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Circular RNAs as biomarkers and therapeutic targets in cancer

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ABSTRACT

Circular RNAs (circRNAs) are a class of single-stranded closed non-coding RNA molecules (ncRNAs), which are formed as a result of reverse splicing of mRNAs. Despite their relative abundance, an interest in understanding their regulatory importance is rather recent. High stability, abundance and evolutionary conservation among species underline some of their important traits. CircRNAs perform a variety of cellular functions ranging from miRNA and proteins sponges to transcriptional modulation and splicing. Additionally, most circRNAs are expressed aberrantly in pathological conditions suggesting their possible exploitation as diagnostic biomarkers. Their covalent closed cyclic structure resulting in resistance to RNases further makes them suitable as cancer biomarkers. Studies involving human tumors have verified differences in the expression profiles of circRNAs, indicating a regulatory role in cancer pathogenesis and metastasis. As endogenous competitive RNA, circRNAs can regulate tumor proliferation and invasion. Further, some circRNAs located in the nucleus can regulate transcription of genes by binding to RNA polymerase II. In this review, we elaborate the characteristics, functions and mechanisms of action of circRNAs in cancer. We also discuss the possibility of using circRNAs as potential therapeutic targets and biomarkers for cancer.

Abbreviations: ABC, ATP-binding cassette; AKT, RAC-alpha serine/threonine-protein kinase; ALDH, Aldehyde dehydrogenase; AMPK, AMP-activated protein kinase; Bcl-2, B-cell lymphoma 2; CDK2, Cell division protein kinase 6; CDK6, Cell division protein kinase 6; CDKN1A, Cyclin-dependent kinase inhibitor 1A; Ci-ANKRD52, Ci-Ankyrin Repeat Domain 52; CicrRNA, Circular RNA; CiRNA, Intron RNAs; CSCs, Cancer stem cells; CXCL10, C-X-C motif chemokine ligand 10; CXCL12, Chemokine (C-X-C motif) ligand 12; DPP4, Dipeptidyl peptidase-4; EcircRNAs, Exon circRNAs; EGFR, Epidermal growth factor receptor; EIciRNA, Exon-intron circRNAs; EMT, Epithelial-mesenchymal transition); ERK, Extracellular signal-regulated kinase; HUVECs, Human umbilical vein endothelial cells; ILK, Integrin linked kinase; IMP3, IGF2BP3 is an insulin-like protein 2 that binds growth factor 3); IRES, Containing internal ribosome entry site; JAK1, Janus kinase 1; LATS1, Large tumor suppressor kinase 1; MAPK, Mitogen-activated protein kinase; MBL, Mannose-binding lectin; miRNA, microRNA; MMP-9, Matrix metallopeptidase 9; mTOR, Mammalian target of rapamycin; NF-kB, Nuclear factor kappa-light-chain-enhancer of activated B cells; NKG2D, Activating receptor natural-killer group 2 member D; PI3K, Phosphoinositide 3-kinase; Pol II, RNA polymerase II; PTEN, Tensin homolog deleted on chromosome 10; qRT-PCR, Real-time quantitative reverse transcription PCR; SiRNA, Small interfering RNA; SnRNPs, Small nuclear ribonucleoproteins; STAT3, Signal transducer and activator of transcription 3; TGF-b, Transforming growth factor beta; VEGF, Factor vascular endothelial growth factor; VEGF-A, Vascular endothelial growth factor A; VEGFR2, Vascular endothelial growth factor receptor 2.

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1. Introduction

Circular RNAs (circRNAs) were previously thought to be malfunctioning splicing processes without function [1], much like the broader class of non-coding RNAs [2]. However, the recent robust development of second-generation sequencing and bioinformatics techniques has allowed researchers to confirm that there are many types of circRNAs with high stability in humans. This has resulted in an interest in the detailed studies of their various functions [3,4], and now more than one hundred thousand circRNAs are believe to exist in cells. They are divided into the following four categories depending on the genome source and biogenesis patterns: circular intron RNAs (ciRNA), exon circRNAs (ecircRNAs), exon-intron circRNAs (EIciRNA), and intergenic circRNAs [5].

Because of their high levels of stability in blood and other body fluids, circRNAs are considered potential biomarkers for predicting cancer risk. Genome-wide analysis has shown a high level of evolutionary conservation and abundance of circRNAs in different species [6]. CircRNAs can act as miRNA sponges or competing endogenous RNAs; bind and isolate proteins; modulate splicing as well as play an important role in cancer pathogenesis with great potential as cancer biomarkers. Here, we discuss the role of circRNAs in cancer, with particular focus on ovarian cancer as proof of principle, and consider their possible role as therapeutic targets.

2. Biogenesis of circular RNAs

There are several pathways that can lead to the formation of circRNAs, depending largely on the origin of the donor transcript (Fig. 1). CircRNAs can be derived from a number of possible sources, including exons, introns, simultaneously from exons and introns, as well as from intergenic regions [7–9]. Intronic circRNAs (intron or exon-intron) are predominantly localized in the nucleus, while exon circRNAs are mainly located in the cytoplasm [10,11]. A length-dependent nuclear export mechanism for circRNAs has recently been described [12]. Most circRNAs are produced dependent on RNA polymerase II (Pol II) from genes encoding a protein. However, unlike linear RNAs, they are not produced by canonical RNA splicing, but instead, most circRNAs are formed from spliced exons, which differ from linear RNA splicing in that the upstream 3′ splicing donor (splicing acceptor) covalently joins the downstream - 5′ splice site (splicing donor) leading to a closed circRNA transcript ligated with a 3′-5′ phosphodiester bond at the junction [13,14]. For most exon and exon-intronic circRNAs, RNA circulation is the most frequently used circulation mechanism [11]. This includes reverse complementary sequences, such as ALU repeats, contained in introns that flank circulating exons [6]. These sequences can form pairs of RNA duplexes that enhance reverse splicing and promote the formation of circRNAs [14,15]. Introns are then removed, and the exon circRNAs are formed, or retained, resulting in exon-intron circRNAs. When flanking introns contain inverted tandem repeats, they are long [10]. Relatively short inverted repeats are also able to stimulate intron base pairing and the formation of circRNAs [16]. However, not all intronic tandem repeats can promote the formation of circRNAs, and in some cases, the increased stability of the RNA duplex inhibits the circulation process [16].

