

The Potent Regulatory Role of Circular RNAs in Breast Cancer Development, Diagnosis and Treatment: An Update

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Abstract: Breast cancer (BC) is one of the most frequent malignant diseases among women worldwide. Circular RNAs (circRNAs) as a novel class of noncoding RNA (ncRNA), display unique features due to their specific circular configuration. One of the important roles of CircRNAs is the regulation of gene expression via different mechanisms, including sponging microRNAs and proteins. Moreover, evidence indicates that circRNAs act as key regulators in the initiation and progression of BC. Currently, many circRNAs have been reported to be associated with different biological processes of BC, such as cell division, migration, invasion, and programmed cell death. The aim of this review was to provide a concise overview of the biogenesis and roles of circRNAs and track the related knowledge in BC development, diagnoses and treatment.

Keywords: CircRNAs, breast cancer, progression, metastasis, therapy, resistance, biomarker.

INTRODUCTION

Breast cancer (BC) is the most commonly diagnosed and the major cause of cancer related mortality among women globally [1]. A high number new cases and deaths due to BC is estimated each year [2]. Tumor resection and preventing recurrence are considered as the main goals of therapy for nonmetastatic BC. By contrast, therapeutic strategies for metastatic BC have planned to prolong survival and control symptoms. At present, metastatic BC are considered incurable [3] and contribute to the high mortality rates of the disease. These are highly resistant to current therapies [4, 5]. Hence, it is of utmost importance to define the molecular mechanisms underlying metastasis and therapy resistance.

It has been shown that aberrant expression of regulatory non-coding RNAs (ncRNAs) such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) can contribute to the progression of BC, through various molecular mechanisms [6, 7]. Circular RNAs (circRNAs) are an emerging type of ncRNA which are generated by joining free 3'-end to 5'-end of RNA backbones and consequent formation of the circular structures [8]. CircRNAs were found out in RNA viruses over 40 years ago [9]. At first, CircRNAs were thought to be by-products of RNA splicing mechanisms [10]. Nevertheless, in 2012, Salzman *et al.* identified circRNAs as prominent spliced transcripts from hundreds of genes in normal and malignant human cells by deep sequencing of RNA [11]. Subsequently, published evidences indicate involvement of circRNAs

in the regulation of gene expression [12, 13]. Recent studies have demonstrated their regulatory roles in the pathogenesis of various cancers, including BC [14, 15].

CircRNAs are protected against the activity of exonucleases or RNase R, because they lack 5' caps and 3' poly-A tails [16] contributed to their higher stability compared with linear RNAs [17]. In consideration of the stable nature of circRNAs and their involvement in various cancer progression, they are an excellent category for biomarker investigations [17-19]. This review aimed to highlight the role, biogenesis as well as functions of circRNAs, and their related applicability as biomarkers in BC the most frequent cancer in females globally.

Circular RNAs: Biogenesis and Classification

CircRNAs are generated by a back-splicing mechanism in such a way that a downstream splice donor site (5') is reversely ligated to an upstream splice acceptor site (3'). The formation of circRNAs via back-splicing is similar to the canonical splicing of linear RNAs since canonical spliceosome machinery is required for pre-mRNA circularization (Figure 1a). Moreover, back-splicing can be adjusted by canonical splicing cis-elements and trans-acting agents [20, 21]. However, splicing regulatory elements and factors differently control the back-splicing process relative to the canonical splicing (linear) [21].

Based on recent studies, three models have been identified for the generation of circRNAs, including lariat-driven (exon-skipping), intron-pairing-driven [22], and RNA-binding protein-driven circularization [23]. In the first model, the exon-skipping event leads to the binding of the splicing donor with splicing acceptor

