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REVIEW

Circular RNA and its potential diagnostic and therapeutic values in breast cancer

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Abstract

Breast cancer (BC) is one of the most common malignant tumors in women and still poses a significant threat to women worldwide. Recurrence of BC in situ, metastasis to distant organs, and resistance to chemotherapy are all attached to high mortality in patients with BC. Non-coding RNA (ncRNA) of the type known as "circRNA" links together from one end to another to create a covalently closed, single-stranded circular molecule. With characteristics including plurality, evolutionary conservation, stability, and particularity, they are extensively prevalent in various species and a range of human cells. CircRNAs are new and significant contributors to several kinds of disorders, including cardiovascular disease, multiple organ inflammatory responses and malignancies. Recent studies have shown that circRNAs play crucial roles in the occurrence of breast cancer by interacting with miRNAs to regulate gene expression at the transcriptional or post-transcriptional levels. CircRNAs offer the potential to be therapeutic targets for breast cancer treatment as well as prospective biomarkers for early diagnosis and prognosis of BC. Here, we are about to present an overview of the functions of circRNAs in the proliferation, invasion, migration, and resistance to medicines of breast cancer cells and serve as a promising resource for future investigations on the pathogenesis and therapeutic strategies.

Keywords circRNA · Breast cancer · Proliferation · Metastasis · Drug resistance · Biomarker

Introduction

Breast cancer is the most common cancer in the world and the leading cause of cancer deaths in women. Despite the progress achieved in surgery, chemotherapy, radiation, endocrine therapy, targeted therapy, immunotherapy and other treatments, the incidence of BC has been on the rise globally over the past decade. The most prevalent cancer among women in the world today is breast cancer, overtaking lung cancer [1]. Based on the expression of estrogen receptors (ER), progestin receptors (PR), KI67, and the human epidermal growth factor receptors (EGFR2/HER2), BC is categorized into four types: luminal A, luminal B, ErbB2 overexpression, and triple-negative breast cancer (TNBC) [2]. Increased mortality in BC patients is associated with tumor recurrence and metastasis to distant organs such as the bone, lungs, brain, and liver [3, 4].

The occurrence of BC is influenced by external elements, familial genetic predisposition, estrogen replacement therapy and long-term high-dose radiation exposure. Mutations in genetic disorders such as P53, BRCA1 and BRCA2 mutations, as well as people with a history of ovarian or breast cancer, are more likely to develop BC [5]. Today, it is believed that epigenetic modifications and genetic alterations play significant roles in the pathogenesis of BC. DNA methylation and histone modification are examples of epigenetic modifications [6]. Additionally, a number of ncRNAs, including long non-coding RNA (lncRNA), microRNA (miRNA) [7], and circular RNA (circRNA) [8] were found to influence the onset and progression of BC.

CircRNA is a kind of covalently closed RNA that was first discovered by Sanger et al. in a plant-infected virus in 1976 [9]. However, due to the inadequate technical conditions at that time, this circRNA was once dismissed as a

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product of exon splicing errors. CircRNA is an endogenous short ncRNA with a closed-loop shape that originates primarily from gene exons [10]. Compared with linear mRNA, circRNA lacks an uncovered 5′ end cap and 3′-polyadenylate terminal structure, resulting in its less susceptible to nucleic acid exonuclease. Many species and types of human cells contain circRNAs, which exhibit plurality, evolutionary conservation, stability, and particularity. CircRNAs were found to be involved in multiple biological processes by acting as competitive endogenous RNAs (ceRNAs) to counteract the effects of miRNAs [11]. In recent years, the role of circRNA in regulating transcription or chelating proteins has been gradually recognized and concerned. CircRNAs also play essential roles in the pathogenesis and expansion of breast cancer. For example, circUBR1 was up-regulated in BC, which can trigger BC cell proliferation and metastasis [12]. Silencing it delayed BC tumor growth in vivo, boosted apoptosis, and reduced BC cell proliferation and metastasis in vitro. Circ_0003645's expression was considerably amplified in both breast cancer cell lines and tissues [13]. Elimination of circ_0003645 hindered the growth of breast cancer cells, leading to their programmed cell death. Circ_0003645 had a positive effect on HMGB1 and facilitated the growth of breast cancer cells by attaching miR-139-3p.

Early detection and prompt treatment can significantly reduce breast cancer mortality rates. However, early-stage breast cancer often does not present obvious symptoms and indications. Hence, women tend to neglect the clinical examination of breast cancer, resulting in breast cancer still being diagnosed at a later stage [14]. As a result, early detection of breast cancer is essential for effective therapy [15]. Circular RNAs have been identified to be differentially expressed in the initial stages of breast cancer, which can act as sponges for miRNAs to affect mRNA expression, contributing to the breast cancer development [16]. Therefore, it is hypothesized that circRNA may serve as a potential diagnostic marker and novel therapeutic approach for early-stage breast cancer.

In the following, we will focus on introducing the main functions of circRNAs and their roles in breast cancer cell proliferation, invasion, metastasis, and drug resistance. In addition, the potential of circRNAs as diagnostic and prognostic markers for breast cancer will also be highlighted.

Introduction of CircRNA

Biogenesis of circRNA

Initially, it was believed that circRNA was generated through the incorrect splicing of exons [17]. With the development of bioinformatics and the maturity of RNA sequencing technology, an increasing number of circRNAs have been discovered in various biological cells [18]. Non-coding RNA of a particular kind called circRNA is commonly expressed in eukaryotic cells. However, unlike the structure of ordinary long non-coding RNA, the circRNA molecule exhibits a covalent bond between its 3′ and 5′ end, resulting in the formation of a covalently closed loop. The absence of a 3′ and 5′ terminus renders it impervious to be digested by RNAase, thereby ensuring its stability in vivo [19]. CircRNAs are spliced in reverse from their mRNA precursors (pre-mRNA). CircRNAs are expressed at low levels in cells [20], but their expression levels appear time and tissue specificity. CircRNAs can be categorized into three subclasses: exon circRNAs (EcRNAs), intron circRNAs (ciRNAs), and exon–intron circRNAs (EIciRNAs), based on their various locations and formation mechanisms [21, 22]. The lasso-driven cyclization model of exon jumping and the intron pairing-driven cyclization model are two hypotheses currently available to explain how exon circular RNAs are generated [23].

