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Review

In silico analysis and comprehensive review of circular-RNA regulatory roles in breast diseases; a step-toward non-coding RNA precision

Nadia M. Hamdy [a,*,1], Mona G. El-Sisi [a], Sherine M. Ibrahim [b], Heba ElNokoudy [c], Ahmad A. Hady [d], Gamal Eldein Fathy Abd-ellatef [e], Al-Aliaa M. Sallam [a,f], Bassant Mohamed Barakat [g,h]

[a] *Biochemistry Department, Faculty of Pharmacy, Ain Shams University, Abassia, Cairo 11566, Egypt*
[b] *Biochemistry Department, Faculty of Pharmacy, October University for Modern Sciences and Arts (MSA), Giza, Egypt*
[c] *Medication Management & Pharmacy Affairs, Egypt Healthcare Authority, Cairo, Egypt*
[d] *Clinical Oncology Department, Faculty of Medicine, Mansoura University, Mansoura, Egypt*
[e] *Therapeutic Chemistry Department, Pharmaceutical and Drug Industries Research Division, National Research Centre, 33 El Bohouth St., Dokki, Giza 12622, Egypt*
[f] *Department of Biochemistry, Faculty of Pharmacy, Badr University in Cairo (BUC), Badr City, Cairo 11829, Egypt*
[g] *Department of Clinical Pharmacy, Faculty of Pharmacy, Al Baha University, Al Baha 1988, Saudi Arabia*
[h] *Department of Pharmacology and Toxicology, Faculty of Pharmacy (Girls), Al-Azhar University, Nasr City, Cairo 11651, Egypt*

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ABSTRACT

In the current comprehensive review, we first highlighted circRNAs, which are key ncRNAs. Next, we discussed the relationships among circRNAs and breast cancer subtypes via *in silico* databases analysis and extensive literature search. CircRNAs, that sponge miRNA axes or act as silencers of oncogenic mRNAs, have been extensively addressed in the context of this review. During BC pathogenesis, the circRNA/microRNA/messenger RNA (mRNA) axis plays a major role in disease growth, progression, and survival/resistance and could be targeted for improved treatment options. This review also aimed to address oncogenic and tumor suppressor mRNAs, which are regulated by various circRNAs in BC. Moreover, we mentioned the relation of different circRNAs with cancer hallmarks, patient survival together with drug resistance. Additionally, we discussed circRNAs as vaccines and biomarkers in BC. Finally, we studied exosomal circRNAs as a hot interesting area in the research.

Review significance: Via using *in silico* databases, bioinformatics analysis, and a thorough literature search to first highlight circRNA as a crucial ncRNA and its biogenesis, and then we explored the connection between circRNA and breast illnesses. In the framework of the review, circRNA sponged-miRNAs axis or as silencers to oncogenic mRNAs were extensively discussed. In the pathophysiology of BC, the circular RNA/microRNA/messenger RNA axis is crucial for the propagation of the disease and resistance that may be targeted for more effective treatment options, in order to confront tumor suppressor and oncogenic mRNAs that are presently regulated by circRNAs in BC. For better patient results, we advised further mechanistic research to elucidate additional ncRNA axis that may be targeted for the therapy of BC and for prognosis/ or early diagnosis.

1. Introduction

1.1. Background

Breast cancer (BC) is the most common malignant disease among females and eventually threatens the health of the majority of women worldwide [1]. Pathologically, BC is characterized by three subtypes: triple negative (TN), estrogen receptor positive (ER+), and ErbB2 overexpressed-HER2 positive (HER2+). TN is the subtype with the highest metastasis, recurrence and mortality rates. TN accounts for approximately 15% of all BC cases, with more aggressive symptoms and a lack of targeted effective therapeutic options [2]. Therefore, targeted treatment and early detection are important, especially for patients with triple-negative BC (TNBC). Traditionally, many pathological features,

* Corresponding author.
E-mail address: nadia_hamdy@pharma.asu.edu.eg (N.M. Hamdy).
[1] orcid.org/0000–0003-2105–107X.

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such as lymph node (LN) status, histological grade and tumor size, are used to predict patient prognosis. Recently, many biomolecular markers, such as microRNAs (miRNAs), tumor-associated macrophages (TAMs), and long noncoding RNAs (lncRNAs), have been identified to have significant prognostic value [3].

1.2. The current problem addressed is BC management

A substantial portion of the human genome undergoes transcription, yielding a diverse array of noncoding RNAs (ncRNAs). Within this spectrum, this discourse focuses on three key types—lncRNAs, microRNAs (miRNAs), and circular RNAs (circRNAs)—that play a fundamental role in cancer pathogenesis. In this review, the authors will focus on the most recent class of ncRNAs, namely, circRNAs. Previously, we investigated whether microRNAs influence tumorigenesis and neoplastic progression or treatment resistance [4] and whether circRNAs regulate gene expression via an extended array of molecular mechanisms and signaling pathways influencing tumorigenesis and neoplastic progression or treatment resistance.

1.3. Review aim(s) and objective(s)

This review succinctly delineates recent advancements in the landscape of circRNAs, followed by an in-depth exploration and *in silico* analysis of the prospect of employing circRNAs as plausible therapeutic targets/agents in BC, with a special focus on BC types and metastatic and/or resistant BC patients. The quadri-negative type included androgen receptor-negative + TNBC.

BC vaccines utilizing circRNAs, accompanied by comprehensive and *in silico* or bioinformatic analysis of the intricate mechanistic frameworks that underlie these interactions.

