

REVIEW

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# circRNAs and their relationship with breast cancer: a review

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## Abstract

**Background:** Recently, an increasing number of studies have been conducted on circular RNAs (circRNAs) that have demonstrated their different roles in a variety of biological processes. Moreover, a large number of circRNAs have been shown to be involved in the occurrence and development of breast cancer (BC).

**Main body:** Both functional and mechanistic experiments have shown that circular RNAs (circRNAs) can act as competing endogenous RNAs by sponging miRNAs, encoding proteins, and regulating parental genes. In doing so, circRNAs modulate the proliferation, migration, apoptosis, and invasion of BC cells in vitro as well as tumor growth and metastasis in vivo. Moreover, scores of circRNAs have been demonstrated to be related to clinicopathological features, prognosis, and treatment sensitivity in patients with BC; many circRNAs have shown potential as biomarkers for diagnosis, drug sensitivity, and prognosis prediction. Furthermore, researchers have focused on circRNAs as potential therapeutic targets.

**Conclusion:** In this review, we briefly summarize the functions and categories of circRNAs, their different roles in BC, and recent research and therapeutic progress related to circRNAs.

**Keywords:** circRNAs, Breast cancer, ceRNA, Clinic

## Background

Cancer remains a serious global problem. According to Global Cancer Statistics for the year 2020 [1], breast cancer (BC) was the most diagnosed cancer and caused the most cancer-related deaths among women. Furthermore, BC is estimated to account for almost one-third of all new cancer diagnoses and has the second highest mortality rate among women in the USA in 2022 [2].

Circular RNAs (circRNAs), characterized by a covalently closed loop structure without a 5'-cap or a 3'-polyadenylated tail, were first reported as viroids in 1976 [3] and are thought to be an error product of RNA splicing [4]. With the development of high-throughput RNA-sequencing technology and bioinformatics tools in recent

years, an increasing number of circRNAs have been discovered and researched. Many circRNAs play important roles in physiological and pathological processes and are characterized by their variety, stable structure, conserved sequences, and specific expression in cells or tissues. In recent years, many studies have shown that circRNAs, as oncogenes or tumor suppressor genes, are closely related to the occurrence of various tumors such as BC [5, 6], endometrial cancer [7], cervical cancer [8], lung carcinoma [9], hepatocellular carcinoma [10], esophageal squamous cell carcinoma [11], and colorectal cancer [12].

CircRNAs are not only involved in regulating proliferation, invasion, and migration of BC cells but may serve as novel molecular markers for early diagnosis and individualized prognosis evaluation of BC. At present, reports on circRNAs related to BC are gradually increasing, but there are few summary articles on these RNAs. Clinical research is still in the early stages, and there remains a lack of comprehensive understanding. This study reviews

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the relationship between circRNAs and BC to provide new ideas for seeking more valuable circRNA-based diagnosis and personalized targeted therapy strategies.

### Biogenesis and classification of circRNAs

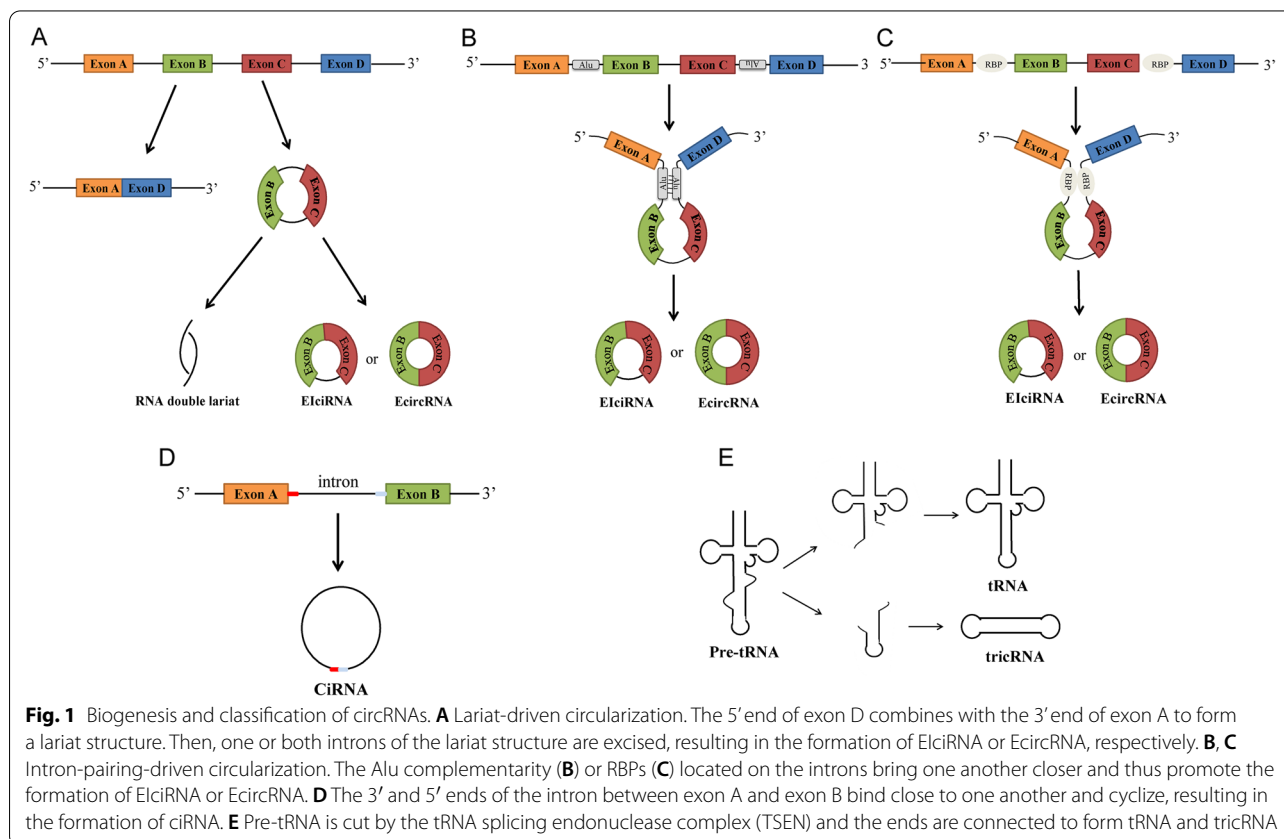
It is generally believed that the majority of circRNAs are generated by back-splicing or other processes of precursor messenger RNAs (pre-mRNAs) and are further processed by enzymes. In 2013, Jeck et al. [13] proposed two models of circRNA generation namely lariat-driven circularization and intron-pairing-driven circularization, which laid the foundation for further exploration of circRNA formation. The former is based on exon-skipping, which results in lariat structure and promotes circularization; the latter is based on Alu complementarity, and other RNA pairings of reverse complement, or repetitive sequences, which allow for circularization [13]. In addition to cis-acting elements (such as Alu-repeats), RNA-binding proteins (RBPs) like muscleblind-like protein 1 (MBNL1) [14], have also been shown to drive circRNA circularization. The canonical spliceosomal machinery can catalyze the process of back-splicing, which is modulated by both intronic complementary sequences and RBPs [15].

