



# Circular RNAs orchestrating breast cancer hallmarks: bridging tumor biology and therapy resistance

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## Abstract

Breast cancer (BC) remains a leading cause of cancer-related mortality among women worldwide, with treatment resistance posing a significant clinical challenge. Circular RNAs (circRNAs), a class of non-coding RNAs, have gained increasing attention as key regulators of gene expression, influencing BC pathogenesis, progression, and therapeutic response. This review explores the mechanistic insights into circRNA functions in BC, focusing on their involvement in tumor proliferation, metabolic reprogramming, epithelial-mesenchymal transition (EMT), angiogenesis, metastasis, and apoptosis. Additionally, we highlight the crosstalk between circRNAs and microRNAs, emphasizing their potential as diagnostic and prognostic biomarkers. Beyond their roles in tumor biology, circRNAs are implicated in drug resistance, modulating responses to chemotherapy, targeted therapy, and endocrine treatment. Despite their promising applications, challenges remain, including the complexity of circRNA interactions, and the development of robust preclinical models. Addressing these challenges through interdisciplinary research integrating genomics, transcriptomics, and functional studies will pave the way for circRNA-based therapeutic strategies and personalized medicine approaches in BC management.

**Keywords** Breast cancer · Drug resistance · Personalized medicine · Biomarkers · Non-coding RNAs (ncRNAs) · CircRNAs

## Introduction

Breast cancer (BC) was the second most commonly diagnosed cancer among women worldwide in 2022, according to GLOBOCAN 2022, with an estimated 2.3 million new cases, representing 11.6% of all global cancer cases. Moreover, it was the fourth leading cause of cancer-related mortality among women, accounting for approximately 666,000 deaths that year (Abdelhamid et al. 2024; Bray et al. 2024). Despite advances in early diagnosis and treatment,

challenges persist, particularly in advanced stages where 5-year survival rates are alarmingly low at 26% mainly due to metastatic disease and resistance to therapy (Malmgren et al. 2018). Multiple factors including female sex, advanced age, family history, and genetic mutations influence BC risk (Łukasiewicz et al. 2021). These challenges highlight the need to develop personalized treatments and reduce reliance on chemotherapy by identifying novel therapeutic targets and biomarkers.

Whole-genome transcriptome analyses have revealed that around 80% of the human genome is transcribed, Yet only 2% encodes proteins, leaving over 90% transcribed into non-coding RNAs (ncRNAs), which do not directly govern protein synthesis (Palazzo and Koonin 2020). Subsequently, ncRNAs have been systematically classified into housekeeping and regulatory groups. Housekeeping ncRNAs consist of tRNAs and rRNAs, small nuclear RNAs (snRNAs) and small nucleolar RNAs (snoRNAs). Regulatory ncRNAs are categorized by their transcript length into short ncRNAs (<200 nucleotides), such as microRNAs (miRNAs), PIWI-interacting RNAs (piRNAs), small

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interfering RNAs (siRNAs), and small nucleolar RNAs (snoRNAs), and long ncRNAs (lncRNAs) (>200 nucleotides). These ncRNAs play crucial roles in RNA maturation, processing, signaling, gene expression, and protein synthesis (Doghish et al. 2025; Rostom et al. 2025).

In tumorigenesis, ncRNAs serve various roles; they can function as tumor suppressors in one type of cancer while facilitating tumor progression in another (Abdelhamid et al. 2024; Assal et al. 2025; Bhan et al. 2017; Doghish et al. 2025; Rostom et al. 2025). Notably, a new subclass of lncRNAs, known as circular RNAs (circRNAs), has garnered significant interest due to their emerging therapeutic potential, high stability, diagnostic and prognostic value and their critical involvement in cellular proliferation and malignant transformation processes (Meng et al. 2017).

CircRNAs represent a distinct class of endogenous non-coding RNAs characterized by a covalently closed loop structure, lacking the 5'–3' polarity and poly-A tail, providing high stability against exonucleases (Meng et al. 2017). While their biogenesis can occur through various mechanisms, backsplicing is the predominant process in humans. Initially considered as mere byproducts of pre-mRNA splicing, circRNAs have since been recognized for their significant roles in regulating gene expression (Verduci et al. 2021). They play a crucial role in serving as microRNA sponges, protein scaffolds, and modulators of mRNA synthesis, splicing, and protein production (Liu et al. 2022). CircRNAs have been found to be associated with many biological processes such as gene expression regulation, protein interaction, encoding for proteins and peptides that inhibit cancer development, in addition to being involved in many physiological functions (Shi et al. 2023).

Research into underlying mechanisms has unveiled the pivotal roles of circRNAs in BC, influencing processes such as cell proliferation, apoptosis, angiogenesis, epithelial to mesenchymal transition (EMT), tumor microenvironment, and drug resistance. Moreover, emerging research into circRNAs in cancer has unraveled their potential as therapeutic targets (Hussen et al. 2023; Kumar et al. 2022). CircRNAs, whether functioning as oncogenes or tumor suppressors, may be harnessed as treatment targets. The unique backsplicing junction sequence of circRNAs allows for precise targeting of these molecules without interference with the corresponding parental mRNA, offering a promising avenue for therapeutic intervention (Beilerli et al., 2022). Despite these findings, the reasons behind the abnormal expression of circRNAs and the regulatory mechanisms governing circRNAs in tumors are still not fully understood (Zeng et al. 2022; H. da Zhang et al. 2018). In this review, we explore the role of circRNAs in BC, focusing on their biogenesis, dysregulation, and interactions with key signaling

pathways. Additionally, we examine the therapeutic potential of circRNAs in overcoming drug resistance and their utility as diagnostic and prognostic biomarkers.

## Classification of circRNAs

CircRNAs are a type of RNA with a covalently closed loop structure, making them more stable than linear RNA (Mumtaz et al. 2020). CircRNAs initially could not be differentiated based on their size and their lack of 5' and 3' ends as well as poly(A) tails made it difficult to identify them by traditional sequencing approaches. However, the advancement in high throughput sequencing methods have allowed for better classification of these circRNAs based on their origin which are derived from specific protein coding regions in the genome (Jeck and Sharpless 2014).

These circRNAs can be classified into 3 types (J. Li et al. 2023), the first type is known as exonic circular RNAs (ecircRNA) which have been found to be derived from the coding region of genes and are predominately localized in the cytoplasm, their primary role is to regulate gene expression following transcription. The second type, intronic circular RNAs (ciRNAs) which originate from intronic regions of genes, the region of genes that do not code for proteins, are mostly located in the nucleus, they actively participate in the coordination of the complex transcription process (Zhang et al. 2013). The third type are known as exon-intron circular RNAs (EiRNAs), these circRNAs can form a composition with exons which interact with RNA polymerase II enabling gene expression coordination (Li et al. 2015; Zhang et al. 2013).

## CircRNAs nomenclature

With the evolving field of research on circRNAs, the absence of standardized nomenclature has been a significant challenge for researchers (Liu et al. 2019; Youness et al. 2024). Current databases, including circBase 0.1 (<http://www.circbase.org/>), use arbitrary numbering and have limited information regarding the host gene and chromosomal locations of certain circRNAs (Youness et al. 2024). Consequently, a new nomenclature system based on the host gene and exact start/end positions within that gene has been developed to solve these issues and to facilitate clear communication between researchers (Moghaddam et al. 2022). The circBank database not only organizes circRNA data comprehensively but also provides detailed knowledge on miRNA binding sites, conservation, circRNA mutations, m6A modifications, protein-coding potential, and predicted

internal ribosome entry sites (IRESs), offering a basis for further development of circRNA nomenclature and functions (Youness et al. 2024).

Human circRNAs are named based on the human genome organization (HUGO) host gene symbol, following this format: “hsa-circHUGO-#”, according to the circBank (Seal et al. 2020). Additionally, circRNAs originating from the same host genes are numbered based on their position within the gene, with the upstream one given the initial number. If circRNAs have the same starting point but different ending point, the one with the earlier ending point gets the lower number (see Fig. 1). For circRNAs with identical starting and ending points, alternative splicing is taken into account. In this regard, the circRNAs nomenclature includes “has-circHUGO-#\_V#”, where “V” represents “variant”, and the number following “V” is determined by the length of the circRNA (Mumtaz et al. 2020; Seal et al. 2020).

For the intergenic circRNAs’ nomenclature, the format “has-circChrom#\_#” is applied, where the first number represents the chromosome number, and the circRNA order number is assigned according to the same rules as those for circRNAs derived from coding genes (Moghaddam et al. 2022).

## CircRNAs biogenesis

The biogenesis of most circRNAs occurs through a co-transcriptional, spliceosome-mediated process known as back-splicing. In this process, a 5′ splice donor site covalently links to an upstream 3′ splice acceptor site in the associated linear RNA, resulting in the circularization of the intervening exon(s) (Nielsen et al. 2022). Consequently, the formation of circRNA hinders the synthesis of mRNAs originating from the same genomic locus. Requirements for the splicing and circularization of exons have been identified by various

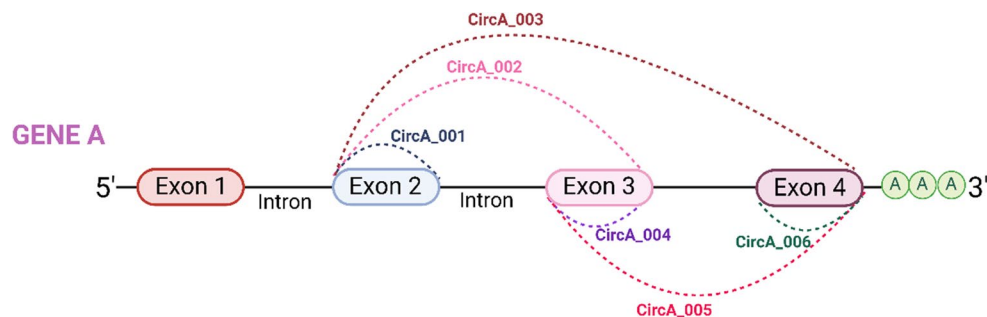
groups, whereby circularization signals reside within the introns flanking circle forming exons where protein factors bind to flanked intron sequences (Patop et al. 2019).

In eukaryotes, pre-mRNAs undergo two distinct splicing processes: “canonical splicing,” which generates linear mRNAs by splicing introns and joining exons, and “non-canonical splicing” or “back splicing,” which produces circRNAs by forming stable, covalently closed-loop structures without 5′ caps or 3′ poly(A) tails (Dawoud et al. 2024; J. Li et al. 2023). CircRNA loop formation involves junctions that are specific to each circRNA. Understanding these mechanisms is pivotal to understanding circRNA functions and enhancing their detection and analysis (Huang et al. 2020). Currently, two widely accepted circularization mechanisms explain this, as illustrated in Fig. 2.

