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REVIEW ARTICLE

Circular RNAs in cancer and diabetes

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Abstract. Circular RNAs (circRNAs) are a class of noncoding RNA molecules formed by the back splicing process. Compared to linear mRNA molecules they are more stable. CircRNA acts as miRNA sponges, regulates translation, epigenetic alterations, etc. However, the most significant aspect of circRNAs has been its role in regulating the hallmark of cancer and diabetes mellitus. Several circRNAs are extensively expressed in individuals with cancer and diabetics. Dysregulated expression of various circRNAs plays a crucial part in the development of type 2 diabetes mellitus. In the present review, we present the current understanding of cricRNAs biogenesis, regulatory mechanisms, reviews of recent findings and circRNA as potential biomarker.

Keywords. tumour; miRNA sponge; back-splicing; biomarker.

Introduction

Circular RNAs (circRNAs) are a family of RNA molecules where a covalent bond connects 3′ and 5′ ends and acts as mammalian gene regulator. They are noncoding, single-stranded and highly stable molecules, first recognized as viroids in plant-based viruses in 1976 and later (1979), it was also found in eukaryotic cells (Kolakofsky 1976; Sanger *et al.* 1976). CircRNAs are mostly formed by the precursor mRNA back-splicing process (Hsu and Coca-Prados 1979). In nature, they are less abundant than the normal linear RNA molecule and, are therefore, considered as rare events (Shan *et al.* 2019; Shang *et al.* 2019; Zhao *et al.* 2019). With the advancement of RNA sequencing techniques and bioinformatics, thousands of individual cricRNAs were discovered in mammalian cells. Following this, extensive research has discovered numerous functions of cricRNAs in recent years. For example, acting as scaffolds in the assembly of protein complexes, sequestrating proteins from their native subcellular localization, modulating parental gene expression, regulating alternative splicing and RNA–protein interactions and functioning as microRNA sponges (Wang *et al.* 2017). Most notably, certain circRNA plays a significant role in tumour initiation and cancer progression. Genomic analysis demonstrates the strong presence of circRNA in different cell types. In low-proliferating cells such as the brain, they have higher levels of expression compared to highly-proliferating liver cells (Haddad and Lorenzen 2019). Notably, enucleated cells such as red blood cells and platelets tend to exhibit higher levels of circRNAs than nucleated (hematopoietic) cells. It has been reported that platelets, in particular, express the highest number of circRNAs, almost twice as many as erythrocytes and five times more than granulocytes (Haddad and Lorenzen 2019; Nicolet *et al.* 2018). In this mini review, we concentrated on the circRNA's biogenesis, functional mechanism and crucial role in the development of two human diseases, i.e. cancer and diabetes.

Characteristics and biogenesis of circRNA

Recent studies have shown that the size of circRNA ranges from a few hundred to thousand nucleotides produced from one to five exons. Since they lack free 5′ and 3′ polarity they are not prone to exonuclease degradation and are much more

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stable than the linear RNA molecule. They primarily reside in the cytoplasm of the cell and some are present in the nucleus as well. Both circRNA and linear RNA originates from the precursor mRNA by back splicing of exons/introns and simple splicing, respectively. CircRNAs are of three different types depending on their origin: exon–intron circRNAs (EIciRNAs), exonic circRNAs (ecircRNAs), and circular intronic RNAs (ciRNAs) (Jeck and Sharpless 2014; Su *et al.* 2019b).