circRNAs can be divided into four main categories: (1) exonic circRNAs (EcircRNAs) are composed of one or more exons, are mainly located in the cytoplasm, and account for over 80% of the known circRNAs [16]; (2) circular intronic RNAs (ciRNAs) are comprised of introns and are mainly located in the nucleus; (3) exonic-intronic circRNAs (EicRNAs) are composed of both exons and introns, and are also mainly located in the nucleus; (4) other circRNAs are generated by cyclization of the viral RNA genome [17, 18] or during the splicing of pre-tRNA [19] (tRNA intronic circRNAs, or tricRNAs). Figure 1 illustrates the biogenesis and classification of circRNAs.

### Properties of circRNAs

Compared to linear RNAs, circRNAs have been shown to be more abundant in eukaryotes. Studies have shown that EcircRNAs appear to be derived from over 14% of transcribed genes in human fibroblasts, and there are more than 25,000 different circRNAs that are expressed at much higher levels than their corresponding canonical mRNA [13, 20]. In some cases, circRNAs can be expressed 10 times more than their associated linear transcripts [13].

circRNAs have been shown to be more stable than the associated linear mRNAs [13]. Because of their



covalently closed loop structure, which lacks a 5'-cap and 3'-polyadenylated tail, circRNAs are resistant to the activity of RNases, debranching enzymes, and RNA exonucleases. As a result, the average half-life of mRNAs in cells (10 h) is much shorter than that of circRNAs (> 48 h) [21]. However, circRNAs can also be degraded by some types of RNase R [22] and are regulated by siRNAs, shRNAs, and miRNAs.

Most circRNAs exhibit tissue-, cell-, and developmental stage-specificity [23, 24]. CiRS-7 has been reported to be overexpressed in brain tissues, compared to non-neuronal tissues with low to no expression [25]. Sequencing of RNA from several organs revealed lower numbers and expression levels of circRNAs in human adult tissues compared to fetal tissues, and 50% of circRNAs showed tissue-specificity expression patterns [26]. Most circRNAs are located in the nucleus, whereas most EcircRNAs are transported to the cytoplasm.

Sequence conservation is another characteristic of the circRNAs. Wang et al. found evidence for circRNAs throughout the eukaryotic tree of life which showed structural features similar to eukaryotes that diverged more than 1 billion years ago [27]. Rybak et al. analyzed the conservation of neuronal circRNAs between mammals using RNase R treatment and Sanger sequencing, which showed that the head-to-tail junction sequences were precisely conserved between humans and mice [28].

circRNAs are mainly released through exosomes, which are primarily derived from multivesicular bodies formed by the invagination of intracellular lysosomal particles. These are released into the extracellular matrix after the fusion of the outer membrane of vesicles with the cell membrane. Exosomes can be shed by most cell types and circulate in bodily fluids such as blood, saliva, breast milk, and urine [29, 30]. After being transported from the nucleus to the cytoplasm, circRNAs are secreted into bodily fluids by the exosomes. It has been reported that circRNAs can be transferred to recipient cells via exosome delivery, indicating that exosomal circRNAs are important for invasion and metastasis [31]. Based on this information, circRNAs are considered potential non-invasive biomarkers for the diagnosis and prognosis of various diseases.

### **Functional mechanisms of circRNAs and the molecular mechanisms in BC**

The biological function of circRNA has been widely studied, and the functional mechanism can be mainly divided into the following three types: miRNA sponging, protein/peptide template, and regulating parental genes. An increasing number of circRNAs have been found to be associated with BC tumorigenesis, progression, and metastasis. Furthermore, various circRNAs

have been reported to be abnormally expressed in BC tissues and cell lines. The circRNAs that have been reported to be associated with BC are summarized and listed in Table 1, and their functions and mechanisms in BC are also demonstrated. In Table 2, the results of RNA-seq or microarray analysis of circRNAs associated with BC that have been reported in the literature are listed, including the total number of circRNAs, number of differentially expressed circRNAs, and cut-off criteria (fold change and *P* value) defining differential expression.