## Lariat-driven circularization

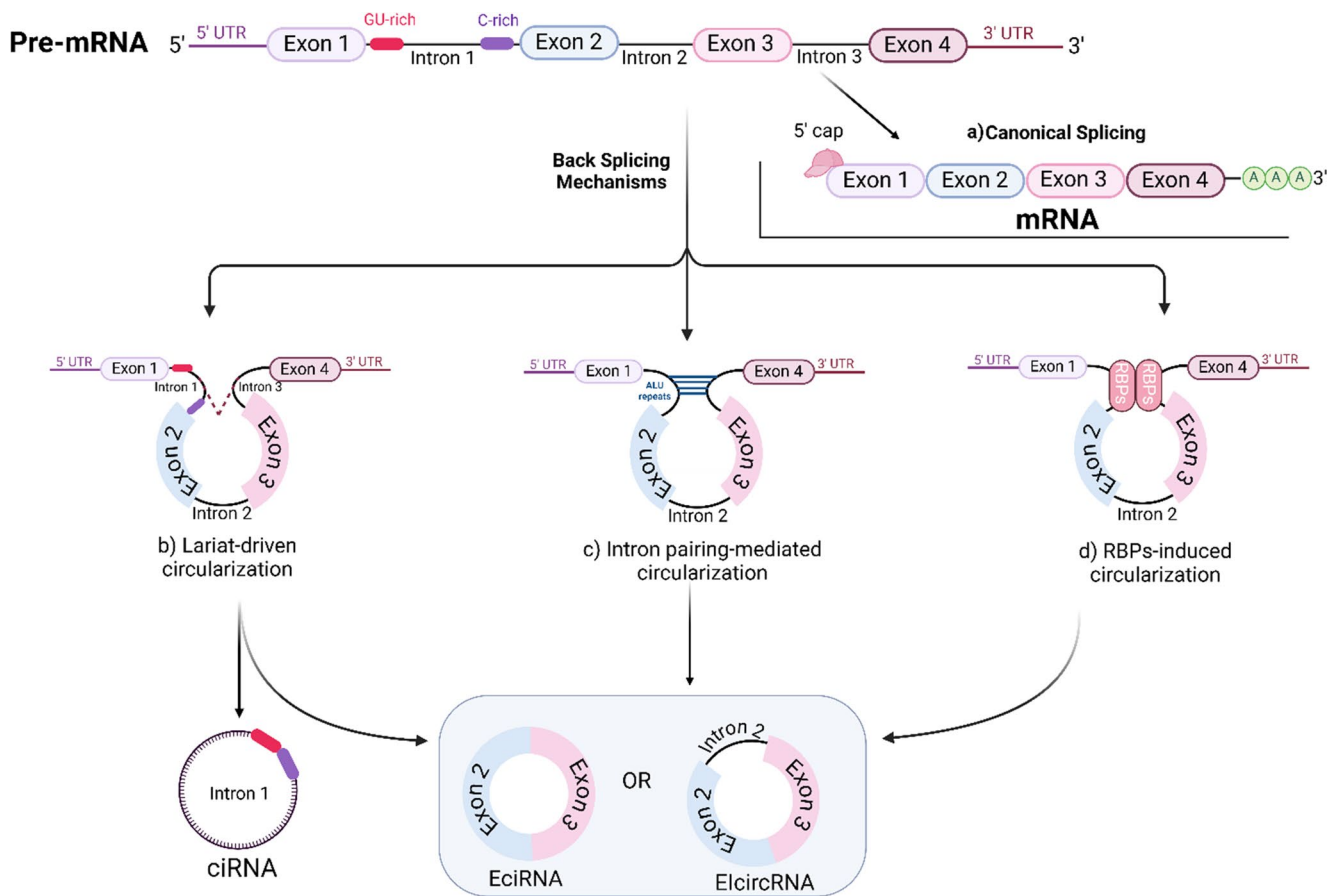
In this circularization model, the pre-mRNA undergoes partial folding in a way that brings the 5′ splice donor (SD) site of a downstream exon into proximity with the 3′ splice acceptor (SA) site of an upstream exon (He et al. 2021a, b). This interaction facilitates exon skipping, leading to the formation of a lariat structure that encapsulates both exons and introns. The resulting lariat, which includes the skipped exon, subsequently undergoes internal splicing to produce ecircRNA through back-splicing (Y. Huang and Zhu 2021). Introns can also be removed by the action of the lariat debanching enzyme (DBR), which linearizes intron lariats for degradation (Carriero and Damha 2003). However, if the introns are not fully removed during this process, an exon-intron circRNA (EircRNA) will be produced instead (Dawoud et al. 2023).

Mechanistic evidence suggests that the generation of a large lariat encompassing the skipped exon is a prevalent and crucial stage in circRNA biogenesis, particularly during



**Fig. 1** Nomenclature of circRNAs in CircBank. Schematic representation of alternative back-splicing events generating multiple circRNA isoforms from GENE A. Exons are represented as colored boxes, and introns as connecting lines. The arcs represent back-splicing junctions. CircA\_001 to CircA\_006 indicate specific circRNA iso-

forms: CircA\_001: circularization of Exon 2, CircA\_002: Exons 2–3, CircA\_003: Exons 2–4, CircA\_004: Exon 3, CircA\_005: Exons 3–4, and CircA\_006: Exon 4. Each circRNA is formed by a back-splicing event that links a downstream 5′ splice donor site to an upstream 3′ splice acceptor site



**Fig. 2** Biogenesis of circRNAs. Pre-mRNA can follow two main processing pathways: (a) canonical splicing, which results in linear mRNA, or (b–d) alternative back-splicing mechanisms that generate circRNAs. (b) Lariat-driven circularization leads to the formation of an exon-containing lariat. During exon-skipping events, producing eciRNA or ecircRNA. In contrast, ciRNAs are derived from intron lariats that evade debranching following canonical splicing, with a dis-

tinctive 7-nucleotide GU-rich motif adjacent to the 5' splice site and an 11-nucleotide C-rich motif near the branch point. (c) Intron pairing-mediated circularization occurs through complementary base-pairing between flanking intronic sequences, such as ALU repeats. (d) RBP-induced circularization is facilitated by RNA-binding proteins (RBPs) that bring splice sites into proximity, promoting circRNA formation

indirect back-splicing processes (Sharpless and Norman 2014; Xiao et al. 2018) lariat, produced by exon skipping, acts as a precursor that undergoes back-splicing, resulting in a mature circRNA molecule (Jiang et al. 2021; Li et al. 2019).

### Direct Back-splicing

In this method, if back-splicing occurs initially, the RNA precursor will directly make a circRNA along with an intermediate that contains both introns and exons. This intermediate is then further processed to produce a linear RNA (Robic and Kühn 2020). The method of “direct back-splicing” can be further classified into two groups based on the differences of the circularization mechanism: “Intron-pairing Driven Circularization” and “RNA-binding proteins (RBP)- Mediated Circularization (Y. Huang and Zhu 2021).

### Intron-pairing driven circularization

Intron-pairing Driven Circularization is triggered by intronic flanks adjacent to circularized exons. A critical element in this process is a conserved motif found in both the upstream and downstream introns, identified as the canonical ALU repeat. Notably, these distinct characteristics of exon and intron length are strongly associated with the production of EicircRNA, where introns are conserved, and ecircRNA, where introns are excised. This observation suggests that the circularization process is highly specific (He et al. 2021a, b).

### RNA-binding proteins (RBP)-induced circularization

The relationship between RNA-binding proteins (RBPs) and circRNAs is bidirectional and context-dependent, with circRNAs also exerting regulatory control over RBP

expression (Jiang et al. 2021). Here, the biogenesis of circRNAs is modulated by RBPs through various mechanisms discussed below (Zang et al. 2020). These proteins play a pivotal role in both promoting and inhibiting the formation of circRNAs, thereby significantly impacting their abundance and functional roles in different cellular contexts. The relationship between RBPs and circRNAs is bidirectional and context-dependent, with circRNAs also exerting regulatory control over RBP expression (Jiang et al. 2021).

One of the primary mechanisms through which RBPs facilitate circRNA formation is by the stabilization of the transient RNA structures necessary for back-splicing (Chen 2020). Double-stranded RNA-binding proteins (dsRBPs) such as NF90/NF110 have been demonstrated to enhance circRNA production by binding to intronic RNA sequences that flank circularized exons (Ren et al. 2022). NF90/NF110, through their dsRNA binding domains (dsRBDs), interact with inverted Alu repeats (IRAlus) within nascent pre-mRNA, thereby stabilizing the back-splicing event and promoting circRNA formation. This stabilization is crucial, as it ensures the correct alignment and pairing of complementary sequences, which are essential for the circularization process (Li et al. 2018).

Conversely, RBPs could also work as inhibitors by destabilizing the RNA duplexes required for back-splicing. For instance, the RNA helicase DHX9, which incorporates both a dsRBD and an RNA helicase domain, has been shown to play a significant role in the regulation of circRNA production by unwinding RNA duplexes that are essential for the back-splicing process, thus preventing the formation of circRNAs (Jiang et al. 2021). Adenosine deaminase acting on RNA 1 (ADAR1) inhibits circRNA production by editing adenosines to inosines in RNA duplexes, reducing sequence complementarity and destabilizing the RNA structure, which impairs circRNA formation. Interestingly, there appears to be a functional interplay between DHX9 and ADAR1 in the regulation of circRNA biogenesis, potentially due to their shared association with Alu elements (Rybak-Wolf et al. 2014).

## Mechanistic insights into circRNAs' role in breast cancer

As previously discussed circRNAs are known for their stability, interact with RBPs and also engage in key growth signaling pathways such as MAPK/ERK and PTEN/PI3K/AKT. CircRNAs engage with RBPs through mechanisms including acting as protein sponges, decoys, scaffolds, or recruiters, thereby influencing the fate of their target mRNAs (Table 1). Additionally, some circRNAs possess an Internal Ribosome Entry site (IRES), enabling them to directly encode proteins (Lei et al. 2020). While circRNAs

primarily function as miRNA sponges, their secondary function involves circRNA-protein interactions. Among the proteins that interact with RNA molecules, RBPs are particularly significant. These proteins play a crucial role in RNA metabolism, including processes such as maturation, transport, localization, and translation of RNAs, and are also involved in the formation of ribonucleoprotein complexes (Ceci et al. 2021). Therefore, circRNAs function through various mechanisms, including sponging miRNAs and interfering with RNA splicing, making them potential biomarkers and therapeutic targets for management of diseases including cancer (Ghazimoradi and Babashah 2022).

### CircRNAs as miRNA sponges

CircRNAs containing multiple miRNA binding sites can function as competing endogenous RNAs (ceRNAs) by binding to miRNAs via miRNA response elements (MREs), thereby inhibiting their activity (Fig. 3) (Singh et al. 2024). For example, a recent study assessing autophagy-associated circRNA circCDYL found that circCDYL promoted autophagic level in BC cells via the miR-1275-ATG7/ULK and may serve as a potential prognostic and predictive marker for BC patients (Liang et al. 2020).

CircIFI30 promotes the progression of triple-negative breast cancer (TNBC) and may function as a ceRNA for miR-520b-3p, counteracting its suppressive impact on the *CD44* gene, thereby promoting the progression of TNBC (Xing et al. 2020). Therefore, the circIFI30/miR-520b-3p/CD44 axis could serve as a novel diagnostic and prognostic marker, as well as a potential therapeutic target for TNBC patients (Xing et al. 2020). Circ\_0006528 contributes to paclitaxel (PTX) resistance in BC by sponging miR-1299, thereby upregulating cyclin-dependent kinase 8 (CDK8) expression, which is linked to poor patient prognosis (Xing et al. 2020). Inhibition of Circ\_0006528 in paclitaxel-resistant BC cells disrupts EMT and enhances tumor cell clearance, while promoting apoptosis and impeding tumor growth, underscoring its potential as a therapeutic target in overcoming drug resistance (Wang et al. 2023a, b) (Table 1).

### CircRNAs as protein sponges

CircRNAs can act as protein sponges or decoys, affecting cellular functions by modulating protein expression and function, while also influencing their own synthesis and degradation through RNA-protein interactions (Fig. 3) (Huang et al. 2020). RBPs are the most common class of proteins which interact with RNA molecules. These proteins play a crucial role in RNA metabolism, including processes such as maturation, transport, localization, and translation of RNAs, influencing their roles in BC (Conlon and Manley

**Table 1** Mechanistic insight into circRNA roles in breast cancer

CircRNA	Functional role	Interaction	Effect	References
circFOXO3	Protein scaffold	p53/p21-CDK2	Inhibits cell proliferation and induces apoptosis	(Du et al. 2017)
circ-0011946	miRNA sponge	miR-145-5p/RFC3	Promotes cell proliferation and migration	(Zhou et al. 2018)
circ-NR3C2	Protein scaffold	NR3C2	Promotes cell survival and resistance to apoptosis	(Fan et al. 2021)
circ-ABCB10	miRNA sponge	miR-1271/ABCB10	Promotes drug resistance and cell survival	(Liang et al. 2017)
circ-DNMT1	miRNA sponge	miR-1236-3p/DNMT1	Inhibits cellular senescence and promotes tumor growth	(Du et al. 2018)
circ-CNOT2	Protein scaffold	CNOT2	Enhances cell proliferation and survival	(Smid et al. 2019)
circAHNAK1	miRNA sponge	miR-421/RASA1	Cell proliferation.	(Xiao et al. 2019)
circ-tada2a-E6	miRNA sponge	miR-203a-3p/TADA2A	Promotes tumor growth and progression	(Xu et al. 2019)
FECR1	Protein recruiter	TET1	Induce invasion, metastasis	(Chen et al. 2018a, b)
circ-Ccnb1	protein scaffold	H2AX, p53; H2AX, Bcl1	Decrease Proliferation, induce apoptosis	(Fang et al. 2018)
circ-IRAK3	miRNA sponge	miR-942/IRAK3	Promotes inflammation and cancer progression	(He et al. 2017)
circ-gfra1	miRNA sponge	miR-34a/GFRA1/TLR4	Enhances cell survival and proliferation and paclitaxel resistance	(He et al. 2017)
circDNMT1	Protein translocation	p53, AUF1	Autophagy mediated cell proliferation, survival, and tumor growth	(Du et al. 2018)
circBACH2	miRNA sponge	miR-186-5p/miR-548c 3p/CXCR4	Cell proliferation, invasion, and metastasis.	(Wang et al. 2021a, b)
Circ-IKBKB	Protein decoy	Decoys NF-κB pathway proteins	Promotes inflammation and cancer progression	(Xu et al. 2021)
circ-PDCD11	miRNA sponge	miR-512-3p/CDCA3/PDCD11	Increased glucose uptake, lactate production, ATP generation, Promote tumorigenesis.	(Xing et al. 2021)
circMTO1	Protein scaffold	TRAF4/Eg5	inhibits cell proliferation	(Liu et al. 2018)
circ-EIF6	Protein-coding	EIF6-224 aa/MYH9	Promotes proliferation and metastasis	(Li et al. 2022)
CircSEMA4B	Protein-coding	SEMA4B-211aa/PI3K/AKT	Negative regulator of PI3K/AKT signaling pathway	(Wang et al. 2022)
circEPSTI1	miRNA sponge	miR-4753/6809-BCL11A	Inhibits cell proliferation, migration, invasion and induces apoptosis	(Chen et al. 2018a, b)