2. Circular RNAs (CircRNAs)

2.1. circRNA history overview and characteristics

A recently discovered class of ncRNA molecules. CircRNAs are a large class of ncRNAs that are produced by a splicing event called back splicing; during splicing, a downstream splice-donor site is linked covalently to an acceptor site. CircRNAs were first discovered by [5] in plant-infected viroids using electron microscopy, and they are considered pathogenic due to their structural similarity to viruses. CircRNAs were subsequently detected by electron microscopy in the cytoplasm of eukaryotic cell lines. However, they are considered to be known as 'junk' obtained by splicing events, and only the mouse testis-specific circRNA obtained from the sex-region Y gene was suggested to have a possible function [6]. Recently, circRNA-specific bioinformatics algorithms and RNA sequencing (RNA-seq) have identified thousands of circRNAs in eukaryotic cells, including those of fungi, worms, plants, fish, mammals and insects. RNA sequencing and microarray technology are used to quantify RNA abundance and identify new RNA species that have identified most circRNAs in human cells [7]. In addition to the advanced bioinformatics algorithms that have been developed to identify circRNAs, such as find-circ, circRNA-finder, and CIRC-explorer, the main methods for validating the expression of circRNAs are quantitative real-time PCR (qRT—PCR) and Northern blotting. Northern blotting is a more efficient method for validating circRNAs than qRT—PCR because it is straightforward and does not involve reverse transcription or amplification steps [8].

***In silico* Database Search** (Accessed September 6th, 2023)

GeneCards Version 5.17 (Updated: Aug 2, 2023) The human gene database https://www.genecards.org/ has 120 circRNAs of the total genes. The percentages of GeneCards for which information was obtained from the corresponding source of 100% of the circRNAs were obtained from the ENA, RNAcentral, and GeneLoc databases.

https://www.genecards.org/List/Statistics#RNAGeneCircRNAs

The **European Nucleotide Archive (ENA)** used a European Bioinformatics Institute (EBI) search to perform a free text search across the ENA data.

https://www.ebi.ac.uk/ena/browser/home last updated December 1st, 2021. Concerning human circRNA

https://www.ebi.ac.uk/ena/browser/text-search?query=human%20circRNA Fifty-one circRNAs with complete sequences (st.), 8 noncoding genes (A985216.1:1.51:ncRNA to A9852122.1:1.51:ncRNA) were identified in Supplementary Table S1, and 945 experiments were performed in 627 studies.

RNAcentral database v22 https://rnacentral.org/ (RNAcentral Consortium 2021) ncRNA sequence database from EBI

https://rnacentral.org/search?q=circRNA%20AND%20so_rna_type_name:%22Circular_ncRNA%22%20AND%20TAXONOMY:%229606%22

The search terms used were as follows: RNA AND so_rna_type_name: "Circular_ncRNA" AND TAXONOMY: "9606" AND rna_type: "circRNA" AND has_genomic_coordinates: "True", where 135 hsa-circRNAs with lengths ranging from 128 to 3626 nucleotides are present.

2.2. State-of-the-art circRNAs in breast cancer

CircRNAs, a novel category of endogenous regulatory RNA molecules, are characterized by their 5' and 3' ends being linked to form a covalently closed single-stranded loop through backsplicing [9]. These genes exhibit disease-specific expression and remarkable expression stability, and they can regulate gene expression both post-transcriptionally and transcriptionally

In various cancers, including breast cancer, circRNAs are abnormally expressed and contribute to the onset and progression of the disease. They influence numerous aspects of breast cancer, such as cell proliferation, the cell cycle, apoptosis, invasion and metastasis, autophagy, angiogenesis, drug resistance, and tumor immunity. Their potential as prognostic and diagnostic markers is currently under investigation [10].

The insights gained into the functions and roles of circRNAs in BC could pave the way for the creation of new diagnostic and predictive biomarkers for this disease [9]. It's noteworthy that biomarkers are defined as biological molecules found in blood, other body fluids or tissues that are signs of a normal or abnormal process/condition or disease. However, there is still an urgent need for accurate identification and annotation of newly emerging circRNAs in this rapidly evolving research field [10].

In a recent study, researchers used circRNA microarray analysis to examine plasma samples from breast cancer patients. They discovered three circRNAs, hsa_circ_0000091, hsa_circ_0067772, and hsa_circ_00005123, that were differentially expressed in tumors. These circRNAs could serve as biomarkers for diagnosing breast cancer [11]. However, further studies are required to confirm these results.

Another study provided a comprehensive review on human circRNAs and their potential clinical implications in BC [12]. These findings emphasize the importance of additional research to elucidate the molecular pathways that contribute to the proliferation and progression of this disease. These recent studies indicate that there is still much to learn about the role of circRNAs in breast cancer. These gaps present opportunities for future research to advance our understanding of the role of circRNAs in breast cancer.

2.3. Biogenesis of circular RNAs

Most circRNAs are expressed from protein-coding genes that consist of a single or multiple exons. Despite the lack of capping and polyadenylation, circRNAs generally localize to the cytoplasm [13]. However, the products of circRNAs that contain sequences derived from both introns and exons, known as exon–intron circRNAs, are derived from internal intron retention, and failure of the debranching process of intronic lariats during back splicing leads to the production of exonic

circRNAs (EcRNAs), circular intronic RNAs (ciRNAs) and exon–intron circRNAs (ElciRNAs); ciRNAs and exon–intron circRNAs reside in the nucleus of the cell, and these circRNAs can enhance the transcription of their parental genes by positively regulating RNA polymerase II or by interacting with the U1 small nuclear ribonucleoprotein (snRNP) [14].

Although back-splicing events are less effective than linear splicing events, circRNAs accumulate in a temporally regulated manner in specific cell types due to their very high stability. This stability occurs due to their closed ring structures, which protect these circRNAs from degradation by exonucleases [15]. In addition to the abovementioned circRNAs, tRNA intronic circular RNAs (tricRNAs) are a class of circular noncoding RNAs that are produced during tRNA metazoan splicing [16]. The biogenesis of tricRNAs requires both conserved tRNA sequence motifs and several processing enzymes, and their expression is regulated in a tissue-specific and age-dependent manner [17].