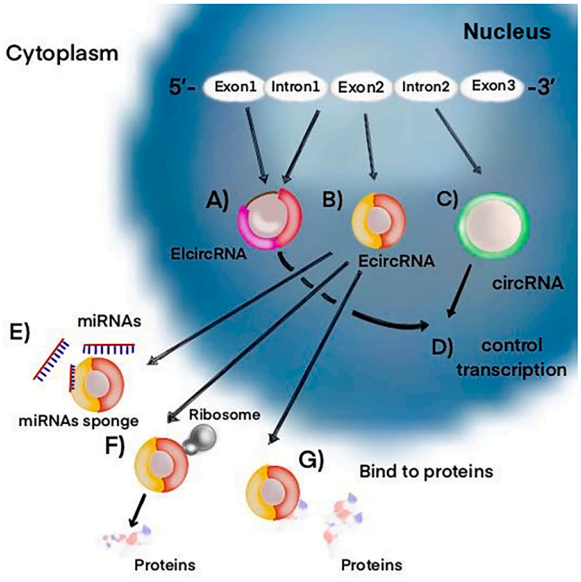

Fig. 1. Biogenesis and regulatory functions of circRNAs. (A) Exon–intron circRNAs (EIcircRNAs) contain both exons and introns. (B) Exonic RNAs (EcircRNAs) are generated from exons. (C) CircRNAs are formed by introns. (D) CircRNAs are able to promote transcription. (E) CircRNAs can act as miRNAs sponges. (F) CircRNAs encode proteins. (G) CircRNAs can bind to proteins.

For most intron RNA circRNAs, circulation involves short, specific, intronic, reverse, complementary sequences that come together to promote circulation [17,18]. These two elements, in close proximity, bind and form a lariat, which in turn is excised by a spliceosome [19]. These lariats then undergo 3′-tail degradation, leading to the formation of the final intron molecule circRNAs. Different mechanisms lead to differences in structure between intron and exon circRNAs. Intronic circRNAs are distinguished by the presence of a 2′-5′-junction arising from the remainder of the original lariat structure, while exonic circRNAs have a 3′-5′-bond at the splicing point [19]. During alternative splicing, circRNAs can be generated [20,21]. When this occurs, snRNPs (small nuclear ribonucleoproteins) are sequentially assembled into pre-mRNAs, promoting the circulation of the lower 5′-splice site of the exon with the 3′-upstream splice site. In addition, some trans-acting RBP activators can specifically bind to flanking intron sequences, forming a bridge that brings the donor and acceptor splice sites closer together to facilitate the formation of circRNAs [21].

3. Biological functions of circular RNAs

RNA-seq analysis has helped identify numerous circRNAs in several model organisms with different cell types, and it was possible to find out that some endogenous circRNAs contain elements of an internal ribosome entry site and AUG sites. However, there is currently limited evidence for their translation in vivo, and the biological role of most circRNAs remains unknown. Recent studies have shown that circRNAs function as microRNA (miRNA) sponges and transcriptional modulators, and that some circRNAs can be translated into peptides or proteins, implying that circRNAs modulate gene expression at several levels (Fig. 1).

3.1. CircRNAs function as miRNA sponges

MiRNAs can modulate gene expression through direct base pairing with target sites in mRNA and are known to be involved in multiple biological and pathological processes, including cancer [22–27]. Most circRNAs are predominantly localized in the cytoplasm, which suggests that they can act as competitive endogenous RNAs and modulators of miRNA activity, competing for miRNA-binding sites [28]. Li et al. Indicated that cir_ITCH inhibits tumor growth by acting as a miRNA sponge [29]. Chen et al. reported that circ_PVT1 could stimulate cell growth by acting as a sponge for members of the miR-125 family [30]. Importantly, several studies have shown that ciRS7 can act as an inhibitor or sponge of miR-7 by decreasing miR-7 activity and increasing the levels of transcripts targeting miR-7 [31].

3.2. CircRNAs as transcription modulators

It is assumed that circRNAs are nuclear limited, which is similar to the observation of nuclear limitation of linear RNAs containing

conserved introns and forms a large number of posttranscriptional modulators [32]. CircRNAs can be poorly enriched for target sites of miRNAs [19]. Significantly, inhibition of such RNAs can lead to a decrease in the expression of their parental genes, causing one potential role for circRNAs as positive modulators of Pol II transcription. In addition, it was also found that ci-Ankyrin Repeat Domain 52 (ci-ANKRD52), one of such RNAs, can interact with the Pol II extension complex and accumulate largely at transcription sites, which stimulates the transcription of its parent gene ANKRD52 [19].

3.3. CircRNAs as protein sponges

CircRNAs can participate in other physiological processes by binding proteins in the form of sponges. The best experimentally confirmed example of such a circRNAs protein is obtained from the mannose-binding lectin (MBL) locus [33]. It is important that modulation of MBL levels significantly contributes to the biogenesis of circ_MBL, and this effect depends on the MBL binding sites [34]. In cancer, circ_FOXO3 can modulate the expression of its binding proteins by regulating protein-protein interactions. It was found that circ_FOXO3 binds both p53 and MDM2, and increases the sensitivity of breast cancer cells to cisplatin and doxorubicin [35]. Schneider et al. focused on IMP3 (IGF2BP3 is an insulin-like protein 2 that binds growth factor 3), an RNA-binding protein and a known tumor marker in order to investigate circ_RNP with a specific protein component [36]. They hypothesized that there are certain circ_RNP families, determined by a common protein component. Both of these studies have demonstrated the dynamics of circRNAs-protein interaction in various tissues and in cancer.

4. The functions of circular RNAs in cancer

The functional significance of circRNAs in cancer is well documented and includes avoidance of growth suppressors and cell death, activation of invasion and metastasis, angiogenesis, and sustained proliferative signaling. In additional, cancer is characterized by aberrant cell cycle activity [37–39]. Many of the examples below point to a critical role of circRNAs in the regulation of signaling pathways in cancer, including the Wnt / beta-catenin, phosphoinositide 3-kinase (PI3K) / AKT, and mitogen-activated protein kinase (MAPK) / extracellular signal-regulated kinase (ERK) signaling pathways [40,41]. In this section, we provide an overview of the current results on delivery methods of miRNA therapeutics agents generated from preclinical models of brain tumors. In this section, we provide an overview of the function of circRNAs in various cancer types.