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covalently. Then, back-splicing occurs in exons comprising lariats to develop circRNAs (Figure 1b). In the secondary model, exon-skipping is not used and the generation of circRNA is mediated by base-pairing between reverse complementary sequences on the flanking introns [22] (Figure 1c). RNA-binding proteins (RBPs) regulate biogenesis of circRNAs (Figure 1d). For instance, the RNA binding protein Quaking (QKI) regulates circRNA biogenesis through binding to the sites flanking circRNA-forming exons. The addition of QKI binding motifs into linear RNAs lead to *de novo* circRNA formation [23]. Conversely, the double-strand RNA-editing enzyme ADAR function as an antagonist of circRNAs production by adenosine to inosine (A-to-I) editing of introns flanking circRNAs [24]. In addition, circRNAs expression is negatively associated with the expression of the enzyme ADAR1, indicating that ADAR1 can repress the biogenesis of circRNAs [24, 25]. Generally, based on the genomic region where they are derived, four distinct types could be distinguished: exonic circRNAs (ecircRNA) [26], exon-intron circRNAs (EicRNAs) [27], circular intronic RNAs (ciRNAs) [28], and intergenic circRNAs or fusion circRNAs (f-circRNAs) [29].

Exonic circRNAs

EcircRNAs are identified as the most plentiful circRNAs forms and are commonly found in the cytoplasm [22, 30]. Exonic circRNAs could contain a single exon or multiple exons [31]. Besides the above-mentioned models of the generation, some studies

proposed another model through resplicing-drive circularization, in which resplicing occurs on spliced mRNA [31] (Figure 1e).

Exon-Intron circRNAs

In some cases, formation of exon-intron circRNAs or EicRNAs occur due to circularization of exons with introns. These circRNAs mostly remain in the nucleus and augment the transcriptional process of parental genes through the interaction with U1 snRNP. In other words, these circRNAs can be involved in regulating of the gene expression in the nucleus [27].

Circular Intronic RNAs

ciRNAs as the subcategories of circRNAs are derived from introns lariats, resulting from a failure in decay and debranching. The ciRNAs are mainly found in the nucleus and have cis-regulatory role in the expression of their parental genes. The production of such ciRNAs is associated with the presence of a 7 nt GU-rich sequence near the 5' splice site and an 11 nt C-rich base in proximity of the branch point site [28].

Fusion circRNAs

Unlike other circRNAs types, fusion circRNAs (f-circRNAs) are intergenic circRNAs. They are formed by transcribed exons of different genes involved in the translocations (Figure 1f). Furthermore, Guarnerio *et al.* indicated the correlation between f-circRNAs originated from chromosomal translocations and