Interestingly, the majority of circRNAs are upregulated during neurogenesis, and some circRNAs are enriched in the synaptic region. Additionally, the mechanisms of action and several functions of circRNAs in the development of neurons are under investigation. Whether circRNAs accumulate in nonproliferating cells due to their very high stability or because circRNAs are generally produced by more differentiated cells in the terminal phase, such as differentiated cells in the nervous system, is still unclear. In contrast to those in the nervous system, circRNAs are downregulated in cancer and other diseases and are associated with high cell proliferation rates, possibly due to dilution by proliferation before they reach a steady-state level [18].

To date, circRNAs have been implicated in many human diseases, including cancer, cardiovascular diseases, neurological disorders, chronic inflammatory diseases and diabetes mellitus, and they also accumulate during aging.

circRNADb version 1.0 (accessed September 6th, 2023) was used to browse protein-coding potential data; there were 72 circRNAs with protein expression evidence and 21 circRNAs with protein coding potential and expression evidence http://reprod.njmu.edu.cn/cgi-bin/circrnadb/broProtein_front.php, but neither were studied in breast tissues nor cell lines.

circSC CircRNAs in Single-cell transcriptomes (accessed September 6th, 2023)

https://ngdc.cncb.ac.cn/circatlas/circSC/data.html

circAtlas 3.0 updated June 30th, 2023 https://ngdc.cncb.ac.cn/circatlas top 30 circRNAs in human breast tissue (Figs. 1 and 2) https://ngdc.cncb.ac.cn/circatlas/top_exp1.php Accessed Sept. 6th, 2023.

Epigenetic alterations that regulate cancer commonly include abnormal DNA methylation and histone alterations that are linked to epigenetic gene expression. *It has been reported that circRNAs play a fundamental role in the etiology of several human diseases, including several oncological conditions.*

3. The functional role of CircRNAs in breast cancer

3.1. BC regulation

However, circRNAs have attracted the attention of researchers due to their roles in the development of various human cancers, including all BC subtypes. Researchers have revealed that circRNAs play important roles in the regulation of several factors at the transcriptional or post-transcriptional level in mammals and that dysregulation of circRNAs may affect gene expression, leading to human cancers. Many studies using microarray and RNA-seq have revealed that the characterization of expression patterns and systematic profiling of circRNAs in different subtypes of BC can be used to distinguish cancer subtypes, indicating that circRNAs may be novel molecular biomarkers [8].

3.1.1. Expression of circRNAs in all subtypes of BC

CircRNAs play a significant role in the regulation of invasion, cell proliferation, metastasis, autophagy, apoptosis, vascularization and the

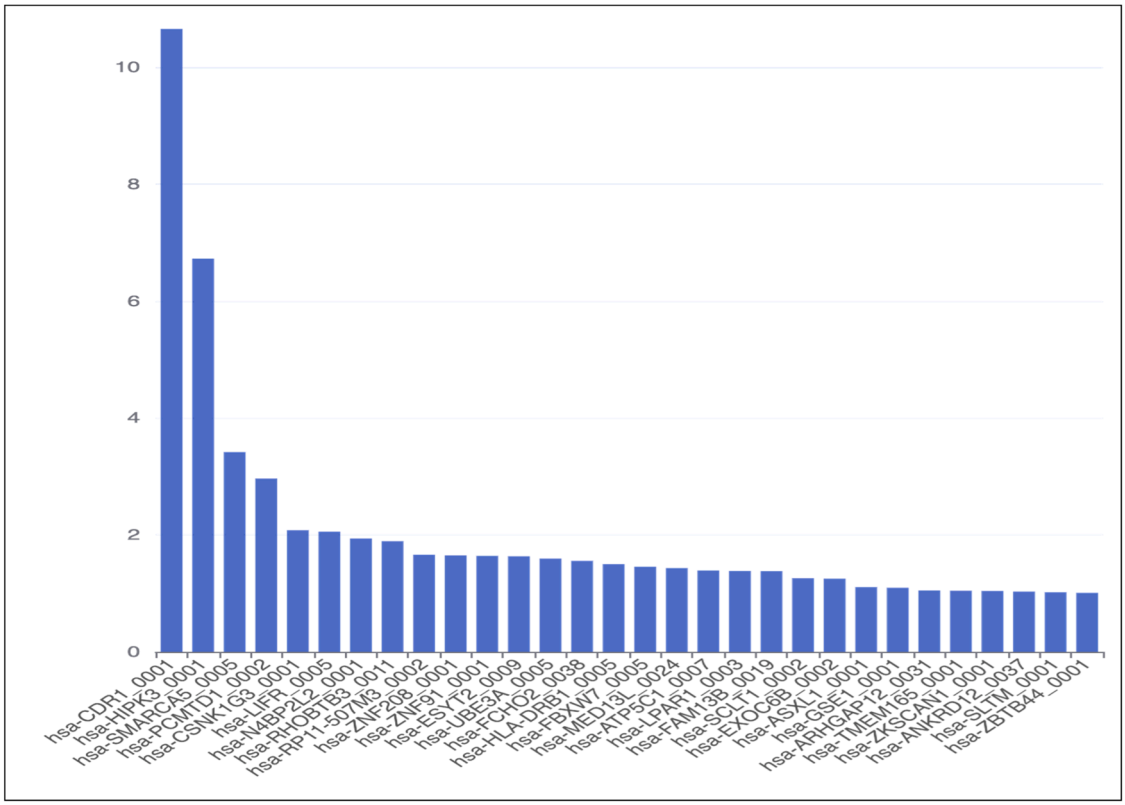

Fig. 1. Top 30 highly expressed circRNAs from preanalyzed datasets of human breast tissue, one-step analysis, expressed as CPM count per million. Accessed Sept. 6th, 2023 https://ngdc.cncb.ac.cn/circatlas/top_exp1.php.