Three possible models of ecircRNA biogenesis have been discovered, namely circularization driven by lariat, intron pairing, and resplicing. The lariat-driven method of circularization is a form of exon skipping (cassette-on) process where the intronic lariat contains the skipped exon(s). If further splicing occurs before the lariat is unravelled by debranching enzymes within it, a stable RNA circle can be formed with the exons skipped. During the process, a linear transcript is also made, excluding the skipped exon(s) (Chen, *et al.* 2015). Circularization driven by intron pairing is independent of exon skipping. It differs from the lariat-driven model of circularization by selecting splice site pairs and lacks a detailed understanding of the corresponding linear product(s). Intronic motifs were proposed to edge the circularized exons(s) and thus join the circularized exons(s) (Chen *et al.* 2015). Resplicing-driven circularization is a two-stage cycle, initial splicing eliminates canonical splicing sites and thus resplicing makes use of cryptic splicing sites on the spliced mRNAs for exon-skipping circularization (Chen *et al.* 2015). Unlike ecircRNAs, EIciRNAs retain those introns that are not completely spliced out (figure 1). Pre-mRNAs contain flanking Alu complementary pairs or pairs other than Alu might facilitate EIciRNA production (Sheng, *et al.* 2018). CiRNAs are being derived from intron lariats that resist normal intron degradation and debranching. Lariat intron excised of reverse complementary sequences from pre-mRNA can pair to generate a close loop structure called ciRNA. The development of ciRNAs is dependent on the presence of GU-rich 7mer sequence near the 5′ splicing site and 11mer C-rich motifs near the 3′ branch site (Su, *et al.* 2019a).

Functional mechanism of circRNAs

CricRNA acts as microRNA sponges (miRNA). miRNA sponges contain multiple sites complementary to a miRNA of interest. A recent study reported that circRNA is rich in miRNA response elements (MREs) and can function as miRNA sponges (Ebert and Sharp 2010; Han, *et al.* 2017). When cricRNA is expressed at a high level, it inhibits the activity of miRNAs sharing the common seed area. MicroRNA plays an important role in posttranscriptional regulation of gene expression by binding to the 3′ untranslated region (3′UTR) of an mRNA. CircRNA acts as sponges and binds to the miRNA complementary sites, withdrawing the miRNAs from their downstream target genes and regulates gene expression. Compared to some of the other miRNA sponges, circRNA can bind more efficiently and effectively to the target, and thus, regarded as a super sponge. The best example is CDR1as, which nurture more than 70 selectively conserved miR-7 binding sites (Schwerk and Savan 2015; Vislovukh, *et al.* 2014). Apart from functioning as a miRNA sponge, some circRNA also has binding sites for RNA-binding proteins and thus functions as protein sponges and regulates gene expression. For example, the PABPN1 locus originating from circRNA (circ-PABPN1) binds to human