As is illustrated in Fig. 1, the lasso-driven cyclization model of exon-skipping begins with the classical splicing of upstream and downstream exons via 3′ and 5′ covalent binding, forming an RNA lasso with exon and intron. Subsequently, the intron breaks down and the exon splices back into exon circRNA [24]. The pairing of complementary sequences on introns outside of the upstream and downstream exons in the intron pairing-driven cyclization model brings the splicing sites near to each other, thereby facilitating the formation of reverse splicing (Fig. 1) [25]. Inverted repeat Alu pairs (IRAlus) were found in the introns upstream and downstream of the ring exon. Its pairing makes the splicing sites outside the upstream and downstream exon to be in a closer position, prompting the formation of reverse splicing. The formation of circular RNA could be facilitated by IRAlus pairing or other complementary sequences [26]. Exon–intron RNA (EIciRNA) is produced by a direct cyclization splicing process after lasso generation without intron degradation [27]. Intron circRNA (ciRNA) is created when introns are partially degraded and then cyclized after lasso formation [28, 29].

Further investigation has revealed that circRNAs have significant impacts on a range of diseases, including the emergence and progression of tumors [30]. CircRNAs have a wide range of biological functions, most commonly as a miRNA sponge that regulates gene expression to mediate the occurrence and development of cancer [31]. Some circRNAs contain miRNA binding regions, which may function as ceRNAs to block miRNAs, thus boosting the expression of the target gene [32]. The circRNA/miRNA/mRNA regulator axis, which resulted from the adsorption of miRNAs by circRNAs, liberated the target mRNA from functional inhibition [33]. Hansen et al. discovered that CIRS-7 was a special sponge for miR-7 that inhibited the production of multiple oncogenes controlled by miR-7 [34].

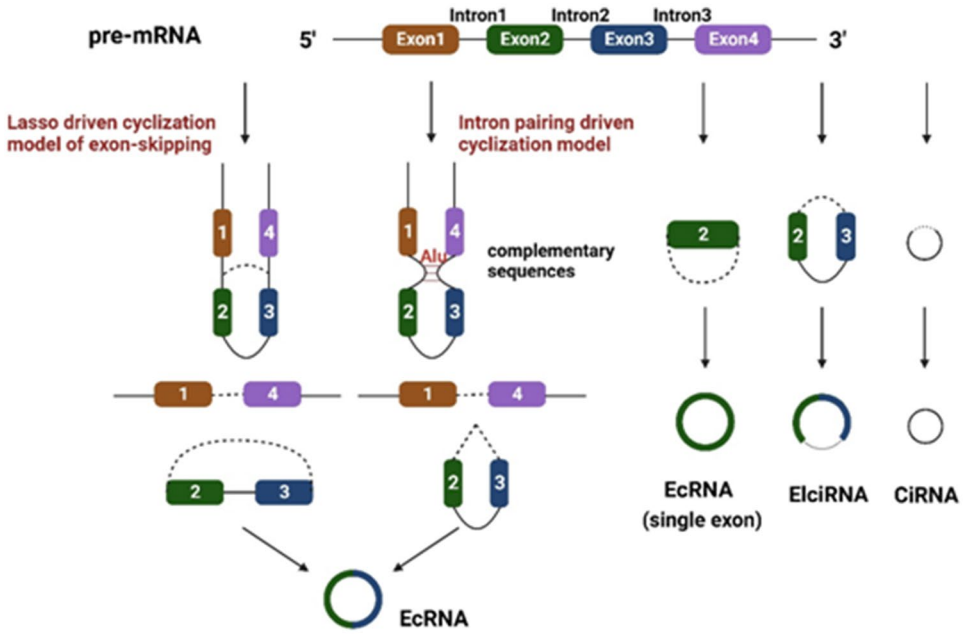

Fig. 1 In the biogenesis of circRNA, Exonic circRNAs (EcRNAs) are created by back-splicing, which can involve either one or several exons. The lasso-driven cyclization model of exon jumping, and the intron pairing-driven cyclization model, are the other two methods for creating ecRNAs. It is the predominant circRNAs form. Exon–intron circRNAs (EIciRNAs) are primarily found in the nucleus and preserve their intronic sequences between the circularized exons. Intronic lariat precursors escape from the debranching stage of conventional linear splicing to become intronic circRNAs (ciRNAs), which are prevalent in the nucleus

In recent years, the role of circRNA and related proteins in controlling protein expression in cancer progression has also been extensively investigated [35]. CircRNAs may adhere to various RNA-binding proteins (RBPs) to perform various functions, including suppressing protein activity, promoting the creation of protein complexes, and enabling cooperation among various proteins [36]. For example, circRNA MBL contains the conserved protein binding sites of muscle blindness (MBL), and the expression levels of MBL strongly influenced circMbl biosynthesis [37]. CircRNA can also regulate gene transcription and influence physiological and pathological processes [38]. CircITCH regulated the expression of ITCH and impeded breast cancer progression by adsorbing miR-214 and miR17 like a sponge [39]. Investigations of circRNA at a translational level uncovered the concealed proteomes and their therapeutic implications for human health [40]. The interaction between circSCRIB and the pre-mRNA of SCRIB hindered the splicing and translation of SCRIB, thus facilitating the advancement of breast cancer [41]. In the last few years, the impact of circRNA on breast cancer has become increasingly well-documented and researched [30].

The main function of circRNA

The ceRNA notion was first proposed by Salmena et al. [32]. They considered that a single miRNA may control various target genes, while the same target gene may be controlled by several different miRNAs. Because of their competitive connection and regulation by the same miRNA, these RNAs are known as ceRNAs. CircRNAs are competitive endogenous RNAs that control a variety of procedures in biology, including the expression of human genes, the growth and spread of cancer, and many other biological processes (Fig. 2A) [42, 43]. For instance, circDDX21 slowed the progression of triple-negative breast cancer (TNBC) by adsorbing miR-1264 as a sponge to regulate the expression of QKI [44]. Circ_0039960 specifically targeted miR-1178 to up-regulate PRMT7 expression, which helped BC cell grow [45]. Numerous disorders have been demonstrated to be influenced by the circRNA/miRNA/mRNA axis [46, 47].

Additionally, circRNA can serve as an RBP sponge. A number of biological functions depend on RNA–protein complexes (RPCs), which are created when circRNAs bind to RBPs [48]. RBPs were responsible for the generation of circRNAs and the regulation of gene expression in transcriptional and post-transcriptional level [49]. For example, RBPs are involved in RNA alternative splicing, which had an impact on the transcription of linear parent genes and controlled the production of affiliated proteins, which were crucial for the development of tumors [50, 51]. CircACTN4 derived from exons 2 to 7 of ACTN4 could interact with far upstream element binding protein 1 (FUBP1) to inhibit the connection between FUBP1 and FIR. Consequently, MYC transcription was triggered to facilitate the emergence and advancement of breast cancer (Fig. 2B) [52]. Circ-Foxo3 was able to attach to several proteins and cooperate with CDK2 and p21 to block the cell cycle and prevent the transition from the G1 stage to the S stage [53]. CircFoxo3 was also found to be able to promote cardiac senescence through binding to as well as inhibiting anti-aging-related proteins (ID1 and E2F1) and anti-stress-related proteins (HIF1a and FAK) in the cytoplasm [54].