#### **miRNA sponging**

miRNAs can base pair directly with target sites within the untranslated regions of mRNAs, and thus play key roles in regulating gene expression at the post-transcriptional level [48]. circRNAs contain miRNA binding sites. Thus, by competitively binding to miRNAs and acting as sponges, circRNAs can degrade mRNAs in a targeted manner and indirectly regulate gene expression, which may have an impact on tumor development and drug resistance [49]. This is the most important mechanism by which circRNAs play the role of regulation.

CiRS-7 was the first circRNA to be validated as a miRNA sponge and was verified to contain more than 70 selectively conserved binding sites for miR-7 [48]. Hsa\_circRNA\_101237 was found to be an important onco-circRNA of non-small cell lung cancer (NSCLC) that sponges miRNA-490-3p and thus promotes the expression of MAPK1 to drive proliferation, migration, and invasion of NSCLC cell lines [50].

A study on circRNA\_0025202 found that its tumor inhibition and tamoxifen sensitization effects on HR-positive BC were achieved through sponging of miR-182-5p, as well as through further regulation of the expression and activity of its target protein FOXO3a [39]. Yang et al. reported that circAGFG1 may act as a competing endogenous RNA (ceRNA) by sponging miR-195-5p and regulating the expression of its target CCNE1, thus promoting triple-negative breast cancer (TNBC) progression [33]. circWAC has also been reported to affect the chemosensitivity of TNBC by sponging miR-142 and regulating its target WWP1 [51]. A study on circANKS1B showed that it was associated with TNBC metastasis, advanced stage, and overall survival (OS) as a result of sponging miR-148a-3p and miR-152-3p [32]. Cao et al. reported that circRNG20 promoted BC proliferation via the circRNF20/miR-487a/HIF-1 $\alpha$ /HK2 axis [6]. circFOXK2 and circRNA\_103809 have also been reported to promote the invasion and migration of BC by sponging miR-370 and miR-532-3p, respectively [35, 37]. Xu et al. reported that circTADA2A-E6 acts as a miR-203a-3p sponge and inhibits the expression of SOCS3, the target gene of

**Table 1** circRNAs associated with breast cancer

circRNA	circRNA ID	Expression in BC	Function					Mechanism				Ref.
			Proliferation	Metastasis	Invasion	Migration	Mobility	Others				
hsa_circ_001783	hsa_circ_001783	↑	✓	✓	✓	✓			Sponging miR-200c-3p	[5]		
circANKS1B	hsa_circ_0007294	↑	✓	✓	✓				Sponging miR-148a-3p and miR-152-3p	[32]		
circAGFG1	-	↑	✓	✓		✓			Sponging miR-195-5p	[33]		
circRNF20	hsa_circ_0087784	↑	✓					Warburg effect	Sponging miR-487a	[6]		
hsa_circ_0005273	hsa_circ_0005273	↑	✓						Sponging miR-200a-3p	[34]		
circFOXK2	hsa_circ_0000816	↑	✓	✓	✓				Sponging miR-370	[35]		
circRHOT1	-	↑	✓	✓	✓				Sponging miR-106a-5p	[36]		
circRNA_103809	circRNA_103809	↓	✓	✓	✓				Sponging miR-532-3p	[37]		
circSMARCA5	-	↓	✓					Cisplatin response	Interacting with host gene	[38]		
hsa_circ_0025202	hsa_circ_0025202	↓	✓		✓			Apoptosis, Tamoxifen Sensitivity	Sponging miR-182-5p	[39]		
circTADA2A-E6	hsa_circ_0006220	↓	✓	✓	✓			Clonogenicity	Sponging miR-203a-3p	[40]		
circNR3C2	hsa_circ_0071127	↓	✓	✓	✓				Sponging miR-513a-3p	[41]		

**Table 2** Overview of circRNAs identified by RNA sequencing and microarrays in BC

Sample	Subtype of BC	Detection method	Number of circRNAs	Number of differently expressed circRNAs (upregulated/ downregulated)	Fold Change	P value	Ref
4 pairs of BC and BCN tissues	TNBC	RNA-seq	–	354 (47/307)	≥ 2	< 0.05	[42]
3 pairs of BC and BCN tissues	TNBC	RNA-seq	69815	5033 (1307/3726)	≥ 2	< 0.05	[32]
4 pairs of BC and BCN tissues	IDC	circRNA microarray	–	1155 (715/440)	≥ 2	< 0.05	[43]
MCF7/TR and MCF7/P cells	HR-positive BC	RNA-seq	36110	465 (352/113)	> 1	< 0.01	[39]
three TNBC cell lines (MDA-MB-231, MDA-MB468 and BT549) and one HME cell line (MCF-10A)	TNBC	circRNA microarray	–	270 (93/174)	> 3	< 0.05	[44]
4 pairs of BC and para-cancer tissues	non-TNBC	circRNA microarray	–	85 (63 /22)	≥ 2	< 0.05	[45]
5 pairs of BC and paired normal tissues	TNBC	RNA-seq	27346	1200 (613/587)	≥ 2	< 0.01	[46]
5 pairs of plasma of BC patients and healthy controls	–	circRNA microarray	–	41 (19/22)	≥ 2	< 0.05	[43]
4 pairs of BC and para-cancer tissues	TNBC	circRNA microarray	–	250 (173/77)	≥ 1.5	< 0.05	[47]
BC and NMGT tissues	TNBC (4 BC, 3 NMGT)	circRNA microarray	–	215 (122/93)	–	–	[40]
	Luminal A (4BC, 3 NMGT)	circRNA microarray	–	73 (55/18)			