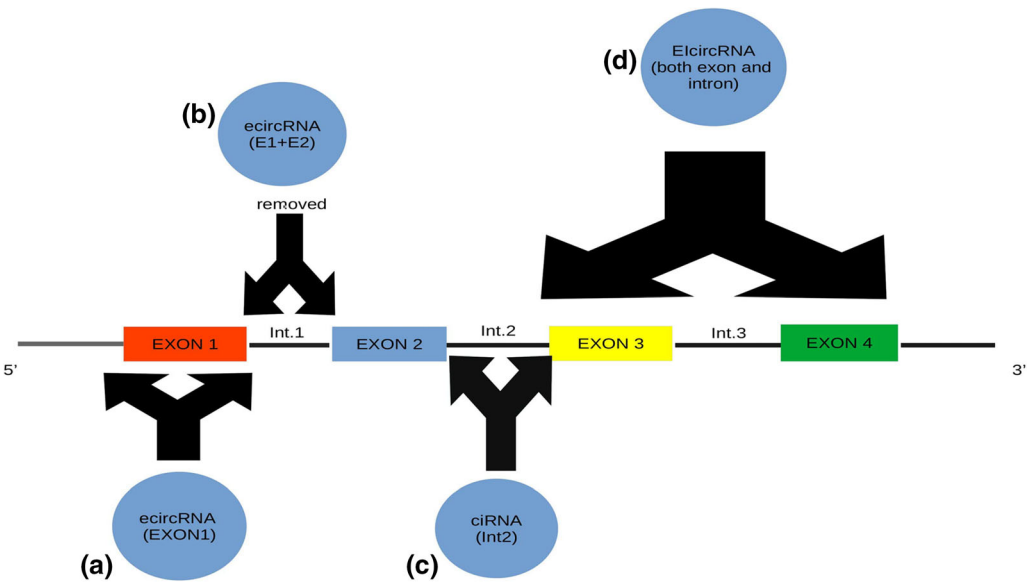

Figure 1. CricRNA formation. (a) Exonic cricRNA (ecricRNA) are formed by the backsplicing of 5′ splice site to a 3′ splice site. (b) The intron is removed and ecricRNA is produced by more than one exons. (c) Formation of ciRNA from intorn lariats. (d) EicricRNA are formed by the circularization of intron retained between the exons.

antigen R / ELAV-like protein 1 (HuR) and avertsHuR from binding to PABPN1 mRNA, thereby suppressing translation of PABPN1 (Su *et al.* 2019a; Zhao *et al.* 2019). CircRNA regulates transcription by combining with RNA polymerase II complex and translating related proteins. For example, circ-PAIP2 and circ-EIF3J were found to interrelate with the RNA polymerase II and U1 snRNPs in the promoter region of the host gene for enhanced transcription of their parental genes, such as EIF3J and PAIP2 (Su *et al.* 2019a; Zhao *et al.* 2019). Recent studies have also shown that circRNA competes with linear mRNA for selective splicing. For example, the circRNA generated from the circularization of the second exon of the muscle blind splicing factor (MBL) competes with the linear MBL mRNA (Ashwal-Fluss, *et al.* 2014; Wu *et al.* 2019).

CircRNAs in cancer

Cancer cells can produce dysregulated growth factors and corresponding receptor molecules, leading to autocrine stimulation. Epidermal growth factor receptor (EFGR) is a type of protein receptor that can trigger a cascade of other growth factors and controls cell growth. EFGR is a target of miR-7 (tumour-suppressor). CDR1as (cricRNA) acts as a sponge of miR-7 and increases the expression level of proto-oncogenes (EGFR, CCNE1 and PIK3CD). Consequently, overexpression of CDR1as results in the suppression of tumour-suppressing activity of miR-7. In addition to CDR1as, a particular kind of circRNA (has_circ_0000284) is overexpressed in CRC tissues and cell lines. The knockdown of this circRNA inhibited the proliferation and induced apoptosis of CRC cells. A recent study also showed that has_circ_0046701 promotes cell proliferation and invasion through regulating ITGB8 expression by sponging the miRNA–miR-142-3p (Du and Lovly 2018; Sever and Brugge 2015; Witsch *et al.* 2010).

Cancer cells can escape antigrowth signals by suppressing the expression of tumour suppressor genes. The antigrowth signals are necessary to block cell proliferation by arresting the cell cycle (Amin *et al.* 2015). The overexpression of the circularized product (Circ-ITCH) inhibits cell proliferation, migration, invasion and metastasis. Phosphatase and tensin homolog (PTEN) and p21 contributes to cell cycle suppression and recent studies have shown that circ-ITCH can sponge miR-17 and miR-224 directly, leading to increased target gene expression, PTEN and p21, respectively. Another type of circRNA known as circRNA-000425 is a target of yes-associated protein 1 (YAP1), a transcriptional coactivator factor that acts as an oncogene associated with cancer malignancy in several cancer types (Su *et al.* 2019a; Yang *et al.* 2018a). By activating CDK4 and CDK6, cyclinD1 facilitates the transition from the G1 phase of the cell cycle to S phase. Several circRNAs regulate tumour growth by regulating Cyclin D1. Xue and colleagues performed microarray research on circRNA and reported that Circ100284 is upregulated in As-HaCaT cells (arsenite-treated HaCaT cells). When icrc100284 was knocked down, it inhibited G1/S transition in As-HaCaT cells (Su *et al.* 2019a).