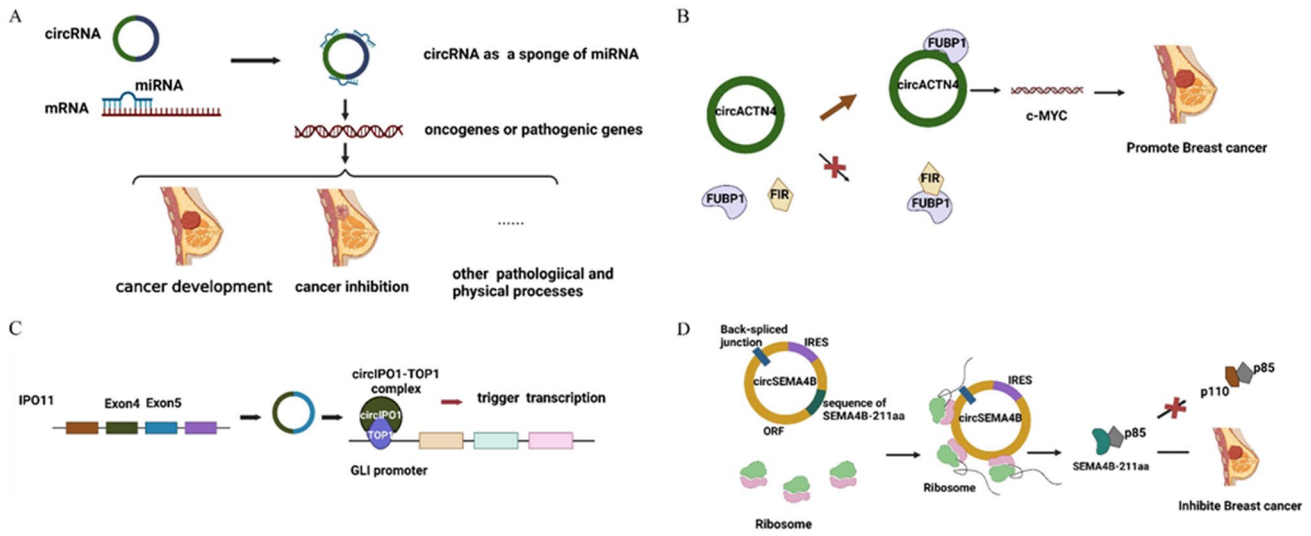

Fig. 2 **A** CircRNA is a miRNA sponge that indirectly controls mRNA expression and a number of biological processes, including the emergence and advancement of breast cancer. **B** By binding circACTN4 to FUBP1, the interaction between FUBP1 and FIR is hindered, leading to the regulation of breast cancer progression. **C** CircIPO11 binds TOP1 to form the CirciPO11-Top1 complex and recruits it to the GLI promoter to trigger its transcription. **D** circSEMA4B containing IRES can translate the producing protein SEMA4B-211aa in the open reading frame (ORF)

CircRNA can also control gene transcription through a variety of methods. CircRNA can manipulate parental genes through the ceRNA mechanism. As an illustration, circGFRA1 might function as a miR-34a sponge to control the production of GFRA1 [55], the parental mRNA, leading to the stimulation of BC cell proliferation and apoptosis blockage. CircIPO11, derived from the IPO11 gene transcript and composed of exons 4 and 5 of the IPO11 gene, recruited TOP1 to the GLI1 (GLI family zinc finger 1) promoter, triggering its transcription and thereby activating the hedgehog signal (Fig. 2C) [56].

For a long time, circRNA has been studied as a non-coding RNA. As a result, its capacity to be translated into proteins has been disregarded. Up until 2017, Legnini et al.'s discovery that circZNF609 could be translated to protein in mouse muscle cells in both a splicing-dependent and a cap-independent way suggested that other eukaryotic circRNAs may encode protein as well [57]. The SEMA4B-211aa protein was translated from an internal ribosome entry site (IRES) sequence of circSEMA4B in a 5′-cap-independent manner. The binding of SEMA4B-211aa to p85 hindered the synthesis of PIP3 and the phosphorylation of AKT, thereby impeding the advancement of breast cancer (Fig. 2D) [58]. By controlling the homeostasis of C-Myc protein, the protein FBXW7 produced by circFBXW7 impeded the onset and progression of glioblastoma [59].

Roles of circRNA in breast cancer

As a new class of epigenetic regulator, circRNA is receiving more and more attention in the process of BC tumor growth, metastasis, chemotherapy resistance, etc. CircRNAs associated with breast cancer mentioned in this paper are listed in Table 1. Because circRNAs have a large number of miRNA binding sites, they can adsorb miRNAs like sponges and prevent them from attaching to target genes, thus affecting tumor formation.

CircRNA is involved in breast cancer development and cell proliferation

Some circRNAs feature miRNA binding sites and can function as ceRNAs to suppress the production of miRNA and increase the production of the target genes [32]. As a result, circRNA can operate as a miRNA sponge to control gene expression, thereby influencing the emergence and advancement of cancer. For instance, P21, a mitosis regulator, could attach to the CDK1/cyclinB1 and prevent CDK1 from activating, hence preventing the growth and proliferation of G2/M breast cancer cells [60]. The low expression of circDDX17 in breast cancer cell lines and tissues [61] was linked to poor long-term survival of

