Review Article

Molecular mechanisms of circular RNA in breast cancer: a narrative review

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Contributions: (I) Conception and design: Z Li, R Zhang; (II) Administrative support: R Zhang, D Li; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: Z Li, R Guo; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background and Objective: Breast cancer is presently the most prevalent cancer and the leading cause of cancer-related deaths in women worldwide. Circular RNA (circRNA) is a class of closed circRNAs lacking a 5'-end cap structure and a 3'-end polyA tail, which is highly stable and widely involved in a variety of pathophysiological processes such as cell proliferation, differentiation, and apoptosis. In recent years, accumulating studies have shown that circRNAs play an important role in the development and prognosis of breast cancer, but there are fewer literature reviews on their intrinsic molecular mechanisms which is the aim of this study.

Methods: This review synthesizes the findings of literature retrieved from searches of PubMed and Google Scholar databases, hand searches, and authoritative texts. Citations mainly originate from the past 3 years. The articles need to describe the role of circRNA in breast cancer; no language restrictions were imposed.

Key Content and Findings: This review summarizes the latest relevant literature and systematically reviews the four main mechanisms of circRNA in breast cancer from the perspective of circRNA function. At the same time, we describe the formation mechanism, characterization, and biological functions of circRNAs.

Conclusions: We reviewed the status of actual knowledge about circRNA biogenesis and functions and summarized novel findings regarding the molecular mechanism of circRNA in breast cancer. Meanwhile, this review explores the possibility of circRNAs for becoming new biodiagnostic indicators and therapeutic targets in breast cancer.

Keywords: Circular RNA (circRNA); breast cancer; molecular mechanisms; biomarkers

Submitted Sep 22, 2023. Accepted for publication Dec 28, 2023. Published online Feb 26, 2024.
doi: 10.21037/tcr-23-1760
View this article at: https://dx.doi.org/10.21037/tcr-23-1760

Introduction

According to global cancer data published by the International Agency for Research on Cancer (IARC), breast cancer is the most common malignancy in the world and the leading cause of cancer death in women (1). The American Cancer Society predicts that the incidence of breast cancer will continue to increase at a rate of 0.5% per year (2). The rising prevalence of breast cancer has imposed a significant burden on patients and society. Timely detection of breast cancer is crucial for enhancing the success and forecasting of breast cancer treatment. However, many patients overlook the optimal treatment window because of the absence of apparent symptoms and precise diagnostic techniques in the initial stage of breast cancer. With the emergence of

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Table 1 The search strategy summary

Items	Specification
Date of search	September 10, 2023
Databases and other sources searched	Electronic searches of PubMed and Google Scholar, hand searches of references of retrieved literature, and authoritative texts
Search terms used	CircRNA, Breast cancer, Molecular mechanisms, Biomarkers
Timeframe	September 2020 to September 2023
Inclusion and exclusion criteria	The articles need to describe the role of circRNA in breast cancer. No language restrictions were imposed
Selection process	Two authors (Z.L. and R.G.) review independently and in duplicate screened articles for inclusion based on title and abstract and reviewed relevant articles as full text. Disagreement during the review process was resolved by consensus through involvement of a third review author (R.Z.)

molecular biology and sequencing technology, an increased number of circular RNA (circRNA) have been identified. These RNAs are classified by their stable structure, significant abundance, and specific expression in varying tissues (3). They are prevalent in various body fluids such as blood, urine, and saliva, and have a longer half-life than linear RNAs (4). The average half-life of circRNAs in cells exceeds 48 hours while mRNAs only last on average for 10 hours (5). Previous studies have demonstrated the crucial role of circRNAs in regulating the proliferation, invasion, metastasis, and drug resistance of breast cancer cells (6-9). They possess the potential to be novel molecular targets for breast cancer treatment, highlighting their importance in the field. Currently, many teams are focusing on circRNAs and their impact on breast cancer, exploring the molecular mechanism of circRNAs in breast cancer. Current research suggests that the molecular mechanisms of circRNAs in breast cancer are both diverse and subtle.