NMGT normal mammary gland tissues, BCN tissues normal breast tissues of patients with breast cancer

miR-203a-3p, thus suppressing cell proliferation, migration, invasion, and clonogenicity in vitro [40]. A study on circCD44 (hsa\_circ\_0021735), a type of EcircRNA that is mostly localized in the cytoplasm, showed that it was associated with TNBC proliferation and malignant characteristics as well as prognosis [52]. Furthermore, circCD44 was predicted to act as a ceRNA and to mediate KRAS degradation through targeting of miR-502-5p [52].

circERPT9, a novel circRNA generated from exon 2 of SERPT9 by back-splicing, is involved in the carcinogenesis and development of TNBC [42]. Functional experiments demonstrated that circERPT9 promotes BC cell proliferation, migration, and invasion while suppressing cell cycle arrest, apoptosis, and autophagy. Further bioinformatic analysis showed that circSEPT9 can sponge miR-637 and activate the LIF-STAT3 pathway through the circSEPT9/miR-637/LIF axis in TNBC. Furthermore, E2F1 and EIF4A3 could promote the expression of circSEPT9, although the mechanism involved remains unclear.

Hsa\_circ\_001783 has a genomic sequence 34460 nucleotides (nt) in length and is a type of EicRNA [5]. Functional experiments showed that transfection of siRNAs targeting the junction site of hsa\_circ\_001783 inhibited the progression of BC cells. Further results showed that hsa\_circ\_001783 could sponge miR-200c-3p and upregulate its targeting genes.

In the analysis of a large cohort, hsa\_circ\_0005273 was substantially expressed in BC tissues. This circRNA is 357 base pairs in length and is derived from the circularization of exons 27–29 of the PTK2 gene. According to functional experiments, by sponging miR-200a-3p, hsa\_circ\_0005273 can boost BC cell proliferation both in vitro and in vivo, thereby regulating the miR-200a-3p/YAP1 axis and inactivating the Hippo signaling pathway [34].

circNFIC (hsa\_circ\_0002018) has the potential to be a new suppressive factor and BC biomarker [53]. Overexpression of circNFIC suppresses proliferation and migration of BC cells both in vitro and in vivo. Both bioinformatic analysis and a series of experiments demonstrated that circNFIC could sponge miR-658 and restore the expression of its target gene, UPK1A. Additionally, further assays revealed that circNFIC overexpression increased the enrichment of circNFIC on Ago2 but decreased that of UPK1A. However, UPK1A expression could be promoted, indicating that circNFIC may act as a ceRNA through the circNFIC/miR-658/UPK1 axis. In summary, circNFIC was demonstrated to be a novel anti-oncogenic circRNA that regulates BC proliferation and migration through the circNFIC/miR-658/UPK1 regulatory network.

circ\_0000442 (hsa\_circ\_0000442), derived from the MED13L gene, is downregulated in BC cells and tissues compared to that in adjacent non-cancerous cells [54]. In a subsequent functional study, results showed that circ\_0000442 suppressed the proliferation of BC



both in vivo and in vitro and thus acted as a tumor suppressor. Furthermore, circ\_0000442 functions as a sponge for miR-148b-3p, which promotes cell proliferation. Further exploration of the underlying mechanism showed that PTEN was the direct target gene of miR-148b-3p, which was identified as a negative PI3K/Akt pathway switch. Overexpression of circ\_0000442 increased the level of PTEN while suppressing phosphorylation of PI3K and Akt; however, overexpression of miR-148b-3p reversed this phenomenon. Taken together, circ\_0000442 may play a role in inhibiting BC tumor progression through the circ\_0000442/miR-148b-3p/PTEN/PI3K/Akt axis.

Recently, the concept of autophagy has been proposed to promote the progression of BC [55, 56]. Autophagy is an important mechanism for the survival of disseminated dormant BC cells and plays a key role in tumor metastasis and recurrence [55]. circCDYL was shown to have up to 3.2-fold higher expression in BC tissues than that in adjacent non-cancerous tissues, and was associated with poor prognosis and clinical response in patients with BC [57]. Overexpression or silencing of circCDYL is related to the level of LC3-II protein, which is an autophagic marker. Biological function experiments showed that circCDYL regulated the proliferation of BC cells through the miR-1275-ATG7/ULK1-autophagic axis.

circANKS1B, arising from exons 5 to 8 of the ANKS1B gene, is markedly overexpressed in TNBC compared to normal tissues and other subtypes of BC [32]. Functional experiments have shown that circANKS1B promotes the epithelial-mesenchymal transition (EMT) to facilitate BC invasion and metastasis both in vitro and in vivo, but has no effect on BC growth. The level of the epithelial cell marker E-cadherin was increased, while the level of mesenchymal cell markers vimentin and fibronectin were decreased. Further mechanistic studies revealed that the ESRP1/circANKS1B/miR-148a/152-3p/USF1 axis regulates BC via TGF- $\beta$ 1-mediated EMT.

circNR3C2, which is generated by back-splicing of the second exon of the nuclear receptor subfamily 3 group C member 2 (NR3C2) located at chr4:149356255–149358014 (1760 nt), was markedly under expressed in TNBC, and a negative correlation was found in clinical data [41]. HMG-CoA reductase degradation protein 1 (HRD1) was also found to be under expressed in TNBC and was negatively correlated with vimentin expression. Functional experiments showed that overexpression of HRD1 suppressed proliferation, migration, and invasion capabilities of BC cells, and these effects were reversed upon overexpression of vimentin. Further mechanistic studies suggested that circNR3C2 regulates the tumor-suppressive effect of HRD1 by sponging miR-513a-3p in TNBC.