Table 1 CircRNAs associated with breast cancer mentioned in this paper

circRNA	Cell line name/animal model/clinical sample	Target miRNA	Target genes of miRNA (s)	Function	Reference
circ-UBR1	T47D, MCF-7, MCF-10A/BALB/c nude mice/30 pairs BC tumor tissues (BC) and adjacent normal tissues (Normal)	miR-1299	CCND1	Promote the proliferation, metastasis, and inhibit apoptosis of BC cells; as a potential prognostic marker and therapeutic target for BC	[12]
circ_0003645	T47D, MCF-7, BT549, MDA-MB-231,Hs-578T;MCF-10A and MCF-12A/45 pairs breast tumor tissues and adjacent breast tissues	miR-139-3p	HMGB1	Promote the proliferation of breast cancer cells	[13]
circITCH	MCF-10A, MCF-7, T47D, SK-BR-3, MDA-MB-231, and BT -549/Female BALB/c nude mice (4–6 weeks old)/275 breast cancer (52 Luminal A, 87 Luminal B, 45 HER-2+, 91 TNBC) and 68 adjacent normal tissues	miR-214; miR-17	ITCH	Inhibit TNBC proliferation, invasion, and metastasis both in vitro and in vivo; a tumor suppressor and a promising prognostic biomarker in TNBC	[39]
circSCRIB	Skbr-3,MDA-MB231, HTB126, Skbr3, MCF-7, BT20, MDA-MB468, and ZR75	–	SCRIB	Promote the progression of BC	[41]
circ_0000514	MCF-7 (ER+/HER2−), BT-474 (ER+/HER2+)/56 pairs BC tissues and adjacent tissue samples of BC patients undergoing tumor resection	miR-296-5p	CXCL10	Promote the proliferation and invasion of BC cells	[42]
circDDX21	MCF7, T47D, SK-BR3, BT474, MDA-MB-231, SUM1315, BT549, MCF10A, 4T1 and E0771 /BALB/c mice (5-week-old)/66 TNBC specimens and paired non-tumour breast specimens	miR-1264	QKI	Inhibit the progression of triple-negative breast cancer (TNBC)	[44]
circ_0039960	BT20, MCF-7, MDA-MB-231, SK-BR-3, MCF-10A/BC patients without receiving any kind of surgery or chemotherapy before	miR-1178	PRMT7	Promote the growth of breast cancer cells	[45]
circACTN4	MCF-7, SK-BR-3, ZR-75-1, BT-474, T-47D, MCF-10A/Female BALB/c nude mice (4-week-old)/80 breast cancer patients without receiving preoperative chemotherapy or radiotherapy	–	–	Promote tumorigenesis and progression of BC	[52]
circGFRA1	SKBR3, T47D, BT474, MCF-7, BT-483, BT-20, BT549, MDA-MB-468, MDA-MB-231, MCF10A and 184A1/Female BALB/c nude mice (4-week-old)/Tumor and paired adjacent normal mammal tissues from TNBC patients	miR-34a	GFRA1	Promote the proliferation of TNBC and inhibit apoptosis	[55]
circSEMA4B	MDA-MB-231, HCC-1937, BT549, MCF-7, SKBR3, MCF-10A/Athymic nude mice (4-week-old)/Tumor tissues and adjacent normal tissues of 110 BC patients	–	–	Inhibit the progression of BC	[58]
circDDX17	MCF-7, MCF-10A, BT474, BT549, HCC2218, HBL-100/Breast cancer tissues and adjacent normal tissues	miR-605	CDK1; p21	Inhibit the proliferation and colony formation and promote apoptosis of BC cells; as a potential prognostic marker and therapeutic target for BC	[61]
circ_103809	sum-1315, MCF7, MDA-MB-231, and MCF10A/Nude mice (6-week-old)/55 pairs BC tissues and adjacent tissues	–	–	Promote the progression of BC	[62]

Table 1 (continued)

circRNA	Cell line name/animal model/clinical sample	Target miRNA	Target genes of miRNA (s)	Function	Reference
circ_0000526	MDA-MB-231, MCF-7, ZR751,MCF-10A/40 pairs BC tissues and adjacent tissues	miR-492	SOCS2	Promote the proliferation and migration of BC cells and inhibit apoptosis	[63]
circ_001569	MCF-7, MDA-MB-468, MDAMB-231, MDA-MB-453, MCF-10A/145 patients underwent breast cancer-associated surgeries without receiving antitumor treatment before surgery	–	–	Promote the progression of BC	[64]
circPTK2	BT-549, SUM-159, MDA-MB-231, MDA-MB-453, MDA-MB-468, MCF-10A/45 pairs BC tissues and paracancerous normal tissues without receiving local or systemic treatment before surgery	miR-136	NFBI	Promote the proliferation, migration, and invasion of TNBC cells; as a potential prognostic marker and therapeutic target for TNBC	[65]
circ_0005273	MDA-MB-231, MCF-7, HCC-1937, SKBR3, MDA-MB-231, MCF-7, HCC-1937, SKBR3, MCF-10A/Athymic nude mice (4–6 weeks old)/120 BC tissues and their adjacent normal tissues of BC patients	miR-200a-3p	YAP1	Promote the proliferation and migration of BC cells	[66]
circRNF20	MCF-7, MDA-MB-468, MDA-MB-231, MDA-MB-453, MCF-10A/Male nude mice (4–5 weeks old)/55 pairs BC tissue specimens and adjacent normal tissue without administrating chemotherapy or radiotherapy before surgical excision	miR-487a	HIF-1α	Promote the proliferation of BC cells	[67]
circZFR	MCF-7, MDA-MB-231, BT-549, T-47D, MCF-10A/Female nude mice (4-week-old)/50 pairs BC tissues and adjacent normal tissues	miR-223-3p	FABP7	Promote the proliferation, migration, invasion, and EMT of BC cells and inhibit apoptosis of BC cells	[68]
circNR3C2	MCF-7, T-47D, BT474, MDA-MB-231, BT549/Female BALB/C nude mice (6-week old)/10 cases of BC samples with each 5 of Luminal or TNBC	miR-513a-3p	HRD1	Inhibit the proliferation, migration, invasion, and EMT of breast cancer cells; as a potential prognostic marker and therapeutic target for BC	[70]
circ_0047604	MDA-MB-231, MCF-7, MCF-10A/Tumor and their adjacent normal tissues from BC patients without any treatment before surgery	miR-548o	DACH1	Inhibit the proliferation and migration of BC cells; as a potential prognostic marker and therapeutic target for BC	[71]
circANKS1B	MCF-7, T47D, SK-BR-3, MDA-MB-231, MDA-MB-468, BT549, MCF-10A/Female BALB/c nude mice/23 pairs fresh frozen TNBC and adjacent normal tissues,165 formalin-fixed, paraffin-embedded (FFPE) BC tissues, and 40 normal tissues	miR-148a-3p; miR-152-3p	USF1	Promote the EMT, invasion, and migration of BC in vitro and in vivo	[72]
circ_0089153	T47D, MCF-7, BT549, and MDA-MB-231, MCF-10A/Female BALB/c-nude mice (4–5 weeks old)/90 pairs tumor/adjacent normal tissues from BCa patients undergoing surgery	miR-2467-3p	E2F6	Promote the proliferation, migration, invasion, and EMT of BC cells	[73]
circ_0001955	MDA-MB-453, SKBR3, MCF-10A/Female BALB/c-nude mice (6-week-old)/51 pairs BC tissues and adjacent normal tissues of BC patients undergoing surgery	miR-1299	GLUT1	Promote the proliferation, migration, and invasion of BC cells	[74]