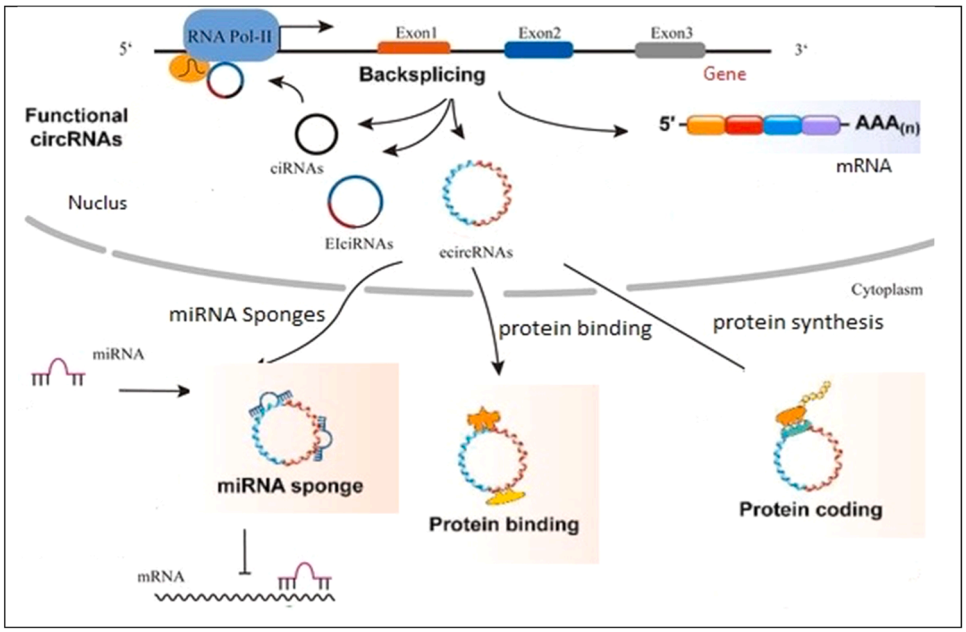

Fig. 2. Molecular mechanisms underlying the regulatory functions of circRNAs, [miRNA; microRNA, circRNA; circular RNA, mRNA; messenger RNA, Pol-II; polymerase II enzyme.].

cell cycle in BC via regulation of the expression of target genes that are involved either directly or indirectly in signaling pathways related to cancer. Accumulating findings have indicated that greater numbers of circRNAs are detected in normal breast tissues than in malignant tissues. Microarray analysis revealed that 41 circRNAs, 22 downregulated and 19 upregulated, were significantly differentially expressed in BC patients compared to healthy controls [19]. Notably, circRNAs in (ER)-positive normal samples are inversely correlated with the risk-of-relapse proliferation (ROR-P) score used for proliferating genes, indicating that circRNAs may be molecular markers for cell proliferation in BC and its subtypes. In a recent study, researchers identified the expression profiles of circRNAs in BC and adjacent normal tissues using microarray analysis. The results indicated that 1155 circRNAs were differentially expressed, including 440 circRNAs whose expression was downregulated and 715 circRNAs whose expression was upregulated in BC tissues [20]. Additionally, a Circ-Seq workflow was developed to identify circRNAs that are specific to malignant breast cancer samples and are unique to each of the three BC subtypes [21]. Another validation study revealed that hsa_circ_104689 and hsa_circ_103110 were upregulated in BC tissues, while hsa_circ_100219 and hsa_circ_006054 were downregulated [22]. Similarly, another study revealed 1314 circRNAs at both lactation stages in lactating rats [23]. With the increasing number of circRNAs discovered in BC, the regulatory role of circRNAs in cancer will receive increasing attention.

From the CircRNADisease v2.0 database [24] (updated in August 2023) http://cgga.org.cn:9091/circRNADisease/ First, according to Disease Ontology (DO) BC is a thoracic cancer that originates in the mammary gland https://disease-ontology.org/?id=DOID:1612. However, BC, which has a material basis in abnormally proliferating cells derived from epithelial cells, is breast carcinoma. https://disease-ontology.org/?id=DOID:3459 The expression of hsa_circ_RPPH1 is upregulated in breast carcinoma patients, where the host gene RPPH1 and the Circ_RPPH1/miR-146b-3p/E2F2 axis can promote the progression of BC.

With respect to Her2-receptor-positive BC https://disease-ontology.org/?id=DOID:0060079, two circRNAs, hsa-circ_CDYL and hsa-circ_ERBB2, whose host genes CDYL and ERBB2, respectively, were upregulated. hsa-miR-92b-3p inhibits the proliferation of HER2-positive BC cells by targeting circCDYL. Circ-ERBB2 sponges miR-136–5p and miR-198, accelerating HER2-positive BC progression through the circ-ERBB2/miR-136–5p/TFAP2C axis or the circ-ERBB2/miR-198/TFAP2C axis.

Luminal breast carcinoma A https://disease-ontology.org/?id=DOID:0060548 is characterized by high expression of luminal epithelial cell genes, including estrogen receptor (ER) genes. Nine circRNAs showed differential expression, 8 of which were upregulated, namely, hsa_circRNA_061260, hsa_circRNA_103933, hsa_circRNA_005239, hsa_circRNA_100689, hsa_circRNA_004087, hsa_circRNA_104420, hsa_circRNA_104421 and hsa_circRNA_101222; only one circRNA was downregulated, namely, hsa_circRNA_104864.

Table 1 lists the circRNA names of dysregulated, upregulated or downregulated circRNA expression patterns, circRNA-associated host genes and sponged microRNAs in TNBC http://cgga.org.cn:9091/circRNADisease/ (accessed September 7th, 2023).

According to earlier investigations, circRNAs are thought to be important in the onset, development, and growth of BC Table 2.