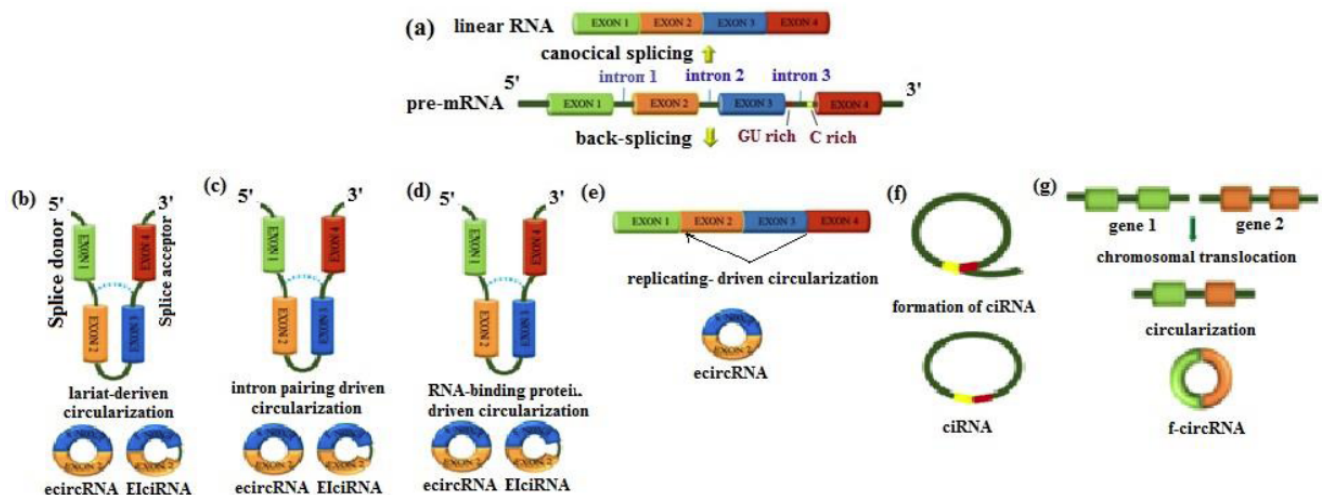


Figure 1: Biogenesis of circRNAs. (a). Linear RNA is formed by canonical splicing of pre-mRNA. (b). Lariat-driven circularization. Following exon-skipping, back-splicing process occurs in exon-consisting lariats leading to the formation of ecircRNA or EicRNA. (c). Intron-pairing-driven circularization. This model is mediated by pairing of bases with the reverse complementary sequences of flanking introns. (d). RNA-binding protein-driven circularization. RNA binding protein (RBP) binds to flanking introns and advances the process of back-splicing. (e). Resplicing-drive circularization. The ecircRNAs might be generated from mRNAs undergoing the back-splicing. (f). Formation of ciRNA. The ciRNAs are formed by intron lariats which escape from the normal intron debranching and decay. (g). Constitution of f-circRNA. Intergenic circRNAs are produced by the exons of different genes.

transformation and resistance to therapy in tumor cells [29].

General Functions of Circular RNAs

The function of circRNAs in various pathophysiological processes has been demonstrated by many studies [32]. They function via affecting various biological axes, including miRNA sponges, protein sponges, protein scaffolding, regulation of splicing and transcription, and translation.

miRNA Sponges

MicroRNAs (miRNAs) are endogenous RNAs with a length of about 23 nt that target 3'-UTR (3' untranslated regions) of mRNAs by direct base pairing, resulting in decreased mRNA stability and transcription repression. Thus, microRNAs may act as main regulators of gene expression after transcription [33]. On the other hand, miRNA activity can be affected by transcripts of miRNA sponge, known as competing endogenous RNA (ceRNA) [13, 34]. CircRNAs have been shown to act as a miRNA sponge because of the presence of miRNA-binding sites, leading to suppression of miRNA activity and increased level of target mRNAs. Consequently, circRNAs may indirectly be involved in regulation of miRNA target genes expression [13] (Figure 2a). A good example is ciRS-7 (known as CDR1as), which possesses over sixty conserved binding sites for miR-7 and functions as an inhibitor or sponge. Additionally, miR-7 can directly target several oncogenes, suggesting that CDR1as can enhance the gene expression levels of miR-7 targets and associate with various human cancers [30, 35]. Another example is Sry circRNA, which harbors 16 miRNA-binding sites for miR-138 to function as a miR-138 sponge [13]. Other investigations have also demonstrated that circPVT1 [36], circHIPK3 [37], circCCDC66 [38], and circITCH [39] can interact with miRNAs and act as a miRNA sponge.

Protein Sponges

It has been shown that some circRNAs contain sites for binding of one or several RNA-binding proteins, which might act as traps or sponges for proteins (Figure 2b). For instance, when circRNA generated from the *PABPN1* gene binds to HuR proteins, inhibits binding of HuR to *PABPN1* mRNA and lead to reduced translation of *PABPN1* [40]. Another demonstration is CircMbl, which contains binding sites for the MBL protein. The binding of MBL to introns flanking circularized exon promotes the biogenesis of circMbl

and decreases MBL mRNA levels to regulate the production of MBL protein [12].

Protein Scaffolding

CircRNAs can also function as scaffolds for proteins and thereby facilitate their interaction (Figure 2c). For example, circFoxo3, a circular RNA decreased in BC, possesses binding sites for MDM2 and P53 and enhances MDM2-mediated p53 ubiquitination and consequent decay. As a result, the expression of circFoxo3 decreases P53 protein levels [14]. Another study demonstrated circFoxo3 can be associated with CDK2 and P21 via formation of triplex complexes and arrest cell cycle progression [41]. In addition, in p53 wild-type cells of BC, circ-Ccnb1 was shown to shape a complex with H2AX and wild-type p53, which results in ineffective tumor suppressing activity of p53 [42].