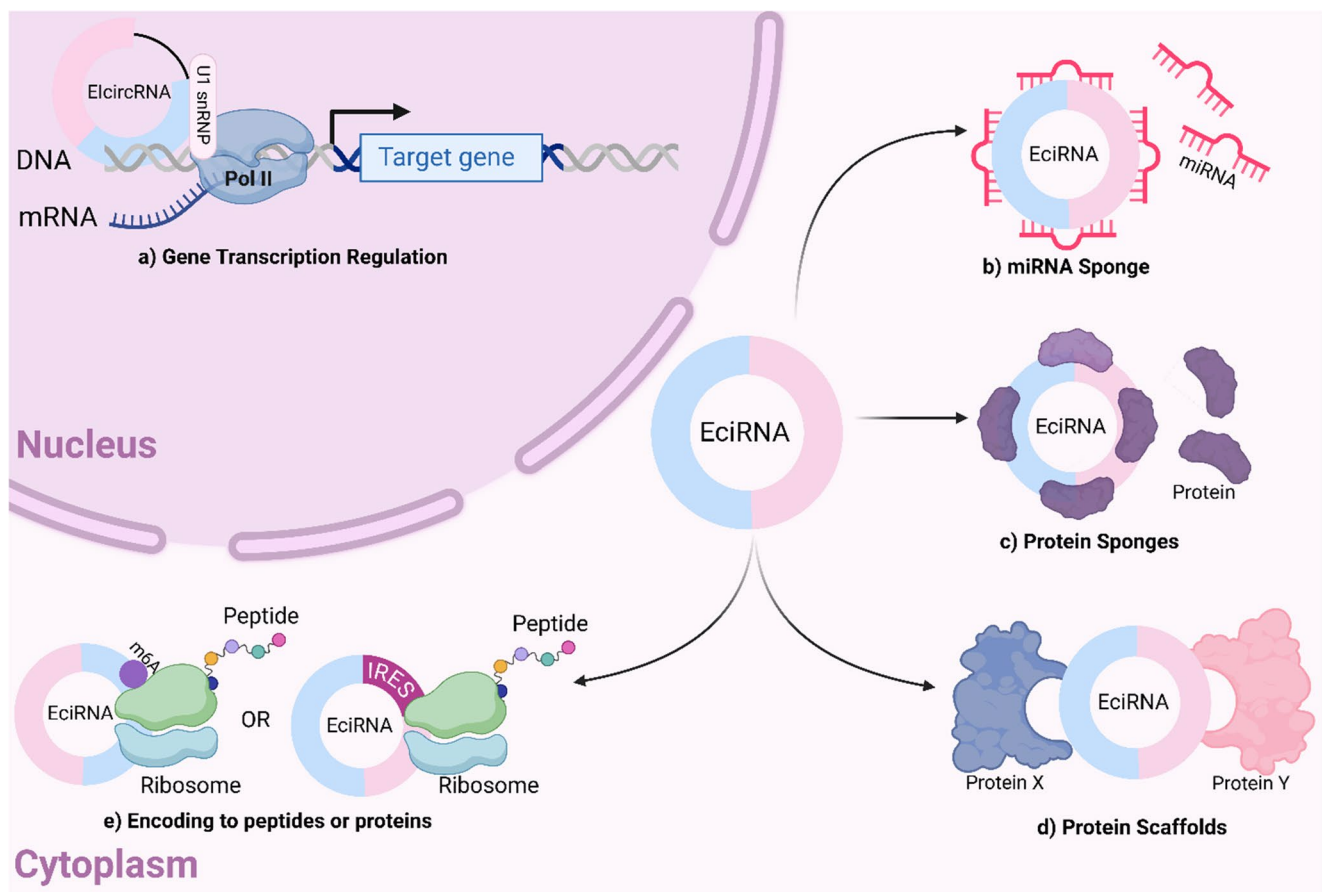
2017). Similarly, circSKA3 enhances tumor progression as it promotes migration and invasion of BC cells and tissues by forming a complex with Tks5 and integrin  $\beta$ 1. This results in the formation of invadopodium which are responsible for cancer invasiveness and metastasis (Du et al. 2020).

Other studies demonstrated circ-Dnmt1 oncogenic behavior in BC, which promotes tumor growth by inhibiting cellular senescence through autophagy modulation. It achieves this by facilitating the nuclear translocation of p53 and AUF1, which interact with circ-Dnmt1 to enhance cell proliferation and survival (Du et al. 2018). CircAMOTL1, a newly identified circRNA, enhances c-Myc nuclear translocation in BC and is linked to increased cell viability, invasion, and Paclitaxel (PTX) resistance. In BC tissues, circAMOTL1 is overexpressed, resulting in a significant increase in both phosphorylated and total AKT protein (Sadlak et al. 2023). Additionally, circAMOTL1 modulates the gene and protein expression of AKT-related pro-apoptotic (BAX and BAK) and anti-apoptotic (BCL-2) factors, indicating its potential role in stabilizing AKT signaling. These results suggest the important role circAMOTL1 may play in the Paclitaxel (PTX) resistance of BC cells. Knockdown of circAMOTL1 disrupts these processes, highlighting its potential as a therapeutic target for BC treatment (Sun et al. 2020) (Table 1).

### CircRNAs as molecular scaffolds

CircRNAs can also function as scaffolds facilitating contact between two or more proteins (Fig. 3) (Zhou et al. 2020a, b). Circ-Ccnb1 functions as a scaffold that modulates interactions between key proteins depending on the p53 mutation status (Almouh et al. 2022). In wild-type p53 cells, circ-Ccnb1 facilitates the interaction between p53 and H2AX, promoting cell survival. However, in p53 mutant cells, circ-Ccnb1 forms a complex with H2AX and Bclaf1, leading to cell death. These findings suggest that Ccnb1 scaffolding could be targeted to develop new therapeutic strategies against p53 mutations (Fang et al. 2018).

Notably, a recent study identified that circEIF3H interacts with the RNA-binding proteins IGF2BP2 and HuR, both of which are known to stabilize mRNAs. Through this interaction, three target genes—HSPD1, RBM8A, and G3BP1 have been identified (Yang et al. 2024). HSPD1 (also known as HSP60) is crucial for protein folding and mitochondrial assembly, and is secreted by cancer cells, contributing to processes such as transformation, angiogenesis, and metastasis (Javid et al. 2022). RBM8A, while associated with poor prognosis and tumor progression in hepatocellular carcinoma has an undetermined role in BC



**Fig. 3** Biological Functions of circRNAs. CircRNAs exhibit multifaceted roles in both the nucleus and cytoplasm. **(a)** ElcircRNAs enhance the transcription of parental genes by interacting with U1 snRNP and Pol II. **(b)** CircRNAs regulate miRNA activity by containing miRNA response elements (MREs), which sequester miRNAs and lead to either translational repression or mRNA degradation. **(c)** Some cir-

crnAs possess internal ribosome entry sites (IRES) or undergo m6A modifications, allowing them to act as templates for peptide or protein synthesis. **(d)** CircRNAs serve as protein scaffolds, promoting the assembly of molecular complexes. **(e)** They also function as sponges for RNA-binding proteins (RBPs), thereby influencing gene expression

(R. Liang et al. 2021a, b). G3BP1, on the other hand, is known to enhance tumor cell proliferation and metastasis while inhibiting apoptosis through pathways involving Ras, TGF- $\beta$ /Smad, Src/FAK, and p53. In BC, G3BP1 drives cell proliferation through the upregulation of PMP22 expression (Song et al. 2022). Together, the oncogenic activity of these genes' underscores circEIF3H's pivotal role in cancer progression and its potential as a target for personalized therapy in TNBC (Table 1) (Song et al. 2022).

### CircRNAs' translational roles

CircRNAs were once presumed to be untranslatable. However, studies have shown that circRNAs possess open reading frame (ORF) features, along with IRES or m6A modifications that can be effectively translated into long proteins in eukaryotic translation systems through a rolling circle amplification (RCA) mechanism potential for

circRNA translation in human cells (Fig. 3) (Chen et al. 2021). For instance, circFBXW7, a circRNA derived from the FBXW7 Gene encodes a 185-amino acid peptide (FBXW7-185aa) with tumor-suppressive properties. This peptide competitively interacts with USP28, counteracting USP28-induced c-Myc stabilization. Notably, the upregulation of FBXW7-185aa has been shown to inhibit the proliferation and migration of TNBC cells by increasing FBXW7 levels and promoting c-Myc degradation (Ye et al. 2019). FBXW7 was found to be downregulated in TNBC therefore upregulation of this circRNA may be used therapeutically (Table 1).

Additionally, increased expression of circ-EIF6 was found to promote cell proliferation and metastasis in TNBC in vivo and in vitro (Li et al. 2022). This circRNA which encodes the novel peptide EIF6-224 amino acid (aa), contains a 675-nucleotide (nt) open reading frame (ORF) with an IRES required for translation initiation. Expression of

EIF6-224aa led to increased cell proliferation and migration mediated by inhibition of the ubiquitin-proteasome pathway and subsequent activation of the Wnt/beta-catenin pathway (Li et al. 2022). Similarly, circSEMA4B has been demonstrated to encode SEMA4B-211aa (Wang et al. 2022). However, mechanistically, SEMA4B-211aa inhibited the generation of PIP3 by competing with p110 to bind to p85, thereby inhibiting the phosphorylation of AKT (Thr308) leading to reduced activation of the PI3K/Akt pathway and inhibition of cell proliferation. Therefore, restoration of circSEMA4B in BC patients with low expression levels may have therapeutical potential (Wang et al. 2022) (Table 1).

### CircRNAs as transcription regulators

CircRNAs are known to modulate the transcription of their host genes either positively or negatively by interacting in a cis acting manner with RNA polymerase II (Pol II) in promotor regions, recruiting various proteins, or forming an R-loop that targets transcriptional regulatory regions of the host genes (García-Muse and Aguilera 2019). Comprehensive research has demonstrated that most EIciRNAs predominantly localize in the nucleus, where they engage with RNA Pol II to modulate host gene transcription in a cis-acting manner, whereas the majority of the ecircRNAs are found to localize in the cytoplasm (Fig. 3) (Wei et al. 2023).

Nuclear run-on assays demonstrated that silencing circEIF3J and circPAIP2 reduced the transcription of their respective parental genes, EIF3J and PAIP2, whereas direct silencing of these genes via siRNA did not significantly affect their transcription. RNA-DNA double FISH confirmed the co-localization of circEIF3J and circPAIP2 with their parental gene loci, suggesting that these circRNAs may regulate their gene expression in a cis-acting manner (Bose and Ain 2018). CircRNAs could also regulate transcriptional gene expression by serving as miRNA sponges as represented in Table 1.

### CircRNAs and the key hallmarks of breast cancer

Research has established that circRNAs play many diverse roles in BC progression. Some studies have discovered specific roles of circRNAs pertaining to certain hallmarks, such as angiogenesis, metastasis, or metabolic reprogramming (Yarmishyn et al. 2022). However, most circRNAs are involved in more than one hallmark of cancer (Table 2). Recent evidence on the roles of different circRNAs in BC hallmarks is summarized below.

### Role of circRNAs in metabolic reprogramming

Cancer cells exhibit heightened rates of cellular division and growth, which increases the cell's metabolic demands and requirements. To satisfy these needs, cancer cells undergo metabolic reprogramming where they change the way they metabolize glucose, fatty acids, and amino acids (Cai et al. 2023). One prominent feature of metabolic reprogramming is the shift of the cancer cell from oxidative phosphorylation to glycolysis for the generation of energy, also known as the Warburg effect (Schiliro and Firestein 2021).