Ferroptosis, a newly discovered form of programmed cell death characterized by the iron-dependent accumulation of lipid reactive oxygen species (ROS), plays an important role in BC and other diseases. Intracellular lipid ROS are catalyzed by Fe<sup>2+</sup>-containing enzymes, and excessive ROS are removed through the antioxidant system. Cell death occurs when the excess accumulation of ROS caused by lipid peroxidation exceeds the safety threshold [58–60]. circRHOT1 has been shown to promote proliferation, invasion, and migration of BC cells both in vivo and in vitro while inhibiting apoptosis and ferroptosis. Furthermore, overexpression of STAT3 and the use of a miR-106a-5p inhibitor reversed BC progression that was mediated by circRHOT1 knockdown and also increased the levels of ROS, iron, and Fe<sup>2+</sup>. Taken together, this study suggests that circRHOT1 promotes BC progression via the miR-106a-5p/STAT3 axis [36].

#### Protein/peptide template

circRNAs were originally considered noncoding RNAs because of their special structure, which does not provide suitable ribosomal entry sites. However, it was first reported in 1995 that circRNAs with internal ribosome entry site (IRES) elements could be translated by eukaryotic ribosomes [61]. Recently, an increasing number of studies have demonstrated that a special group of circRNAs can encode proteins [62–64].

circ-ZNF609 was found to contain an open reading frame (ORF) spanning the start codon that could be translated into protein in a splicing-dependent and cap-independent manner [62]. Another study showed that circ-SHPRH contains an ORF driven by an IRES. Thus, circ-SHPRH can be translated into a novel protein, shprh-146aa, which is a tumor suppressor in human glioblastoma [63]. Another recent study showed that circDIDO1, a circRNA containing IRES, ORF, and m6A modification, could generate a 529 amino acid tumor suppressor protein that inhibits the activity of poly ADP-ribose polymerase 1 through direct interaction [65].

#### Regulating parental genes

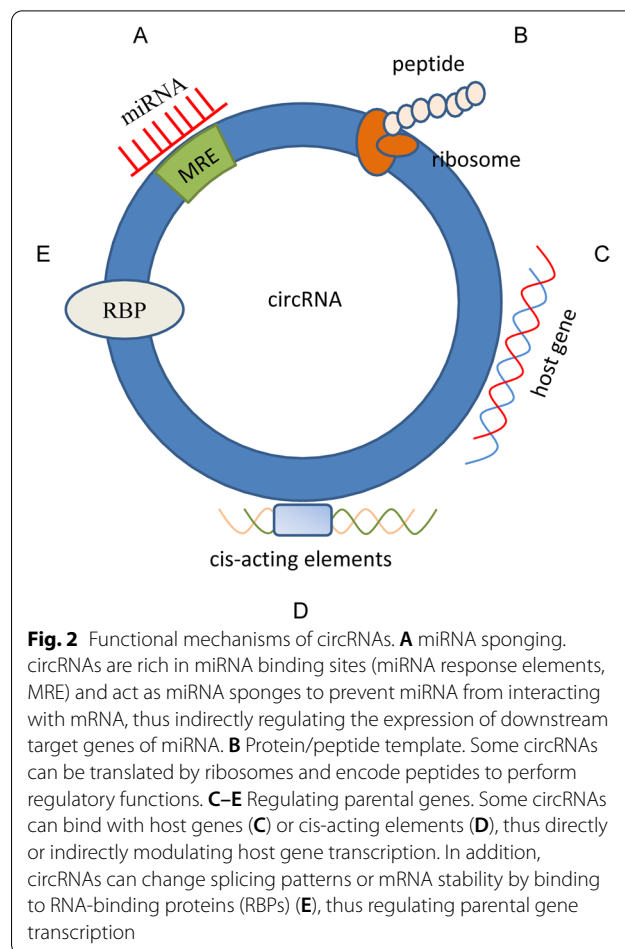
Another important function of circRNAs is the regulation of parental gene expression. First, circRNAs can directly interact with host genes. A study showed that the circRNA generated from exon 6 of the SEPALLATA3 gene in plants binds to its cognate DNA locus to form RNA: DNA hybrids or R-loops, resulting in transcriptional pausing; whereas, cognate linear RNA binds less strongly to DNA [66]. This was the first time that circRNA manipulation was found to mediate phenotypes