Regulation of Transcription and Splicing

CircRNAs could act as main contributors in the regulation of transcription in the nucleus (Figure 2d). For instance, ElciRNAs could interact with U1 snRNA in the nucleus and regulate the RNA polymerase II transcription of genes in cis by RNA-RNA interaction [27]. Another study reported that ci-ankrd52 can serve as an appropriate regulator of its parental gene transcription via interaction with RNA polymerase II [28]. Therefore, the transcription of genes are regulated by circRNAs via interacting with transcription related components. On the other hand, there is evidence that the formation of circRNAs competes with the canonical pre-mRNA splicing, indicating their important regulatory role in gene expression [12].

Translation

In addition to the aforementioned, emerging evidence suggests most of circRNAs are derived from coding genes, therefore, it is expected to be translated into proteins (Figure 2e). Internal ribosomal entry sites (IRESs) are particular elements that can induce the initiation of circRNA translation via a cap-independent mechanism [43, 44]. For example, it was shown that circ-ZNF609 can be translated to a protein into a splicing dependent and cap-independent way (IRES-driven mechanism) [45]. A study has shown that circ-SHPRH contains an ORF driven by the IRES and can be translated into a functional protein [46]. Importantly, another study proved that short sequences containing N6-methyladenosine (m6A) as IRESs can efficiently promote the translation of circRNAs in human cells [47]. Accordingly, these findings indicate circRNAs can function as a template for translation.

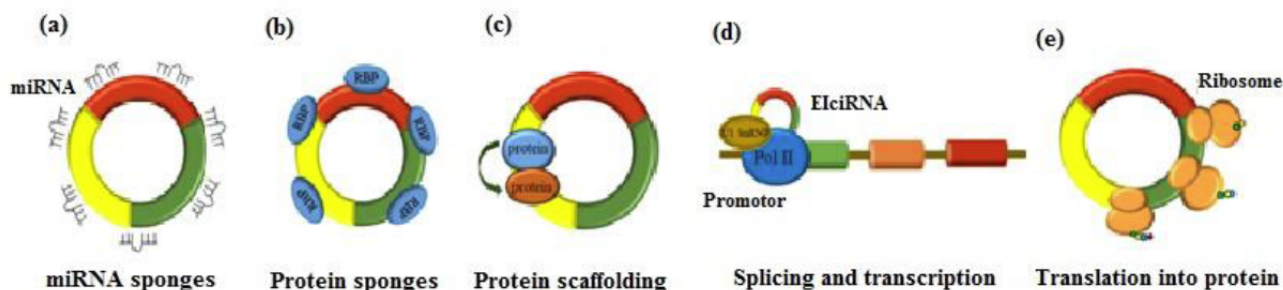


Figure 2: Roles of circRNAs. (a). CircRNAs sponge miRNA to regulate the expression of target genes. (b). CircRNAs may sequester and serve as sponges or traps for proteins. (c). CircRNAs bind to several proteins and build complexes or scaffolds for protein-protein interaction. (d). CircRNAs can adjust the transcription and splicing processes of their parental genes by interacting with the RNA polymerase II or transcription related factors. (e) CircRNAs translate to proteins with a cap-independent mechanism.

Circular RNAs and Breast Cancer

Numerous investigations have clearly indicated that circRNAs are differently expressed in tumorous not in normal tissues [48]. By the advancement of high-throughput sequencing, some circRNAs have also been found to be involved in BC. For example, by means of circ-seq data from 885 samples, Nair *et al.*

identified specific and novel circRNAs in breast tumors and normal-adjacent breast tissue. They also categorized 256, 288, and 411 tumor-specific circRNAs for BC subtypes, triple-negative (TN), estrogen receptor-positive (ER+), and HER2-positive (HER2+), respectively [49]. By using the circRNA microarray analysis, Yin *et al.* reported a different expression