3.2. *Involvement of circRNAs in BC development and progression (Table 2)*

3.2.1. *CircRNAs serving as miR sponges*

MiRNAs are responsible for the negative regulation of mRNA expression through base pairing with mRNAs located in 3′ untranslated regions, which opposes translation and decreases the stability of mRNAs. The competing endogenous RNA (ceRNA) theory states that other RNAs accompanied by miRNA target sites can compete for the binding of miRNAs to mRNAs [25,26]. Furthermore, most circRNAs found in the cytoplasm function as miRNA sponges by interacting with miRNAs, suppressing the inhibitory effect of miRNAs on target genes in many cancers. In doing so, circRNAs may act as lncRNAs that sponge various miRs in various cancer types, such as NOTCH lncRNAs. The similarity between circRNAs and NOTCh-related lncRNAs should be examined in BC,[2] such as CRC [27].

Accumulating data have revealed that miRNAs can directly regulate gene expression during the process of transforming normal cells into

[2] research gap #1

Table 1
CircRNAs in TNBC (40) retrieved from the circRNADisease v2.0 bioinformatics database search.

Expression pattern	CircRNA	host Gene	hsa-miRNA
Down	hsa_circ_ITCH	ITCH	hsa-miR-214, hsa-miR-17
	hsa_circ_FBXW7	FBXW7	hsa-miR-197–3p
	hsa_circ_WAC	WAC	hsa-miR-142
	hsa_circ_TADA2A	TADA2A	hsa-miR-197–5p
	hsa_circ_CREIT	CREIT	-
	hsa_circ_VEGFA	VEGFA	-
	hsa_circ_CLASP1	CLASP1	-
Up	hsa_circ_CDR1	CDR1	hsa-miR-1299
	hsa_circ_EPSTI1	EPSTI1	hsa-miR-4753, hsa-miR-6809
	hsa_circ_UBAP2	UBAP2	hsa-miR-661
	hsa_circ_AGFG1	AGFG1	hsa-miR-195–5p
	hsa_circ_KIF4A	KIF4A	-
	hsa_circ_PLK1	PLK1	hsa-miR-296–5p
	hsa_circ_TFCP2L1	TFCP2L1	hsa-miR-7
	hsa_circ_GNB1	GNB1	hsa-miR-141–5p
	hsa_circ_SEPT9	SEPT9	hsa-miR-637
	hsa_circ_TCONS_00016926	TCONS_00016926	hsa-miR-1297
	hsa_circ_MAP3K4	MAP3K4	hsa-miR-2682
	hsa_circ_UBE2D2	UBE2D2	hsa-miR-512–3p
	hsa_circ_HIF1A	HIF1A	-
	hsa_circ_PSMA1	PSMA1	hsa-miR-637
	-	-	hsa-miR-152–3p
	-	-	hsa-miR-1296
	hsa_circ_ERBB2	ERBB2	hsa-miR-136–5p
	hsa_circ_PDCD11	PDCD11	hsa-miR-432–5p
	hsa_circ_EIF6	EIF6	-
	hsa_circ_WHSC1	WHSC1	hsa-miR-212–5p
	hsa_circ_METTL3	METTL3	hsa-miR-34c-3p
	hsa_circ_INTS4	INTS4	hsa-miR-129–5p
	hsa_circ_ELP3	ELP3	-
	hsa_circ_UBR5	UBR5	hsa-miR-1179
	hsa_circ_TRIO	TRIO	hsa-miR-432–5p
	hsa_circ_CSNK1G1	CSNK1G1	hsa-miR-28–5p
	hsa_circ_AR	AR	hsa-miR-665, hsa-miR-671–5p
	hsa_circ_TBC1D14	TBC1D14	-
	hsa_circ_KIF4A	KIF4A	-
	hsa_circ_MYC	MYC	-
	hsa_circ_SNX25	SNX25	-
	hsa_circ_CAPG	CAPG	-

The expression pattern was either upregulated (UP) or downregulated (Down) http://cgga.org.cn:9091/circRNADisease/ Accessed September 7th, 2023.

cancerous ones (carcinogenesis). In-depth studies have shown that some circRNAs may regulate copying DNA and splitting into 2 cells (proliferation), extension & penetration into neighboring tissues in cancer (invasion) and forming new tumors in other parts of the body (metastasis) by functioning as miRNA sponges. Similarly, another study indicated the essential role of circular homeodomain-interacting protein kinase 3 (CHIPK3), which is an abundant circRNA derived from exon 2 in the *HIPK3* gene, which was proven via a luciferase screening assay to sponge 9 miRNAs with 18 binding sites. Specifically, this study indicated

Table 2
List of circRNAs reported as potential biomarkers in breast cancer.

circRNA and/or circBase ID	Clinical interest	Experimental approach	Ref.
circHIPK3/ hsa_circ_0000284	diagnosis, prognosis	*ex vivo, in vitro, in vivo, in silico*	[36]
circRPPH1_015/ hsa_circ_0000517	diagnosis, prognosis	*ex vivo, in vitro, in vivo, in silico*	[36]
hsa_circ_0005046	-	*ex vivo, in vitro, in vivo*	[37]
hsa_circ_104821	-	*ex vivo, in silico*	[20]
hsa_circ_0005230	-	*ex vivo, in vitro, in silico*	[38]
hsa_circ_0006743	Early-stage diagnosis	*ex vivo, in silico*	[39]
circLARP4	diagnosis, prognosis	*ex vivo, in vitro, in silico*	[40]
hsa_circ_0072309	diagnosis, prognosis	*ex vivo, in vitro, in silico*	[41, 42]
hsa_circ_103110	diagnosis	*ex vivo, in silico*	[20]
hsa_circ_103552	diagnosis, prognosis	*ex vivo, in vitro, in silico*	[43]
circCCDC85A	diagnosis	*ex vivo, in vitro, in vivo, in silico*	[44]
circLARP4	diagnosis, prognosis	*ex vivo, in vitro, in silico*	[40]
circVRK1/ hsa_circ_0141206	diagnosis, prognosis	*ex vivo, in vitro, in silico*	[42]
circAGFG1	diagnosis, prognosis	*ex vivo, in vitro, in vivo, in silico*	[41] [45]
circFBXW7/ hsa_circ_0001451			
circKIF4A			[46]
circPDCD11/ hsa_circ_0019853			[46]
circUBAP2/ hsa_circ_0001846			[47]