CircRNAs play crucial roles in metabolic reprogramming. For example, circSIPA1L3 boosts the rate of glycolysis in TNBC. This leads to an increase in the production of lactate and a subsequent attraction of tumor-associated macrophages and tumor metastasis (Liang et al. 2024a, b). Increased glutamine metabolism in BC has been extensively studied and characterized, offering targetable metabolic dependencies (Li et al. 2023) (Table 2). CircSEPT9 was found to upregulate solute carrier family 1 (neutral amino acid transporter), member 5 (SLC1A5) expression by sponging of miR-149-5p in TNBC (X. Wang et al. 2021a, b). Knockdown of circSEPT9 led to reduced glutamine uptake and cell proliferation and increased cell apoptosis (X. Wang et al. 2021a, b). Similarly, in TNBC, circ\_0062558 was found to enhance glutamine metabolism by sponging of miR-876-3p which leads to enhanced expression of SLC1A5. This led to an increase of cell proliferation, survival, migration and invasion of TNBC cells (Yuan et al. 2022). For fatty acid metabolism, circMYC was found to be upregulated in TNBC, which binds to human antigen R (HuR) protein. This improves the binding affinity of HuR to the sterol regulatory element binding protein 1 (SREBP1) mRNA and increases its stability (S. Wang et al. 2023a, b). The enhanced stability of the SREBP1 mRNA leads to increased lipogenesis, ultimately leading to cancer progression (S. Wang et al. 2023a, b) (Table 2).

### Role of circRNAs in apoptosis

Normal cells activate apoptosis, or programmed cell death, once they accumulate increasing amounts of mutations or aberrations (Obeng 2021). However, one of the hallmarks of cancer is resistance to apoptosis, where the cells lose the ability to self-destruct (Neophytou et al. 2021). Studies have shown that circRNAs also play an influential role in enabling BC cells to escape apoptosis. CircZEB1, for instance, was found to be overexpressed in BC, increasing the sponging of miR-448, leading to a subsequent increase in eukaryotic elongation factor 2 kinase (eEF2k) (Pei et al. 2020). A recent study also discovered that circARHGER28

**Table 2** CircRNAs in breast cancer and their targets

CircRNA	Regulation	Target miRNA	Pathway	Reference
Circ_JMJD1C	Up	miR-182-5p	JMJD1C and SOX4	(Xu et al. 2024)
Circ_0008717	Up	miR-326	GATA6	(L. Yang and Chen 2023)
NR3C2	Down	miR-513a-3p	HRD1	(Fan et al. 2021)
CircFOXO	Down	WHSC1	Zeb2	(Chen et al. 2024a, b)
CircIKBKB	Up	IκBα	NF- κB pathway	(Xu et al. 2021)
CircHIF1A	Up	miR-149-5p	AKT/STAT3 pathway	(Chen et al. 2021; Zepeda-Enríquez et al. 2023)
Circ-0100519	Up	USP7	USP7 and NRF2	(Zhuang et al., 2024)
CircCAPG	Up	STK38 SMURF1	MEKK2-MEK1/2-ERK1/2 pathway	(Song et al. 2023)
Circ_0059457	Up	miR-140-3p	UBE2C	(Huang et al. 2024)
Hsa_circ_0001925	Up	miR-1299	YY1	(Shen et al. 2023)
Hsa_circ_0008673	Up	miR-578	GINS4	(Sun et al. 2023)
CircRPPH1	Up	miR-556-5p	YAP1/Hippo signaling pathway	(Y. Zhou et al. 2020a, b)
CircBRAF	Up	KDM4B IGF2BP3	MMP9 ADAMTS14	(Lan et al. 2024)
CircZEB1	Up	miR-337-3p	YBX1 and OGT	(D. Wang, Chen et al. 2024a, b)
Circ_0002496	Up	miR-433-3p	YWHAZ Bax And Bcl-2	(Yang et al. 2023)
Circ_0045881	Down	miR-214-3p	Unknown	(Ren et al. 2024)
CircNFIB	Down	Encodes a 56 amino acid protein	Arachidonic acid synthesis	(Zhong et al. 2024)
Circ_0009910	Up	miR-145-5p	MUC1	(Abtin et al. 2024)
CircRREB1	Up	GNB4	ERK1/2 pathway	(H. Chen et al. 2024a, b)
CircHSDL2	Up	miR-7978	ZNF704 and MST2	(Wang et al. 2024)
hsa_circ_0003528	Up	miR-215	Unknown	(Chang et al. 2024)
Circ_0104345	Up	miR-876-3p	ZBTB20	(Wu et al. 2023)
CircZEB1	Up	miR-448	eEF2k	(Pei et al. 2020)
CircARHGGER28	Up	Unknown	PI3K/AKT/mTOR pathway	(Tao et al. 2024)
CircSPECC1	Up	miR-1236-3p	CBX8	(Zhang et al. 2024)
CircCDYL	Down	miR-190a-3p	TP53INP1	(Wang et al. 2020)
Circ_0058063	Up	miR-557	DLGAP5	(Zhu et al. 2024)
CircSEPT9	Up	miR-625-5p	PTBP3	(Shi et al. 2024)
CircSIPA1L3	Up	miR-665	SLC16A1 RAB11A (glycolysis)	(Yuan et al. 2022)
CircPRKC1	Up	miR-545-3p	AKT phosphorylation	(X. Wang, Song et al. 2022)

overexpression increases apoptosis of BC cells (Tao et al. 2024).

Another recent study found circSPECC1 to be overexpressed in BC tissues and that its downregulation led to an increase in apoptosis by increasing the expression of miR-1236-3p (Zhang et al. 2024). Conversely, the overexpression of circ\_0058063 was found to enhance apoptosis by reducing miR-557 expression which leads to an increase in discs large-associated protein 5 (DLGAP5) expression (Zhu et al.

2024). DLGAP5 plays a role in polymerizing microtubules and formation of spindle fibers, which enables the cell to transition from the G2 phase of the cell cycle to the mitotic phase. In addition to the previous circRNAs, the overexpression of circCDYL was found to enhance apoptosis by binding to miR-190-3p and increasing the expression of tumor protein p53 inducible nuclear protein 1 (TP53INP1), a prominent tumor suppressor. Research has also revealed that inhibition of circSEPT9 increases apoptosis through

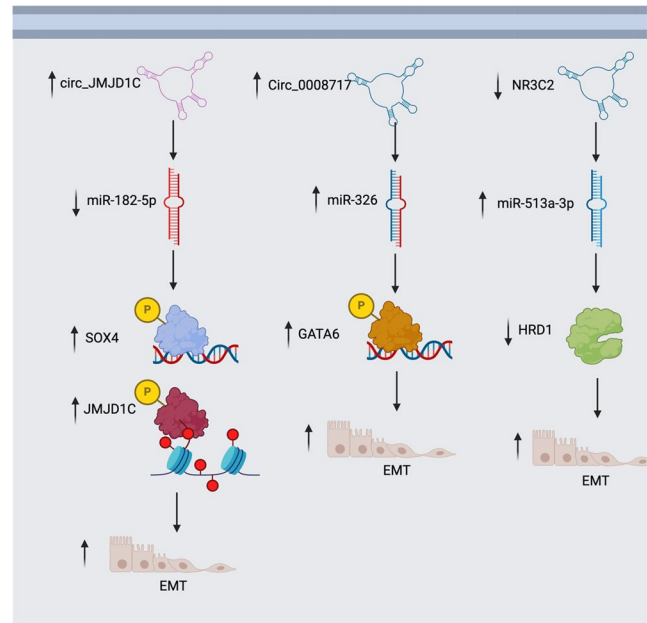
the elevation of miR-625-5p expression (Table 2) (Shi et al. 2024).

### Role of circRNAs in the epithelial mesenchymal transition (EMT)

One of the initial stages of metastasis is the EMT, where the cancer cell changes its morphology and develops the capacity to separate from the extracellular matrix (ECM) and migrate into neighbouring tissues (Xu et al. 2024). Numerous studies have demonstrated that circRNAs play a role in the EMT process thus enabling or suppressing metastasis (Ashrafzadeh et al. 2024). One of the main mechanisms through which this takes place is by sequestering microRNAs and regulating the expression of oncogenes or tumor suppressor genes. A recent study highlighted the role of the circRNA for Jumonji C (JmjC) domain-containing (JMJD) demethylases (circ\_JMJD1C) in EMT where it absorbs miR-182-5p leading to increased expression of JMJD1C and SRY-related HMG-box transcription factor 4 (SOX4) (Xu et al. 2024).

While previous studies show that circ\_JMJD1C can function as either a tumor promoter or suppressor in different cancers (Manni et al. 2022), SOX4 is a transcription factor that was shown to promote cellular migration by activating the transcription of chemokine Ligand 12 (CXCL12) (Tsai et al. 2020). Circ\_JMJD1C has been demonstrated to not only regulate EMT, but that it also increases tumor growth and reduces programmed cell death (Xu et al. 2024). Circ\_0008717 is another circRNA that plays a role in EMT as well as migration, angiogenesis, and invasion. Circ\_0008717 achieves this effect by decreasing miR-326 leading to increase of GATA6. GATA6 is an oncogenic transcription factor that increases EMT by increasing the expression of Slug, another transcription factor (Fig. 4) (L. Yang and Chen 2023).

Another circRNA implicated in EMT is Nuclear Receptor Subfamily 3, Group C, Member 2 (NR3C2), which was found to be downregulated in TNBC. Its low expression in BC undermines the capacity of ERAD-associated E3 ubiquitin-protein ligase HRD1 (HRD1) to suppress tumor EMT by increasing the availability of miR-513a-3p (Fig. 4) (Fan et al. 2021). On the other hand, circANKS1B was found to be overexpressed in TNBC, which in turn leads to increased EMT by increasing the expression of transforming growth factor beta 1 (TGF- $\beta$ 1). TGF- $\beta$ 1 is a growth factor known to play a positive role in EMT by activating transcription regulators such as Smad2 and Smad3. In turn, Smad2 and Smad3 interact with transcription factors to activate the expression of mesenchymal genes and reduce the expression of epithelial genes (Xu et al. 2009). (Table 2).



**Fig. 4** CircRNAs are implicated in epithelial mesenchymal transition (EMT) in breast cancer. CircJMJD1C upregulation leads to increased sponging of miR-182-5p, which increases the expression of SOX4 and JMJD1C, leading to increased EMT. Increased expression of circ\_0008717 leads to increased expression of miR-326, negatively affecting the expression of GATA6, which, in turn, increases EMT. The expression of NR3C2 is downregulated in BC, leading to increased availability of miR-513a-3p. This reduces the expression of HRD1, and leads to increased EMT

### Role of circRNAs in breast cancer tissue invasion

Studies have found that circRNAs can also contribute to the capacity of BC cells to invade surrounding tissues. In TNBC, circ\_0045881 was demonstrated to be downregulated. However, increasing the expression of circ\_0045881 resulted in decreased expression of miR-214-3p, leading to decreased tumor-cell invasion capacity (Ren et al. 2024). Another study reported that there was lower circNFIB expression in BC tissues compared to control tissues, which was found to lead to increased metastasis. This observed increase in metastasis is thought to be mediated through reduced arachidonic acid (AA) synthesis (Zhong et al. 2024), which, in turn, leads to increased activation and expression of inflammatory cytokines and angiogenic factors. Tumor invasion of the lymph nodes was found to be correlated with increased expression of circ\_0009910 and decreased expression of miR-145-5p (Abtin et al. 2024). Among the positive contributors is also circRREB1, which causes increased invasion, growth, and metastasis in BC by binding to guanine nucleotide-binding protein subunit beta-4 (GNB4) and activating the extracellular regulated kinase 1/2 (ERK1/2) pathway (Table 2) (H. Chen et al. 2024a, b).

Aside from the aforementioned circRNAs, increased circHSDL2 in BC patients was found to enhance the cancer's capacity to invade in the matrigel and the transwell assays by sequestering miR-7978, leading to increased expression of Zinc Finger Protein 704 (ZNF704) and reduced expression of mammalian ste20-like kinase 2 (MST2) (Wang et al. 2024). MST2 is a well-known component of the Hippo pathway, which plays a role in cancer growth and invasion (Elemam et al. 2024; Wang et al. 2024b). Recent evidence also pointed to an increase in hsa\_circ\_0003528 expression in TNBC corresponding to a decrease in miR-215, leading to increased proliferative potential, migration abilities, and invasive capacities of TNBC cells (Table 2) (Chang et al. 2024).