B-cell lymphoma is an anti-apoptotic molecule that protects the cell from apoptosis, whereas BCL-2 associated X protein is a proapoptotic gene. It has been documented that CircRNA Hsa circ 0007534 is overexpressed in CRC tissues (Geng *et al.* 2018). When it was silenced, it inhibited proliferation of CRC cells while promoting apoptosis. Microarray studies performed by Zhang *et. al.* (2017) showed that circUBAP2 was the most significantly overexpressed circRNA in osteosarcoma (Zhang *et al.* 2017a). The knockdown of circUBAP2 inhibited cell proliferation and promoted cell apoptosis. Hsa_circ_0009910 is another type of circRNA that was upregulated in osteosarcoma cells and its knockdown inhibited cell proliferation. In autophagy, circRNA also plays a very important role. Circ-Dnmt1 was found to be upregulated in the breast cancer tissue and cell lines. Overexpression of circ-Dnmt1 increases the survival and proliferation of breast cancer cells (Straten and Andersen 2010; Um 2016).

One of the major factors driving the growth and proliferation of tumour cells is angiogenesis, which creates new blood vessels to supply oxygen and nutrients to the tumour and to dispose toxic tumour waste. CircRNA-MYLK is a product of the myosin light chain kinase gene that is significantly overexpressed in breast cancer tissues and cell lines. CircRNA-MYLK acts as a sponge miRNA and binds directly to miR-29a, relieving the suppression of target vascular endothelial growth factor A (VEGFA) and activating the signalling pathway VEGFA/VEGFR2 which produces several cellular responses relevant to angiogenesis. Another kind of cirRNA, i.e. Cznf292 plays a very important role in the progression of glioma tube formation (Bielenberg and Zetter 2015; Su *et al.* 2019a). CircRNA is also known to regulate the stemness of cancer. Yang and colleagues reported 27 circRNA expressed in breast cancer stem cells (BCSCs) (Yan *et al.* 2017). They observed that circVRK1 was downregulated, inhibiting the expansion and self-renewability of BCSCs. The knockdown of circVRK1 increases the stemness of BCSCs (Yan *et al.* 2017). CircRNA–Hg19_circ_0005033 is upregulated in TDP cells and promotes cell proliferation and resistance to chemotherapy and radiotherapy (Ma *et al.* 2020; Su *et al.* 2019a). Liu *et al.* (2018a, b) found that circRNA-MTO1 is upregulated in monastrol-resistant BC cells that promoted cell cytotoxicity caused by monastrol and reversed monastrol resistance (Liu *et al.* 2018b). Peng and colleagues identified circRNA - circBA9.3 which contributes to increased leukaemia cell proliferation and anti-apoptotic capacity (Kun-Peng *et al.* 2018; Su *et al.* 2019b).

CricRNAs are a good candidate for biomarker studies because of their stability and tissue-specific expression. These are relatively present in high quantities in body fluids such as saliva, plasma, serum and exosomes and act as

noninvasive biopsy biomarkers for cancer. CircZEB1.33 may serve as a biomarker in the prediction of HCC prognosis, as it is overexpressed in human HCC tissues. Hsa_circRNA_002059 is overexpressed in gastric cancer and thus it has been proposed as a potential biomarker. Hsa_circRNA_0067934 can also serve as a novel biomarker for disease progression or as a therapeutic target in the case of squamous cell carcinoma. Hsa_circ_0000190 was downregulated in GC tissues and plasma samples (Fang *et al.* 2019). In another study, hsa_circ_0000745 is lowly expressed in GC tissues and plasma samples (Huang *et al.* 2017). Its expression is correlated with tumour differentiation and tumour-node-metastasis stage. The stability, universality, conservativeness and specificity of circRNAs make it a better-trusted diagnostic and prognostic biomarker for cancer, and the regulatory roles of circRNAs in tumour cells make it an important candidate for cancer treatment (Su *et al.* 2019b). The role of different circRNAs in cancer based on recent research is shown in table 1.

