-13, KYSE-410, ECA-109, TE-1, HEEC	(Xia et al., 2016)
circ-SMAD7	Up		Human, *In vitro*	KYSE30, KYSE 70, KYSE 140, KYSE 150, KYSE 180, TE10, TE12, HET-1-A	(Zhang et al., 2019b)
ITCH	–	Wnt/β-catenin pathway	Human, *In vitro*	Eca-109, TE-1	(Li et al., 2015a)
Circ-TTC17	Up		Human, *In vitro*	HET-1A, KYSE30, KYSE450	(Wang et al., 2019d)

0.720 for hsa_circ_16245-1 and 0.656 for hsa_circ_0091579. For hsa_circ_0091579, the sensitivity and specificity were 0.4 and 0.97 respectively. The specificity and sensitivity of hsa_circ_16245-1 were 0.63 0.83 respectively. 75 pairs of HCC specimens were tested to validate the prognostic value of these circRNAs. Hsa_circ_0091579 expression was remarkably increased in HCC tumor tissue in comparison to the levels in adjacent non-tumor tissues. They could not detect hsa_circ_16245-1 in a number of the HCC samples. Thus, hsa_circ_0091579 up-regulation serves as a potential prognostic marker for individuals with HCC, and is related to overall survival (Zhang et al., 2018a). Hsa_circ_0001649 expression was considerably down-modulated and was correlated with tumor size in 89 HCC tissues in comparison to adjacent non-tumor tissues (Qin et al., 2016). Microarray analysis of circRNAs revealed that the expression of hsa_circ_0004018 was lower in HCC than non-tumor tissues. Hsa_circ_0004018 expression was also associated with TNM stage, differentiation, and tumor diameter (Fu et al., 2017b).

The microRNA sponging function of circRNAs is involved in HCC development, and various pathways have been reported to be regulated by this mechanism. circMTO1 (mitochondrial translation optimization1 homologue) and hsa_circRNA_0007874/hsa_circRNA_104135 were detected to be remarkably down-modulate in HCC tissues, and were linked to shortened survival. MiR-9 was found to bind tocircMTO1, and circMTO1 silencing in HCC cells could down-modulate p21, the oncogenic miR-9 target, leading to HCC invasion and proliferation promotion. Furthermore, an inhibitor of miR-9 blocked the tumor-promoting impact of circMTO1 silencing (Han et al., 2017). The expression of CircTRIM33–12 in HCC tissues was investigated, and it was revealed that circTRIM33–12 is down-regulated in HCC cell lines and tissues. CircTRIM33-12 can sponge miR-191, and its inhibition increased immune evasion, tumor invasion, migration, and proliferation (Zhang et al., 2019a). Compared to the adjacent non-tumor tissues, Cdr1as expression is up-regulated in HCC tissues, and its suppression inhibits miR-7 expression and increased tumor cells invasion and proliferation. Mentioned findings propose that Cdr1as acts as an oncogene in HCC, partly by targeting miR-7 (Yu et al., 2016). Expression analysis of circRNA-101368 showed that this circRNA is considerably up-modulated in HCC tissue samples, and the higher expression of hsa-circ-101368 was related to poor prognosis in patients with HCC. Hsa-circ-101368 was confirmed that directly binds to miR-200a and both could negatively modulate each other. The expression of miR-200a was negatively related to hsa-circ-101368 expression in tissue samples. Hsa-circ-101368 inhibition blocked migration, which could be partially attenuated *via* miR-200a suppression (Li et al., 2018d).

CircSETD3 (hsa_circRNA_101436/hsa_circRNA_0000567) was remarkably down-regulated in HCC cell lines and tissues, and was correlated with larger tumor size and poor HCC differentiation in affected subjects. CircSETD3 could suppress the proliferation of HCC cells and induced G1/S cell cycle arrest. Furthermore, it was shown that circSETD3 could act as a sponge for miR-421, which targets MAPK14 signaling (Xu et al., 2019b). MAPK14 may facilitate tumor cells proliferation and survival, and contribute to the progression of some tumor types (Igea and Nebreda, 2015).Yu et al. reported that hsa-circ-104718 was physically associated and co-expressed with microRNA-218-5p in HCC. They found that exogenously expressed hsa-circ-104718 accelerated cell proliferation, migration, invasion, and inhibited apoptosis. Hsa-circ-104718 over-expression could increase tumor size and metastasis, while its silencing had the opposite effect. Conversely, miR-218-5p over-expression could decrease the proliferation, migration, invasion, and increase apoptosis (Yu et al., 2019).