Furthermore, circ\_0104345 expression in BC cells was found to support their ability to not only survive apoptosis, but also to proliferate, move, and invade surrounding tissues. Circ\_0104345 achieves this through sponging miR-876-3p, thereby increasing the expression of Zinc finger and BTB domain-containing protein 20 (ZBTB20), (Wu et al. 2023) (a transcription factor that reduces the expression of inhibitor of kappa B (I $\kappa$ B). This reduction in I $\kappa$ B leads to an increase of nuclear translocation of nuclear factor kappa B (NF- $\kappa$ B), which is thought to mediate an increase in matrix metalloproteinase 2 and 9 (MMP2 and 9) and increased cellular migration (Stoyanov et al. 2023). In Human epidermal growth factor receptor 2 (HER2)-positive BC cells, upregulation of circEPSTI1 was found to promote cell proliferation, migration and invasion mediated by miR-145 sponging, leading to increased expression of Erb-B2 Receptor Tyrosine Kinase 3 (ERBB3), a tyrosine kinase receptor involved in the growth and survival of breast epithelial cells (Hamburger 2008; Zhang et al. 2022). In TNBC, circPRKC1 (hsa\_circ\_0067934) was demonstrated to upregulate WW domain binding protein (WBP2) and promote protein kinase B (AKT) phosphorylation through sponging of miR-545-3p leading to increased cell proliferation and migration (Table 2) (X. Wang, Song et al. 2022).

### Role of circRNAs in breast cancer metastasis

Regarding the involvement of circRNAs in metastasis, recent studies have shown that the downregulation of circFOXO, when observed in TNBC, is connected to metastasis of the breast tumor to lymph nodes resulting in a negative prognosis for patients. The downregulation of circFOXO resulted in an increase in the translocation of Wolf-Hirschhorn Syndrome Candidate 1 (WHSC1) to the nucleus, leading to an increase in the expression of zinc finger E-box binding homeobox 2 (Zeb2) and increased metastasis (Chen et al. 2024a, b). Studies suggest that Zeb2 increases metastasis by altering the expression of cell-cell junctions (Korpal et al.

2008). However, one study by Burks et al. (2021) suggests that Zeb2 does not alter the expression of epithelial or mesenchymal genes, although it does observe that Zeb2 plays a role in metastasis (Table 2).

One study demonstrated circIKBKB's ability to promote the metastasis of BC to bone by activating the NF- $\kappa$ B pathway through the phosphorylation and inhibition of inhibitor of nuclear factor kappa B alpha (I $\kappa$ B $\alpha$ ) (Xu et al. 2021). By activating the NF- $\kappa$ B pathway, circIKBKB promotes cancer-related inflammation and metastasis as a consequence (Liu et al. 2015). Other studies have demonstrated that circHIF1A contributes to the metastasis of BC to lymph nodes by binding to miR-149-5p and inhibiting cyclin-dependent kinase inhibitor 1 (P21), the main target of P53. The biogenesis of circHIF1A takes place through the activation of fused in sarcoma (FUS) protein, which is activated by nuclear factor 1 B (NF1B), which in turn increases the activity of the protein kinase B/signal transducer and activator of transcription 3 (AKT/STAT3) pathway. At the same time, circHIF1A itself modulates the activity of NF1B, creating a positive feedback loop that increases circHIF1A and increases the activity of AKT/STAT3 pathway (Table 2) (Chen et al. 2021; Zepeda-Enrquez et al. 2023).

Another recent study found that circ-0100519 expression was increased in BC, increasing metastasis by secretion into exosomes and an increase of the de-ubiquitination of nuclear factor-like 2 (NRF2) by the ubiquitin specific protease 7 (USP7) in macrophages (Zhuang et al., 2024). Moreover, circCAPG encodes a polypeptide which increases tumor growth by blocking the binding of the serine/threonine kinase (STK38) and SMAD-specific E3 ubiquitin protein Ligase 1 (SMURF1) in TNBC (Song et al. 2023). This results in reduced degradation of mitogen-activated protein kinase kinase kinase 2 (MEKK2) and a subsequent increased activation of the mitogen-activated protein kinase (MEKK2-MEK1/2-ERK1/2) pathway (Song et al. 2023). Studies indicate that this pathway can promote metastasis by upregulating matrix metalloproteinases (Kciuk et al. 2022; Rocca et al. 2022). Moreover, circ\_0059457 promotes metastasis as well as proliferation of BC cells through the sequestration of miR-140-3p, which increases the expression of ubiquitin-binding enzyme 2 C (UBE2C) (Huang et al. 2024). UBE2C was previously shown to promote tumor invasion and proliferation by activating protein kinase B/mammalian target of rapamycin (AKT/mTOR) pathway (Table 2) (Lu et al. 2021).

### Role of circRNAs in angiogenesis

As the tumor grows and migrates, it undergoes what is known as the "angiogenic switch", where growth of blood vessels around the tumor is induced to provide the tumor

with additional nutrients (Lugano et al. 2020). Recent studies have indicated that circRNAs also play a crucial role in angiogenesis. The upregulation of Hsa\_circ\_0001925 in TNBC tissues was found to play a role in angiogenesis, tumor growth and migration. This takes place through increasing the expression of Yin Yang 1 (YY1) by sequestering miR-1299 (Table 2) (Shen et al. 2023).

Previous studies stated that YY1 can contribute to angiogenesis and other hallmarks of cancer through the activation of epidermal growth factor receptor (EGFR) and human epidermal growth factor 2 (HER2) (Guo et al. 2020). Similarly, an increase in Hsa\_circ\_0008673 expression was associated with increased angiogenesis and tumor growth through elevated levels of GINS Complex Subunit 4 (GINS4) and reduced miR-578 absorption (Sun et al. 2023). Although the role of GINS4 in the angiogenesis of BC is unknown, it was previously shown to promote gastric cancer by activating Rac1 and cell division control protein 42 (CDC42) suggesting this might be its potential mechanism in increasing angiogenesis (Zhu et al. 2019). However, this requires further research (Table 2).

In addition to the aforementioned circRNAs, circRPPH1 was observed to increase angiogenesis of TNBC by sequestering miR-556-5p which enhances the expression of Yes-associated protein 1 (YAP1) and activation of Hippo signaling pathway (Zhou et al. 2020a, b). YAP1 is a key component of the Hippo pathway, which mediates the effects of angiogenic molecules such as vascular endothelial growth factor (VEGF) by regulating the transcription of key genes (Table 2) (Boopathy and Hong 2019).

In BC, circBRAF was demonstrated to be a key player in angiogenesis, metastasis, and proliferation of BC whereby it boosts the modification of histone H3K9me3 by increasing lysine demethylase 4B (KDM4B) recruitment (Lan et al. 2024). It also interacts with insulin-like growth factor 2 binding protein 3 (IGF2BP3). The histone modification in turn leads to increased expression of matrix metalloproteinase 9 (MMP9) and ADAM metalloproteinase with thrombospondin type 1 motif 14 (ADAMTS14), enzymatic components of the ECM (Table 2) (Lan et al. 2024).

In another study, circZEB1 was found to be upregulated in BC cells and that its downregulation reduced angiogenesis and invasion potential of the cancer cells by increasing miR-337-3p and subsequently inhibiting the expression of O-GlcNAc transferase (OGT). This inhibits the O-GlcNAcylation of YBX1 leading to its degradation (D. Wang, Chen et al. 2024a, b). Although the exact mechanism by which YBX1 affects BC is not known, several oncogenes were found to be targets of YBX1, such as cellular myelocytomatosis oncogene (c-myc) and AKT, among others. More research is needed to identify how YBX1 can promote

angiogenesis through the transcriptional regulation of oncogenes. Another circRNA that was found to play a positive role in angiogenesis is Circ\_0002496 (Table 2) (Yang et al. 2023).

## CircRNAs as potential diagnostic markers in breast cancer

CircRNAs have been identified as promising biomarkers and can be used to diagnose BC. They are found in abundance and are expressed in various tissues. CircRNAs can be obtained from body fluids (blood, plasma, and exosomes) and are more stable than linear RNA as they are more resistant to exonuclease-mediated degradation due to their covalent closed continuous loop structure (Fontemaggi et al. 2021). Studies have shown that the dysregulation of circRNAs can be used as tools for early detection of BC. Numerous studies have demonstrated the dysregulation of circRNAs in BC tissues and their potential utility as diagnostic and prognostic markers. For example, hsa\_circ\_0000615 was found to be highly expressed in blood samples and the receiver operator characteristic (ROC) showed the value of the area under curve (AUC) was 0.904, with a sensitivity of 76.8%, and specificity of 88.4% (Liu et al. 2021a, b, c). The authors conducted a dual comparison approach that utilized blood samples drawn from age-matched healthy control volunteers as well as adjacent normal tissues from the same BC patients. The study illustrated that hsa\_circ\_0000615 had superior sensitivity and specificity in comparison to traditional tumor markers (e.g., including CA153, CA125, and CEA), highlighting its potential as a more accurate biomarker in diagnosing BC (Liu et al. 2021a, b, c). hsa\_circ\_0008673 was found to be upregulated in plasma samples of BC patients (Y. Hu et al. 2020a, b). Conversely, hsa\_circ\_0006220 was significantly down-regulated, a 27-fold decrease compared to healthy tissues, in BC tissues (C. Liu et al. 2021a, b, c). Furthermore, three circRNAs: circ\_0000745, circ\_0001531, circ\_0001640 were identified to be strongly upregulated in whole blood samples of BC patients, suggesting their potential use as novel biomarkers (Table 3) (Fig. 5) (Wang et al. 2021a, b).

Moreover, circ\_0005046 and circ\_0001791 were found to be upregulated in tissues of BC patients, illustrating their potential as biomarkers for early cancer detection (Ameli-Mojarad et al. 2021). It is also worth discussing that hsa\_circ\_0006743 and hsa\_circ\_0002496 were reported to be upregulated in BC cells obtained from tissues, supporting their promising potential as biomarkers for early detection of BC (Rao et al. 2021). Additionally, circ\_0076611, was

**Table 3** CircRNAs as diagnostic biomarkers in breast cancer

CircRNA	Expression	Source	Reference
CircRPPH1	Upregulated	Tissue	(Huang et al. 2021a, b)
hsa_circ_0000615	Upregulated	Blood	(Liu et al. 2021a, b, c)
hsa_circ_0008673	Upregulated	Plasma	(Y. Hu et al. 2020a, b)
hsa_circ_0006220	Downregulated	Tissue	(Liu et al. 2021a, b, c)
circ_0000745	Upregulated	Blood	(Wang et al. 2021a, b)
circ_0001531			
circ_0001640			
circ_0005046	Upregulated	Tissue	(Ameli-Mojarad et al. 2021)
circ_0001791			
hsa_circ_0006743	Upregulated	Tissue	(Rao et al. 2021)
hsa_circ_0002496			
circ_0076611	Upregulated	Serum	(Turco et al. 2022)
circ_0001522	Upregulated	Serum	(Awata et al. 2025)
circ_0001278			
circ_0001801			

detected in serum samples since it is released from TNBC cells into exosomes (Turco et al. 2022). Overall, the differential expressions of circRNAs demonstrate promising potential to be utilized as biomarkers for early detection of BC (Table 3) (Fig. 5).

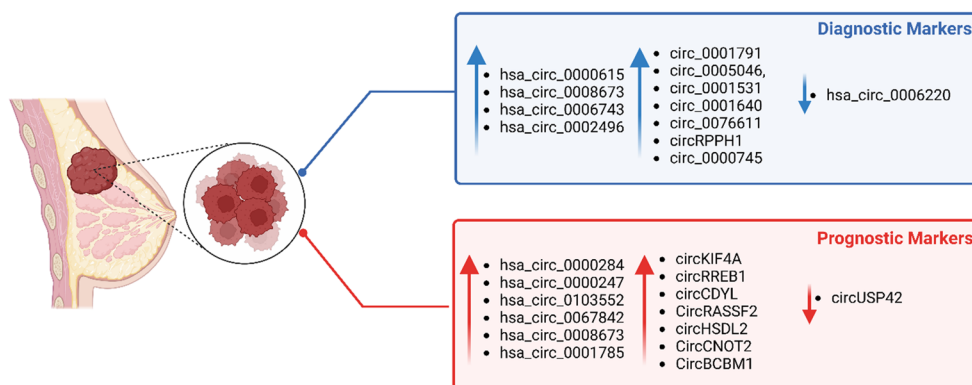
Recently the roles of circ\_0001522, circ\_0001278, and circ\_0001801 as promising diagnostic and prognostic biomarkers were investigated by Awata et al. (2025) and were found to be positively correlated with poor-relapse free survival. Moreover, the circRNAs demonstrated significant overexpression in tumor tissues in comparison to the adjacent sample tissues of the same patient, indicating the critical role of these circRNAs as key breast cancer hallmarks in promoting TNBC proliferation, migration and 3D-growth and suggesting their role as a potential biomarker (Table 3).