[circRNAs; circular RNAs, N; normal breast tissue, T; breast tumor tissue]

that circHIPK3 inhibits miR-124 activity and binds directly to miR-124, which induces BC proliferation [28]. According to RT—PCR follow-up validation, circ-ABCB10 was significantly upregulated in a cell line and in a large sample size. Notably, loss-of-function experiments indicated that circ-ABCB10 knockdown increased the apoptosis of BC cells, revealing the essential role of circ-ABCB10 in the development of cancer by sponging miR-1271 [29]. Additionally, another rescue and loss-of-function experiment was conducted to determine the biological functions of the miRNA sponge properties of hsa_circ_0001982 in the progression and development of carcinogenesis. The results indicated that hsa_circ_0001982 knockdown induced apoptosis and suppressed the proliferation and invasion of BC cells by targeting miR-143, suggesting a novel approach for the pathogenesis of BC [22]. In summary, accumulated data have shown that circRNAs can regulate cancer development and progression by sequestering certain miRNA species that are responsible for the differentiation, proliferation, and migration of cancer cells.

3.2.2. *CircRNAs influencing BC-associated signaling pathways*

An increasing amount of data has revealed the relationships between several novel circRNAs and cancer-associated signaling pathways. Growing evidence has suggested that circRNAs play essential roles in the initiation, metastasis, proliferation and invasion of BC via regulation of target genes either directly or by interacting with miRNAs that are associated with cancer signaling pathways. As a known tumor suppressor miRNA, miR-7 gene expression is reduced in malignant breast tissue compared to normal tissues, and forced miR-7 gene expression in aggressive BC cell lines leads to suppression of malignant cell migration, proliferation and invasion [30]. Recently, miR-7 has been shown to be involved in various signaling pathways that are associated with cancer via the downregulation of the expression of oncogenic factors such as FAK, HER2D16 and SETDB1, which indicates an obvious role for miR-7 as a tumor suppressor [31]. Another newly identified circRNA known as ciRS-7, which is an inhibitor of circular miR-7, was proven to be

involved in several cancer-associated signaling pathways. Similarly, another study indicated that miR-7, which was downregulated in BC cells obtained from the human MDA-MB-231 and MCF-7 cell lines, suppressed cell metastasis and invasion and reversed the epithelial-to-mesenchymal transition in the MDA-MB-231 cell line by targeting the specific oncogene SETDB1, which leads to the suppression of STAT3 [32]. Thus, ciRS-7 can act as an inhibitor of miR-7 to reduce miR-7-mediated suppression of the STAT3 signaling pathway. Additionally, CiRS-7 can enhance cell proliferation in BC through miR-7, which in turn inhibits MCF-7/HER2 cell migration via suppression of the miR-7 target gene endothelial growth factor receptor (EGFR) [33]. Many studies have indicated that circRNAs might enhance the development and progression of BC through cancer-associated signaling pathways. However, other studies have shown the opposite results. The PI3K/AKT/FOXO signaling pathway has been shown to be involved in BC initiation via integration of a genomic approach. Foxo3 has been identified as a tumor suppressor gene due to its downregulation of gene expression in the development of cancer due to either loss of PTEN or increased Akt activity [34]. Similarly, another study revealed that circ-Foxo3 may upregulate the protein levels of Foxo3 by binding to several miRNAs that are shared with linear Foxo3 mRNA, leading to the induction of cell apoptosis and the inhibition of BC progression via the PI3K/AKT/FOXO signaling pathway [35]. Finally, with the progress of research methods for the identification of circRNAs, identifying circRNAs might be a tremendous approach in clinical diagnosis and treatment for cancer therapy.

3.3. CircRNAs and the underlying molecular mechanisms in BC

In peripheral blood, Xu et al. discovered that circRNAs can typically be expressed more than their host linear genes [48]. One of their interests was the circRNA SWI/SNF Related, Matrix Associated, Actin Dependent Regulator of Chromatin, Subfamily A, Member 5 (circSMARCA5). In contrast to the host gene SMARCA5, circSMARCA5 expression is lower in breast cancer tissues than in nearby normal tissues. *In vitro* and *in vivo* drug sensitivity of breast cancer cell lines was increased by the forced expression of circSMARCA5. In addition, they showed that this circRNA can connect to the parent gene locus, producing an R-loop that causes SMARCA5 exon 15 to pause transcription. The overexpression of that circRNA was sufficient to increase sensitivity to cytotoxic medicines, and it caused the downregulation of the gene and the formation of a truncated nonfunctional protein. Thus, circRNAs are thought to interact with host genes to prevent DNA damage repair.

Another molecular mechanism to be mentioned is sponging miRNAs. Circular RNAs function as competing endogenous RNAs (ceRNAs) that bind to miRNAs to indirectly control gene expression and function [49]. According to circRNA/miRNA analysis, hsa_circ_0001944 may contribute to breast cancer brain metastasis (BCBM) by sponging miR-509 and hindering its ability to bind to its downstream targets [50]. The same is true for circBCBM1 [51]. It was found to promote BCBM by modulating miR-125a. Ma and his colleagues also showed that three circRNAs (hsa-circ-0083373, hsa-circ-0083374, and hsa-circ-0083375) are important in the pathophysiology and development of breast cancer and that they regulate the genetic expression of some genes via miR-511 [52].