Table 1: List of circRNAs Associated with Breast Cancer

CircRNA	Dysregulation	Putative function	Reference
circ-Foxo3	down regulated	association with Foxo3, MDM2 and p53 proteins	[14]
circ-Ccnb1	down regulated	association with H2AX and p53proteins	[42]
circ-ABCB10	up regulated	sponge to miR-1271	[53]
circ-GFRA1	up regulated	sponge to miR-34a	[54]
circMYO9B	up regulated	sponge to miR-4316	[55]
circ-DNMT1	up regulated	association with AUF1and p53 proteins	[56]
circCDYL	up regulated	sponge to miR-1275	[57]
circWWC3	up regulated	sponge to miR-26b-3p and miR-660-3p	[58]
circRNA_0001283	down regulated	sponge to miR-187	[59]
circRNA_000911	down regulated	sponge to miR-449a	[60]
circDENND4C	up regulated	sponge to miR-200b and miR-200c	[62, 63]
circ-RNF20	up regulated	sponge to miR-487a	[64]
circIRAK3	up regulated	sponge to miR-3607	[66]
circSKA3	up regulated	association with Tks5 and integrin β 1 protein	[67]
circANKS1B	up regulated	sponge to miR-152-3p and miR-148a-3p	[69]
circ-0011946	up regulated	sponge to miR-26a/b	[70]
circ_0006528	up regulated	sponge to miR-7-5p	[72]
circKDM4C	down regulated	sponge to miR-548p	[73]
circBMPR2	down regulated	sponge to miR-553	[74]
circRNA_0025202	down regulated	sponge to miR-182-5p	[75]
CDR1as	up regulated	sponge to miR-7	[78]
circRNA-MTO1	up regulated	association with TRAF4	[79]
circFBXW7	down regulated	sponge to miR-197-3p	[93]

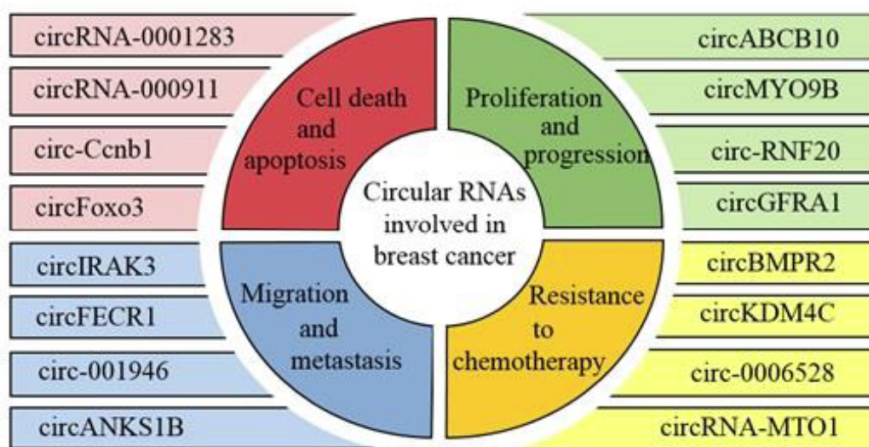


Figure 3: The roles of circular RNAs in breast cancer. CircRNAs have been indicated to contribute to various biological processes of breast cancer.

paradigm of circRNAs in plasma of BC patients compared with healthy individuals, including nineteen upregulated and twenty two downregulated circRNAs [50]. Table 1 shows several circRNAs and their potential roles implicated in breast cancer.

The Roles of Circular RNAs in Breast Cancer

It is documented that circRNAs can regulate the various cellular functions such as cell division, invasion, migration, and programmed cell death in BC tissues. Moreover, some circRNAs can have an important role in sensitivity and resistance to therapy [51] (Figure 3).

CircRNAs Regulate the Proliferation and Progression of Breast Cancer

Proliferation serves as an important step in the progression and development of BC [52]. Some circRNAs can regulate proliferation and progression in BC. For example, the expression of circRNA circ-ABCB10 (hsa_circ_008717) was increased in BC tissues and knockdown of this circRNA *in vitro* inhibited proliferation of BC cells and increased programmed cell death, indicating a regulatory role of circ-ABCB10 in BC progression by sponging miR-1271 [53]. Circ-GFRA1 was shown to be upregulated in BC. The Knockdown of circ-GFRA1 suppressed proliferation and increased apoptosis. Also, circ-GFRA1 was observed to regulate the expression of *GFRA1* via sponging miR-34a [54]. Another survey demonstrated that the expression of circMYO9B was directly associated with the prognosis of BC patients. This circRNA promoted the proliferation of BC cells and invasiveness through circMYO9B/miR-4316/FOXP4 axis, indicating a main function of circMYO9B in the regulation of progression [55]. Circ-Dnmt1 as a circRNA could augment proliferation in breast cancer. It