CircRNAs in diabetes

Diabetes mellitus, commonly called diabetes, is a metabolic condition that causes high sugar in the blood, one of the most important health issue worldwide. Type 2 diabetes mellitus (T2DM) in China shows a rapid increase due to the prevalence of poor lifestyle, the ageing population and changes in dietary structure. The incidence of T2DM in adults is as high as 11.6%, which is expected to increase (Wu *et al.* 2014). Perusal of literature suggested that dysregulation of circRNA is one of the indicative feature of metabolic disorders (table 2). CircRNA seems to play a significant role in the pathogenesis of diabetes and related metabolic disorders thus acts as a potential biomarkers. For example, the level of hsa_circ_0054633 in peripheral blood was reported to be associated with diabetes and might serve as a diagnostic biomarker of prediabetes (Zhao *et al.* 2017). Another circRNA, Cdr1as, can improve the development and secretion of insulin by targeting Pax6 and Myrip in mouse β cells, respectively via miR-7 as a mediator, suggesting that this circRNA may be a new therapeutic target for diabetes. Diabetic vascular complications are the major causes of disability and high mortality among patients with diabetes (Zaiou 2020). Mitogen-activated protein kinase (MAPK) pathway plays a crucial role in gene expression and cytoplasmic activities. CircRNA may affect the status of diabetes by chipping in the MAPK pathway (Kono *et al.* 2006). CircRNAs are usually observed to be upregulated or downregulated in various specimens from diseased patients, such as tissue, plasma, peripheral blood, and saliva, which are easy and suitable to obtain for quantification via painless and minimally invasive methods. Some circRNA have shown efficacies as a biomarker for other types of diseases (Zhang *et al.* 2018b). Altered expression profile of circRNA in the blood of patients with T2DM was confirmed of which hsa_circ_0054633 was proposed to be a potential diagnostic biomarker for prediabetes and type-2 diabetes (Zhao *et al.* 2017). CircRNA can regulate insulin signalling and can be used as a biomarker as well for cell metabolism and T2DM. Peripheral blood has-circ000094 could be used as a diagnostic marker for T2DM. Dammann *et al.* (2018) found the elevated expression of has-circ000094 in patients with T2DM inhibited the expression of P21 by repressing hsa-miR-370-5p, in turn leading to the deactivation of kinase PAK1 (Dammann, *et al.* 2018). One of the rno_circRNA_008565 target genes, MAPK8 (JNK) had the highest score with autophagy. miRNA binding prediction found that rno-miR-504 had most binding sites (four sites) with this target and had the most stable binding structure, which suggests that it may regulate MAPK8 (JNK) and the autophagy of rat islet β-cells by inhibiting rno-miR-504 (Bai *et al.* 2019). CircRNA biomarkers allow early precise diagnosis, appropriate therapy selection and monitoring that can be detected effectively in body fluid, extracellular vesicles or circulating cells in various types of diseases (Zhang *et al.* 2018b).

Conclusion

At first, circRNA was considered to be an error during the splicing process. However, with the advancement of RNA sequencing techniques and bioinformatics, various important roles of circRNA have been highlighted, in particular their function in diseases ranging from cancerous to non-cancerous pathologies and their growth and progression, which is still less understood. CircRNA is now known to be an abundant, stable and highly expressed class of mRNAs serving as miRNA sponges, interacting with RNA binding proteins, controlling splicing and translations etc. CircRNA's most important functions are that they act as a potential biomarker in cancer and diabetes due to their stability and tissue-specific expression, making them an appropriate candidate for biomarker studies. Now it is commonly accepted that eukaryotic spliceosomes exhibit a certain degree of flexibility in the choice of splice sites, resulting in widespread alternatively spliced isoforms in transcriptomes, including circRNAs. In the coming days, enhanced bioinformatics techniques related to circRNA along with faster sequencing techniques are believed to discover more circRNA functions that will eventually enable us to better understand the origin of circRNAs. Different types of circRNA are overexpressed in different cancer and diabetic cell lines and, if guided, can regulate the growth and proliferation of these diseased cells. Further studies on this ancient RNA will provide a significant perspective in cancer and diabetes research.