### CircRNAs as potential prognostic markers in breast cancer

The upregulation of various circRNAs, as discussed thus far, suggests their potential prognostic value in BC. For instance, circKIF4A was found to be significantly upregulated in TNBC, which correlated to large tumor size and lymph node metastasis (Tang et al. 2019). Knockdown of this circRNA also led to a significant decrease of TNBC cell proliferation, suggesting its role in cancer progression.

In another study, circRREB1, a novel circRNA that is upregulated in BC, was identified to promote increased tumor growth and metastasis through extracellular signal-regulated kinase 1/2 (Erk 1/2) signaling pathway by interaction with GNB4 and is associated with poor prognosis in BC patients (H. Chen et al. 2024a, b). The elevated expression of circRREB1 correlates with advanced stages of BC and shorter survival times according to the Kaplan-Meier survival analysis. On the other hand, the expression of circUSP42 was strongly downregulated in TNBC tissues (Yu et al. 2020). The downregulation was associated with lymph node metastasis, suggesting that the dysregulation of circUSP42 is involved in the progression of TNBC (Table 4) (Fig. 5) (Yu et al. 2020).

Hsa\_circ\_0000284 was found to be upregulated in tissues of BC patients, which also promotes cell proliferation, migration, and invasion of BC by regulating signaling pathways that are crucial for cancer progression. Upregulation of this circRNA predicted a poor prognosis in BC patients (Luo et al. 2021). Similarly, another circRNA, circHMCU (hsa\_circ\_0000247) also demonstrated an upregulation in BC tissues with high metastatic potential. This circRNA enhances BC cell growth, increases migration and invasion, and suppresses the expression of let-7 MicroRNA. Downregulation of let-7 can lead to increased expression



**Fig. 5** CircRNAs as Potential Prognostic and Diagnostic Markers in Breast Cancer. The blue box lists diagnostic markers, including upregulated (e.g., hsa\_circ\_0000615, circ\_0005046) and downregulated (e.g., hsa\_circ\_0006220) circRNAs. The red box lists prognostic

markers, including upregulated (e.g., hsa\_circ\_0000284, circCDYL) and downregulated (e.g., circUSP42) circRNAs. Arrows indicate expression changes. Data reflects reported expression patterns in breast cancer tissue

**Table 4** CircRNAs as prognostic biomarkers in breast cancer

CircRNA	Expression	Source	Prognosis	Reference
circKIF4A	Upregulated	Tissue	Poor	(Tang et al. 2019)
circRREB1	Upregulated	Tissue	Poor	(H. Chen et al. 2024a, b)
circUSP42	Downregulated	Tissue	Poor	(Yu et al. 2020)
hsa_circ_0000284	Upregulated	Tissue	Poor	(Luo et al. 2021)
hsa_circ_0000247	Upregulated	Tissue	Poor	(Song et al. 2020)
hsa_circ_0103552	Upregulated	Tissue	Poor	(Huang et al. 2021a, b)
hsa_circ_0067842	Upregulated	Tissue	Poor	(Li et al. 2023)
hsa_circ_0008673	Upregulated	Plasma	Poor	(Y. Hu et al. 2020a, b)
circCDYL	Upregulated	Tissue	Poor	(Liang et al. 2020)
circRASSF2	Upregulated	Serum	Poor	(Zhong et al. 2021)
circHSDL2	Upregulated	Serum	Poor	(S. Yang and Tang 2020)
hsa_circ_0001785	Upregulated	Plasma	Poor	(Yin et al. 2018)
circCNOT2	Upregulated	Plasma	Poor	(Smid et al. 2019)
circBCBM1	Upregulated	Serum	Poor	(Fu et al. 2021)
circGSK3 $\beta$	Upregulated	Tissue	Poor	(Liang et al. 2024a, b)
circ_0022382	Upregulated	Tissue	Poor	(Liu et al. 2024)
circFOXK2	Upregulated	Tissue	Poor	(Yi et al. 2025)

of oncogenes such as *MYC*, *HMG2A*, and *CCND1* (Song et al. 2020).

In another study, *hsa\_circ\_0103552* was found to be upregulated in BC cells and associated with cancer cell proliferation and cell metastasis resulting in poor prognosis for BC patients (Huang et al. 2021a, b). Furthermore, *hsa\_circ\_0067842* was also highly upregulated in BC tissues (Table 4) (Fig. 5) (Li et al. 2023). This circRNA is strongly associated with poor prognosis, as it can promote cancer cell proliferation and metastasis as well as enhance the migration and invasion of BC cells, thereby contributing to immune escape.

Likewise, *hsa\_circ\_0008673* located in the plasma of BC patients was found to be upregulated compared to normal cells. This circRNA was also reported to be associated

with increased tumor size and distant metastasis (Y. Hu et al. 2020a, b). Knockdown of *hsa\_circ\_0008673* led to the disruption of tumor cell proliferation and metastasis. The study suggests that *hsa\_circ\_0008673* could be used as a biomarker and that its presence contributes to poor prognosis in patients. In BC tissues, *circCDYL* was found to be dysregulated in comparison to Healthy tissues and was found to be elevated by 3.2 folds. The increased expression of this circRNA has been associated with increased cell autophagy and BC malignancy. Furthermore, the increased levels of *circCDYL* are correlated with poor prognosis in BC patients (Liang et al. 2020).

*CircRASSF2* was found to be significantly elevated in both serum and tissues of BC patients. Increased levels of *circRASSF2* have also been associated with enhanced tumor size, distant metastasis and lymph node metastasis, which lead to a decrease in overall survival for BC patients. Targeting *circRASSF2* will allow for novel therapeutic approach and novel prognostic biomarkers (Table 4) (Fig. 5) (Zhong et al. 2021).

Additionally, (Liang et al. 2024a, b) reported that *CircGSK3 $\beta$*  plays a pivotal role in promoting BC progression and aided in cell immune progression, highlighting its potential as a promising prognostic biomarker. Additionally, the study found that it was highly expressed in various BC cell lines including MDA-MB-231 and MCF7 compared to normal control cell lines. Knockdown of the circRNA led to a substantial reduction in aggressive BC progression and migration capabilities. Moreover, its role in immune evasion was highlighted by the upregulation of PD-L1 through miR-338-3p/PRMT5 interaction. PD-L1 is expressed upon the binding of PRMT5, a type II enzyme, to its promoter increasing its transcription through histone H3K4 trimethylation (H3K4me3) which leads to cancer invasion and immune evasion (Table 4) (Liang et al. 2024a, b).

Recent findings have identified *circ\_0022382* as an oncogenic circRNA that is significantly upregulated in BC tissues and cell lines (MDA-MB-231, MCF-7) compared to adjacent normal tissues. Knockdown of this circRNA resulted in the inhibition of the proliferation and migration of BC cells both in vitro and in vivo (Liu et al. 2024). *Circ\_0022382* serves as a promising biomarker in BC diagnosis due to its essential role in cancer cell progression. Furthermore, the study also revealed that *circ\_0022382* can act as a sponge for let-7a-5p miRNA which is often downregulated in BC cells and promotes downstream oncogenic signaling. The circRNA affects the PI3K/AKT/mTOR signaling pathway as well as the upregulation of SLC7A11, essential for tumor metabolism. Upon knocking down this circRNA, reduced phosphorylation of AKT and SLC7A11 was observed. Contribution to disulfidptosis was also observed, a type of

cell apoptosis that is triggered by the accumulation of cysteine and altered glucose metabolism. The study also noted that the expression of circ\_0022382 is promoted upstream by EIF4A3, an RNA helicase that is often reported to be expressed in BC cells. Targeting pathways such as PI3K/AKT/mTOR and SLC7A11 could potentially serve as a novel therapeutic approach in BC treatment (Table 4) (Liu et al. 2024).

Moreover, Yi et al. (2025) recently characterized circFOXX2 as a hallmark driver in advancing the proliferation, and aggression of ER-positive BC. The increase of circFOXX2 expression in both cell lines and BC tissues is associated with CCND1, which is a key regulator in cell cycle transition. Unlike most circRNAs mentioned in this review, circFOXX2 does not act as a sponge for miRNA, rather, it directly binds to the CCND1 mRNA, specifically, the 3' UTR region through RNA-RNA pairing. The circRNA also recruits ELAVL1 which is an RNA-binding protein that stabilizes CCND1 mRNA as well as increasing its expression. Elevation of CCND1 protein levels can activate the CCND1-CDK4/6-pRB-E2F signaling cascade which in turn promotes the transcription of *E2F* target genes that promote tumor growth. The study also suggested that circFOXX2 can serve as a potential therapeutic target using antisense oligonucleotide (ASO-circFOXX2) which can lead to the suppression of ER-positive BC growth and can be used synergistically alongside tamoxifen. The study discussed that the combination of ASO-circFOXX2 and tamoxifen was capable of resensitizing tamoxifen resistant ER-positive BC cells (Table 4).

## The role of circRNAs in breast cancer cells' drug resistance

Drug resistance is a major cause of cancer therapy failure; however, the underlying mechanisms remain to be fully elucidated. CircRNAs can either promote or inhibit resistance to traditional chemotherapy, endocrine therapy, and even targeted therapies across various types of tumors, suggesting their potential as a novel focus for research into overcoming drug resistance. This highlights the promise of circRNAs as potential therapeutic targets to combat chemoresistance in BC (Misir et al. 2022). The following sections highlight the involvement of circRNAs in resistance to commonly used BC drugs in three major categories: chemotherapy, endocrine therapy, and targeted therapy.

### Chemotherapy resistance

Chemotherapy is vital for breast cancer treatment, but chemoresistance limits its efficacy. CircRNAs regulate

resistance by modulating apoptosis, autophagy, and drug efflux, often acting as ceRNAs to sequester miRNAs, thereby influencing drug resistance-associated gene expression (Ghazimoradi and Babashah 2022; He et al. 2021a, b).

### Adriamycin (Doxorubicin)

Doxorubicin, also known as adriamycin (ADM), belongs to a class of chemotherapy drugs known as anthracyclines. It works by slowing or halting the growth of cancer cells through the inhibition of topoisomerase 2 (Granados-Principal et al. 2010). This medication is commonly used in the treatment of Estrogen receptor-positive breast cancer (ER+BC) (Pritchard et al. 2012). ADM is an antibiotic that does not target a specific phase of the cell cycle. ADM functions by blocking the synthesis of DNA and RNA, thereby impeding tumor progression (He et al. 2021a, b).