Table 1 (continued)

circRNA	Cell line name/animal model/clinical sample	Target miRNA	Target genes of miRNA (s)	Function	Reference
circCD44	Hs578T, BT-549, MDA-MB-468, MDA-MB-231, MCF-10A/Female BALB/c nude mice (4-week-old)/All samples were obtained from the Department of Breast	miR-502-5p	KRAS	Promote the tumorigenesis, cell migration, and invasion of BC; as a potential prognostic marker and therapeutic target of BC	[75]
circHIPK3	MCF7, SK-BR-3, BT549, BT20, MDA-MB-231, MDA-MB-453, MCF-10A/48 pairs BCa tissues and adjacent tissues (ANT)	miR-326	SOX12	Promote the proliferation, migration, invasion, and EMT of BC cells	[76]
circ_0000511	MCF-7, SK-BR-3, MDA-MB-231, MDA-MB-468, MCF-10A/Female BALB/c nude mice (4-week-old)/50 pairs BC tissue specimens and adjacent normal tissue specimens (5 cm from tumor tissues)	miR-326	TAZ	Promote the proliferation, migration, and invasion of BC cells, and inhibit apoptosis of BC cells; as a potential prognostic marker and therapeutic target for BC	[77]
circ_0000518	BT549, MDA-MB-231, MDA-MB-468, MDA-MB-453, MCF-10A/Specimens of tumor tissues and paracancerous tissues of 43 BC patients without undergoing preoperative anti-cancer treatment	miR-1225-3p	SOX4	Promote the growth, infiltration, and migration of BC cells	[78]
circ_0001667	MCF-7, MDA-MB-231, MCF-7/ADM, MDA-MB-231/ADM)/Female BALB/c mice (6–8 weeks old)/61 pairs BC tissues and normal tissues of BC patients who were diagnosed and received therapy received ADM-based chemotherapy before the surgical operation	miR-4458	NCOA3	Promote the resistance of BC cells to ADM	[79]
circ_0092276	MCF-7, MDA-MB-468, MCF-7/DOX, MDA-MB-468/DOX/Male BALB/c nude mice (4–6 weeks old)	miR-384	ATG7	Promote the apoptosis of BC cells and the resistance to ADM	[80]
circUBE2D2	BT-549, SUM-159, MDA-MB-231, MDA-MB-468, HCC38, MCF-10A/Female BALB/c nude mice (5-week-old)/66 pairs BC tissues and paracancerous tissues of patients without receiving local or systemic treatment before surgery	miR-512-3p	CDCA3	Promote the progression of TNBC and the resistance to ADM	[81]
circ_0025202	MCF7, T47D/Female BALB/c nude mice (5-week-old)/230 BC tissues and 44 adjacent breast tissues of patients receiving surgical treatment	miR-182-5p	FOXO3a	Promote the apoptosis and sensitivity to TAM	[82]
circ_0025202	T47D, MCF7, MCF-10A/Female BALB/c nude mice (5 weeks old)/32 BC tissues, and matched normal tissues	miR-197-3p	HIPK3	Enhance the resistance to TAM and promote BC cell proliferation	[83]
circUBE2D2	MCF-7, T47D/Female BALB/c nude mice (5 weeks old)/BC tissues of 54 patients undergoing surgical resection	miR-200a-3p	–	Enhance the resistance to TAM in BC	[84]
circ_0006528	MCF10A, BT-549, and ZR-75-30/Male BALB/c nude mice (4 weeks old)/Tumor tissues and corresponding normal tissues of 48 BC patients (33 PTX-chemosensitive patients and 15 PTX-chemoresistance patients)	miR-1299	CDK8	Promote the proliferation, migration, invasion, and autophagy of PTX-resistant BC cells and inhibit apoptosis	[85]

Table 1 (continued)

circRNA	Cell line name/animal model/clinical sample	Target miRNA	Target genes of miRNA (s)	Function	Reference
circHIPK3	MDA-MB-231, MCF-7 BC, MDA-MB-231/PTX, MCF-7/PTX)/Female BALB/c nude mice (5-week-old)/76 clinical specimens, including 13 PTX-sensitive BC tissues, 25 PTX-resistant BC tissues, and 38 adjacent normal BC samples	miR-1286	HK2	Promote the invasion and autophagy of BC cells and resistance to PTX	[86]
circABCB10	MDA-MB-468, MDA-MB-453, MCF-7, MDA-MB-231, MCF-10A/BALB/c nude mice/30 PTX-sensitive BC patients or 30 PTX-resistant BC patients	Let-7a-5p	DUSP7	Promote the invasion and autophagy of BC cells and resistance to PTX	[87]
circRNF111	MCF-7, MDA-MB-231, MCF-10A, MCF-7/PTX, MDA-MB-231/PTX/BALB/c nude mice (6-week-old)/30 PTX-resistant BC patients and 30 PTX-sensitive BC patients	miR-140-5p	E2F3	Promote the resistance to PTX in BC	[88]
circMMP11	MDA-MB-231, MCF-7, MCF-10A/Female BALB/C nude mice (3–4 weeks old)/27 drug-resistant patients and 21 drug-sensitive patients of advanced BC after treatment with lapatinib-based molecular targeted therapy, followed by the collection of tissue samples	miR-153-3p	ANLN	Promote the resistance of BC cells to lapatinib	[89]
circ_0007874	MDA-MB-231, MCF-7, MDA-MB-453, SKBR-3, T47D, MDA-MB-468	–	–	Inhibit BC cell viability and promote monastrol-induced cytotoxicity	[90]
circ_0103552	BT-20, T47D, MFC-7, SKBR-3,MDA-MB-231, MCF-10A/57 pairs BC and nontumor tissues of BC patients	miR-1236	–	As a potential prognostic marker and therapeutic target for BC	[92]
circCDYL	mCherry-GFP-LC3-labeled MDA-MB-231/Female BALB/c nude mice (4-week-old)/3 independent cohorts of BC patients	miR-1275	ATG7; ULK1	As a potential prognostic marker and therapeutic target for BC	[93]
circ_0069094	MCF-7, MDA-MB-231, MDA-MB-468, T47D, MCF-10A/Female BALB/c nude mice (4–6 weeks)/Tissue specimens of 60 BC patients who were diagnosed at stage I, II, or III and underwent radical surgery	miR-59	HK2	As a potential prognostic marker and therapeutic target for BC	[94]
circYY1	MCF7, BT549, MDA-MB-231, MDA-MB-468, T47D, MCF10A/Female BALB/c nude mice (4–6 weeks)/70 BC tissues and matched neighboring normal tissues of BC patients without receiving radiotherapy, chemotherapy, or other anti-tumor therapies and undergoing BC surgery	miR-769-3p	YY1	As a potential prognostic marker and therapeutic target for BC	[95]
circUBAP2	T47D, BT-20, SK-BR-3, MCF-7, MCF-10A, MDA-MB-468, and MDA-MB-231/Female BALB/c nude mice/78 pairs of TNBC and normal specimens	miRNA-661	MTA1	As a potential prognostic marker and therapeutic target for BC	[96]
circSEPT9	MDA-MB-231, BT-549, MDA-MB-468, MDA-MB-453, SUM-159, MCF-10A/Female BALB/c nude mice(4-week-old)/The TNBC tissues and paracancerous tissues of TNBC patients undergoing surgical resection	miR-637	LIF	As a potential prognostic marker and therapeutic target for BC	[97]