5.5. Role of circRNAs in gallbladder cancer

Gallbladder cancer (GBC), the most prevalent biliary tract cancer, accounts for more than 80 % of biliary tract malignancies (Lai and Lau, 2008). GBC has only a 6 month mean overall survival, while the 5-year survival rate remains low at about 5 %. A genetic predisposition,

Table 6
Role of circRNAs in hepatocellular carcinoma.

circRNAs	Dysregulation	Target	Model	Type of cell line	Ref
Hsa_circ_0091579	Up		Human	–	(Zhang et al., 2018a)
Hsa_circ-101368	Up	HMGB1/RAGE signaling	Human, In vitro	HCCLM3	(Li et al., 2018d)
CircSETD3 (hsa_circRNA_0000567/hsa_circRNA_101436)	Down		Human, *In vitro*		(WHO, 2019)
Hsa_circRNA-104718	Up	miR-218-5p/TXNDC5 signaling pathway	Human, *In vivo*	SMMC-7721, HepG2, MHCC-LM3, and SK-Hep1, HEK293 T	(Yu et al., 2019)
Hsa_circ_0003570	Down	alpha-fetoprotein	Human, *In vitro*	HepG2, SMMC-7721, MHCC97 L, MHCC97H, and HCCLM3, L02	(Fu et al., 2018)
Hsa_circ_0068669	Down		Human, *In vitro*	HCC	(Yao et al., 2018)
Hsa_circ_0078602	Down		Human		(Kou et al., 2019)
Circ5379–6	Down		*In vitro, In vivo*	hepG2, 293 T, Huh-7, SK-hep-1	(Zhang et al., 2018b)
CSMARCA5 (hsa_circ_0001445)	Down	TIMP3, Sponging miR-17-3p and miR-181b-5p	Human, *In vitro, In vivo*		(Yu et al., 2018)
CircPTGR1	Up	miR449a-MET pathway	*In vitro*	HepG2, L-O2, SMCC-7721, HEP3B, HUH7, MHCC97-L (97 L), MHCC 97H (97 H), HCC-LM3 (LM3)	(Wang et al., 2019b)
Hsa_circ_0079929	Down	PI3K/AKT/mTOR signaling pathway	Human, *In vitro, In vivo*	SK-Hep-1, SMMC-7721, 7702, LM-3, PRL-RF5	(Zheng et al., 2019)
CircHIPK3	Up	miR-124, AQP3	Human, *In vitro*	Huh7, MHCC-LM3, HepG2, SMMC-7721, PLC, L02, HEK293 T	(Chen et al., 2018a)
Hsa_circ_0070269	Up	miR-182/NPTX1 axis	Human, *In vitro*	(Hep-3B, SMMC-7721, HepG2, PLC, Huh-7, LO2	(Su et al., 2019)
Hsa_circ_0028502, hsa_circ_0076251	Down		Human	–	(Jiang et al., 2019a)
circular RNA PVT1	Up	miR-203/HOXD3 pathway	Human, *In vitro*	Huh7, Sk-hep1, SMMC-7721, HepG2, L-02	(Zhu et al., 2019a)
Circ_0015756	Up	miR-7	Human, *In vitro*	WRL-68, MHCC97H, Bel-7402, Huh-7, Bel100	(Liu et al., 2019b)
hsa_circ_0085616	Up	β-catenin, p-ERK,p-AKT,	Human, *In vitro*	HepG2, MHCC-97 L, MHCC-97H, Huh7, LM3	(Li et al., 2019)
Hsa_circ_0003998	Up	AFP,	Human, *In vitro*	HepG2, HuH7, MHCC97H, PLC/PRF/5, L02	(Qiao et al., 2019)

Table 7
CircRNAs as biomarkers in hepatocellular carcinoma.