Moreover, CircNR3C2 (hsa_circ_0071127), which is noticeably downregulated in TNBC, has a negative correlation with the mortality of invasive breast cancer and distant metastases [53]. By sponging miR-513a-3p, overexpressing circNR3C2 *in vitro* and *in vivo* results in a critical increase in the tumor-suppressive activity of HRD1. Circ_0068871 sponges miR-181a-5p to control the expression of fibroblast growth factor receptor 3 (FGFR3) in BC cells [54].

Notably, according to a recent study by Wang et al., hsa_circ_0000911 regulates the pathogenesis of BC by sponging miR-449a [55]. On the other hand, circRNA muscleblind (circMbl) competes with pre-mRNA splicing to regulate its gene MBL [56].

In addition to the list of different circRNAs in different breast disease subtypes presented in Table (2), when the androgen receptor (AR) is not expressed, TNBC is classified as **quadruple negative breast cancer (QNBC),** which affects its growth, tumorigenesis, and prognosis [57]. Compared to TNBC, QNBC exhibits a greater Ki-67 index, indicating that this molecular subtype is more sensitive to chemotherapy [58]. However, it has been noted that only partial chemoresistance should be considered for the QNBC subtype because chemoresistance in TNBC due to aberrant expression of noncoding RNAs (ncRNAs) is becoming a global challenge [57]. There is currently little information on potential biomarkers, including the ncRNAs in QNBC that could be exploited as therapeutic targets, as a result of the lack of studies on QNBC. To date, however, no study has discussed the functions of lncRNAs and circRNAs in QNBC [57].

4. Exosomal circRNAs as new hot area of research

Two protein-coding exosomal circRNAs were upregulated in BC, as shown in Table 3 retrieved from exoRBase v2.0 [59] (accessed September 7th, 2023). However, 14 genes were downregulated in both the benign and BC urine and blood samples, per *in silico* database search for exosomal circRNAs in BC http://www.exorbase.org/exoRBaseV2/browse/toIndex?kind=circRNA

http://www.exorbase.org/exoRBaseV2/browse/toIndex?kind=circRNA Accessed Sept. 7th, 2023.

Hallmark pathways involving exosomal circRNAs regulated (according to the ssGSEA score) in BC biological fluid samples retrieved from exoRBase v2.0, where Kras pathway hallmark is noted for benign cases and for BRCA upregulation, the top pathways are Myc target, IFN-alpha response, oxidative phosphorylation, ROS pathway, and heme metabolism; however, for BRCA downregulation, the top pathways are protein secretion, complement, UV response, hypoxia, cholesterol homeostasis, and Kras signaling (Accessed September 7th, 2023)

http://www.exorbase.org/exoRBaseV2/browse/toIndex?kind=circRNA

CIRI-hub https://ngdc.cncb.ac.cn/CIRIhub/index.html **through circAtlas 3.0 was** updated on June 30th, 2023. A background dataset (BRCA) for biological analysis of circRNAs based on RNA-seq or microarray datasets was generated using 237 breast invasive carcinoma (BIC) samples and 15 matched normal tissue samples. After one-stop analysis, specific circRNAs were analyzed, and the input used was the genomic position of the circRNA.

5. Different BC hallmark pathways involving circRNAs

Studies have shown that circular RNAs (circRNAs) can control the degree to which messenger RNAs (mRNAs) express carcinogenic components by sponging microRNAs (miRNAs), which are directly associated with the occurrence and progression of breast cancer (BC) [60]. On the other hand, as circRNAs and miRNAs share binding sites, they are able to interact in a competitive manner, and circRNAs behave as sponges, changing how target genes are regulated by miRNAs. How the circRNA regulatory network functions in diverse tumor types has been widely documented. The regulatory network plays a role in numerous biological processes in BC, including preventing tumorigenesis, invasion, and migration.

5.1. CircRNAs promoting vs inhibitory effects on BC growth

BC cell proliferation is accelerated by many circRNAs, one of which is hsa_circ_0003645. Hsa_circ_0003645 was more strongly expressed in BC tissues and cell lines than in normal breast tissue and MCF-10a breast epithelial cells [61].

Moreover, circRNA DDB1 and CUL4-associated factor 6 (circ_DCAF6) increase BC cell proliferation and stemness by competitively

Table 3
CircRNAs in extracellular vesicles (exosomal circRNAs) that are downregulated (14) or upregulated (2) in blood and urine samples from the BRCA and benign groups. The detection frequency ranged from 0 to 1, and the data were retrieved from exoRBase v2.0.

Down circBase ID/ CircID	Genomic position	Strand	Gene symbol	Gene type
hsa_circ_0000778/ exo_circ_24162	chr17:47402132–47414919	+	EFCAB13	Protein coding
hsa_circ_0001177/ exo_circ_38858	chr21:14968297–15043574		AF127577.2	lncRNA
hsa_circ_0002711/ exo_circ_38873	chr21:14991201–15043574	-	AF127577.2	lncRNA
hsa_circ_0004771/ exo_circ_38881	chr21:15014344–15043574	-	NRIP1	protein coding
hsa_circ_0052621/ exo_circ_40900	chr2:10788697–10790833	-	PDIA6	protein coding
NA/ exo_circ_51688	chr3:3150883–3167793	-	CRBN	protein coding
NA/ exo_circ_68334	chr7:24623663–24650712	+	MPP6	protein coding
hsa_circ_0008297/ exo_circ_78984	chrY:12909360–12913062	+	DDX3Y	protein coding
hsa_circ_0005757/ exo_circ_78986	chrY:12912963–12914649	+	DDX3Y	protein coding
NA/ exo_circ_78999	chrY:13323555–13326350	-	UTY	protein coding
hsa_circ_0009024/ exo_circ_79050	chrY:19587210–19587507	+	TXLNGY	Pseudogene
NA/ exo_circ_79057	chrY:20507352–20521300	-	TTTY10	lncRNA
hsa_circ_0001953/ exo_circ_79066	chrY:2953909–2961646	+	ZFY	protein coding
hsa_circ_0007907/ exo_circ_79068	chrY:2961074–2961646	+	ZFY	protein coding
hsa_circ_0006322/ exo_circ_79082	chrY:7341115–7371889	+	PRKY	Pseudogene
UP circBase ID/ CircID	**Genomic position**	**Strand**	**Gene symbol**	**Gene type**
hsa_circ_0050334/ exo_circ_28381	chr19:29971193–29986417	+	URI1	Protein coding
hsa_circ_0007755/ exo_circ_30364	chr1:145839890–145842477	+	POLR3C	