at the organismal level [66]. It was recently reported that circSMARCA5 inhibits the expression of SMARCA5 by forming R-loops with its parent gene. This results in a transcriptional halt at exon 15 of SMARCA5, thereby inhibiting its DNA damage repair function in cancer cells [38]. Second, circRNAs can combine with cis-acting elements (e.g., promoters) directly or indirectly to modulate host gene transcription. A previous study illustrated that circTulp4, which is mainly located in the nucleus, regulates the function of the nervous system and is likely involved in the development of Alzheimer's disease. This regulation occurs via interactions with U1 small nuclear ribonucleoprotein particles and RNA polymerase II at the promoter to regulate the transcription of its parental gene [67]. Third, circRNAs can bind to RBPs to regulate transcription. RBPs play key roles in regulating RNA at the post-transcriptional level and are involved in tissue development and disorders [68]. By interacting with specific cis-regulatory elements, RBPs assemble the ribonucleoprotein complex to bind RNA sequences and influence the expression and function of their target RNAs [69]. A previous study proposed that the connection between HuR and PABPN1 mRNA could be prevented, and the translation of PABPN1 could be reduced due to the wide binding of circPABPN1 to HuR. This provided the first concrete example of translation affected by the competition between a circRNA and its cognate mRNA to bind to RBP [70]. Similarly, cia-cGAS inhibits cGAS gene expression by binding to the cGAS protein, thereby further inhibiting the generation of type I interferon and ultimately dormant hematopoietic stem cells in the bone marrow [71]. Figure 2 shows the main functional mechanisms of circRNAs.

### Correlation between circRNA expression and clinicopathological features of BC

circRNAs can promote or suppress BC progression by sponging miRNAs, encoding proteins, and regulating parental genes. These effects are reflected in the modulation of proliferation, migration, and invasion in vitro and in vivo through regulation of tumor growth, metastasis, and other clinicopathological features. The reported circRNAs associated with clinicopathological features of BC are listed in Table 3. Additionally, the number of cases, subtypes of BC, and related clinicopathological features are also demonstrated.

A study conducted on a cohort of 120 patients with BC showed that hsa\_circ\_0005273 expression was positively associated with lymph node metastasis, tumor size, TNM stage, and distant metastasis but was not correlated with age [34]. A comparison of 60 TNBC



samples and adjacent non-cancerous tissues showed that circSEPT9 was positively correlated with T, N, and TNM stages [42]. A cohort of 240 BC tissues demonstrated that circACTN4 expression was positively correlated with T, N, and TNM stages [45]. A study showed that circAGFG1 expression level is associated with poor prognosis as well as the T and N stages of the TNM staging system [33]. circNFIC was also reported to be downregulated in BC, and negatively correlated with lymph node metastasis ( $P = 0.021$ ) as well as poor prognosis ( $P = 0.002$ ) [53].

### CircRNAs as diagnostic and prognostic biomarkers for BC

Early diagnosis and prognosis are two of the most important issues for patients with BC, and circRNAs show great potential as biomarkers. Clinical diagnostic and prognostic values of circRNAs have been explored in several studies. The reported circRNAs with diagnostic and prognostic potential and their related indicators are listed

**Table 3** circRNAs and clinicopathological features of breast cancer

CircRNA	Expression in BC	Subtype of BC	Clinicopathological features					Number of cases	Ref.
			Tumor size and TNM stage	Metastasis	IHC and subtype	Grade	Others		
circSEPT9	↑	TNBC	T, N, TNM					60	[42]
hsa_circ_001783	↑	-	T, N, TNM		ER, PR, Ki-67, molecular subtype			136	[5]
circRNF20 (hsa_circ_0087784)	↑	-	tumor size	LN				50	[6]
hsa_circ_0005273	↑	-	tumor size, TNM	LN, distant				120	[34]
circACTN4	↑	Non-TNBC	T, N, TNM					240	[45]
hsa_circ_0001785	↑	-	TNM	Distant		Histological grade		57	[43]
circHMCU (hsa_circ_0000247)	↑	-	T, N	LN	ER, PR, HER2	Histological grade		267	[72]
circKIF4A (hsa_circ_0007255)	↑	TNBC	Tumor size, TNM	LN				240	[73]
circMMP11 (hsa_circ_0062558)	↑	-	TNM	LN				113	[74]
circEPST11 (hsa_circ_000479)	↑	TNBC	Tumor size, TNM	LN				240	[75]
circLARP4	↑	-	Tumor size, T, N, TNM					283	[76]
circPLK1 (hsa_circ_0038632)	↑	TNBC	Tumor size, TNM	LN				240	[75]
circRNA_100395	↓	-	T					52	[77]
hsa_circ_0025202	↓	HR-positive BC		LN		Histological grade,		230	[39]
hsa_circ_0001073	↓	-	Tumor size	LN			age	132	[78]

LN lymph node, IHC immunohistochemistry, ER estrogen receptor, PR progesterone receptor, HER2 human epidermal growth factor receptor 2

in Tables 4 and 5, demonstrating that circRNA has great potential for the diagnosis and prognosis of BC.

Receiver operating characteristic (ROC) curve analysis was used to assess the diagnostic value of circSEPT9 for TNBC screening. The area under the curve (AUC) of circSEPT9 was 0.711, and its specificity and sensitivity were 75.0% and 63.3%, respectively, with a cut-off value of 1.971; these values indicate that circSEPT9 may be an effective biomarker for TNBC diagnosis [42]. In a study conducted by Lü et al. [79], a circRNA microarray was used to identify differentially expressed circRNAs between BC and adjacent non-cancerous tissues. Validation experiments demonstrated upregulated expression of hsa\_circ\_103110, hsa\_circ\_104689, and hsa\_circ\_104821 in BC tissues, along with downregulated expression of hsa\_circ\_006054, hsa\_circ\_100219, and hsa\_circ\_406697. The AUC values were 0.63, 0.61, 0.60, 0.71, 0.78, and 0.64, respectively. In contrast, when hsa\_circ\_006054, hsa\_circ\_100219, and hsa\_circ\_406697 were used in combination, the AUC value increased to 0.82 (95% CI 0.73–0.90), providing strong evidence for circRNAs as diagnostic markers. Yin et al.