We provide a narrative review of the recent advances in circRNA research from the perspective of the molecular mechanism of circRNAs in breast cancer. In addition, we discuss the limitations of the current knowledge and the prospects for the clinical application of circRNAs in the diagnosis and treatment of breast cancer. We present this article in accordance with the Narrative Review reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1760/rc).

Methods

We synthesized the results of literature obtained by searching computerized databases, hand searches, and authoritative texts. The cited literature was mainly from the last 3 years. We summarized and distilled the retrieved literature and then wrote this review. The specific search strategy is detailed in the search strategy summary in *Table 1*.

Overview of circRNA

Biogenesis

Covalently closed, single-stranded circRNAs were initially discovered in plant-infected viruses (10). However, the technical limitations at that time led to the neglect of this type of circRNA as an abnormal product of the splicing process or misexpression. With the advancement of second-generation sequencing and bioinformatics, it is increasingly acknowledged that circRNAs have a significant impact on human diseases and are recognized as crucial regulators of many types of cancer (11). CircRNAs are primarily derived from protein-coding exons but can also originate from introns, untranslated regions (UTRs), or spacer regions of the genome (5). Currently, three main hypothetical models exist to explain the potential mechanisms of exonic circRNA production (12). One is reverse complementary pairing, i.e., intron pairing cyclization (13). The reverse complementary match (RCM) sequence exists in the two flanking introns of the precursor messenger RNA (pre-mRNA), and this reverse complementary pairing mediates the formation of circRNAs, in which the Alu repeats containing reverse complementary pairing play an important role (14). Secondly, the exon jumping, i.e., lasso-driven circularization (14,15). The model suggests that pre-mRNAs are in a semi-folded state, and in the transcription process, exons that are not adjacent to each other come close to each other, and the lasso is generated by exon jumping driven by trans-acting

factors, and then circRNAs are formed by splicing and removing intronic sequences in the lasso structure. Third, RNA binding protein (RBP)-mediated cyclization, RBP can connect the two non-adjacent introns at both ends of the column to promote the proximity of the two ends to form a loop, and then splicing to form an exonic circRNA (16,17).

Characterization

CircRNA can be classified into four types (18): exon circRNAs (ecircRNAs) (19), circular intronic RNAs (ciRNAs) (16), exon-intron circRNAs (EIciRNAs), and intergenic or fusion circRNAs (f-circRNAs) (20). The majority of circRNAs are located in the cytoplasm, with some intron-forming circRNAs found in the nucleus (21). It is noteworthy that the structure of circRNAs exhibits a stable loop structure, higher resistance to RNA exonucleases, and an extended half-life, which may be significant in various cellular processes. CircRNAs with closed-loop structure avoid degradation reactions such as deadenylation and decapitation due to the lack of a 5' cap and 3' tail structure similar to that of mRNAs (22), making them more stable in the body compared to mRNA. Most circRNAs produced by different species are relatively evolutionarily conserved, while the existence and expression of circRNAs in organisms are widespread, and can be found in a variety of body fluids in the human body, such as plasma, saliva, and exosomes (23,24). In addition, different cells and tissues have specific expression profiles at different developmental stages, and circRNAs play specific functions at different developmental stages of cells (3).

Functions

CircRNA serves four primary biological functions. MicroRNA (miRNA) sponges: circRNAs act as miRNA sponges by competitively binding to miRNAs, effectively protecting target mRNAs from miRNA degradation or translation. This mechanism is known as the competitive endogenous RNA (ceRNA) mechanism or miRNA sponge (10). MiRNAs are important post-transcriptional regulators of gene expression and function by direct base pairing with target sites in the UTR of mRNAs (18). CircRNAs contain a large number of miRNA-binding sites, which allows miRNAs to deregulate their target *genes* and thus play important regulatory roles (25).