has been shown that the expression of this circRNA was increased in BC cells and breast carcinoma patients and its silencing suppressed cell proliferation and survival. Moreover, circ-Dnmt1 could bind with both AUF1 and p53, resulting in increased nuclear translation of both proteins. Cellular autophagy was promoted by nuclear translocation of p53. On the other hand, Nuclear translocation of AUF1 could decrease Dnmt1 mRNA instability, promoting the proliferation of BC cells [56]. Up-regulation of circular RNAs such as circCDYL in BC tissues relative to the adjacent normal tissues is shown to be involved in the progression and proliferation of BC cells through miR-1275-ATG7/ULK1-autophagic axis [57]. Moreover, it was shown that the expression of circWWC3 was upregulated in BC tissues leading to increase in the expression of multiple oncogenes of *Ras* signaling pathway by sponging miR-26b-3p and miR-660-3p, indicating an oncogenic role of circWWC3 in progression of BC [58]. On the other hand, downregulation of circRNA-0001283 was shown in BC tissues. Elevated expression of circRNA-0001283 led to inhibition of proliferation and invasion and increase in apoptosis of BC cells [59]. Similar observation was reported for circRNA-000911 [60].

Based on accumulating evidence, hypoxia is greatly interfere in modulation of the proliferation of BC cells [61]. For instance, one study documented the overexpression of HIF1 α -associated circDENND4C in BC cells under hypoxic conditions. Interestingly, the knockdown of this circRNA suppressed the cells proliferation in a hypoxic environment [62]. Moreover, negative association of circDENND4C with decreased expression of miR-200b and miR-200c in BC under hypoxia was reported [63]. CircRNF20 was also one of the upregulated circRNAs in BC that increased the

proliferation and Warburg effect of BC cells. CircRNF20 could act as a sponge for miR-487a in the miR-487a/HIF-1 α axis and subsequently HIF-1 α could bind to the *HK2* promoter and increase its expression, indicating the important role of circRNF20 by the circRNF20/miR-487a/HIF-1 α /HK2 axis in the progression of BC [64]. The above examples indicate that circRNAs have great potential for the regulation of proliferation and disease progression.

CircRNAs Regulate the Metastasis of Breast Cancer

Recent reports indicate that circRNAs modulate breast cancer-derived metastasis. Chen *et al.* showed that the expression of *FLI1* was upregulated in metastatic breast cancers and advanced stage. Notably, circFECR1 (derived from the *FLI1* gene) required TET1 DNA demethylase to the *FLI1* promoter to induce CpG demethylation and thereby activated *FLI1*. CircFECR1 also downregulated DNMT1 DNA methyltransferase in trans. Therefore, circFECR1 could function as an upstream regulator to promote metastasis in BC by using epigenetic regulation of the *FLI1* gene [65]. In another study, the results revealed upregulation of circIRAK3 in metastatic BC cells and was associated with the prognosis of recurrence in other organs. Moreover, this study showed that circIRAK3 might act as a sponge of miR-3607 to enhance the expression of *FOXC1* via circIRAK3/miR-3607/*FOXC1* signaling axis, resulting in the migration and metastasis. Therefore, circIRAK3 might act as a regulator in BC metastasis [66]. Upregulation of circSKA3 was also shown in BC cell lines and tissues. Positive association of elevated expression of circSKA3 with invasion and induction of the formation of invadopodia through interacting with Tks5 and integrin β 1 was demonstrated [67].

Epithelial to mesenchymal transition (EMT) is a critical component of the metastatic process in BC [68]. Zeng *et al.* reported that circANKS1B enhanced BC metastasis and invasion by inducing EMT. This circRNA bound to both miR-152-3p and miR-148a-3p and enhanced the expression of transcription factor USF1, which led to rise in the expression of TGF- β 1 and thereby promoted EMT through activating TGF- β 1/Smad signaling [69]. Moreover, the results of another study indicated that loss-of-function of circ-0011946 inhibited the move and invading of the BC cell line MCF-7. This circRNA could target replication factor C subunit 3 (RFC3) by sponging miR-26a/b. On the other hand, association of the overexpression of RFC3 was shown with metastasis and poor prognosis through

EMT [70, 71]. These results indicate the potential therapeutic value of circRNAs for BC patients with metastasis.