Table 1 (continued)

circRNA	Cell line name/animal model/clinical sample	Target miRNA	Target genes of miRNA (s)	Function	Reference
circGNB1	MCF-10A, MDA-MB-231, BT549, HCC1806, HCC38, MCF-7, T47D, BT474, SKBR-3, and MDA-MB-361/ Female BALB/c nude mice/Fresh breast cancer samples	miR-141-5p	IGF1R	As a potential prognostic marker and therapeutic target for BC	[98]
circIFI30	MDA-MB-231, MDA-MB-468, BT-549, MCF-10A/Female BALB/c mice (4–6 weeks old) /38 pairs samples of TNBC tissues and adjacent normal tissues	miR-520b-3p	CD44	As a potential prognostic marker and therapeutic target for BC	[99]
circKIF4A	MCF-7, T47D, BT474, SKBR3, MCF10A, MDA-MB-453, MDA-MB-468, MDA-MB-231, BT549 and HCC38/ Female BALB/c nude mice (4-week-old)	miR-375	KIF4A	As a potential prognostic marker and therapeutic target for TNBC	[100]
circBMPR2	MCF-7, MDA-MB-231, MDA-MB-468, T47D, SKBR3, ZR-75-1/Tumor tissues, and paired adjacent non-tumorous tissues of BC patients receiving treatment	miR-553	USP4	As a potential prognostic marker and therapeutic target for BC	[101]
circ_0006220	BT-549, MDA-MB-231, MDA-MB-468, SK-BR-3, T47D, MCF-7, MCF-10A/57 primary female BC patients receiving treatment	miR-197-5p	CDH19	As a potential prognostic marker and therapeutic target for BC	[102]

breast cancer patients. CircDDX17 controlled cyclization factors (CDK1 and P21) by sponging miR-605, which in turn promoted apoptosis and reduced cell proliferation. Circ_103809 prevented breast cancer cell lines from reproducing. By disrupting the EMT signal cascade, low expression of circRNA_103809 could impede the G2/M phase and reduce the growth and spread of BC cells [62]. The amplification of circ_0000526 drastically reduced miR-492 production and increased the production of suppressor of cytokine signaling 2 (SOCS2) through the sponge effect, thereby preventing the proliferation and metastasis of breast cancer cells and encouraging cell death [63]. Circ_001569 expression was significantly up-regulated in BC tissues and cell lines [64]. The elevated expression of circ_001569 was associated with lymph node metastases, increased clinical stage, and decreased overall lifespan. It promoted BC progression through PI3K-AKT pathway. CircUBR1 was also up-regulated in BC [12]. Blocking circUBR1 expression prevented BC tumor growth in vivo, induced apoptosis in vitro, and reduced BC cell proliferation and metastasis. The dual-luciferase reporter gene assay confirmed that circUBR1, potentially acting as a miR-1299 substrate, stimulated the synthesis of its target Cyclin D1 (CCND1) and enhanced the proliferation and metastasis of BC cells. A high-throughput microarray of circRNAs and qRT-PCR research revealed that circGFRA1, derived from the GFRA1 gene, was significantly increased in breast cancer [55], while increased expression of circGFRA1 was associated with a decreased overall survival. CircGFRA1 up-regulated the expression of GFRA1 by adsorbing miR-34a to promote breast cancer cell proliferation and inhibit apoptosis. Silencing circGFRA1 inhibited proliferation and promoted apoptosis by releasing more miR-34a to down-regulate GFRA1 expression in BC. In BC tissues and cell lines, circPTK2 expression was increased [65]. By sponging miR-136 to modulate NFBI and AKT/PI3K pathway, it could dramatically promote the growth, spread, and invasion of TNBC cells. Elevated levels of circ_0005273 in breast cancer cells up-regulated the expression of YAPl (yes-associated protein1) through the adsorption of miR-200a-3p, and then inactivated the Hippo-YAP1 signaling route, which contributes to breast cancer cell multiplication and migration [66]. Besides, the reduction of circ_0005273 inhibited BC cell expansion, migration, cell cycle, and tumor formation in vivo.

The Warburg effect, also known as aerobic glycolysis, is a unique pattern of cell metabolism in cancer cells that shows an escalating rate of glucose uptake and lactic acid fermentation in an aerobic environment. Unlike normal cells, which undergo both oxidative phosphorylation and glycolysis, cancer cells tend to undergo glycolysis in both an anoxic and aerobic microenvironment. CircRNF20 was elevated in BC tissues and cells and served as a sponge for miR-487a,

which targeted hypoxia-inducible factor-1 (HIF-1) in BC cells. HIF-1 was a transcription factor targeting the promoter of hexokinase II (HK2) to speed up transcription and promote glycolysis in BC cells. Consequently, circRNF20 could stimulate the proliferation of BC cells by means of Warburg effect (aerobic glycolysis) [67]. In contrast to nearby tissues, Li et al. discovered that circ_0000514 was increased in BC tissues [42]. They found that circ_0000514 could increase the expression of CXCL10 by sponging miR-296-5p to promote BC cell invasion and proliferation. Targeting miR-223-3p, circZFR enhanced the production level of FABP7 in breast cancer, boosting the growth, migration, invasion, and EMT of BC cells while blocking apoptosis [68]. Inhibiting circZFR significantly impeded the growth of tumor cells.

CircRNA is involved in breast cancer invasion and metastasis

One of the major causes of death in breast cancer is metastasis. Breast cancer cell metastasis relies on a mechanism known as epithelial–mesenchymal transformation (EMT), and it was reported that circRNA participated in this process [69]. CircNR3C2 was significantly reduced in BC and was inversely correlated with distant metastasis and mortality in invasive breast cancer [70]. By serving as miR-513a-3p's sponge, circNR3C2 increased the levels of E3 ubiquitin-ligase HRD1. This hindered the expansion, migration, invasion, and EMT of breast cancer cells by generalizing Vimentin and inducing its degradation through the proteasome. Through sponging miR-548o, circ_0047604 directly targeted DACH1 in breast cancer cells, thus preventing the growth and spread of tumor cells [71].

miR-148a-3p and miR-152-3p could be adsorbed by circANKS1B, boosting the production of the transcription element USF1, which then raised the transcription of TGF-1, triggering the TGF-1/Smad signal and encouraging EMT [72]. Circ_0089153 was highly expressed in BC tissues. It increased the expression of E2F6 by serving as the miR-2467-3p sponge to stimulate BC cell growth, migration, invasion, and EMT [73]. Circ_0001955 was also found to be up-regulated in breast cancer cells. It increased the generation of GLUT1 by enhancing miR-1299 and supported angiogenesis, migration, invasion, survival, and glycolytic metabolism in BC cells [74].