Binding proteins: CircRNAs can directly or indirectly bind to specific RBPs, forming RNA-protein complexes. Through the enhancement or weakening of protein mRNA binding capacity, circRNA mainly affects the translation of mRNA (26). CircRNA can serve as a scaffold between proteins, RNAs, and DNAs to facilitate the interaction between two molecules (12).

Translation: the function of circRNA-encoded proteins was first demonstrated in the hepatitis D virus, and thousands of circRNAs have now been tested to contain open reading frames (ORFs). It has been demonstrated that circRNAs can undergo translation through two distinct mechanisms. One method relies on internal ribosome entry sites (IRES) (27), and the other is the addition of m6A RNA for modification (28), which further initiates translational function through both methods. Rolling circle amplification (RCA) (27) is also recognized as a form of polypeptide production. Polypeptides produced by RCA may possess differing structures from the host gene and perform independent functions.

Regulation of gene transcription: moreover, circRNAs regulate gene transcription. In southern mustard, circRNA can strongly bind to the DNA sites of host genes to form the R-loop structure of RNA, and the R-loop structure can inhibit the transcription of the region (29). An earlier study discovered that circRNA can interact with U1 small nuclear RNA (snRNA), forming the EIciRNA-U1 snRNA complex. This interaction promotes the transcription of parental genes (20).

Molecular mechanism of circRNA in breast cancer

CircRNA as miRNA sponges

According to the ceRNA theory, the primary mechanism of circRNA in breast cancer is to interact with miRNAs via various types of miRNA response elements within the circRNA. This interaction eliminates the inhibitory effects of miRNAs on their target *genes*, thereby achieving effects on breast cancer proliferation, progression, metastasis, and drug resistance.

Circ_0001667

To investigate the regulatory mechanism of breast cancer progression by circ_0001667, Zhang *et al.* utilized starBase 3.0 to predict its target miRNA as miR-6838-5p. The analysis revealed that circ_0001667 acts as a sponge for miR-6838-5p. The study involved identifying the top 50 most highly expressed genes in breast cancer using the

GEPIA database, as well as the target gene for miR6838-5p through starBase 3.0. The CXCL10 gene was found to be common among both of these groups. Further correlation analysis established that miR-6838-5p directly targets CXCL10, and confirmed a correlation between miR-6838-5p, CXCL10, and biological behavior in breast cancer cells. Ultimately, the researchers concluded that Circ_0001667 impacts the progression of breast cancer by stimulating CXCL10 expression through miR-6838-5p sponge and playing a role in the proliferation of breast cancer cells and angiogenesis (30).

CircRRM2

Hao *et al.* found that circRRM2 expression in breast cancer patients' tumor tissues was upregulated. Furthermore, high expression of circRRM2 was significantly associated with more advanced N stage in breast cancer patients. CircRRM2 was found to promote cell migration and invasion and function as an oncogene in breast cancer, as shown through gain- and loss-of-function experiments. Mechanistic studies indicate that circRRM2 competes with miR-31-5p/miR-27b-3p to upregulate IGF2BP1 expression. In addition, the study found that IGF2BP1 increases the expression of circRNA RRM2 (circRRM2) by interacting with MYC, a transcription factor for circRRM2. Their experiments identified a positive feedback loop consisting of circRRM2/IGF2BP1/MYC, which may be a potential target for breast cancer therapy (31).

CircHMCU

To elucidate the molecular mechanisms underlying the regulation of breast cancer cell by circHMCU, Qiu *et al.* observed that miR-4458 was highly expressed in circHMCU-silenced MCF-7 cells. Additionally, the researchers found that miR-4458 mimics reduced luciferase activity in the circHMCU wild-type group, indicating that circHMCU binds to miR-4458 through a paired site. And then, they found that miR-4458 contained the complementary region of PGK1 3'UTR and miR-4458 mimics inhibited the luciferase activity of PGK1 3'UTR wt. Furthermore, the knockdown of miR-4458 rescued the downregulation of PGK1 in si-circHMCU-transfected breast cancer cells. Overall, the study confirmed that circHMCU reduction limited breast cancer cell proliferation, migration, invasion, and glycolysis, and induced breast cancer cell apoptosis through the miR-4458/PGK1 axis (32).