CircRNAs Regulate the Resistance to Chemotherapy in Breast Cancer

Several investigations have shown the expression of circRNAs can influence the sensitivity and resistance of tumors to chemotherapy. Gao *et al.* demonstrated a higher level of circ_0006528 expression in cell lines and tissues resistant to Adriamycin (ADM) compared to the groups with ADM sensitivity. Importantly, the downregulation of circ_0006528 enhanced the sensitivity of ADM resistant cells. Moreover, further investigations revealed an important regulatory role of circ_0006528/miR-7-5p/Raf1 axis in ADM resistant BC, suggesting a substantial role of circ_0006528 in combating chemoresistance in BC [72]. The expression of circKDM4C, as a tumor suppressor, was found to be downregulated in BC tissues and suppressed doxorubicin resistance *in vivo* and *in vitro* through regulating the miR-548p/PBLD axis, indicating that circKDM4C might be a potential target for BC treatment [73]. CircBMPR2 is another example that was downregulated in human BC tissues. Additionally, the knockdown of circBMPR2 increased tamoxifen resistance of BC cells by suppressing apoptosis. In contrast, circBMPR2 overexpression decreased tamoxifen resistance by circBMPR2/miR-553/USP4 axis. Therefore, circBMPR2 might be a potent therapeutic goal for BC [74]. A decreased expression level of circRNA_0025202 was observed in BC tissues. This circRNA could inhibit tumor growth and increase tamoxifen efficacy through the miR-182-5p/FOXO3a axis. Thus, circRNA_0025202 could regulate tamoxifen sensitivity and act as a novel biomarker for tamoxifen-resistant in BC [75]. Mediatory role of circAMOTL1 in the resistance of BC cells to paclitaxel (PAX) treatment via regulation of the AKT protein and its signaling pathway was shown previously [76]. This effect might be due to overexpression of circAMOTL1 in cancer cells leading to up-regulation of anti-apoptotic gene *BCL2* and down-regulation of pro-apoptotic gene *BAX* and *BAK* by activating AKT [76]. Similar observation was reported for Circ-ABCB10 through binding to let-7a-5p in cancer cells leading to up-regulation of the expression of *DUSP7* by Let-7a-5p/*DUSP7* axis [77]. CircRNA CDR1as could enhance the resistance of BC cells to cisplatin. CDR1as competitively suppressed miR-7 and subsequently increased the expression of *REGy*. Therefore, silencing CDR1as might decrease the expression of *REGy* by sponging miR-7 and enhance the sensitivity of cisplatin-resistant BC cells

Table 2: circRNAs Involved in Chemotherapy Resistance of Breast Cancer

CircRNA	Corresponding drugs	Mechanism	Reference
circ_0006528	Adriamycin	miR-7-5p/Raf1 axis	[72]
circKDM4C	Doxorubicin	miR-548p/PBLD axis	[73]
circBMPR2	Tamoxifen	miR-553/USP4 axis	[74]
circRNA_0025202	Tamoxifen	miR-182-5p/FOXO3a axis	[75]
circAMOTL1	Paclitaxel	AKT signaling pathway	[76]
circ-ABCB10	Paclitaxel	Let-7a-5p /DUSP7 axis	[77]
CDR1as	Cisplatin	miR-7/ REGγ axis	[78]
circRNA-MTO1	Monastrol	TRAF4/Eg5 pathway	[79]

[78]. Finally, the expression of circRNA-MTO1 was increased in monastrol-resistant BC cells. CircRNA-MTO1 inhibited cell viability and increased monastrol-induced cell cytotoxicity by sequestering TRAF4 to bind to the *Eg5* gene, resulting in the reduction of *Eg5* translation. Thus, circRNA-MTO1 could reverse resistance to monastrol via the TRAF4/*Eg5* axis [79]. In general, these findings may indicate that circRNAs participate in sensitivity and resistance to current chemotherapies drugs. Table 2 shows influential circRNAs involved in chemotherapy resistance.