Circular RNA	Expression in HCC	miRNA sponge	Model /Source	Type of cell line	Ref
hsa_circ_0005075	Up	–	Human/HCC tissues (n = 63)	–	(Zeng et al., 2018)
circRNA_100338	Up	miR-141-3p	*In vitro*, Human/HCC tissues (n = 4)	BEL7402, Hep3B, HCCLM6, MHCC97H	(Huang et al., 2017b)
circ_0067934	Up	miR-1324	*In vitro*, Human HCC tissues (n = 49)	BEL7402, HuH7, MHCC97-L, Hep3B	(Zhu et al., 2018b)
ciRS-7 (Cdr1as)	Down		*In vitro*, Human HCC tissues (n = 108)		(Xu et al., 2017a, b)
hsa_circ_0005986	Down	miR-129-5p	*In vitro*, Human HCC tissues (n = 81)	HepG2, Huh7, SMMC7721, HCCLM3, MHCC97 L, MHCC97H	(Fu et al., 2017a)
hsa_circ_0004018	Down	–	*In vitro*, Human HCC tissues (n = 102)	Huh7, HepG2, HCCLM3, MHCC97H, SMMC7721	(Fu et al., 2017b)
circMTO1	Down	miR-9	*In vitro*, Human HCC tissues (n = 289)	QGY-7701, HepG2, SK-Hep1, SMMC-7721	(Han et al., 2017)
cSMARCA5	Down	miR-181b-5p, miR-17-3p	*In vitro*, Human HCC tissues (n = 208)	HCCLM3	(Yu et al., 2018)
circRNA_0046367	Down	miR-34a	Human HCC tissues (n = 5)	–	(Guo et al., 2017b)
hsa_circ_0001649	Down	–	HCC tissues (n = 89)	–	(Qin et al., 2016)
circC3P1	Down	miR-4641	Human/HCC tissues	Cell line (???)	(Zhong et al., 2018a)
circ-ITCH	Down	–	Human/HCC tissues (n = 1600)	–	(Guo et al., 2017a)
circZKSCAN1	Down		*In vitro*, Human/HCC tissues (n = 102)	BEL-7402, Huh7, SMMC-772, Hep3B, HepG2	(Yao et al., 2017)

congenital biliary tract anomalies, female sex, and age are considered to be the main risk factors for GBC development. Based on the geographical and ethnical considerations, the mentioned factors are different among populations (Hundal and Shaffer, 2014). This malignancy is most often diagnosed at late stages, frequently proving fatal. Although surgical resection is the only treatment option, only 10 % of affected subjects are candidates for surgery with curative intent at initial presentation (Kanthan et al., 2015). The development of diagnostic markers is essential for improved GBC management, and could lead to the development of screening programs for individuals at risk.

Some evidence has shown that circRNAs are involved in GBC development. However, much remains unknown about the role of circRNAs in GBC, and further investigation is needed to clarify possible circRNA regulatory pathways in the initiation and development ofGBC. CircHIPK3 was found to be up-regulated in human GBC cells. Silencing of circHIPK3 using siRNA, induced apoptosis and suppressed proliferation and survival of both primary and established human GBC cells. The opposite effects occurred with circHIPK3 over-expression (Xu et al., 2013). Further investigation showed that circHIPK3 could sponge tumor-suppressive microRNA-124 resulting in enhanced miR-124 gene targets expression, such as CDK6 (rho-associated protein kinase) and ROCK1 (rho-associated protein kinase 1) (Pierson et al., 2008). They concluded that, through sponging miR-124, circHIPK3 could promote GBC cell growth (Kai et al., 2018). CircHIPK3 was also observed to sponge miR-379, and miR-379 up-regulation rescued the phenotype induced by over-expression of circHIPK3 (Tian et al., 2017).

5.6. Role of circRNAs in pancreatic cancer

Pancreatic cancer is the fourth most frequent cause of malignancy-associated mortality in USA. Although the approaches for management and detection of this cancer have been developed, 5-year survival remains at only 4 %. The lethality is mainly caused by its propensity to rapidly metastasize to the lymphatic system and distant organs (Iovanna et al., 2012). The main risk factors for developing pancreatic cancer are high-fat diet, African-American ethnic origin, obesity, diabetes mellitus, male sex (Vincent et al., 2011), smoking, age, and family history of chronic pancreatitis (Klein et al., 2004). Up to now, surgical resection is the only therapeutic approach for pancreatic cancer, and it responds poorly to chemotherapeutic agents (McGuigan et al., 2018). Understanding the underlying mechanism contributing to pancreatic cancer is essential to develop new treatment strategies.