CircBRWD3

Meng *et al.* discovered circBRWD3 is expressed nearly 3-fold in breast cancer tissues compared to normal tissues, and the significant increase was positively correlated with the poor prognosis of breast cancer patients. circBRWD3 knockdown inhibited cell proliferation and metastasis while promoting apoptosis. Consistent with this, an *in vivo* circBRWD3 deficiency model showed suppression of tumor metastasis and tumorigenesis. Mechanistic studies indicate that circBRWD3 inhibits both miR-142-3p and miR-142-5p to regulate RAC1 expression, which in turn activates the RAC1/PAK1 signaling pathway and promotes tumorigenesis and progression in breast cancer. Additionally, the researchers discovered that the RNA-binding protein EIF4A3 stimulates circBRWD3 expression by targeting BRWD3 pre-mRNA upstream (33).

Hsa_circ_0002082

Liu *et al.* experimentally confirmed that hsa_circ_0002082 targeted miR-508-3p in breast cancer cells. According to the results, only CENPF had a putative conserved target of miR-508-3p, and further experimental validation revealed that miR-508-3p targeted CENPF. CENPF is a highly expressed transient fusogenic protein in the G2/M phase. The elevated expression of CENPF is linked to a negative prognosis for breast cancer and speeds up the proliferation and metastasis of breast cancer cells. This investigation presents, for the first time, that hsa_circ_0002082 promotes breast cancer progression by acting oncogenes through the miR-508-3p/CENPF axis (34).

Circ-TRIO

Triple-negative breast cancer (TNBC) is one of the most challenging breast cancer subtypes, and similarly, the study of the mechanism of circRNA action in TNBC has been widely conducted. Wang *et al.* found the expression of circ-TRIO in TNBC tissues, which was associated with TNBC patient recurrence and prognosis. Down-regulation of circ-TRIO impeded TNBC cell proliferation, migration, and invasion, while overexpression had the opposite effect. Mechanically, the dual luciferase reporter gene assay and RNA immunoprecipitation revealed that circ-TRIO interacted with miR-432-5p, thereby controlling the expression of the coiled-coil structural domain containing 58 (CCDC58). Overall, this study indicated that circ-TRIO had a significant role in advancing TNBC through the regulation of the miR432-5p/CCDC58 axis (35).

Hsa_circ_0001925

In their study on the molecular mechanism of hsa_circ_0001925 in TNBC tissues and cells, Shen *et al.* discovered that Hsa_circ_0001925 acted as a miRNA sponge for miR-1299. They observed that miR-1299 interacted with the 3'UTR of YY1, and overexpression of YY1 partially counteracted the effect of miR-1299 overexpression on breast cancer progression. Silencing Hsa_circ_0001925 could reduce YY1 expression by decreasing sponge miR-1299, thereby inhibiting cell proliferation, migration, and angiogenesis and promoting apoptosis *in vitro* (36).

Circ-CSNK1G1

Zan *et al.* found that circ-CSNK1G1 expression was upregulated more than 4-fold in TNBC tissues compared to normal tissues. circ-CSNK1G1 knockdown inhibited cancer cell proliferation, migration, invasion, and glycolytic energy metabolism, promoted apoptosis, and blocked tumor growth *in vivo*. Further studies revealed multiple binding sites between the circ-CSNK1G1 sequence and miR-28-5p, as well as between miR-28-5p and LDHA 3'UTR sequence. and subsequent experiments verified that LDHA expression attenuated by circ-CSNK1G1 knockdown was inhibited by miR-28-5p inhibition, leading to the conclusion that circ-CSNK1G1 promotes cell proliferation, migration, invasion, and glycolytic metabolism during TNBCrux development by regulating the miR-28-5p/LDHA pathway (37).