CircRNAs Regulate the Resistance to Radiotherapy

Radiotherapy is one of the most important therapeutic strategies for BC [80-82]. Accumulating reports demonstrated a predominant regulatory role for circRNAs in response to radiation therapy through various signaling pathways. For instance, the Wnt signaling pathway was shown to be associated with the resistance of malignant cells to radiotherapy [83]. Correspondingly, the results of a study revealed the different expression pattern of circRNAs in radioresistant cell lines originated from esophageal cancer compared to the wild type cell lines (fifty seven upregulated and seventeen downregulated circRNAs). Subsequently, pathways analysis showed that these dysregulated circRNAs may interfere in the Wnt signaling pathway [84]. Another study also indicated that circATRNL1 was downregulated after irradiation treatment in oral squamous cell carcinoma (OSCC). Moreover, overexpression of this circRNA promoted the radiosensitivity of OSCC cells by sponging miR-23a-3p. Indeed, circATRNL1 could bind to miR-23a-3p to enhance *PTEN* expression, indicating the function of circATRNL1 in moderating the radiosensitivity of OSCC [85]. In addition, the association between circRNAs and radiotherapy has also been reported for other human cancers, such as hepatocellular and nasopharyngeal carcinoma, pancreatic and colorectal cancer and also

glioma [86-90]. In general, these findings emphasize that circRNAs can be an important regulator in cancer responsiveness to radiotherapy; therefore it may also be proposed their possible involvement in radiation resistance or augmentation of radiosensitivity in BC.

Diagnostic and Prognostic Value of circRNAs in BC

As mentioned earlier, development of BC is associated with dysregulation of circRNAs. Increasing evidence suggests circRNAs as ideal biomarkers for diagnosis and prognosis of BC. On the other hand, due to the presence of circRNAs in the extracellular fluid such as blood or plasma and saliva [18, 91], they may be considered as non-invasive molecular biomarkers for disease diagnosis. For instance, the level of hsa_circ_0001785 in plasma of postoperative patients was remarkably decreased compared with preoperative patients, providing a potential diagnostic and prognostic bioindicator for BC. The results of the analysis demonstrated that this circRNA had better diagnostic accuracy than other biomarkers, including carcinoembryonic antigen (CEA) and carbohydrate antigen 15-3 (CA 15-3). Importantly, association of hsa_circ_0001785 with histological grade, TNM stage, and distant metastasis was reported [50]. Moreover, circular RNA hsa_circ_0008673 was shown remarkably up-regulated in the plasma of BC patients, well correlated with tumor size, ER+, PR+ status and distant metastasis. Therefore, hsa_circ_0008673 can be considered as a potential noninvasive biomarker for diagnosis and prognostic of BC patients [92]. It has been proposed circGFRA1, circKDM4C, and circFBXW7 could also be served as potent diagnostic and prognostic bioindicators for BC [54, 73, 93]. Taken together, these results highlight the capability of circRNAs as biological markers for diagnosis and prognosis in BC. However, further research is needed to implement circRNAs in routine clinical practice.

CONCLUSION

The present review implicated the biogenesis, classification, and biological functions of circRNAs and explored their significant role in the tumorigenesis of different cancers. Here, we highlighted the impact of inappropriate expression of circRNAs in the progression of BC through regulating various biological phenomena such as cell division, cell death, invasion, migration. Moreover, it was implicated that circRNAs can be involved in chemotherapy resistance through modulating different signaling pathways and physiological processes. Similarly, we illustrated the role of circRNAs in radiation therapy for other types of cancers to explain the potential role of circRNAs in radiotherapy of breast cancer. Therefore, circRNAs can provide effective approaches for the treatment of BC in the near future. On the other hand, due to their unique structure and stability in body fluids, plasma, and blood, circRNAs can be proposed as promising biomarkers for the management of BC through liquid biopsies. However, it is important to note that circRNAs research is still in the initial stages and currently, compared with other noncoding RNAs such as miRNAs and lncRNAs, our knowledge of circRNAs is still very limited. Thus, further investigations would be necessary to determine the precise mechanisms of circRNAs in the progression of BC.

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CONFLICTS OF INTERESTS

None to declare.

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