4.1. Effect of circular RNAs on proliferation, invasion, and metastasis

Oncogenesis is usually triggered by dysregulation of signaling pathways that mediate cell proliferation, invasion, and cancer metastasis. These pathways include nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), transforming growth factor beta (TGF-b), integrin linked kinase (ILK)-regulated EMT (Epithelial-mesenchymal transition) and PI3K/AKT/JAK/STAT. Today it is known that circRNAs play an important role in the proliferation, invasion, and metastasis regulating by the major signaling pathways of oncogenesis [42]. It has been shown that hsa_circ_0001649 has a tumor suppressing effect in several types of cancers. Xing et al. found that its suppression could lead to poor prognosis of retinoblastoma along the RAC-alpha serine/threonine-protein kinase/ mammalian target of rapamycin (AKT / mTOR) pathway [43]. Other studies have shown that circ-CBFB and circ-ITCH can regulate the Wnt / beta-catenin pathway associated with tumor cell proliferation by binding miRNAs [44]. This regulation by circRNAs is particularly important given the interplay of miRNAs and Wnt signaling in aggressive cancers [45]. In addition, circRNAs also affect the proliferation of cancer cells by regulating NOTCH and Janus Kinase 1 / signal transducer and activator of transcription 3 (JAK1 / STAT3) signaling pathways [46,47]. Wang et al. found that, in addition to affecting tumor proliferation, circ_HIAT1 could influence the invasion and metastasis of renal cell carcinoma. The mechanism is that it directly increases the stability of mir-195-5p / 29a-3p / 29c-3p, acting as a “microRNA reservoir” [48].

The vast majority of studies to-date that have determined the functional role of circRNAs in cancer have been based on the miRNA sponge activity of these molecules. In gastric cancer, it was shown that circRNAs LARP4 inhibits proliferation and invasion of tumor cells by regulating miR-424-5p levels and expression of its target gene large tumor suppressor kinase 1 (LATS1) (49). In vivo deposition was used to identify miR-9 as a target for circMTO1, and inhibition of this circRNAs was found to suppress cyclin-dependent kinase inhibitor 1A (CDKN1A) (p21), a confirmed target for miR-9, in addition to increasing cell proliferation and invasion in vitro. Also in hepatocellular carcinoma, Huang et al. used microarrays to identify 226 differentially expressed circRNAs between 4 patients and paired precancerous tissues (50). Also in hepatocellular carcinoma, Huang et al. used microarrays to identify 226 differentially expressed circRNAs between 4 patients and paired precancerous tissues (50). Overexpression or inhibition of circ_ZKSCAN1 regulated proliferative, migratory, and invasive properties of cells in vitro and tumor growth in vivo. Yang et al. used a proteomic approach to identify 322 differentially expressed proteins through the regulation of CDR1as in hepatocellular carcinoma cells (51). They demonstrated that the effect of CDR1as on cell proliferation was mediated through the regulation of epidermal growth factor receptor (EGFR) expression, and this expression of CDR1as regulated miR-7, which had previously been shown to target EGFR, although no direct link was shown in this publication. In bladder cancer, microarrays have been used to identify 469 differentially expressed circRNAs between 4 tumors and adjacent non-tumor material (52). Six of these were confirmed by real-time quantitative reverse transcription PCR (qRT-PCR) in 40 paired samples, and in silico analysis was used to predict the interaction between circ_TCF25 and miR-107, miR-103a-3p, and that both of these miRNAs could target the CDK6 gene. The authors demonstrated that overexpression of circ_TCF25 increases levels of the CDK6 protein in vitro, and that cells have increased migratory and invasive properties.

Using paired RNA sequencing, Ahmed et al. Found that circRNAs were highly expressed in ovarian epithelial carcinoma samples and increased even more dramatically in different lesions (primary sites, abdominal metastases, and lymph nodes) compared to mRNA [49]. Meanwhile, high levels of mRNA expression have been associated with decreased levels of circRNAs. For example, miRNA let-7, which negatively regulates RAS and MYC (2 proto-oncogenes), shows a clearly lower level of expression in the primary injury than metastases to the peritoneal cavity. However, the gene encoding circRNAs containing several let-7 binding sites was highly expressed in the primary lesion, which can be explained by the fact that circRNAs can act as a sponge of miRNAs [49]. Using RNA sequencing for the primary lesion, metastases to the abdomen and lymph nodes, epithelial ovarian carcinoma (stage IIIC), the researchers found upregulation of mRNA and downregulation of circRNAs that bind NF-kB, PI3k / AKT and TGF-b (both contain multiple miR-24 / let - 7 binding sites). This indicated that circRNAs could use their circulation to competitively inhibit linear splicing and function as sponges of miRNAs, modulating the expression of genes that induce metastasis, thus promoting metastatic ovarian cancer.

4.2. Regulation of apoptosis and cell cycle by circular RNAs

Recent advances in uncovering molecular mechanisms, playing a key role in oncogenesis, stimulated the search and creation of drugs for targeted therapy. A special place among these targets is the genes that regulate the functioning of various links of apoptosis [50]. Reactivation of apoptosis in cancer cells using targeted therapy opens up new possibilities in the treatment of many cancers, since the cytotoxic effect of such drugs is highly selective (cells of normal tissues are not damaged)

and effective even in the case of chemotherapy-resistant tumors. In addition, apoptosis reactivators can be used in combination with widely used antitumor agents, significantly enhancing their cytotoxic effect [51,52]. The mechanism that triggers apoptosis that transmits signals between regulators and effectors are controlled by the balance between pro-apoptotic and anti-apoptotic regulatory proteins that make up the B-cell lymphoma 2 (Bcl-2) family [53]. In addition, the study of dysregulated phases of the cell cycle can provide valuable data on the biology of cancer development for the development of new therapies.

It has been reported that circRNAs (circ_UBAP2, hsa_circ_0001649, hsa_circ_0007534) can influence cell apoptosis by regulating the Bcl-2 / caspase-3 pathway [54,55]. Liu et al. found that circ_ZFR can modulate phosphatase and tensin homolog deleted on chromosome 10 (PTEN) and miR-130a / miR-107, which promotes tumor cell apoptosis, inhibits cell proliferation, and plays a role in tumor inhibition [56]. It is reported that hsa_circ_0014717 can influence the tumor cell cycle by regulating the expression of p16 [57]. It was demonstrated that circ_ZEB1.33 could increase the proportion of S-phase cells and promote cell proliferation along the circ_ZEB1.33 / mir-200a3p / cell division protein kinase 6 (CDK6) axis [58]. It was shown that circ_FOXO3 can form a circ_FOXO3-p21- cell division protein kinase 6 (CDK2) complex with p21 and CDK2, which blocks the cell cycle by inhibiting the function of CDK2 [59]. In addition, it has been confirmed that circRNAs can encode proteins. FBXW7-185aa is a protein encoded by circ_FBXW7 that inhibits the proliferation of cancer cells and blocks the development of the cell cycle [60].