Studies have suggested that circRNAs could serve as diagnostic or predictive biomarkers for pancreatic cancer, and could provide new insights especially in pancreatic ductal adenocarcinoma (PDAC) (Tables 8 and 9) (Qu et al., 2015). Microarray analysis of circRNAs in 6 PDAC and paired non-tumor tissues revealed that 351 circRNAs were differentially expressed between PDAC and the healthy tissue, of which 142 circRNAs were down-regulated and 209 circRNAs were up-regulated in tumor samples. Some differentially expressed circRNAs were evaluated by qRT-PCR in 20 paired tissues. Bioinformatics analysis predicted that hsa_circ_0005785 (one of the differentially expressed circRNAs) was potentially able to bind miR-181a and miR-181b (Li et al., 2016a). MiR-181a has a crucial role in modulating the migration as well as growth of pancreatic cancer cells (Zhang et al., 2015). MiR-181b is related to pancreatic cancer cell resistance to gemcitabine chemotherapy (Takiuchi et al., 2013). Gue et al. investigated the circRNA profile in 20 pancreatic cancer tissues and corresponding adjacent tissues. They reported that 128 circRNAs were up-regulated and 161 circRNAs were down-regulated in cancer tissues (Guo et al., 2018). Moreover, these authors predicted circRNA-miRNA interactions, and identified eight circRNAs that bound to miR-15a.Three of these were up-regulated (hsa_circ_100435, hsa_circ_103076, hsa_circ_103309) and five were down-regulated (hsa_circ_000780, hsa_circ_101252, hsa_circ_102374, hsa_circ_104433, hsa_circ_104882).Moreover, four up-regulated circRNAs bound to miR-506 (hsa_circ_101717, hsa_circ_104084,

Table 8
Circular RNAs in pancreatic cancer.

circRNAs	Dysregulation	miRNA sponge	Related molecules or pathways	Model	Type of cell line	Ref
circ-LDLRAD3	Up	miR-137-3p	pleiotrophin (PTN)	*In vitro*	PANC-1, SW1990	(Yao et al., 2019)
hsa_circRNA_0007334	Up	hsa-miR-144-3p, hsa-miR-577	–	Human	–	(Yang et al., 2019)
circ_0007534	Up	miR-892b, miR-625	–	*In vitro* Human	Capan-2, BxPC3, SW1990, AsPC-1, PANC1	(Hao et al., 2019)
ciRS-7	Up	miR-7	EGFR/STAT3 signaling pathway	Human	–	(Liu et al., 2019a)
circ_0030235	Up	miR-1294, miR-1253		*In vitro* Human	AsPC-1, SW1990, Capan-2, PANC1, BxPC-3	(Xu et al., 2019c)
circZMYM2 (hsa_circ_0099999)	Up	miR-335-5p	JMJD2C	*In vitro* Human	CFPAC-1, PANC-1	(An et al., 2018)
circRHOT1	Up	miR-330, miR-26b, miR-382, miR-125a	–	Human	PANC-1, Capan-1, Capan-2, AsPC-1, SW1990, BxPC-3	(Qu et al., 2019)
hsa_circ_0000977	Up	miR-874-3p	PLK1	*In vitro*	–	(Huang et al., 2018b)
circ-IRAS	Up	miR-122	ZO-1, RhoA, F-actin	*In vitro* Human	AsPC-1, Hs 766 T	(Li et al., 2018a, b)
hsa_circ_0006215	Up	–		Human	–	(Zhu et al., 2018a)
circ-PDE8A	Up	miR-338	MACC1/MET pathway	*In vitro* Human	BxPC-3, Capan-1, Hs 766 T, Aspc-1, Hs 766 T, HEK-293	(Li et al., 2018i)
CircRNA_100782	Up	miR-124	IL6-STAT3 pathway	Human	BxPC3, HPDE	(Chen et al., 2017a)

hsa_circ_100646, hsa_circ_102213). It has been reported that miR-15a could inhibit the proliferation of pancreatic cancer cells and the EMT, and that miR-506 could suppress progression and chemoresistance (Guo et al., 2014b; Li et al., 2016b). Gue et al. speculated that circRNAs could regulate gene expression *via* the miRNA sponging effect and may have a role in the progression of pancreatic cancer (Guo et al., 2018).