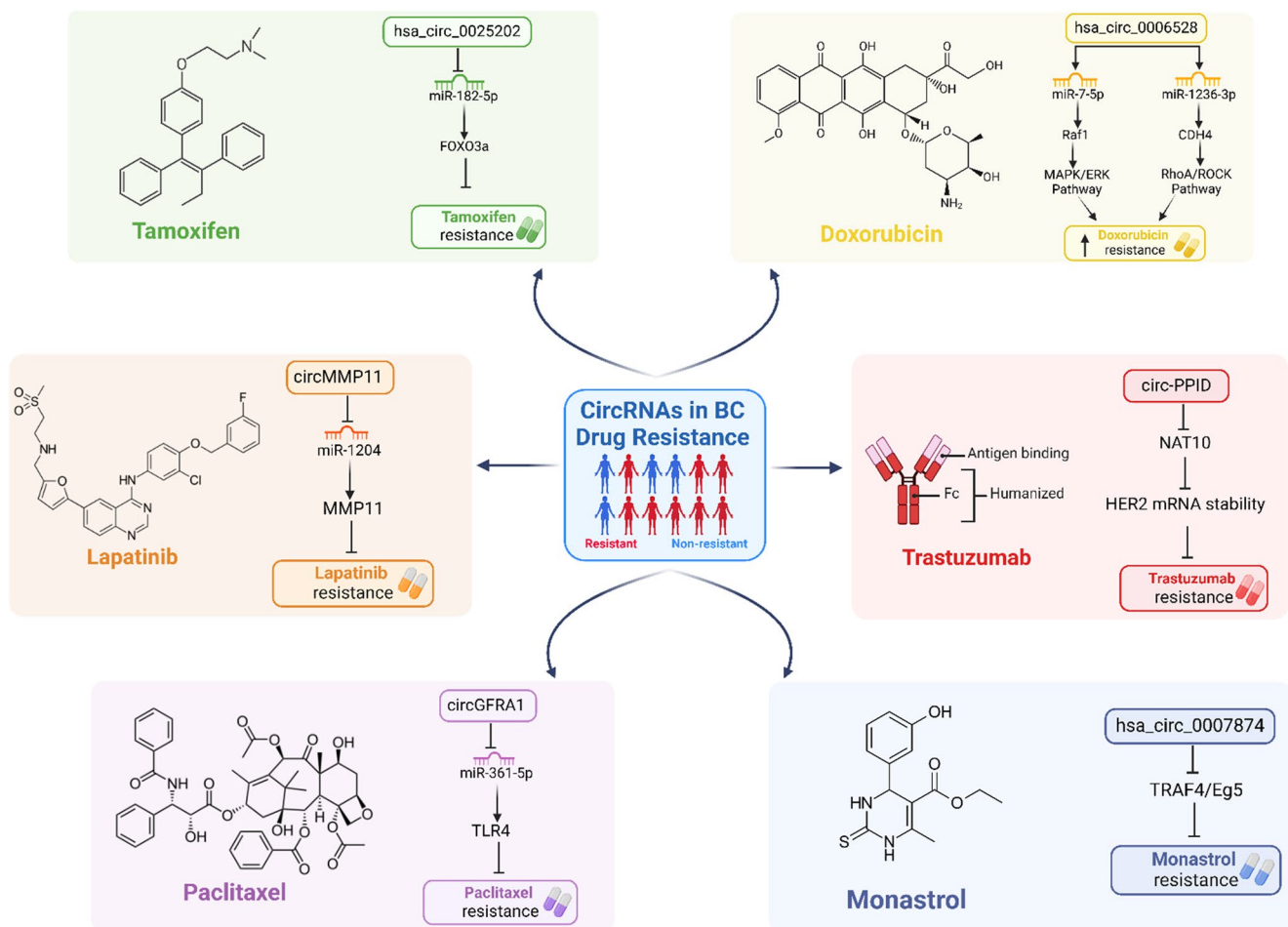
**Hsa\_circ\_0006528** Researchers have identified that hsa\_circ\_0006528 is elevated in (ADM)-resistant BC cells (Afzal et al. 2022). Previous studies indicate that hsa\_circ\_0006528 sponges miR-7-5p, leading to Raf1 activation, leading to the activation of the downstream MAPK/ERK signaling pathway, making it a potential therapeutic target for reducing recurrence and metastasis (He et al. 2021a, b). Additionally, it is also considered a promoter of the RhoA/ROCK pathway by sponging miR-1236-3p, increasing CHD4 expression (Table 5) (Ghazimoradi and Babashah 2022).

**Hsa\_circ\_0001839 (CircKDM4C)** ADM-resistant cells were found to have lower levels of circKDM4C compared to their sensitive parental counterparts (De Palma et al. 2022). The knockdown of circKDM4C led to a significant increase in ADM resistance, while its overexpression resulted in decreased resistance by interacting with miR-548p. This interaction results in upregulation of phenazine biosynthesis-like domain-containing (PBLD) expression, which was established to function as tumor suppressor in BC tumorigenesis. Additionally, the overexpression of circKDM4C reduced the migration and invasion capabilities of ADM-resistant BC cells, highlighting the connection between metastasis and chemoresistance. (Fig. 6) (Table 5) (Liang et al. 2021a, b).

**Circ\_0085495** Circ\_0085495, located in the cytoplasm, is overexpressed in ADM-resistant BC. Silencing it has been shown to reduce ADM resistance by modulating the miR-873-5p/integrin  $\beta$ 1 signaling pathway (Xie and Zheng 2022). miR-873-5p inhibits integrin  $\beta$ 1, a protein associated with cancer cell metastasis and resistance. Therefore, lowering circ\_0085495 levels can help reduce both drug

**Table 5** CircRNAs involved in drug resistance mechanisms in breast cancer

CircRNA	miRNA sponges	Target Pathway	Dysregulation	Drug resistance	Mechanism	References
hsa_circ_0006528	miR-7-5p	raf1 & MAPK/ERK	Upregulation	ADM	Increases resistance of BC to ADM by interacting with miR-7-5p and raf1	(Gao et al. 2019)
hsa_circ_0006528	miR-1236-3p	RhoA/ROCK	Upregulation	ADM	Increases CH4 expression	(Ghazimoradi and Babashah 2022)
hsa_circ_0001839	miR-548p	PBLD	Downregulation	ADM	Increases resistance of BC to ADM by sponging miR-548p to increase the PBLD expression	(De Palma et al. 2022)
Circ_0085495	miR-873-5p	Integrin $\beta$ 1	Upregulation	ADM	Promotes resistance by sponging miR-873-5 which inhibits integrin $\beta$ 1	(Ghazimoradi and Babashah 2022; Xie and Zheng 2022)
Circ_0001667	miR-4458	NCOA3	Upregulation	ADM	Promotes resistance by binding to miR-4458, which typically suppresses NCOA3. NCOA3 is a protein that helps cancer cells grow and resist endocrine therapies	(Cui et al. 2022; Ghazimoradi and Babashah 2022)
Circ_0001667	miR-193a-5p	Rap2A	Upregulation	ADM	Leads to the downregulation of Rap2A mRNA and protein levels by targeting the 3'UTR of Rap2A	(Xu et al. 2023)
CircRNA-CREIT		PKR/eIF2 $\alpha$	Downregulation	ADM	CircRNA-CREIT enhances HACE1-mediated PKR degradation, inhibiting the PKR/eIF2 $\alpha$ signaling axis and SG formation	(Wang et al. 2022)
hsa_circ_0025202	miR-182-5p	FOXO3a	Downregulation	TAM	Exert tumor inhibition and TAM sensitization effects via the miR-182-5p/FOXO3a axis	(He et al. 2021a, b)
Circ_UBE2D2	MiR-200a-3p	ER $\alpha$	Upregulation	TAM	Resist TAM by sponging miR-200a-3p, miR-200a-3p	(He et al. 2021a, b)
CircBMPR2	MiR-553	USP4	Downregulation	TAM	Reduces the inhibition of apoptosis induced by tamoxifen and regulate miR-553	(Y. Liang et al., 2019)
circRNA-SFMBT2		ER $\alpha$	Upregulation	TAM	CircRNA-SFMBT2 recruit RNF181 to ER $\alpha$ -positive cells, forming a complex that prevents ER $\alpha$ from being degraded through ubiquitination	(Z. Li et al. 2023a, b, c, d)
circBACH1	miR-217	G3BP2	Upregulation	PTX	PTX-induced exosomal circ-BACH1 promoted stemness and migration of BC cells by sponging miR-217 to upregulate the expression of G3BP2	(He et al. 2024)
CircGFRA1	miR-361-5p	TLR4	Upregulation	PTX	CircGFRA1 sponges miR-361-5p, preventing it from inhibiting TLR4, a protein linked to cancer cell survival and drug resistance	(Misir et al. 2022)
circ-MMP11	miR-153-3p	ANLN	Upregulation	Lapatinib	Elevates lapatinib resistance by regulating the miR-153-3p/ANLN axis in breast cancer cells	(Wu et al. 2021)
hsa_circ_0007874		TRAF4/Eg5	Downregulation	Monastrol	Sequesters TRAF4 from binding to EG5 protein	(W. Liu et al. 2021a, b, c).



**Fig. 6** The Role of CircRNAs in Breast Cancer Cells' Drug Resistance. This figure illustrates the involvement of circRNAs in mediating resistance to common breast cancer treatments, including doxorubicin, tamoxifen, paclitaxel, monastrol, lapatinib, and trastuzumab

resistance and cancer cell growth (Table 5) (Ghazimoradi and Babashah 2022).

### Paclitaxel (PTX)

Paclitaxel (PTX) was first segregated from the bark of pacific yaw trees; it was identified as a tetracyclic diterpenoid compound. As it is known for its low toxicity, high effectiveness, and wide-ranging anti-cancer properties, PTX has been widely used against BC. The mechanism of action of PTX involves various pathways in which it affects cellular processes resulting in apoptosis (Y.-H. Yang et al. 2020).

**CircGFRA1** CircGFRA1 has been identified as a key factor contributing to the resistance to PTX in TNBC cells by sponging miR-361-5p, which normally inhibits TLR4, a protein associated with cancer cell survival and drug resistance. When circGFRA1 is knocked down, the resistance of TNBC cells to PTX is reduced due to a decrease in TLR4 expression (Lyu et al. 2021). Thus, circGFRA1 can function

as a regulator of miR-361-5p/TLR4 and by blocking TLR4, the responsiveness of TNBC cells to PTX could be significantly enhanced, improving their sensitivity to the drug in BC treatment (Fig. 6) (Table 5) (Misir et al. 2022).

**CircBACH1** CircBACH1 has been shown to promote colorectal cancer progression by lowering let-7a-5p levels, leading to elevated expression of CREB5, a transcription factor involved in eukaryotic gene regulation. CREB5, a protein-coding gene, plays a key role in controlling cellular processes through its function as a transcription factor (J. Li et al. 2020a, b). However, the way exosomal circBACH1 influences chemoresistance and metastasis in BC are still unclear. Recent research revealed that circBACH1 levels are higher in exosomes from PTX-treated BC cells and BC tissues. The ability of circBACH1 to sponge miR-217, leading to the upregulation of G3BP2 expression, highlights a potential therapeutic target for combating PTX resistance and BC progression through the circBACH1/miR-217/G3BP2 axis. Moreover, studies confirmed that reducing

circBACH1 levels enhances sensitivity to PTX by inhibiting the viability, stemness, migration, and angiogenesis of BC cells, making it a potential multifaceted target in BC management (Table 5) (He et al. 2024; J. Li et al. 2020a, b).

### Monastrol

Monastrol causes mitotic arrest at the G2/M phase by targeting the kinesin-5 motor protein, known as Eg5 (KIF11). By inhibiting its basal and microtubule functions, monastrol disrupts Eg5's ability to maintain bipolar spindles, leading to cell apoptosis (Galeano et al. 2024). However, its drug resistance limits the application in BC therapy (He et al. 2021a, b).

Hsa\_circ\_0007874 (Circ\_MTO1).

Circ\_MTO1 was found to be downregulated in cell lines that have developed resistance to monastrol. It influences the TRAF4/Eg5 axis by binding TRAF4 to the Eg5 gene, which in turn inhibits BC cell activity and enhances the cytotoxic effects of monastrol (He et al. 2021a, b). When circMTO1 is silenced, cancer cell viability increases. Conversely, overexpression of circMTO1 leads to increased cell death by sequestering TRAF4 in the cytoplasm during monastrol treatment, thereby preventing Eg5 expression, which is essential for bipolar spindle separation (Das et al. 2021). Therefore, circMTO1 may play a crucial regulatory role in BC, and regulating its levels could be a promising approach to overcoming chemoresistance (Fig. 6) (Table 5) (W. Liu et al. 2021a, b, c).

### Endocrine therapy resistance

Endocrine therapy is essential for HR-positive patients and is a widely used and effective treatment. However, resistance to this therapy still occurs in about 20–30% of patients (Cen et al. 2023). Recent studies suggest that circRNAs are closely linked to endocrine therapy response, influencing resistance by modulating estrogen receptor signaling and apoptosis pathways (Y. Liang et al., 2019; Yao et al. 2020).

### Tamoxifen

Tamoxifen (TAM) is a crucial treatment for women with estrogen receptor-positive (ER+) BC. It is both affordable and lifesaving, with minimal side effects for most individuals (Shagufta and Ahmad 2018). However, drug resistance limits its efficacy, making it essential to find ways to overcome tamoxifen resistance in BC (Yao et al. 2020).

**CircBMPR2** CircBMPR2 expression is markedly reduced in tamoxifen-resistant BC cells and tissues, indicating a potential tumor-suppressive function in this setting.

Functional studies have demonstrated that overexpression of circBMPR2 not only suppresses BC cell motility but also enhances their sensitivity to tamoxifen by promoting apoptosis, thereby improving therapeutic efficacy (Ghazimoradi and Babashah 2022). In contrast, circBMPR2 knockdown promotes tamoxifen resistance through the inhibition of tamoxifen-induced apoptosis (Liang et al. 2019b). Additionally, CircBMPR2 diminishes the motility of BC cells, hence constraining their metastatic capability, and enhances their sensitivity to tamoxifen by facilitating tamoxifen-induced apoptosis. The silencing of circBMPR2 enhances tamoxifen resistance by suppressing apoptosis. miR-553 enhances proliferation, metastasis, and tamoxifen resistance while establishing a negative feedback loop with circBMPR2, somewhat mitigating its effects (Table 5) (Y. Liang et al., 2019).