4.3. Circular RNAs in cancer angiogenesis

The ability to induce and maintain angiogenesis is a critical stage in tumor development. Angiogenesis is a complex process in which new blood vessels are formed from pre-existing ones through the sprouting, remodeling, and expansion of primary vascular networks [61]. Angiogenesis underlies the development of methods for targeting this process as a means of cancer therapy. In terms of possible drug development, several molecular targets and cellular pathways have been identified. One of these targets is pro- angiogenic factor vascular endothelial growth factor (VEGF) [62]. CircRNAs in cancer cells regulate the expression of pro- or anti-angiogenic factors, thereby modulating the proliferation and migration of endothelial cells in a paracrine manner. Endothelial circRNAs regulate the response of endothelial cells to multiple angiogenic stimuli, mainly by acting autonomously on growth factor receptors and signaling molecules [62]. As shown in the study, Zhong et al. upregulating circRNA-MYLK promoted the growth, angiogenesis, and metastasis of bladder carcinoma through modulating vascular endothelial growth factor A (VEGF-A) / vascular endothelial growth factor receptor 2 (VEGFR2) signaling pathway [63]. In another study, upregulated of circHIPK3 effectively inhibits migration, invasion, and angiogenesis of bladder cancer cells in vitro and suppresses bladder cancer growth and metastasis in vivo [64]. In addition, they demonstrated that two binding sites were critical for circHIPK3 to sponge miR-558. Furthermore, this study showed that high expression of circHIPK3 efficiently interacted with miR-558 and subsequently downregulated the expression of HPSE and its downstream targets matrix metallopeptidase 9 (MMP-9) and VEGF to attenuate the promoting effect of miR-558 on bladder cancer cell migration, invasion, and angiogenesis. Chen et al. identified circ-ASH2L that was closely associated with pancreatic ductal adenocarcinoma [65]. They detected that circ-ASH2L plays an important role in pancreatic ductal adenocarcinoma progression such as angiogenesis. The qRT-PCR results indicated that circ-ASH2L showed high expression in pancreatic ductal adenocarcinoma cells. When human umbilical vein endothelial cells (HUVECs) were transfected with circ-ASH2L, the tube-like structures were significantly enhanced compared to the normal or sh-circ-ASH2L groups. The results above suggest that circ-ASH2L could promote angiogenesis in pancreatic ductal adenocarcinoma.

4.4. Circular RNAs in cancer immunity regulation

There is extensive research that has contributed to the description of the tumor microenvironment and has improved our understanding of cancer. We are only now beginning to understand how the stromal cell-mediated immune response determines the onset and progression of cancer. Many factors are involved in this process, including non-coding RNAs [66]. Non-coding RNAs not only regulate the development and maturation of immune cells but also control the activation of immune cells and their subsequent action as pro- or antitumor factors [66]. Although circRNAs have been reported to contain many potential functions in carcinogenesis and the immune system, these functions are not fully understood. To date, there is a small amount of research on the role of the circRNAs in cancer and immunity regulation. For instance, Zhang et al. demonstrated that the overexpression of circTRIM33–12 reversed the oncogenic function of miR-191 and thus inhibited the progression of hepatocellular carcinoma [67]. Their results suggest that circTRIM33–12 may exert its antitumor effects by protecting TET1 via sponging miR-191. To further explore the relationship between circTRIM33–12 and immune evasion, they examined the expression of activating receptor natural-killer group 2 member D (NKG2D) in cancer tissues. It is known that the NKG2D and its ligands play vital roles in immune responses to cancers. As a result, a scatter plot analysis revealed a positive correlation between circTRIM33–12 expression and NKG2D-positive cell number in cancer tissues [68]. These results reveal the important role of circTRIM33–12 in the cancer progression and immune evasion abilities of hepatocellular carcinoma cells and provide a new perspective on this circRNA as therapeutic target. Wei et al. indicated that circ_0020710 was overexpressed in melanoma, and high level of this circRNA was positively correlated with malignant phenotype and poor prognosis of melanoma patients [69]. Moreover, elevated circ_0020710 level upregulated chemokine (C-X-C motif) ligand 12 (CXCL12) expression to promote melanoma progression and induce immune evasion by sponging miR-370-3p. In addition, in another study circMET was an oncogenic circRNA that induces hepatocellular carcinoma development and immune tolerance via the Snail/dipeptidyl peptidase-4 (DPP4)/ C-X-C motif chemokine ligand 10 (CXCL10) axis [70]. Studies about circRNAs functions [71–91] in cancer are listed in Table 1.

5. Role of circular RNAs in drug resistance

Drug therapy in modern oncology is a highly effective and promising method. The expansion of its capabilities in recent years has been due to the improvement of standard techniques and the creation of anticancer agents, fundamentally new in terms of the mechanism of action. Currently, drug therapy for cancers includes targeted therapy, chemotherapy and immunotherapy [92–94].

The problem of drug resistance in cancer is multifaceted [95,96]. Although advances in surgery have improved the prognosis of patients with early-stage cancer, the majority of patients are diagnosed at the advanced stages of the disease and thus have to undergo chemo- and radiotherapy [95]. However, the 5-year-survival rate has not improved significantly due to the development of chemoresistance to anti-cancer drugs. Drug resistance, which is frequently observed in cancers, threatens the success rate of therapy and the survival of patients [97]. Therefore, the underlying mechanisms of drug resistance in cancer remain to be fully understood [98,99]. One of the well-known mechanisms of drug resistance is the modulation of the EMT process, which converts epithelial cells into mesenchymal cells [100]. Studies have confirmed that EMT can induce drug resistance by slowing the rate of proliferation of cancer cells, enhancing the expression of ATP-binding cassette (ABC) transporters that mediate drug efflux, and increasing the expression of anti-apoptotic proteins [101]. It has also been demonstrated that EMT can reconstruct the tumor microenvironment, thereby inducing resistance to immunotherapy [100]. Another known

Table 1
circRNAs in cancer.