Table 1. Circular RNAs and their role in different cancer types.

Cancer type	CircRNA	Target genes/proteins/mode of action	Role	References
Hepatocellular carcinoma (HCC) (liver cancer)	Circ-MTO1	Targets miR-9 and affects the expression of downstream P21 protein	Tumour suppressor, prognostic biomarker	Li *et al.* (2020)
Prostate cancer	CircFoxo3	Sponges miR-29a-3p	Affects the cell cycle and cell apoptosis in PCa through transcriptional upregulation of SLC25A15	Kong *et al.* (2020)
Nonsmall-cell - lung carcinoma (NSCLC)	Circ_0067934	MiR-1182	Regulates the miR-1182/KLF8 axis and activates Wnt/β-catenin pathway	Zhao *et al.* (2020)
Glioblastoma	SHPRH-146aa	Ubiquitinates proliferating cell nuclear antigen (PCNA)	Protects SHPRH from degradation by ubiquitin protease	Zhang, *et al.* (2018a)
Lung squamous cell carcinoma (LUSC) tissues	CircTP63	Binds to miR-873-3p	Upregulates CENPA and CENPB, and finally facilitates cell cycle progression by preventing *miR-873-3p* to decrease the level of FOXM1	Cheng *et al.* (2019)
Bladder cancer	Circ-ZKSCAN1	Sponging miR-1178-3p	Upregulates p21 expression	Bi *et al.* (2019)
HCC	CircRNA-MYLK	MiR-362-3p	Suppress the expression of Rab23, thus inhibiting the growth and proliferation of Hep3B cells	Li *et al.* (2019)
HCC	CircASAP1	Sponges miR-326 and miR-532-5p	Regulating the miR-326/miR-532-5p-CSF-1 pathway and mediates tumour-associated-macrophage infiltration	Hu *et al.* (2020)
Breast cancer	FECR1	Downregulate DNA methyltransferase 1 (DNMT1) and causes DNA demethylation of FLI1	Increase the invasiveness of breast cancer cells and promotes cell metastasis	Chen *et al.* (2018)
Ovarian cancer	hsa_circ_0061140	Regulation of the miR-370/FOXM1 pathway-mediated EMT	Promote cell migration and invasion	Chen *et al.* (2018)
HCC	Circ-10720	Sponge miRNAs that targets Vimentin	Twist1-mediated regulation of vimentin during EMT	Meng *et al.* (2018)
Chronic myelogenous leukaemia (CML)	CircBA9.3	Enhance the expression of oncoprotein - BCR-ABL1	Increases proliferation and anti-apoptotic capacities of leukaemic cells	Pan *et al.* (2018)
Breast cancer	Circ-Ccnb1	Interacts with Bclaf1	Induction of cell death in breast cancer	Yang *et al.* (2017)
Breast cancer	Circ-EPSTI1	Targets miR-4753 and miR-6809	Regulate BCL11A expression and affect TNBC proliferation and apoptosis	Chen *et al.* (2018)
Lung cancer	Circ-0006916	Sponge miR-522-3p and inhibits PHLPP1 activity	Tumour suppressor	Dai *et al.* (2018)
HCC (liver cancer)	cSMARCA5	Binds to miR-181b-5p and miR-17-3p (sponging), thereby regulating TIMP3 expression	Inhibits the proliferation and metastasis of HCC	Yu *et al.* (2018)
Gliomalc tumourigenesis	Circ-FBXW7	Encode a novel 21-kDa protein	Reduced the half-life of c-Myc by antagonizing USP28-induced c-Myc stabilization	Yang *et al.* (2018b)
Colorectal cancer	Circ-HIPK3	Sponge miR-7 targeting proto-oncogenes	Promote proliferation, migration, invasion, and inhibit apoptosis in vitro and promote colorectal cancer growth and metastasis *in vivo*	Zeng *et al.* (2018)
Bladder cancer	Circ-ITCH	Sponging miR-17/miR-224	Regulates p21 and PTEN expression induces cell cycle arrest and apoptosis	Yang *et al.* (2018b)