Hsa_circ_0006215 was shown to be remarkably up-regulated in pancreatic cancer tissue. Based on bioinformatics analysis, it was proposed that hsa_circ_0006215 most likely regulated the expression of miR-378a-3p (Zhu et al., 2018a). Expression analysis of circ-IARS in human microvascular vein endothelial (HUVECs) cells, Hs 766 T, Hs 766 T-L2 pancreatic cancer cells, plasma exosomes, and PDAC tissues revealed that the expression of circ-IARS is up-modulated in plasma exosomes and in pancreatic cancer cells/tissues of metastatic disease patients (Zhang et al., 2018a). Also, the expression of circ-IARS is positively linked to TNM stage, vascular invasion and liver metastasis, and negatively associated with postoperative survival time. Circ-IARS sponges miR-122, and its overexpression considerably down-regulates miR-122. Taken together, it was proposed that circ-IARS promotes tumor metastasis and invasion (Zhang et al., 2018a). The expression of ciRS-7 and MiR-7 in 41 pairs of PDAC tumors and their adjacent tissues revealed that the expression of ciRS-7 is remarkably greater in PDAC tissue. However, the expression of miR-7 demonstrated the conflicting trend. Moreover, ciRS-7 suppression inhibits invasion and proliferation of PDAC cells. Using functional analysis they proposed an oncogenic role for ciRS-7 in PDAC, which could act partially through modulating the EGFR/STAT3 pathway as well as targeting miR-7 (Liu et al., 2019a). Qu and colleagues indicated that circRHOT1 was up-regulated in pancreatic cancer. CircRHOT1 could bind to miR-382, -330, -125a, and -26b, leading to modulate various tumor-related pathways. Moreover, circRHOT1 knockdown could inhibit pancreatic cancer cell proliferation, invasion and migration (Qu et al., 2019).

Gemcitabine (2',2'-difluoro 2'-deoxycytidine, dFdC) (a cytidine analogue) is a cornerstone of PDAC therapy at all stages. Unfortunately, chemoresistance development within weeks of treatment initiation has limited its clinical use (Amrutkar and Gladhaug, 2017). Shao et al. reported that the circRNA signature was different between the gemcitabine-resistant PANC-1-GR cell line and the gemcitabine-sensitive PANC-1 counterpart (Shao et al., 2018). Differential analysis of gene expression between PANC-1 and PANC-1-GR cells showed that 126 circRNAs had significantly different expression between these two cell lines, with 68 up-regulated and 58 down-regulated in PANC-1-GR cells in comparison with PANC-1 cells. In another investigation, the expression levels of circ-LDLRAD3 were examined in 31 plasma samples from normal cases 31 plasma samples from pancreatic cancer patients, cell lines and 30 paired pancreatic cancer and adjacent non-tumor tissues (Yang et al., 2017). Their results showed that Ccirc-LDLRAD3 is up-regulated in plasma samples tissues and cell lines of pancreatic cancer. Besides, the expression of circ-LDLRAD3 is significantly associated with metastasis, as well as venous and lymphatic invasion.

6. Conclusions

CircRNAs, once thought to be merely random errors in transcription, have now been realized to be important players in cell biology and regulation of gene expression. The mechanism by which they regulate gene expression, and their overall function are not yet fully understood. Recent studies have clarified that these transcripts are dysregulated in many cancers, and play an essential role in cancer-related signaling pathways. Taken together, these findings highlight the important and diverse role of circRNAs in cancer initiation and progression. Accumulating evidence suggests that one important mechanisms of action for circRNAs is by acting as microRNA sponges, thus having the opposite effect on gene expression as manifested by the corresponding miRNAs involved. The present review has shown that circRNAs are involved in many different GI cancers, including esophagus, stomach,

Table 9
Circular RNAs as biomarkers in pancreatic cancer.