circRNA	Gene-Target	Type of cancer	Biological function	Regulation	Phenotype	Model used	Ref.
circ_0072995	miR-147a/ CDK6	OC	Promote cell proliferation and invasion and suppress apoptosis	Up	Oncogenic	In vitro, in vivo and human	[71]
circ_0009910	miR-145	OC	Promote cell proliferation and tumor metastasis. Decrease the overall survival	Up	Oncogenic	In vitro and human	[72]
circ_MTO1	miR-182-5p/ KLF15	OC	Inhibits cell proliferation and invasion	Down	Tumor suppressor	In vitro and human	[73]
circ_ITCH	miR-10a	OC	Suppresses cell proliferation and promote apoptosis	Down	Tumor suppressor	In vitro	[74]
circ_0078607	miR-518a-5p/Fas	OC	Suppresses cell proliferation and promotes apoptosis	Down	Tumor suppressor	In vitro and human	[75]
circ_0025033	miR-330-5p/ KLF4	OC	Promote migration, invasion, and EMT transition and suppress apoptosis	Up	Oncogenic	In vitro, in vivo and human	[76]
circ-001971	miR-29c-3p	CC	Modulate cancer growth, metastasis, and angiogenesis	Up	Oncogenic	In vitro and human	[77]
circRNA_002178	miR-328-3p/ COL1A1	BC	Promote cell proliferation, energy metabolism and angiogenesis. Decrease the overall survival	Up	Oncogenic	In vitro, in vivo and human	[78]
circ_0000936	miR-582-3p/ HUR/VEGF	GC	Promote cell proliferation, migration, invasion and angiogenesis	Up	Oncogenic	In vitro, in vivo and human	[79]
circ_0000515	miR-296-5p/ CXCL10	BC	Promote cell proliferation, invasion, angiogenesis, inflammatory response and cell cycle progression. Decrease the overall survival	Up	Oncogenic	In vitro, in vivo and human	[80]
circRNA-100338	MMP9/ MVD/ VE-Cadherin /ZO-1	HCC	Promote invasion, metastasis and angiogenesis	Up	Oncogenic	In vitro, in vivo and human	[81]
circPRRC2A	TRPM3	RCC	Promote angiogenesis and metastasis	Up	Oncogenic	In vitro, in vivo and human	[82]
circSEMA5A	miR-330-5p/ ENO1/ SEMA5A	Bladder cancer	Promote cell proliferation, suppressed apoptosis, facilitated migration, accelerated invasion, enhanced angiogenesis, and promotes glycolysis	Up	Oncogenic	In vitro, in vivo and human	[83]
circRNA_001587	miR-223/ SLC4A4	PC	Inhibit migration, invasion and angiogenesis	Down	Tumor suppressor	In vitro, in vivo and human	[84]
circ_001653	miR-377/ HOXC6	PDAC	Promote cell proliferation, invasion, angiogenesis, cell cycle progression and inhibit apoptosis	Up	Oncogenic	In vitro, in vivo and human	[85]
circ-CPA4	let-7 miRNA/PD-L1	NSCLC	Promote cancer growth, suppress apoptosis and immune evasion	Up	Oncogenic	In vitro, in vivo and human	[86]
circ_0000977	miR-153/HIF1A/ ADAM10	PC	Immune evasion. Cancer cell immunoresistance to antitumor cytokines, including IFN-γ, IL-2, and TNF-α. Inhibits the killing effect of NK cells on cancer cells	Up	Oncogenic	In vitro and human	[87]
circ_0058124	NOTCH3/ GATAD2A	PTC	Promote cell proliferation, metastasis and invasion, cell cycle progression and inhibit apoptosis	Up	Oncogenic	In vitro, in vivo and human	[88]
circPTPRA	miR-96-5p /RASSF8	NSCLC	Suppresses EMT and metastasis	Down	Tumor suppressor	In vitro, in vivo and human	[89]
circ_0091581	miR-591/FOSL2	HCC	Promote metastasis, cell cycle progression and inhibit apoptosis	Up	Oncogenic	In vitro, in vivo and human	[90]
circTADA2A	miR-203a-3p/ CREB3	Osteosarcoma	Promote metastasis and inhibit apoptosis	Up	Oncogenic	In vitro, in vivo and human	[91]

Abbreviation: miRNA, microRNA; circRNA, circular RNA; CDK6, Cyclin Dependent Kinase 6; KLF15, Kruppel-like factor 15; KLF4, Kruppel-like factor 4; Fas, Fas Cell Surface Death Receptor; CC, Colorectal cancer; BC, Breast cancer; GC, Gastric cancer; HCC, Hepatocellular carcinoma; RCC, Renal cell carcinoma; PC, Pancreatic cancer; PDAC, Pancreatic ductal adenocarcinoma; NSCLC, Non-small-cell lung carcinoma; PTC, Papillary thyroid cancer; COL1A1, Collagen, type I, alpha 1; HUR, Human antigen R; VEGF, Vascular endothelial growth factor; CXCL10, C-X-C motif chemokine ligand 10; MMP9, Matrix metallopeptidase 9; MVD, Mevalonate diphosphate decarboxylase; VE-Cadherin, Vascular endothelial-cadherin; ZO-1, Zonula occludens-1; TRPM3, Transient receptor potential cation channel subfamily M member 3; ENO1, Alpha-enolase; SEMA5A, Semaphorin 5A; SLC4A4, Solute carrier family 4 member 4; HOXC6, Homeobox C6; PD-L1, Programmed cell death 1; HIF1A, Hypoxia-inducible factor 1-alpha; ADAM10, A Disintegrin and metalloproteinase domain-containing protein 10; NOTCH3, Neurogenic locus notch homolog protein 3; GATAD2A, GATA zinc finger domain containing 2A; RASSF8, Ras association domain-containing protein 8; FOSL2, Fos-related antigen 2; CREB3, Cyclic AMP-responsive element-binding protein 3; EMT, Epithelial–mesenchymal transition.

mechanism is cancer stem cells (CSCs). CSCs are a population of cells with a high carcinogenic potential in tumors, and these cells modulate the initiation, development, and metastasis of cancer [102]. Numerous studies have shown that CSC induces drug resistance by displacing intracellular therapeutic drugs into the extracellular space through transport proteins [103,104]. In addition, the high activity of aldehyde dehydrogenase (ALDH) is another element associated with drug resistance in CSCs [105]. A number of studies have indicated that circRNAs

are involved in the development of drug resistance in different types of cancer via numerous mechanisms. These mechanisms contribute to the involvement of a large and complex network of circRNAs in drug resistance. As shown in Table 2, we summarize the potential mechanisms of circRNAs in drug-resistant cancer to provide evidence for clinical treatment strategies [106–122].