Table 1 (*contd*)

Cancer type	CircRNA	Target genes/proteins/mode of action	Role	References
Nonsmall cell lung cancer (NSCLC)	CDR1as	MiR-7 sponging	Upregulation of proliferation index Ki-67, EGFR, CCNE1 and PIK3CD levels inhibit tumour suppressor miR-7	Zhang *et al.* (2018a)
Gastric cancer (GC)	Circ-ZFR	Binds with miR-130a/miR-107,	Targets PTEN and hampered apoptosis	Liu *et al.* (2018a)
HCC	Circ-ZEB1.33	MiR-200a-3p	Downregulate CDK6 transcription by targeting its 3′UTR	Gong *et al.* (2018)
Breast cancer	CircRNA-MTO1	Suppress expression of Eg5	Suppressed cell viability, promoted monastrol-induced cell cytotoxicity and reversed monastrol resistance.	Liu *et al.* (2018a)
Glioma	hsa_circ_0046701	Sponging miR-142-3p	Regulates ITGB8 (integrin beta) expression and promote cell proliferation and invasion	Li *et al.* (2018)
Laryngeal squamous cell carcinoma (LSCC)	hg19_circ_0005033	Binds to miR-4521	Increased cell proliferation, migration and colony-formation ability as well as resistance to chemotherapy and radiotherapy	Wu *et al.* (2018)
Nonsmall-cell - lung carcinoma (NSCLC)	CircPTK2 (hsa_circ_0008305)	Sponge or binds to miR-429/miR-200b-3p	Inhibits TGF-β-induced EMT and metastasis by controlling TIF1γ in NSCLC	Wang *et al.* (2018b)
HCC	CircSMAD2 (hsa_circ_0000847)	suppress the expression of miR-629	Inhibits the migration, invasion, and EMT (epithelial-mesenchymal transition) of HCC	Zhang *et al.* (2018a)
HCC	Circ-C3P1	Sponges miR-4641 in HCC cells	Promotes PCK1 expression	Zhong *et al.* (2018)
Colorectal cancer	Circ-CCDC66	Sponges to to miR-33b, miR-93, and miR-185	Protect a group of oncogenes from being attacked by a panel of miRNAs	Hsiao *et al.* (2017)
Bladder cancer	Circ-HIPK3	Binds to miR-558 and can suppress HPSE expression (heparanase)	Inhibit migration, invasion and angiogenesis of bladder cancer cells	Li *et al.* (2017)
Bladder cancer	CircRNA- BCR4	Binds and regulates miR-101	Regulate cell apoptosis and signalling	Li *et al.* (2017)
Colorectal cancer	CDR1as	Inhibition of miR-7	Suppression of EGFR and IGF-1R expression	Tang *et al.* (2017)
Breast cancer (BC)	Circ-Amotl1	Binds to c-myc	Promote c-myc stability and upregulate c-myc targets	Yang *et al.* (2017)
Breast cancer stem cells (BCSCs)	CircVRK1	Acts as miRNA sponge	Suppress BCSC's expansion and self-renewal capacity	Yan *et al.* (2017)
Colorectal cancer cells (CRCs)	hsa_circ_0020397	Binds to miR-138 and and increase the expression of its target genes	Promotes viability of CRCs and inhibited apoptosis	Zhang *et al.* (2017c)

Table 2. Role of circRNAs in diabetes, their target genes/miRNAs.