[43] found that a novel circRNA, hsa\_circ\_0001785, was upregulated in the plasma of patients with BC via microarray analysis. ROC curve analysis of 20 paired plasma samples showed that the AUC value of hsa\_circ\_0001785 was 0.771 (95% CI 0.592–0.915). Another analysis of 57 paired plasma samples showed that the AUC values of CEA, CA-153, and hsa\_circ\_0001785 were 0.562, 0.639, and 0.784, respectively. The AUC value of the combination of the three potential biomarkers was 0.839, indicating their potential as biomarkers for BC.

Kaplan–Meier analysis performed on a large cohort suggested that BC patients with higher levels of hsa\_circ\_001783 were more likely to have poor disease-free survival (DFS) ( $P < 0.001$ ). Multivariate analysis showed that the expression level of hsa\_circ\_001783 was an independent risk factor for BC prognosis (HR 9.114; 95% CI 2.428–34.206,  $P = 0.001$ ) [5].

circTADA2A-E6, a circRNA spliced from exon 6 of TADA2A (chr17, 35766977–35839830), suppresses cell proliferation, migration, invasion, and clonogenicity in vitro. Combined with clinical data, downregulation



**Table 4** Diagnosis efficiency of circRNAs for breast cancer

CircRNA	Expression in BC	Subtype of BC	Sample	AUC	Sensitivity	Specificity	Cut-off	Number of cases	Ref.
circACTN4	↑	non-TNBC	Tissue	0.719	0.7	0.7	12.77	80	[45]
hsa_circ_0001785	↑	–	Plasma	0.771	0.786	0.756	–	20	[43]
				0.784	0.764	0.699	0.981	57	
circSEPT9	↑	TNBC	Tissue	0.711	0.633	0.75	1.971	60	[42]
hsa_circ_103110	↑	IDC	Tissue	0.63	0.63	0.63	8.97	51	[79]
hsa_circ_104689				0.61	0.57	0.55	7.67		
hsa_circ_104821				0.60	0.57	0.57	6.04		
hsa_circ_006054	↓			0.71	0.65	0.69	14.84		
hsa_circ_100219				0.78	0.69	0.71	8.95		
hsa_circ_406697				0.64	0.63	0.63	14.24		
hsa_circ_0001073	↓	–	Tissue	0.9898	0.9242	0.9737	6.68	132	[78]
circVRK1	↓	–	Tissue	0.72	0.617	0.791	0.425	350	[80]

IDC invasive ductal carcinoma

**Table 5** circRNAs and prognosis of breast cancer

CircRNA	Expression in BC	Subtype of BC	Sample	Survival	P value	HR (95%CI)	Number of cases	Ref.
circANKS1B	↑	–	Tissue	OS	0.002	3.29 (1.75–8.23)	165	[32]
circCDYL	↑	–	Tissue	DFS	0.0036	2.85 (1.415–5.739)	113	[57]
		MBC	Serum	OS	0.002	3.748 (1.233–11.239)	30	
circAGFG1	↑	TNBC	Tissue	OS	< 0.0001	–	80	[33]
circKIF4A	↑	TNBC	Tissue	DFS, OS	< 0.01	–	240	[73]
circFBXW7	↑	TNBC	Tissue	OS	0.001	0.215 (0.119–0.387)	473	[81]
circ_0001073	↓	–	Tissue	RFS	0.038	–	132	[78]

RFS relapse-free survival, DFS disease-free survival, OS overall survival, MBC metastatic breast cancer

of circTADA2A-E6 is associated with poor prognosis for TNBC [40].

circRGP6 was dramatically reduced in BC tissues compared to healthy tissues [82]. Kaplan-Meier survival analysis suggests that BC patients with high expression of circRGP6 or YAF2 are more likely to have superior DFS and OS than those with low expression, whereas miR-26b showed the opposite phenomenon. Further analysis and experiments revealed that transcript variant (TV) circRGP6 suppresses BC stem cell-mediated metastasis through the miR-26b/YAF2 axis, further explaining these results. These findings further demonstrate that many circRNAs show great value in the prognosis of BC.

### circRNAs expression and treatment of BC

#### circRNAs predict drug sensitivity for BC

Given their high stability, abundance, and sequence conservation, circRNAs are considered to be potential biomarkers of drug sensitivity. For instance, a study of hsa\_circ\_0025202 demonstrated that overexpression of hsa\_circ\_0025202 sensitized cells to tamoxifen treatment [39].

TNBC tissues lack expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). Therefore, we believe that anti-HER2-targeted therapy is not beneficial for patients with TNBC. However, Lee et al. found that circ-HER2 is enriched in TNBC, which in turn encodes HER2-103. In vitro experiments showed that HER2-103 promotes proliferation, invasion, and metastasis of TNBC cells. HER2-103 binds to EGFR and/or HER3 and activates the PI3K-Akt pathway, thereby promoting TNBC occurrence and progression. Pertuzumab has been shown to significantly reduce tumor growth and inhibit lung metastasis of TNBC cells with high HER2-103 expression in animal models [46].