CircEPSTI1

In investigating circEPSTI1's mechanism in Her2-positive breast cancer, Zhang *et al.* found that when co-transfected with a luciferase reporter gene and a miR-145 mimic, luciferase intensity was decreased, and RIP experiments showed that miR-145 was predominantly enriched in the MS2bs-circEPSTI1 group, suggesting a circEPSTI1-specific interaction with miR-145. Subsequently, the researchers discovered that the expression of ERBB3 was suppressed by miR-145 and verified that circEPSTI1 impacted ERBB3 by absorbing miR-145. This process ultimately enhanced the proliferation, migration, and invasion of HER2-positive breast cancer cells. Moreover, ERBB3, as a member of the ErbB family, has been extensively studied for its therapeutic mechanism and efficacy in targeting Her2-positive breast cancer. This study adds to the understanding of the development of Her2-positive breast cancer and offers a potential marker and therapeutic approach (38).

CircRNA as translation template

CircRNAs were previously thought to be unique endogenous non-coding RNAs that could not translate proteins due to the lack of 5–3 polarity, polyadenylated tails, and IRES. However, studies have revealed that certain cytoplasmic circRNAs can be efficiently translated into detectable polypeptides (39,40). In their study, Abe *et al.* showed for the first time that circRNAs synthesized *in vitro* can be translated in living human cells in the absence of specific elements used for internal initiation (27). A number of circRNAs have now been found to be translatable into proteins and to exert effects in breast cancer.

CircFBXW7

CircFBXW7 was reported to be a tumor suppressor circRNA that is abundantly expressed in normal brain tissue and down-regulated in gliomas. Ye *et al.* initially evaluated its expression levels in different cell lines and discovered low expression in breast cancer cell lines, specifically TNBC cell lines. Furthermore, circFBXW7 exhibited a negative correlation with tumor size and lymph node metastasis and was an independent prognostic factor in TNBC patients. Studies of the molecular mechanism of circFBXW7 provide experimental confirmation of the interaction between circFBXW7 and miR-197-3p. circFBXW7 functions as a miR-197-3p sponge reducing the expression of the tumor suppressor gene FBXW7. Meanwhile, they discovered that circFBXW7 can encode the protein FBXW7-185aa, which inhibits TNBC cell proliferation and metastasis by down-regulating c-Myc expression. Protein blot analysis demonstrated that overexpressing FBXW7-185aa augmented FBXW7 abundance and caused degradation of c-Myc. Therefore, circFBXW7 sponges miR-197-3p and encodes FBXW7-185aa protein, which suppresses TNBC advancement by upregulating FBXW7 expression. circFBXW7 may be a novel prognostic biomarker and potential therapeutic strategy for TNBC (40).

Hsa_circ_0060055

By comparing and screening, Li *et al.* discovered that the expression of hsa_circ_0060055 (circ-EIF6) was elevated in TNBC cells and positively correlated with metastatic ability, and silencing of circ-EIF6 inhibited the proliferation, migration, and invasion of TNBC cells, suggesting that circ-EIF6 may play a role in TNBC metastasis. The results from later experiments suggest that circ-EIF6 expression was correlated with histological grading and distant

metastasis of patients. Circ-EIF6 and distant metastasis status were independent prognostic factors affecting overall survival. The subsequent experimental studies on the molecular mechanism of circ-EIF6 demonstrated that circ-EIF6 interacts with ribosomes and is translated into a new 224-amino-acid peptide called EIF6-224aa. Whereas it is EIF6-224aa, not circ-EIF6, that promotes the proliferation and metastasis of TNBC cells, EIF6-224aa directly interacts with the MYH9 protein and inhibits the proteasomal degradation of MYH9 by reducing its ubiquitination, which subsequently activates the Wnt/β-linker pathway to promote the oncogenic function of circEIF6 (41).