Diabetes type	CircRNA	Target miRNAs/genes	Role	Reference
Diabetic retinopathy	cZNF532	Sponges miR-29a-3p	Coordinates pericyte biology and vascular homeostasis by inducing increased expression of NG2, LOXL2, and CDK2	Jiang *et al.* (2020)
Diabetic retinopathy	cPWWP2A	MiR-579 sponge	Promote the DR-induced retinal vascular dysfunction by upregulating the expression of angiopoietin 1, occludin and SIRT1	Yan *et al.* (2020)
Diabetes mellitus type 2 (T2DM)	rno_circRNA_008565	Target miRNA	Involve in MAPK signalling pathway, apoptosis, and Ras signalling pathway and regulate the autophagy of islet β-cells	Bai *et al.* (2019)
Diabetes mellitus type 2	has-circ-000094	Repressing hsa-miR-370-5p	Inhibits the express-ion of P21 gene and deactivation of PAK1 kinase	Bai *et al.* (2019)
Diabetic cardiomyopathy	hsa-circ-0076631 (CACR) caspase-1-associated circRNA (CACR)	Inhibits the expression of miR-214-3p sponge	pyroptosis via the miR-214-3p/caspase-1 pathway	Zaiou (2020)
Diabetic nephropathy	cirRNA_15698	Sponges miR-185	(i) Regulates the transforming growth factor-β1 (TGF-β1) protein expression (ii) CircRNA_15698/miR-185/TGF-β1 pathway promoted extracellular matrix (ECM)-related protein synthesis	Hu *et al.* (2019)
Diabetes mellitus	CircHIPK3	Sequestering of miR-124-3p and miR-338-3p	Regulation of β-cells genes Slc2a2, Akt1 and Mtpn	Stoll *et al.* (2018)
Diabetes mellitus correlated vasculopathy	CircWDR77	Targets miR-124 and fibroblast growth factor-2 (FGF-2)	Regulates proliferation and migration of high glucose-induced VSMCs	Chen *et al.* (2017)
Diabetic retinopathy	hsa_circRNA_063981; hsa_circRNA_ 404457; hsa_circRNA_100750; hsa_circRNA_406918; hsa_ circRNA_104387; hsa_circRNA_103410; hsa_circRNA_ 100192	hsa-miR-29a-5p hsa-miR-126-5p hsa-miR-146a-3p hsa-miR-215-3p	Upregulated in diabetic retinas and retinal endothelial cells	Gu *et al.* (2017)
Diabetes mellitus type 2	hsa_circRNA_003251 hsa_circRNA_015115 hsa_circRNA_100918 hsa_circRNA_005019	hsa-miR-3191-5p hsa-miR-33b-5p hsa-miR-761 hsa-miR-298	(i) Participate in the thyroid hormone, Wnt, ErbB, and mitogen-activated protein kinase signalling pathways (ii) Targets to treat depressive disorders	Jiang *et al.* (2017)
Diabetes mellitus-related retinal vascular dysfunction	cZNF609	Inhibits miR-615-5p	Increased MEF2A expression that could rescue cZNF609 silencing-mediated effects on endothelial cell migration, tube formation, and apoptosis	Wang *et al.* (2018a)
Diabetes mellitus-related retinal vascular dysfunction	CircHIPK3	Inhibits miR-30a-3p activity	Increased vascular endothelial growth factor-C FZD4 and WNT2 expression	Shan *et al.* (2017)
Diabetes mellitus	hsa_circ_0054633	-	Potential diagnostic biomarker of prediabetes and T2DM	Zhao *et al.* (2017)

Table 2 (*contd*)

Diabetes type	CircRNA	Target miRNAs/genes	Role	Reference
Diabetic retinopathy	Circ_0005015	Inhibits miR-519d-3p activity	Increased expression of MMP-2, XIAP, and STAT3. Facilitates endothelial angiogenic function via regulating endothelial cell proliferation, migration and tube formation	Zhang *et al.* (2017b)
Diabetic cardiomyopathy	CircRNA_01057	Sponge miR-141 and targets TGF-β1	Involves in pathogenesis of myocardial fibrosis	Zaiou (2020)
Diabetes mellitus	CDR1as/ciRS-7	Inhibits miR-7 function in islet cells	Improves insulin secretion	Xu *et al.* (2015)

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