6. Circular RNAs in cancer metabolism

Research on tumor growth in recent decades has been mainly focused on understanding the increased function of oncogenes and/or loss of function of oncosuppressor genes in tumor cells. Although this paradigm is the leading one in the biology of tumors, today it is becoming evident that other factors involved in the mechanisms of carcinogenesis cannot be ignored. Thus, it has recently become clear that the reprogramming of energy metabolism is a hallmark of tumors caused by genome instability [123]. Where, deregulated metabolism, which is widespread during tumor progression, is an important source of tumor cell growth and division [123]. One of the main goals of reprogramming is to provide a quick and readily available supply of metabolic intermediates for cell growth. Tumors are capable of reprogramming many different aspects of cell metabolism to fuel their increased energy needs. For instance, tumors are thought to reprogram glucose metabolism through a variety of mechanisms, including an increase in glucose transporters expression (e.g. GLUT1 to GLUT4) that increase glucose import into the cytoplasm, regulating and enhancing the expression of key glycolytic enzymes and disrupting key molecules in the oxidative phosphorylation pathways [124]. Altered lipid metabolism is also a key feature of cancer cells. Increasing lipid synthesis is not only important for cell proliferation, but lipid catabolism can generate bioactive molecules that usually act as signaling molecules, and in the context of cancer development, lipid metabolism can play a role in regulating cancer metastasis [125]. Similarly, amino acid metabolism plays an essential role in carcinogenesis [126]. Therefore, in order to develop effective therapeutic strategies for the treatment of cancer, it is extremely important to investigate the mechanism underlying the violation of the metabolism of cancer cells.

The current literature on the role of circRNAs in cancer metabolism is growing, and a number of studies regularly confirm the impact circRNAs can have in energy reprogramming in cancer. CircRNAs have been widely implicated in cancer regulation and can regulate almost all cancer hallmarks [127]. The increased interest has focused on the ability of circRNAs to regulate the metabolic activity, either directly, by modulating the expression of a gene-targets that encode for metabolic transporters or metabolic enzymes, or indirectly, by regulating the expression of transcription factors or signaling proteins that act as major regulators of metabolism [128]. It is rational to hypothesize that circRNAs may regulate cancer metabolism through regulating transcription by interacting with mRNAs or long non-coding RNAs (lncRNAs), sponging miRNAs, RNA binding proteins, or other targets [128]. It has been shown that some circRNAs can control enzyme activation by altering cellular conditions and allowing cells to adopt certain phenotypes. For example, one of the metabolic enzymes that play a crucial role in maintaining energy homeostasis is the AMP-activated protein kinase (AMPK). AMPK acts as a critical sensor of cellular energy status and plays a multifaceted role in glycolysis and lipolysis [129, 130]. Li et al. identified circACC1 as an activator of AMPK signaling, whose expression was elicited by metabolic stress conditions and function was to promote fatty acid b-oxidation and glycolysis in a tumor xenograft model [131]. In addition, circRNAs has been shown to alter CSCs, which play an important role in tumor development, by regulating their metabolic profile [132]. Exosomal circRNAs may also play a critical role in cell-to-cell communication in the cancer microenvironment and may be an attractive pathway for the delivery of metabolic signals to other cancer cells [133]. Hereinafter, we illustrate the effects of circRNAs and their target-genes in the metabolism of cancer (Table 3) [134–148].

7. Diagnostic and prognostic potential of circular RNAs in cancer

A number of research groups have reported on the potential of circRNAs as biomarkers for cancer diagnosis and prognosis. Due to their circular structure, circRNAs are protected from degradation by exonucleases, and their half-life is much longer than that of the parent mRNA, ie, about 48 h compared to 10 h for mRNA [11]. In addition, they are stably found in body fluids such as saliva and blood, fluids that can be accessed non-invasively for diagnostic purposes, so-called liquid

Table 2
CircRNAs involved in Cancer Drug-Resistance.

CircRNA	Cancer types	Regulation	Signaling pathway	Drug resistance	Ref.
circ_0004015	NSCLC	Upregulated	miR-1183/PDPK1	Gefitinib	[106]
circ_0076305	NSCLC	Upregulated	miR-296-5p/STAT3	Cisplatin	[107]
circ_0063809	OC	Upregulated	miR-1252/FOXR2	Paclitaxel	[108]
circ_0007031	CRC	Upregulated	miR-885-3p/AKT3/BCL2	5-Fluorouracil	[109]
circ_0000504		Upregulated	miR-485-5p/STAT3/AKT3/BCL2		
circ_0048234		Downregulated	miR-671-5p/EGFR		
circ-PRKDC	CRC	Upregulated	miR-375/FOXM1 and Wnt/β-Catenin	5-Fluorouracil	[110]
circ-FBXW7	CRC	Downregulated	miR-128-3p	Oxaliplatin	[111]
circ_0025202	BC	Downregulated	miR-182-5p/FOXO3a	Tamoxifen	[112]
circKDM4C	BC	Downregulated	miR-548p/PBLD	Doxorubicin	[113]
circMTO1	BC	Upregulated	TRAF4/Eg5	Monastrol	[114]
circELP3	Bladder cancer	Upregulated	Targeting cancer stem-like cells	Cisplatin	[115]
circ_0000285	Bladder cancer	Downregulated	miR-124 and miR-558	Cisplatin	[116]
circFoxo3	PC	Downregulated	FoxO3	Docetaxel	[117]
circ_0060060	TC	Upregulated	miR-144-3p/TGF-α	Cisplatin	[118]
circ_001569	Osteosarcoma	Upregulated	Wnt/β-catenin	Cisplatin	[119]
circ_0001258	Osteosarcoma	Downregulated	miR-744-3p/GSTM2	Doxorubicin, cisplatin, methotrexate	[120]
circAKT3	GC	Upregulated	miR-198/ PIK3R1	Cisplatin	[121]
circ_0026359	GC	Upregulated	miR-1200/POLD4	Cisplatin	[122]

Abbreviation: miRNA, microRNA; CircRNA, Circular RNA; NSCLC, Non-small cell lung cancer; OC, Ovarian cancer; CRC, Colorectal cancer; BC, Breast cancer; PC, Prostate cancer; GC, Gastric cancer; PDPK1, 3-Phosphoinositide dependent protein kinase-1; STAT3, Signal transducer and activator of transcription 3; FOXR2, Forkhead Box R2; AKT3, AKT serine/threonine kinase 3; BCL2, B-cell lymphoma 2; EGFR, Epidermal growth factor receptor; FOXM1, Forkhead Box M1; PBLD, Phenazine biosynthesis like protein domain containing; TRAF4, tumor necrosis factor receptor-associated factor 4; Foxo3, Forkhead box O3; TGF-α, Transforming growth factor alpha; GSTM2, glutathione S-transferase Mu 2; PIK3R1, Phosphoinositide-3-kinase regulatory subunit 1; POLD4, DNA polymerase delta 4.