Chemotherapeutic resistance is a critical aspect of TNBC treatment, and an effective biomarker for chemotherapeutic resistance prediction would play a key role in individualized treatment. circWAC is highly expressed and is negatively associated with prognosis in patients with TNBC [51]. Functional experimental data showed that circWAC had no obvious effect on metastasis and cell invasion but showed a strong relationship with

chemosensitivity to paclitaxel. Subsequent studies have demonstrated that circWAC increases cisplatin resistance in BC cells, both in vivo and in vitro. Bioinformatic analysis and functional experiments further supported that circWAC can regulate chemotherapeutic resistance, specifically by sponging miR-142 and further targeting WWP1. Further analysis and experiments showed that miR-142 overexpression inhibited the PI3K/AKT signaling pathway. In summary, the circWAC/miR-142/WWP1 axis can affect TNBC chemosensitivity by regulating the PI3K/AKT signaling pathway.

#### **circRNAs as potential therapeutic targets for BC**

As the regulatory roles of circRNAs are gradually being discovered, some may be investigated as effective therapeutic targets [20]. With increased biotechnological developments, many researchers have focused on circRNA-directed therapeutics [41, 45, 83]. For example, circDnmt1 is significantly upregulated in BC and promotes tumor growth and autophagy. Combining gold nanoparticles (PEG-AuNPs) with short interfering RNA (siRNA) targeting circDnmt1 was shown to inhibit these effects in mice [84]. circSka3 is highly expressed in patients with BC, and experiments have shown that it can promote tumor invasion and metastasis. In vivo experiments in nude mice confirmed that silencing circSka3 with siRNA could reverse these effects. Therefore, circSka3 may become a potential target in BC [85].

Currently, circRNA-targeted therapy research is in full swing, though it remains in the stage of preclinical animal model experiments [86]. Oncogenic circRNAs can be selectively inhibited or degraded using antisense RNA technology, such as RNA interference (RNAi) [87], CRISPR/Cas9 [88], CRISPR/Cas13 [89], and conditional circRNA knockout or knockdown [90]. Anti-oncogenic circRNAs can also be overexpressed using circRNA expression vectors [91], direct synthesis, and purification [92]. In addition, nanoparticle [93] and exosome [94] drug delivery systems are also being developed vigorously, providing a more solid foundation for the realization of circRNA-targeted therapy.

Researchers developed a versatile transcript variant (TV) amplifier delivery system, which targeted transgene expression in breast tumors with activity comparable to or stronger than the cytomegalovirus promoter in cancer cells [82, 95, 96]. A TV delivery system for microRNA (miR)-34a has also been developed, which reduced the proliferation of breast cancer stem cells (BCSCs) [23]. Furthermore, a new TV-circRGP6 nanoparticle that selectively expresses circRGP6 in metastatic BCSCs was generated recently [82] and inhibited both the tumor-promoting effect of BCSCs in vitro as well as the BC tumor metastasis-promoting effect in vivo. This

nanoparticle also inhibited the proliferation and metastasis of BC via synergistic action with docetaxel. In conclusion, the development of TV-circRGP6 nanoparticles may help reduce BC metastasis and provides a novel direction along with a potential tool for BC treatment.

#### **Conclusion and perspective**

circRNAs are a group of novel RNAs that play key roles in tumorigenesis and progression of many types of benign and malignant tumors. Thus, research on their functions and mechanisms has increased and has provided more extensive information about circRNAs. Researchers have discovered that circRNAs can act as ceRNAs by sponging miRNAs, encoding proteins, and regulating parental genes. However, there are still many phenomena that cannot be explained by existing theories and hypotheses. Furthermore, circRNAs are being integrated into clinical data reporting. Thus, circRNAs are showing great potential as biomarkers for the diagnosis and prognosis of BC. Some circRNAs have also shown the potential to predict therapeutic outcomes and may become new therapeutic targets in the future. However, in general, research related to circRNA in tumors is still in its infancy, and the precise mechanisms involved have not been fully elucidated, which suggests that we still need to carry out many exploratory experiments. It is undeniable that circRNAs show great potential in tumor diagnosis, prognosis, and treatment, and they also have high clinical value. It is believed that with the unremitting efforts and practical exploration of scientists, circRNAs will open up a new field for tumor research, hopefully creating a new starting point for precision medicine in clinical diagnosis and treatment.

#### **Abbreviations**

circRNAs: Circular RNAs; BC: Breast cancer; ceRNA: Competing endogenous RNA; pre-mRNAs: Precursor messenger RNAs; RBPs: RNA-binding proteins; ICSS: Intronic complementary sequences; EcircRNAs: Exonic circRNAs; ciRNAs: Circular intronic RNAs; ElciRNAs: Exonic-intronic circRNAs; tricRNAs: tRNA intronic circRNAs; NSCLC: Non-small cell lung cancer; TNBC: Triple-negative breast cancer; ORF: Open reading frame; IRES: Internal ribosome entry site; RNP: Ribonucleoprotein; HR: Hazard ratio; FUBP1: Far upstream element binding protein 1; FUSE: Far upstream element; FIR: FBP interacting repressor; EMT: Epithelial-to-mesenchymal transition; NR3C2: Nuclear receptor subfamily 3 group C member 2; HRD1: HMG-CoA reductase degradation protein 1; ROS: Reactive oxygen species; AUC: Area under the curve; CI: Confidence interval; DFS: Disease-free survival; OS: Overall survival; ER: Estrogen receptor; PR: Progesterone receptor; HER2: Human epidermal growth factor receptor 2; TV: Transcript variant; miRNA: MicroRNA; NMG1: Normal mammary gland tissues; RFS: Relpase-free survival; BCSCs: Breast cancer stem cells.

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