CircSEMA4B

The Semaphorin 4B (*SEMA4B*) gene's product, circSEMA4B, was notably downregulated in both breast cancer tissues and cell lines. Cellular experiments conducted *in vitro* demonstrated that circSEMA4B substantially suppressed breast cancer cell proliferation while inhibition of circSEMA4B expression led to a rise in the invasive capacity of MDA-MB-231 cells. In addition, the deletion of circSEMA4B promoted breast cancer cell migration compared to the control group, while overexpression of circSEMA4B significantly decreased cell migration in MDA-MB-231 cells. Therefore, circSEMA4B acts as a tumor suppressor in breast cancer cells. Mechanistically, Wang *et al*. found that circSEMA4B encodes a new protein, SEMA4B-11aa, driven by active IRES. SEMA4B-211a hinders the formation of the p85/p110 complex by binding with p85, resulting in a decrease in the formation of phosphatidylinositol-3,4,5-trisphosphate (PIP3). This reduction inhibits AKT (Thr308) phosphorylation, thus exerting an inhibitory effect on breast cancer cells. On the other hand, the study discovered that circSEMA4B has the ability to inhibit AKT phosphorylation (Ser473) via the miR-330-3p/PDCD4 axis. It can be concluded that circSEMA4B is a novel negative regulator of the PI3K/Akt signaling pathway, and both circSEMA4B and SEMA4B-11aa significantly inhibited breast cancer proliferation and migration *in vitro* and *in vivo* (42).

Circ-HER2

The analysis of the circ-HER2 sequence revealed the presence of an ORF, which potentially produces HER2-103, a 103 amino acid protein. This ORF is regulated by the IRES. In clinical samples, HER2-103 was expressed in 41% of randomly selected TNBC cancer tissues, while no detectable HER2-103 was found in the paired normal breast tissues. To gauge the role played by circ-HER2/HER2-103 in TNBC, Li *et al*. (43) constructed MDA-MB-231 and MDA-MB-468 HER2-103 stable knockdown cells. Knockdown of circ-HER2 inhibited TNBC cell proliferation, invasion, and tumorigenesis both *in vitro* and *in vivo*, indicating a crucial role for circ-HER2/HER2-103 in TNBC tumorigenicity. Mechanism of studies revealed that HER2-103 enhances EGFR/HER3 interaction and activation in TNBC. In the absence of HER2, EGFR can form EGFR/EGFR homodimers or heterodimers with HER3 to activate downstream signaling cascades. EGFR is overexpressed at a higher frequency in TNBC than in other subtypes of breast cancer and is thought to be a factor in poor prognosis (44). It is possible that resistance to EGFR-targeted therapy in TNBC is driven by the upregulation of HER3 and its participation in heterodimerization with EGFR (45). This study confirms that circ-HER2 encodes a novel HER2 variant, HER2-103. HER2-103 promotes EGFR/HER3 interaction and activation in TNBC. Deprivation of HER2-103 inhibited cell proliferation, invasion, and tumorigenicity of TNBC *in vitro* and *in vivo*. HER2-103 shares the same amino acid sequence as HER2 CR1 and can be antagonized by pertuzumab. Their findings suggest that TNBC patients expressing circ-HER2/HER2-103 may benefit from pertuzumab, a clinically approved HER2 antibody. This undoubtedly offers hope for the treatment of TNBC.

CircRNA binds RBPs

CircRNAs have the ability to bind to proteins both directly or via RNA, and can also act as competing elements, thus isolating proteins to inhibit their effects (46). Recent research indicates that circRNAs can bind with various kinds of proteins, impacting protein regulation, localization, and interaction with other proteins.

CircFoxo3

A case in point is the circRNA-protein interaction by circFoxo3, whose high expression significantly promotes apoptosis in TNBC cells. CircFoxo3 expression was found to be notably low in patient tumor samples and a panel of cancer cells. However, its expression was significantly heightened during cancer cell apoptosis. Furthermore, silencing of endogenous circFoxo3 increased cell viability, while ectopic expression of circFoxo3 induced stress-induced apoptosis and suppressed tumor graft growth. Mechanistically, in MDA-MB-231 cells, circFoxo3 showed a preference to bind MDM2 and p53 over Foxo3. The induction of the circFoxo3-

MDM2 complex resulted in low-affinity binding of Foxo3 to circ-Foxo3, which prevented Foxo3 ubiquitination and degradation. Overexpression of circFoxo3 led to MDM2-induced p53 ubiquitination and degradation while competing to prevent MDM2-mediated Foxo3 ubiquitination and degradation. This competition resulted in elevated levels of Foxo3 protein. Ultimately, the upregulation of PUMA, a downstream target of Foxo3, led to apoptosis (47).