**Hsa\_circ\_0025202** Hsa\_circ\_0025202 was found to be downregulated in BC tissues, particularly in tamoxifen (TAM)-resistant BC cells. Loss-of-function experiments revealed that when hsa\_circ\_0025202 is silenced in BC cells, the IC<sub>50</sub> value for TAM increases, indicating enhanced resistance to the drug (Li et al. 2021). Hsa\_circ\_0025202 can act as a miRNA sponge, specifically targeting miR-182-5p. The interaction between miR-182-5p and FOXO3a plays a key role in cancer development and progression by influencing pathways that regulate the cell cycle and enhance cell survival (He et al. 2021a, b). FOXO3a, a member of the forkhead box O (FOXO) transcription factors, is known as a tumor suppressor in various cancers. It was shown to enhance TAM sensitivity by functioning as a competing endogenous RNA (ceRNA) for miR-182-5p, which modulates the expression and activity of FOXO3a, thereby potentially inhibiting tumor progression in hormone receptor-positive BC patients undergoing TAM therapy (Fig. 6) (Table 5) (Sang et al. 2019).

**Circ\_UBE2D2** Circ\_UBE2D2 is elevated in TAM-resistant BC tissues. Exosomes from these resistant cells are rich in circ\_UBE2D2 and can transfer this RNA to BC cells, increasing their TAM resistance (Hu et al. 2020a, b). However, overexpression of miR-200a-3p inhibits circ\_UBE2D2, leading to lower vimentin levels and increased E-CAD and ER $\alpha$  expression, which are associated with reduced drug resistance (Ghazimoradi and Babashah 2022). Therefore, reducing circ\_UBE2D2 may offer a potential strategy to overcome hormone therapy resistance (Table 5).

### Targeted therapy resistance

Targeted therapy is a cancer treatment approach that focuses on specific genes or proteins driving tumor growth. Unlike

traditional chemotherapy, it selectively attacks cancer cells while sparing normal cells. In BC treatment, targeted therapies such as HER2 inhibitors and tyrosine kinase inhibitors (TKIs) play a paramount role. These therapies align with personalized medicine by tailoring treatment to a patient's molecular profile, improving precision and efficacy. However, circRNAs contribute to resistance by interacting with oncogenic pathways, underscoring the need to develop strategies that directly target circRNAs to overcome resistance and enhance the effectiveness of personalized therapies (Wu et al. 2021).

### Lapatinib

Lapatinib is a small molecule dual tyrosine kinase inhibitor (TKI) that targets Human Epidermal growth factor Receptor 1 (HER1) and Human Epidermal growth factor Receptor 2 (HER2). It works by binding reversibly to the cytoplasmic ATP-binding site of the tyrosine kinase domains of HER1 and HER2, thereby blocking the activation of downstream cascades (Voigtlaender et al. 2018).

**Circ-MMP11** In human BC tissue, circMMP11 is significantly elevated and associated with lymph node metastasis and clinical stage. The circMMP11/miR-1204/MMP11 axis promotes BC progression through the ceRNA mechanism (Li et al. 2020a, b). Additionally, exosomal circMMP11 levels are higher in lapatinib-resistant (LR) BC tissues. Knockdown of circMMP11 enhances lapatinib sensitivity and induces apoptosis in resistant BC cells. Notably, circ-MMP11 is transferable via exosomes, highlighting its role in cancer progression. Its contribution to lapatinib resistance, cell growth, and metastasis is potentially mediated by the miR-153-3p/ANLN axis in LR BC cells (Fig. 6) (Table 5) (Wu et al. 2021).

### Trastuzumab

Trastuzumab is a monoclonal antibody used primarily to treat BC and certain types of gastric cancer. It specifically targets the HER2 protein (Maadi et al. 2021).

**Circ-PPID** Low expression levels of circ-peptidylprolyl isomerase D (circ-PPID) have been identified to contribute to trastuzumab resistance in HER2 BC. The restoration of circ-PPID was demonstrated to significantly enhance trastuzumab sensitivity by promoting HER2 mRNA decay, mediated by circ-PPID binding to N-acetyltransferase 10 (NAT10) in the nucleus and inhibition of the interaction between NAT10 and HER2 mRNA, reducing N4-acetylcytidine (ac4C) modification on HER2 exon 25 (Wang et al. 2024a, b, c). These findings highlight the potential

therapeutic role of circRNAs in overcoming cancer therapy resistance. Therefore, a comprehensive investigation of how miRNAs and circRNAs regulate responses to targeted therapies could offer crucial insights for enhancing BC-targeted treatments (Fig. 6) (Table 5).

## Computational approaches for circRNAs detection and validation

Detecting circRNA from RNA sequencing data primarily involves two key approaches: candidate-based and segmented read-based methods. The candidate-based method relies on a predefined list of potential back-splicing junction (BSJ) sequences, which is usually created by combining all pairs of known annotated exons within a gene. However, this approach is limited to species with annotated genomes and can only identify circRNAs that share the same splicing sites as linear RNAs. On the other hand, the segmented read-based method involves breaking down unmapped sequencing reads into shorter fragments, which are then realigned to the reference genome (Rebolledo et al. 2023).

When predicting the sub-cellular localization of circRNAs, methods utilizing residue frequency-based sequence descriptors and tree-based classifiers have proven more effective (Asim et al. 2022). Among the various tools available, Circall stands out for its high sensitivity and precision in simulation studies, surpassing other circRNA detection methods in experimental dataset analysis. The efficiency of Circall is further enhanced by its use of an ultra-fast quasi-mapping algorithm, making it particularly well-suited for analysing large datasets (Nguyen et al. 2021).

LLCDC which can preserve local information During the encoding process was used in predicting circRNAs associated with BC with an AUC value of 0.9177 (Ge et al. 2020). Furthermore, SIMCCDA effectively predicted circRNA-disease associations, identifying 29 top candidates linked to BC in related studies (He et al. 2021a, b).

Moreover, circRNAs identified by a single method tend to include more false positives, suggesting that circRNAs detected by multiple tools are more dependable. CirComPara2 is a computational tool designed to aggregate expression estimates from various circRNA detection methods into a single, unified value. It does this by eliminating redundant counts of back-splicing junctions (BSJs) detected by multiple tools, without requiring additional read re-alignment. CirComPara2 incorporates nine different circRNA detection methods and examines circRNAs that might have been missed by one or more tools (potential false negatives). Interestingly, only 4% of circRNAs in the false-negative set were missed by all methods, while 96% were detected by at least one of the nine tools (Gaffo et al. 2022). This indicates

that selecting circRNAs predicted by at least two methods can lead to more accurate results (Vromman et al. 2023).

## Challenges and future perspectives of circRNAs in breast cancer: from pathogenesis to therapeutic potential

Despite the growing recognition of circRNAs as key regulators in BC pathogenesis, several challenges hinder their full clinical translation. Understanding the intricate roles of circRNAs in gene regulation, splicing, and cellular pathways remains complex, especially given their diverse and overlapping functions. While numerous circRNAs exhibit dysregulated expressions in BC, the precise mechanisms driving these alterations and their functional consequences in tumor suppression or promotion are not yet fully elucidated.

High-throughput sequencing and bioinformatics analyses have significantly advanced circRNA research, identifying multiple circRNA–miRNA–mRNA regulatory axes involved in BC development. Notably, several circRNA/miRNA axes, including circIFI30/miR-520b-3p, CircCDYL/miR-1275, and circ-DNMT1/miR-1236-3p, have been implicated in BC progression and therapy resistance (Du et al. 2018; Liang et al. 2020; Liu et al. 2020; Shi et al. 2024; Wang et al. 2023a, b; Xing et al. 2020; Xu et al. 2019). These interactions highlight the significance of these interactions in BC development and their potential as therapeutic targets.

Beyond their fundamental roles in tumor biology, circRNAs are also implicated in therapy resistance. Approximately 30% of BC patients exhibit resistance to treatment, with TNBC showing a particularly poor response (Ortega et al. 2021; Reitz et al. 2021). CircRNAs such as hsa\_circ\_0006528, hsa\_circ\_0001839, and circ\_0085495 have been linked to altered drug sensitivity, suggesting their potential as therapeutic targets (De Palma et al. 2022). This underscores the promising role of circRNAs in improving BC management by modulating treatment responses. However, further research is required to determine whether circRNA-based interventions could effectively counteract therapy resistance across different BC subtypes.

Future studies should prioritize interdisciplinary approaches integrating circRNA analysis with genomics, transcriptomics, proteomics, and metabolomics to uncover the broader regulatory networks influencing BC. Advanced preclinical models, such as patient-derived xenografts and organoids, will be instrumental in assessing circRNA function across BC subtypes and exploring their roles in chemoresistance. Additionally, the role of circRNAs in immune regulation and metabolic reprogramming warrants further

exploration, particularly in the context of tumor microenvironment interactions.

From a clinical perspective, circRNAs hold immense promise as biomarkers for non-invasive BC detection, given their high stability in body fluids and exosomes. Exosomal circRNAs, in particular, offer a novel avenue for early diagnosis and personalized therapy, as they are protected from degradation and can effectively modulate gene expression in recipient cells (Hussen et al. 2023; Kumar et al. 2022). However, while many studies have demonstrated the potential diagnostic and prognostic value of circRNAs, large-scale clinical validation is still required before they can be integrated into routine clinical practice.

Therapeutic strategies targeting circRNAs remain in their infancy. Approaches such as synthetic inhibitors for oncogenic circRNAs and overexpression of tumor-suppressive circRNAs present promising avenues for BC treatment. However, most studies have been limited to preclinical models, and the feasibility of translating these findings into effective therapies remains uncertain. Nevertheless, optimizing delivery systems for circRNA-modulating compounds and ensuring their specificity in targeting BC cells are critical challenges that must be addressed before clinical implementation. Large-scale clinical trials are crucial to evaluate the efficacy, safety, and long-term benefits of circRNA-targeted therapies in BC patients.

To surpass the existing limitations in circRNA therapy, genome-scale RNA-targeting CRISPR/Cas13d screens have been incredibly potent. Zhang et al. (2021) conducted a CRISPR/Cas13d screen in hepatocellular carcinoma cells and uncovered circRNAs whose knockdown sensitized cells to sorafenib, illustrating that Cas13d libraries can target thousands of circRNAs with higher specificity than shRNA methods. Expanding on this, Wang et al. (2022a) employed triple-negative breast cancer patient-derived organoids and xenografts to demonstrate that circCREIT overexpression (through vector delivery) re-sensitized doxorubicin-resistant tumors to chemotherapy, illustrating how 3D and in vivo models can confirm functional circRNA targets in BC. Furthermore, nanoparticles based on lipid and polymer that deliver siRNAs targeting oncogenic circDnmt1 have effectively inhibited breast tumor growth in mouse models, illustrating feasible delivery methods for circRNA suppression (A. T. He et al. 2021a, b). Candidate prioritization is further enabled by large-scale functional screens and computational pipelines. An shRNA-based screen in prostate cancer cells identified 171 circRNAs required for proliferation, the majority independent of their linear isoforms, offering a roadmap for similar BC screens (A. T. He et al. 2021a, b). Additionally, one study demonstrated that transformer-based models and convolutional neural networks can effectively predict circRNA–miRNA and circRNA–protein

interactions, quickly proposing regulatory axes for experimental validation (Zhao and Wang 2025). Combining these AI-powered predictions with CRISPR/Cas13d assays, organoid/patient-derived xenograft (PDX) validation, and nanoparticle delivery will establish a powerful pipeline to test and translate circRNA-based therapies in breast cancer.

In conclusion, while circRNAs represent a promising frontier in BC diagnosis, prognosis, and treatment, addressing existing challenges related to standardization, mechanistic insights, and clinical validation is crucial for their successful translation into clinical practice. Future advancements in genomics, precision medicine, and interdisciplinary research will be instrumental in harnessing the full therapeutic potential of circRNAs. Additionally, circRNA-targeted strategies may further enhance therapeutic outcomes, paving the way for circRNA-driven personalized medicine in BC management.

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## Declarations

**Ethical approval** Not applicable “No experiments on human subjects or animals were done in this study”.

**Human and animal ethics** Not applicable.

**Consent for publication** Not applicable.

**Competing interests** The authors declare no competing interests.

**Clinical trial number** Not applicable.

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