circRNAs	Dysregulation	miRNA sponge	Model	Type of cell line	Ref
circRNA-ASH2L	Up	miR-34a	*In vitro*, Human	BxPC-3, AsPC-1, Capan-1, PANC-1, Hs 766 T, and SW1990	(Jiang and Bu, 2019)
circ-LDLRAD3	Up	–	*In vitro*, Human	HPDE6-C7, HPC-Y5	(Yang et al., 2017)
circRNA_102213	Up	miR-506	Human	–	(Guo et al., 2018)
circRNA_100646	Up	miR-506	Human	–	(Guo et al., 2018)
circRNA_104084	Up	miR-506	Human	–	(Guo et al., 2018)
circRNA_101717	Up	miR-506	Human	–	(Guo et al., 2018)
hsa_circ_0001946	Up	–	Human	–	(Li et al., 2016a)
hsa_circ_0005397	Up	–	Human	–	(Li et al., 2016a)
circRNA_104882	Down	miR-15a	Human	–	(Guo et al., 2018)
circRNA_104433	Down	miR-15a	Human	–	(Guo et al., 2018)
circRNA_102374	Down	miR-15a	Human	–	(Guo et al., 2018)
circRNA_101252	Down	miR-15a	Human	–	(Guo et al., 2018)
circRNA_000780	Down	miR-15a	Human	–	(Guo et al., 2018)
hsa_circ_0001649	Down	–	*In vitro*, Human	PANC1, BxPC3	(Jiang et al., 2018b)
hsa_circ_0008719	Down	–	Human	–	(Li et al., 2016a)
hsa_circ_0041150	Down	–	Human	–	(Li et al., 2016a)
hsa_circ_0005785	Down	–	Human	–	(Li et al., 2016a)
hsa_circ_0000257	Down	–	Human	–	(Li et al., 2016a)
hsa_circ_0006913	Down	–	Human	–	(Li et al., 2016a)

pancreas, liver, gallbladder and colorectal cancer. The fact that these cancers arise from several different cell types and have different risk factors for cancer development, underlines the likelihood that circRNAs may be involved in general signaling pathways in cancer, such as cell cycle regulation, cell death, proliferation, migration and metastasis. On the other hand, some circRNAs show tissue or malignancy-specific expression patterns, and may function in a single type of cancer or even a single-subtype. The fact that expression levels of many circRNAs can be detected in serum or plasma samples encourages the development of non-invasive screening or biomarker studies. High-throughput screening of thousands of circRNAs together with sophisticated computer algorithms may allow prognostic predictions, and monitoring of the development of treatment resistance. Inhibitors (small molecules or nucleic acid-based) of those circRNAs that function as oncogenes may be developed in the future. Clarifying the roles of circRNAs in GI cancers could open a new window in management and the development of new therapeutic strategies. Further investigation in the field of circRNAs and cancers is needed to fully characterize their role in carcinogenesis.

Funding

MRH was supported by US NIH GrantsR01AI050875 and R21AI121700. Scientific Advisory Boards: Transdermal Cap Inc, Cleveland, OH; BeWell Global Inc, Wan Chai, Hong Kong; Hologenix Inc. Santa Monica, CA; LumiThera Inc, Poulsbo, WA; Vielight, Toronto, Canada; Bright Photomedicine, Sao Paulo, Brazil; Quantum Dynamics LLC, Cambridge, MA; Global Photon Inc, Bee Cave, TX; Medical Coherence, Boston MA; NeuroThera, Newark DE; JOOVV Inc, Minneapolis-St. Paul MN; AIRx Medical, Pleasanton CA; FIR Industries, Inc. Ramsey, NJ; UVLRx Therapeutics, Oldsmar, FL; Ultralux UV Inc, Lansing MI; Illumiheal & Petthera, Shoreline, WA; MB Lasertherapy, Houston, TX; ARRC LED, San Clemente, CA; Varuna Biomedical Corp. Incline Village, NV; Niraxx Light Therapeutics, Inc, Boston, MA. Consulting; Lexington Int, Boca Raton, FL; USHIO Corp, Japan; Merck KGaA, Darmstadt, Germany; Philips Electronics Nederland B.V. Eindhoven, Netherlands; Johnson & Johnson Inc, Philadelphia, PA; Sanofi-Aventis Deutschland GmbH, Frankfurt am Main, Germany. Stockholdings: Global Photon Inc, Bee Cave, TX; Mitonix, Newark, DE.

Declaration of Competing Interest

MRH declares the following potential conflicts of interest.

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