CircDNAJC11

Wang *et al.* (48) discovered that circDNAJC11 expression was noticeably elevated in breast cancer cells and tissues. Moreover, it was positively associated with advanced tumor stage and poor prognosis. The multivariate Cox regression model determined that circDNAJC11 expression level functioned as an independent prognostic factor affecting breast cancer patients. Additionally, they investigated the circRNA's mechanism of action. Further analyses including RNA pull-down, mass spectrometry, RNA immunoprecipitation, rescue experiments, and fluorescence *in situ* hybridization revealed that circDNAJC11 interacts with TATA-box-binding protein associated factor 15 (TAF15). TAF15 is a member of the conserved FUS-EWS-TAF15 (FET) family of RNA-binding proteins that play crucial roles in regulating gene expression such as polyadenylation, spin-capping, RNA splicing, modification, localization, export, translation, and flipping (49,50). CircDNAJC11 maintains MAPK6 mRNA stability through TAF15. CircDNAJC11 overexpression reduces the degradation rate of MAPK6 mRNA and activates the MAPK6 signaling pathway, which significantly increases proliferation, migration, invasion, and growth of breast cancer cells while inhibiting apoptosis.

Circ-Ccnb1

Circ-Ccnb1 is dramatically down-regulated in cancer tissues. Circ-Ccnb1 is derived from exon 4 and exon 5 of the *CCNB1* gene. Circ-Ccnb1 is found at higher levels in many cancers, especially breast cancer. Fang *et al.* found that circ-Ccnb1 precipitates p53 in p53 wild-type cells, and precipitates Bclaf1 in p53 mutant cells. Further experiments have revealed that H2AX proteins act as a bridge, linking the interaction of circ-Ccnb1 with wild-type p53. This leads to the binding of Bclaf1 to Bcl2 and thus to cell survival. In p53 mutant cells, circ-Ccnb1 forms a complex with H2AX and Bclaf1, leading to cell death (51).

Hsa_circ_000023

Hu *et al.* discovered that hsa_circ_000023 exhibited high expression levels in both breast cancer cells and breast cancer tissues. Furthermore, the knockdown of hsa_circ_0000231 inhibited the proliferation, migration, and invasion of breast cancer cells, and induced apoptosis and G1-phase block of the cell cycle. Detection of the related protein table of hsa_circ_0000231 action revealed that hsa_circ_0000231 interacted with HnRNPK. Further experiments have revealed that HnRNPK protein co-localizes with hsa_circ_0000231 in the nucleus. The interaction between HnRNPK protein and hsa_circ_0000231 enhances the expression of c-Myc, which promotes the occurrence and development of breast cancer. Knocking down hsa_circ_0000231 impedes breast cancer cell proliferation, migration, and invasion. It induces apoptosis, blocks the cell cycle, and inhibits the growth of transplanted tumors *in vivo* (52).

CircRNA-MTO1

In the study of the regulatory role of circRNAs on breast cancer cell viability and monastrol resistance, Liu *et al.* found that circRNA-MTO1 (hsa_circRNA_007874) is a circRNA with increased expression levels in drug-resistant cells. Mechanistic studies revealed that circRNA-MTO1 targets Eg5 functionally. MTO1 inhibited the levels of Eg5 protein, but not mRNA levels. RNA pull-down experiments and mass spectrometry analysis showed that MTO1 interacts with tumor necrosis factor receptor-associated factor 4 (TRAF4), which prevents TRAF4 from activating the translation of Eg5. As a result, Eg5 protein levels decrease, leading to the resistance of TNBC cells to monastrol (53).