Elevated circCD44 expression in BC cells was negatively correlated with patient prognosis [75]. As a competitive endogenous RNA, circCD44 inhibited miR-502-5p-mediated KRAS degradation by directly attaching to miR-502-5p. Additionally, it could also bind to IGF2BP2 in TNBCs to maintain the stability of Myc mRNA, thus promoting the breast cancer cell's spread, invasion and tumorigenesis. CircHIPK3 was highly expressed in BC cytoplasm, which specifically targeted miR-326 [76]. Down-regulation of circHIPK3 dramatically reduced BC cell proliferation, migration, invasion, and EMT. Endogenous expression of miR-326 partly counteracted the impacts of circHIPK3 on apoptosis and EMT-related proteins.

By targeting miR-326, circ_0000511 controlled the expression of TAZ in BC cells, thus promoting the expansion, migration, and invasion of BC, while inhibiting BC cell death [77]. Circ_0000518 could adsorb endogenous miR-1225-3p and block its biological activity. MiR-1225-3p was able to increase the expression of SOX4 mRNA, thereby promoting the growth, infiltration, and migration of BC cells [78].

CircRNA is involved in chemotherapy resistance

CircRNAs were found to be expressed in chemotherapy-resistant breast cancer, suggesting that circRNAs may be involved in promoting or reversing chemotherapy resistance in BC cells. Medication resistance-associated circRNAs are promising diagnostic and therapeutic indicators that may improve the clinical management of BC by boosting chemotherapy sensitivity, predicting the efficacy of chemotherapeutic agents in resistant populations, and so on. The most commonly reported drugs associated with circRNAs in recent chemotherapy for BC patients are adriamycin (ADM), tamoxifen (TAM), and paclitaxel (PTX).

BC cells that exhibited resistance to ADM displayed a robust expression of circ_0001667 [79]. The target of circ_0001667, miR-4458, had decreased levels in ADM-resistant carcinoma tissues and cells. Knockdown of circ_0001667 reduced the production of NCOA3 by releasing miR-4458, resulting in a significant decrease in the growth, migration, invasion, and ADM resistance of MCF-7/ADM and MDA-MB-231−/− ADM cells. Circ_0092276 up-regulated ATG7 expression by adsorbing miR-384, thereby enhancing the autophagy of BC cells, augmenting the resistance of MCF-7 and MDA-MB-468 cells to adriamycin (ADM), and preventing apoptosis [80]. In patients with TNBC, elevated circUBE2D2 expression was strongly correlated with progressed TNM staging, lymph node metastases, and worsened prognosis [81]. CircUBE2D2 could protect CDCA3 by working as a miR-512-3p sponge to accelerate the development of BC and adriamycin resistance. The chemo tolerance to ADM in BC cells was decreased by circUBE2D2 knockdown, which also inhibited cell growth, migration, and invasion.

In TAM-resistant BC cells, the expression of circ_0025202 was dramatically reduced [82]. Circ_0025202 could function as a sponge for miR-182-5p, hindering cell proliferation, colony formation, and migration, while also enhancing cell apoptosis and susceptibility to tamoxifen. It could also further stimulate FOXO3a, the direct target gene of miR-182-5p. Meanwhile, circ_0025202 could also

target miR-197-3p [83]. Overexpression of miR-197-3p enhanced TAM resistance and promoted the proliferation of BC cells. Circ_0025202 targeted miR-197-3p, thereby enhancing HIPK3 expression, and diminishing TAM resistance and tumorigenesis in BC cells. Both in TAM-resistant breast cancer cells and their exosomes, circUBE2D2 was significantly up-regulated [84]. By adsorbing miR-200a-3p, exosome-mediated circUBE2D2 induced tamoxifen resistance in breast cancer cells.

Circ_0006528 was highly expressed in PTX-resistant breast cancer tissues and cells, which directly targeted miR-1299 and increased CDK8 expression by sponging miR-1299 to promote the proliferation, migration and invasion of PTX-resistant breast cancer cells [85]. Silencing circHIPK3 led to paclitaxel-resistant BC cells more susceptible to treatment through the alteration of HK2 via miR-1286 [86]. In PTX-resistant BC tissues and cells, circHIPK3 expression was in a high level. CircHIPK3 specifically targeted miR-1286 to increase the expression of HK2, which therefore aided in the formation of BC tumors and decreased the susceptibility of BC cells to PTX. LeT-7A-5P/DUSP7 axis was the mechanism through which circABCB10 increased PTX resistance in breast cancer [87]. CircABCB10 knockdown increased PTX susceptibility and death while preventing invasion and autophagy in PTX-resistant BC cells. CircRNF111 levels were also elevated in paclitaxel-resistant BC tissues and cells [88]. CircRNF111 boosted the production of E2F3 by directly aiming at miR-140-5p to induce PTX resistance in breast cancer. Silencing circRNF111BC resulted in a significant decrease in PTX resistance, cell survival, invasion, colony formation, and glycolysis in BC cells.

The miR-153-3p/ANLN axis was controlled by circMMP11 to influence lapatinib resistance in breast cancer cells [89]. CircMMP11 increased the production of ANLN by functioning as a miR-153-3p sponge, causing BC cells more resistance to lapatinib. Knockdown of circMMP11 showed an increased sensitivity to lapatinib, which inhibited the survival, motility and invasion of breast cancer cells, as well as induced their apoptosis. In monastrol-resistant cell lines, circ_0007874 expression levels were down-regulated. Circ_0007874 controlled the TRAF4/Eg5 axis by acting on the Eg5 protein and preventing TRAF4 from interacting with the Eg5 gene [90], thereby reducing BC cell activity and enhancing monastrol-induced cytotoxicity.

Potential of circRNAs as diagnostic and prognostic markers

Prognostic assessment plays a crucial role in prolonging the survival rate of cancer patients. Multiple studies have suggested that circRNAs might be involved in a variety of breast cancer diseases. Circular RNAs have thus drawn further consideration as potential prognostic indicators for breast cancer [91]. CircRNAs are very common and extremely durable molecules that express themselves in particular ways depending on the stage of cell, tissue, and development. CircRNAs are well conserved across species, and resistant to RNaseR action [14]. Therefore, circRNAs have the potential to be utilized as cancer biomarkers because of their distinctive metabolic characteristics.