Table 3
Evidence supporting involvement of circRNAs in the reprogramming of cancer metabolism.

CircrRNA	Cancer type	Regulation	Target	Metabolism	Model used	Ref.
circ-ENO1	LUAD	Upregulated	miR-22-3p/ENO1	Glucose metabolism reprogramming (modulate glycolysis)	In vitro, in vivo and human	[134]
circMAT2B	HCC	Upregulated	miR-338-3p/PKM2	Glucose metabolism reprogramming (modulate glycolysis)	In vitro and in vivo	[135]
circ_0025039	Melanoma	Upregulated	miR-198/CDK4	Glucose metabolism reprogramming (modulate glycolysis)	In vitro and in vivo	[136]
4circDENND4C	BC	Upregulated	miR-200b/c	Glucose metabolism reprogramming (modulate glycolysis)	In vitro and human	[137]
circRNA_100290	OSCC	Upregulated	miR-378a/GLUT1	Glucose metabolism reprogramming (modulate glycolysis)	In vitro and in vivo	[138]
circRNA_CDR1as	NPC	Upregulated	miR-7-5p/ E2F3	Glucose metabolism reprogramming (modulate glycolysis)	In vitro, in vivo and human	[139]
circECE1	OS	Upregulated	c-Myc	Glucose metabolism reprogramming (modulate glycolysis)	In vitro, in vivo and human	[140]
circ_0079593	Melanoma	Upregulated	miR-516b/GRM3	Glucose metabolism reprogramming (modulate glycolysis)	In vitro and in vivo	[141]
circ_0006168	EC	Upregulated	miR-384/RBBP7, S6K/ S6	Glucose metabolism reprogramming (modulate glycolysis)	In vitro and human	[142]
circ-ZNF609	PC	Upregulated	miR-501-3p/HK2	Glucose metabolism reprogramming (modulate glycolysis)	In vitro, in vivo and human	[143]
circFARSA	NSCLC	Upregulated	miR-330-5p/ miR-326/FASN	Lipid metabolism (Promoting FAS)	In vitro and human	[144]
circGFRA1	Triple negative BC	Upregulated	miR-34a/GFRA1	Lipid metabolism (Promoting lipophagy)	In vitro, in vivo and human	[145]
circ-DB	HCC	Upregulated	miR-34a/ USP7/Cyclin A2	Lipid metabolism (Promoting FAS)	In vitro and in vivo	[146]
circ_0033988	LSCC	Upregulated	MRE	Lipid metabolism (Promoting FA degradation)	Human	[147]
circHMGCS1	HB	Upregulated	miR-503-5p/IGF-PI3K-Akt	Involved in glutamine metabolism (promote glutaminolysis)	In vitro, in vivo and human	[148]

Abbreviation: miRNA, microRNA; circRNA, circular RNA; LUAD, Lung adenocarcinoma; HCC, Hepatocellular carcinoma; BC, Breast cancer; OSCC, Oral squamous cell carcinoma; NPC, Nasopharyngeal carcinoma; OS, Osteosarcoma; EC, Esophageal cancer; PC, Prostate cancer; NSCLC, Non-small cell lung cancer; LSCC, Laryngeal squamous cell carcinoma; HB, Hepatoblastoma; ENO1, Enolase 1; PKM2, Pyruvate kinase muscle isozyme 2; CDK4, Cyclin Dependent Kinase 6; GLUT1, Glucose transporter 1; E2F3, E2F Transcription Factor 3; GRM3, Glutamate metabotropic receptor 3; RBBP7, RB binding protein 7; S6K, Ribosomal protein S6 kinase beta-1; S6, Ribosomal protein S6; HK2, Hundred-kilobyte kernel; FASN, Fatty acid synthase; GFRA1, GDNF family receptor alpha-1; USP7, Ubiquitin-specific-processing protease 7; MRE, miRNA response element; IGF, Insulin-like growth factor; PI3K, Phosphoinositide 3-kinase; Akt, RAC-alpha serine/threonine-protein kinase.

biopsies (Fig. 2). CircRNAs can be further detected in the serum of exosomes, and analysis of the content of circRNAs in these vesicles can distinguish colon cancer patients from healthy people [149]. It has already been shown that some circRNAs have a prognostic value, both individually and synergistically with known cancer markers [150]. Especially in cases where traditional biomarkers are lacking, circRNAs may be useful, but the reproducibility and specificity of detecting circRNAs has yet to be confirmed in larger studies before they can make it into cancer diagnostics and may serve as predictors. A representing summary of recently reported potential biomarkers for different cancers

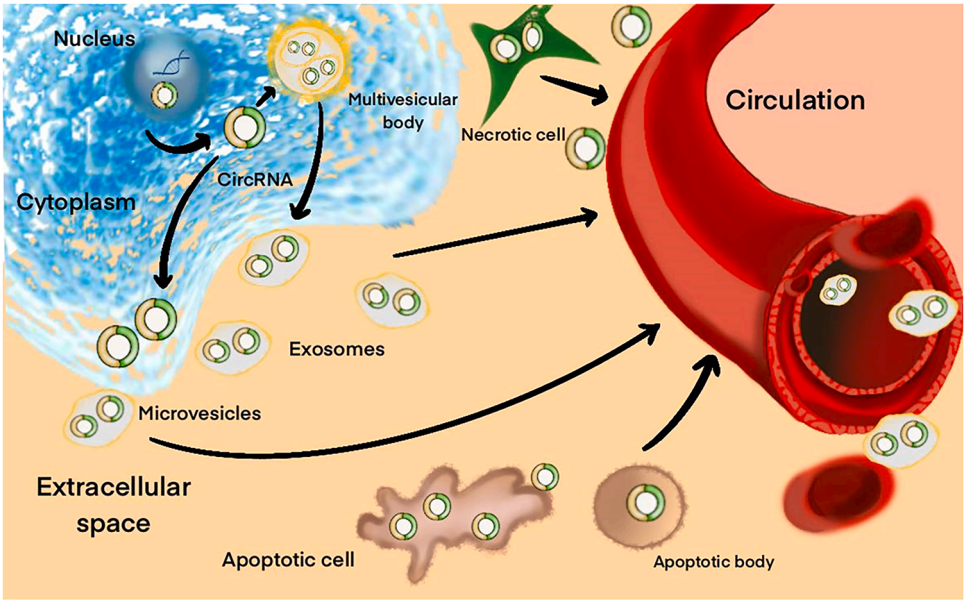

Fig. 2. Possible mechanisms for circRNA secretion. CircRNAs formed by nuclear back-splicing events are eliminated from cells by incorporation into vesicles that are released, such as extracellular vesicles (exosomes or microvesicles). CircRNAs can also be found in apoptotic bodies and necrotic cells.