CircRNA regulates gene expression

CircRNAs have been shown to directly interact with the genomic DNA of host genes in plants, resulting in alterations in parental gene expression (29). However, the interaction between circRNAs and host gene DNA has been less examined in human cancers.

CircSMARCA1

Xu *et al.* discovered that circRNA from *SMARCA5* (circSMARCA1) was considerably reduced in breast carcinoma cell lines and breast carcinoma samples (54).

Previously, circSMARCA5 was identified as a ceRNA by binding to miRNA molecules (55,56). However, this study reveals that circSMARCA5 is also involved in regulating DNA repair capacity by binding directly to exonic DNA. Previous studies have demonstrated that *SMARCA5* plays a critical role in regulating DNA repair processes and maintaining genome stability, and affects breast cancer progression (57,58), circSMARCA5 overexpression increased the sensitivity of MCF-7 cells to cisplatin or bleomycin. To clarify the mechanism of action of circSMARCA5, Xu *et al.* demonstrated that circSMARCA5 helps terminate the transcriptional elongation of *SMARCA5* exon 15 by modeling the regulation of circRNAs and the transcription of certain exons. CircSMARCA5 is recruited to its parental motifs, resulting in the formation of an R-loop, transcriptional termination, and subsequent non-functional truncation of the Δ SMARCA5 protein. This leads to the upregulation of circSMARCA5 and reduced expression of *SMARCA5*, potentially enhancing the DNA damage repair capacity and drug sensitivity of breast cancer cells. The results confirm that overexpression of circSMARCA5 is sufficient to increase the chemosensitivity of breast cancer cells *in vitro* and *in vivo*, which not only elucidates an important regulatory mechanism of circRNAs in breast cancer but also suggests that circSMARCA5 is a promising therapeutic target for breast cancer.

Conclusions

In summary, circRNAs have emerged as a prominent field in medical research, exhibiting immense potential and clinical significance in the diagnosis, treatment, and prognosis of breast cancer. We reviewed the status of actual knowledge about circRNA biogenesis and functions and summarized novel findings regarding the molecular mechanism of circRNA in breast cancer. CircRNAs can impact the progression of breast cancer through their role as miRNA sponges, protein sponges, translational templates, or regulators of gene expression. Our study offers a novel perspective on the molecular mechanism of breast cancer, and circRNAs will soon be used as new therapeutic targets in drug design, early diagnosis, and prognostic evaluation.

Nevertheless, research on circRNAs in breast cancer remains insufficient and the application of circRNAs in clinical practice for diagnosing, treating, and monitoring breast cancer will require further development. First, the existing studies have mostly explored the mechanism of a single pathway, but the interaction and influence of multiple pathways should not be neglected, and we need more in-depth studies to improve the understanding of the molecular mechanism of the circRNA network. Second, the exosomal circRNAs require special attention and their unique biological functions will show great potential in the diagnosis and treatment of breast cancer. Third, our research on circRNAs is currently limited to cellular experiments, blood tests, and animal experiments. We require more clinical studies and multi-center clinical trials to further enhance our comprehension of circRNAs, alongside advanced technology to explore the unknown field of circRNAs, so that circRNAs can be used as a new diagnostic and therapeutic strategy in the clinic as soon as possible, opening up a new field for the diagnosis and treatment of breast cancer.

Acknowledgments

The authors thank the reviewers for their useful feedback and constructive comments.
Funding: The present study was supported by the Inner Mongolia Autonomous Region Natural Science Foundation Project (grant No. 2022MS08010) and the Inner Mongolia Autonomous Region Science and Technology Programme (grant No. 2023YFSH0039).

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1760/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1760/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1760/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Li Z, Zhang R, Li D, Guo R. Molecular mechanisms of circular RNA in breast cancer: a narrative review. Transl Cancer Res 2024;13(2):1139-1149. doi: 10.21037/tcr-23-1760