CircRNAs up-regulated in BC and their diagnostic and therapeutic values in BC

Breast tumors exhibit a differential expression of circRNAs. Some circRNAs have been found to be highly expressed in BC and be capable of promoting the development of BC, suggesting that they may one day be served as prognostic indicators and therapeutic targets for BC. For instance, enhanced production of circ_0103552 in BC tissue samples is associated with poor prognosis in BC patients [92]. The results of loss-of-function study on MCF7 cells and gain-of-function experiments on MDA-MB-231 cells revealed that the survival probability of MCF7 cell line was considerably reduced after silencing circ_0103552. Circ_0103552 greatly increased cell viability and metastasis of MDA-MB-231 cells, while decreased their apoptosis by sponging miR-1236. Silencing circUBR1 in BC hindered the proliferation and metastasis of BC cells, triggered apoptosis in vitro, and impeded the expansion of BC cancer in vivo [12]. By controlling TAZ expression, circ_0000511 promoted the expansion, migration, and invasion of BC cells, while inhibiting BC cell autophagy [77]. In BC patients, circCDYL expression levels in serum and tissues were markedly up-regulated, and this up-regulation was closely correlated with medical tumor staging, metastasis, and patient survival. Through adsorbing miR-1275, circCDYL controlled the production of ATG7 and ULK1, and then affected BC cell autophagy and proliferation [93]. BC patients with high circ_0069094 expression appeared a poor prognosis. Circ_0069094, as a suppressor of miR-59, increased the expression of HK2 to promote glycolysis. The increased rate of glycolysis altered the tumor microenvironment and enhanced the aggressiveness of cancer cells [94]. CircYY1 was expressed at an increased level in BC tissues and cells, and individuals with increased circYY1 expression had a poor prognosis. By adsorbing miR769-3p, circYY1 increased the production of the oncogene YY1 to support tumorigenesis and glycolysis in BC cells [95]. Therefore, up-regulation of all circRNAs mentioned heretofore, including circUBR1, circ_0000511, circCDYL, circ_0069094, and circYY1 can be used as prognostic indicators and therapeutic targets for BC.

Increased tumor size, lymph node spread, advanced TNM staging, aggressiveness of tumors, and poor prognosis were all substantially correlated with elevated levels of

circUBAP2 [96]. CircUBAP2 could increase the production of the carcinogen MTA1 by absorbing miRNA-661, promoting BC cell migration and expansion. The expression of circSEPT9 was higher in BC tissues than that in normal ones. This finding was positively correlated with a severe disease stage and a poor prognosis [97]. Knockdown of circSEPT9 had a profound impact on the spread, migration, and invasion of BC cells, causing BC cell death and autophagy, and preventing tumor growth and spread in vivo. E2F1 and EIF4A3 promoted BC malignancy and progression via the circSEPT9/miR-637/LIF axis.

In BC tissues and cell lines, circGNB1 was substantially expressed, and its expression was strongly linked with tumor volume size and TNM phase [98]. To facilitate the development of BC cells, circGNB1 elevated the production of the oncogene protein IGF1R by targeting miR-141-5p. Furthermore, a strong correlation was observed between circIFI30 and poor prognoses in BC tissues and cell lines. It might function as an absorbent for miR-520b-3p to increase the level of CD44 and hasten the EMT of BC cells and the emergence of an aggressive phenotype [99]. KIF4A has been shown to be a promising indicator of prognosis and treatment targets for cancer. CircKIF4A was highly expressed in BC and played a regulatory role in controlling BC progression by controlling KIF4A production through adsorbing miR-375 [100]. Therefore, circUBAP2, circSEPT9, circGNB1, circIFI30, and circKIF4A are all excellent candidates for targeted therapies and diagnostic and prognostic biomarkers for BC patients.

CircRNAs down-regulated in BC and their values in the treatment of BC

Some circRNAs are down-regulated in BC and prevent breast cancer from growing and progressing, suggesting that these circRNAs could be new BC therapeutic agents. For instance, BC patients with low circDDX17 expression usually had poor long-term survival [61]. By sponging miR-605, it altered the cell cyclization factors (CDK1 and P21) to reduce BC cell proliferation and increase apoptosis. By increasing the production of ubiquitin-specific protease 4 (USP4) through the absorption of miR-553 [101], circBMPR2 prevented the evolution of BC and TAM resistance. BC patients with decreased DACH1 expression had a poor survival rate [71]. By functioning as the sponge for miR-548o, circ_0047604 specifically targeted DACH1 in BC, thus preventing cancer cell proliferation and migration. Therefore, the down-regulation of circDDX17, circBMPR2, and circ_0047604 can be employed as possible prognostic indicators for BC while they could also be investigated as new treatment medicines for BC.

CircNR3C2 was considerably decreased in BC and showed an inverse linkage with the spread and death of invasive breast cancer [70]. By sponging miR-513A-3p, circNR3C2 increased HRD1 production, which in turn prevented migration, invasion and EMT progression of breast cancer cells. In the meantime, it could generalize Vimentin in breast cancer and cause its degradation through the proteasome, thereby impeding the progression of BC. The expression of circ_0006220 was significantly reduced in BC [102]. It was a miR-197-5p absorbent and effectively controlled CDH19 expression, thereby inhibiting the development of BC development. Consequently, circPTK2, circNR3C2, and circ_0006220 are considered to be promising biomarkers for the diagnosis and therapy of BC.

Although numerous circRNAs possess potential for BC diagnosis and treatment, how to utilize them clinically remains unclear, and still needs further research.

Summary and prospects

Because of their distinctive characteristics, circRNAs have garnered a lot of interest and have recently emerged as a new research hotspot. CircRNAs are important regulators of many physiological and pathological processes. They are uniquely expressed in tissues, and are expressed in different ways in both tumor and non-tumor tissues. Due to their abundance in bloodstream fluid, saliva, and exosomes, circRNAs can be used as potential diagnostic or predictive biomarkers for diseases, particularly in the emergence, progression, and prognosis of malignant tumors [103]. CircRNAs are now new options for the early identification of BC and development of prognostic indicators, owing to their aberrant expression in BC and high specificity and sensitivity in detection.

Despite the progress made in the field of circRNA, there are still numerous issues that require further investigation. Our current knowledge of circRNA is still relatively shallow compared to coding RNA, miRNAs, and lncRNAs. The biological function of most circRNAs in physiological and pathological processes and how to apply them clinically still need further research. Additionally, there is still a lack of knowledge regarding the regulatory processes and functions of BC circRNA-miRNA-mRNA regulatory system. Considering that there are multiple subtypes of breast cancer, each with different clinical treatments and disease prognosis, exploring the distinctively expressed circRNAs of each subtype and targeting them will undoubtedly become a hotspot of research in the diagnosis, treatment and prognosis of breast cancer. Target investigation and early mechanism validation are the main areas of concern in current research. Therefore, it will be important to focus on other mechanisms in-depth, combine laboratory and clinical research, and endeavor to translate experimental findings into clinical application and practice in addition to the exploration

and preliminary mechanism verification of circRNA in the future.

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