Table 4
Summary of recent studies on circulating circRNAs as potential biomarkers of different preoperative cancers. Note: AUC: area under ROC curve, AUC > 0, 70 is considered diagnostically significant for the biomarker; Kaplan-Meier curves and log rank tests were used in articles to evaluate the prognostic significance of circulating circRNAs in cancer; /, not mentioned in article; comb., combined.

circRNA	Cancer type	Sample	Diagnostic	Prognostic	Sensitivity %	Specificity %	AUC	Regulation	Ref.
Exosomal circ_MYC	NPC	Serum	Yes	Yes	90.24	94.51	0.945	Up	[151]
circ_SLC7A5	ESCC	Plasma	Yes	Yes	/	/	0.771	Up	[152]
circ_ERBB2	GC	Plasma	No	Yes	/	/	/	Up	[153]
circ_KIAA1244	GC	Plasma	Yes	Yes	77.42	68.00	0.75	Down	[154]
circ_0005962 circ_0086414	LUAD	Whole blood	Yes	Yes	77.80	72.22	Comb. 0.81	Up Down	[155]
circ_FARSA	NSCLC	Plasma	Yes	No	/	/	0.71	Up	[144]
Exosomal circ_0004771	CRC	Serum	Yes	No	/	/	0.92	Up	[156]
circ_0081001	OS	Serum	Yes	Yes	/	/	0.898	Up	[157]
circ_0101996 circ_0101119	CSCC	Whole blood	Yes	No	/	/	0.906 0.887 Comb. 0.81	Up	[158]
circ_Foxp1	EOC	Serum	No	Yes	/	/	/	Up	[159]
Exosomal circ_PDE8A	PDAC	Plasma	No	Yes	/	/	/	Up	[160]
Exosomal circ_AKT3	HCC	Serum	No	Yes	/	/	/	Up	[161]
circ_SETDB1	SOC	Serum	Yes	Yes	78.33	73.33	0.803	Up	[162]
circ_BNC2	EOC	Plasma	Yes	No	96.4 and 95.2	80.7 and 85.5	0.879 and 0.923	Up	[163]
Exosomal circ_MYC	MM	Serum	No	Yes	/	/	/	Up	[164]
circ_0001785	BC	Plasma	Yes	No	/	/	0.771	Up	[165]

Abbreviation circRNA, circular RNA; NPC, Nasopharyngeal carcinoma; ESCC, Esophageal squamous cell carcinoma; GC, Gastric cancer; LUAD, Lung adenocarcinoma; NSCLC, Non-small cell lung cancer; CRC, CRC, Colorectal cancer; OS, Osteosarcoma; CSCC, Cervical squamous cell carcinoma; EOC, Epithelial ovarian cancer; PDAC, Pancreatic ductal adenocarcinoma; HCC, hepatocellular carcinoma; SOC, serous ovarian cancer; MM, Multiple myeloma; BC, Breast cancer.

are listed in Table 4 [144,151–165].

8. Circular RNAs as therapeutic targets in cancer

Both oncogenic and tumor suppressive circRNAs can potentially serve as therapeutic targets in cancer. The back splicing junction sequence is unique to specific circRNAs and allows specific targeting of specific circRNAs without affecting the parental mRNA. Therefore, oncogenic circRNAs can be a target for small interfering RNAs (siRNAs) and undergo Ago2-mediated degradation [166]. Conversely, ectopic expression of tumor-suppressing circRNAs can be achieved using expression vectors with long reverse complementary sequences that facilitate the circulation of the enclosed sequence [14]. Since mammalian cells are able to distinguish their circRNAs from foreign ones, the use of in vitro generated circRNAs should be avoided in order to bypass the activation of the innate immune system [167]. The fact that not all circRNAs are non-coding adds another layer of complexity to this region, and the first circRNA-derived protein with tumor suppressive properties has already been identified [60]. Thus, the use of translational circRNAs may be another therapeutic strategy. CircRNAs containing internal ribosome entry site (IRES) can be translated using the cell's normal ribosomal machinery. CircRNAs with an infinite open reading frame without a stop codon were able to produce a repeating peptide sequence in the form of a "rotating circle" [168]. This can be used to generate peptide sequences that bind and block oncogenic proteins. Thus, the first studies of circRNAs in cancer have shown promising results, and ongoing comprehensive analyzes will improve our understanding of the effect of unregulated expression of circRNAs on tumorigenesis, which will also improve our overall understanding of the role of circRNAs. In the long term, circRNAs have the potential to become part of routine clinical research and improve patient management, offering new perspectives for improving diagnostics, individualizing predictive outcomes, and providing targets for innovative therapeutic approaches.

9. Conclusions

Although circRNAs were previously thought to be "mistakes" in RNA splicing, thousands of endogenous circRNAs have been identified in mammalian cells, which are highly conserved. CircRNAs can be stable and effective miRNA inhibitors. However, there are still many questions that need to be clarified regarding the role of circRNAs. First, like long noncoding RNAs, circRNAs can function as tumor suppressors or tumor promoters in human cancer [169] which calls for a better understanding of the tumor promoting vs. tumor suppressor functions of individual circRNAs. Ideally, the targeting of oncogenic circRNAs should be done in such a way as not to interfere with the expression of linear mRNA. Second, circRNAs are increasingly being proposed as potential cancer biomarkers but the studies are still preliminary to be relevant to clinical use. Further verification requires additional work with larger sets of samples. Finally, it is important to develop a standard nomenclature system. Addressing these issues will provide a fresh look at the role of circRNAs in cancer biology. Thus, there is growing evidence of an important role for circRNAs in tumorigenesis, but research on circRNAs is still in its infancy. We remain cautiously optimistic that diagnostic and therapeutic strategies based on circRNAs may play an important role in cancer therapy in the near future.

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Declaration of Competing Interest

The authors declare that no conflicts of interest exists.

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