binding to miR-616–3p and activating the Hedgehog pathway [62]. According to a study by Cai et al., high expression of the gene hsa_circ_0000515 is linked to a poor prognosis in BC patients. The oncogene chemokine (C-X-C motif) ligand 10 (CXCL10) was made more active by Hsa_circ_0000515, which sped up BC cell proliferation and promoted angiogenesis [63].

On the other hand, circRNAs have been implicated in anticancer activities in BC according to numerous investigations. Conflicting cell processes of apoptosis and growth. The balance between apoptosis and proliferation influences tumor growth and decreases to some extent. Analysis of microarray data revealed that the expression of hsa_circRNA_000554 was much lower in BC tissues than in normal tissues. Circ_000554 is overexpressed and interacts with miRNA-182 to inhibit it, increasing the production of zinc finger protein 36 (ZFP36), which prevents BC cell proliferation, epithelial–mesenchymal transition (EMT), and cell death [64].

According to related research, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) can prevent BC cells from proliferating [65] When exposed to TCDD, the expression of the circRNA BRCA1-associated RING domain 1 (circBARD1/circ_0001098) is upregulated, which decreases BC cell growth and promotes apoptosis by controlling miR-3942–3p and BARD1 [66]. Examples can be seen in Table (1).

5.2. CircRNAs promoting and inhibitory effects on BC migration

Hsa_circ_002178 expression is markedly elevated in BC, and this increase is strongly linked to patient survival, lymph node metastasis, tumor size, and TNM stage. By selectively binding to miR-1258, Hsa_circ_002178 promotes BC development and metastasis by decreasing the inhibitory effect of miR-1258 on lysine demethylase 7 A (KDM7A) [67]. Zinc finger E-box binding homeobox 1 (ZEB1) is a transcription factor that causes EMT by binding to miR152, inhibits BC cell death, and promotes cell metastasis. The circRNA kinesin family member 4 A (circKIF4A/hsa_circ_0007255) can increase ZEB1 expression in BC [68]. Additionally, by interacting with miRNAs to control the expression of their target mRNAs, circKIF4A can facilitate the onset and progression of gliomas, ovarian cancer, and bladder cancer [69–71].

Moreover, circRNA Polo-Like Kinase 1 (circPLK1) controls Insulin-like Growth Factor 1 (IGF1) expression by absorbing miR-4500, an inhibitor of oncogenes. The poor prognosis of BC patients is positively linked with the degree of IGF1 expression. Through the miR-4500/IGF1 axis, CircPLK1 promotes BC cell motility, invasion, and proliferation [72–74]. The circRNA ubiquitin protein ligase E3 component N-Recognin 1 (circ-UBr1) can be used to increase the expression of Cyclin D1 (CCND1) and promote BC cell proliferation and migration by acting as a molecular sponge for miR-1299, which is a tumor inhibitor [75]. The aberrant expression of CCND1, a member of the highly conserved cyclin family, can alter the cell cycle. According to related research, CCND1 is a proto-oncogene that promotes the growth and spread of tumors [76,77].

CircRNA SET domain containing 2 (circ_SETD2/hsa_circ_0065173) is a differentially expressed gene with low expression in luminal A breast cancer and TNBC patients according to the findings of gene chip research [78]. Circ_SETD2 targets miR155–5p and upregulates the expression of SCUBE2, which prevents BC cells from migrating [79]. The likelihood of patient death and the expression of the circRNA nuclear receptor subfamily 3 group C member 2 (circNR3C2/hsa_circ_0071127) are adversely linked with BC transfer. By sponging miR-513a-3p, the overexpression of circNR3C2 reduces BC cell migration, proliferation,

and EMT, which improves the ability of HRD1 to limit tumor growth [53].

5.3. CircRNA involvement in BC invasion

The role of many circRNAs in BC invasion have been studied. One of these genes was Hsa_circ_0136666, which is considerably more highly expressed in BC tissues and cell lines, and its expression is strongly associated with cyclin-dependent kinase 6 (CDK6) expression. Through sponge adsorption of miR-1299, the transcription factor Hsa_circ_0136666 increases CDK6 expression and enhances BC cell invasion [80].

As stated by Zhang et al., Circ_0072995 serves as a miR-30c-2–3p85 sponge, promoting BC cell invasion and migration [81]. It can also upregulate CDK6 and target MIR-147A to support the development of epithelial ovarian cancer cells [82]. High expression of circANKS1B (hsa_circ_0007294) is associated with lymph node metastasis and clinical stage. By sponging miR-152–3p and miR-148A-3p, CircANKS1B increases the expression of upstream transcription factor 1 (USF1) and promotes BC invasion and migration [83].

According to Yin et al., the expression of hsa_circ_0001785 is low in the peripheral blood of BC patients, and this expression level is closely correlated with patient prognosis, distant tumor metastasis, and TNM stage [84]. The miR-94 target gene suppressor of cytokine signaling 3 (SOCS3) is indirectly upregulated by the sponge hsa_circ_0001785, which also suppresses BC cell proliferation and migration [85]. In most BC cell lines, hsa_circ_0087378 is expressed at a low level, and an investigation by Yuan et al. supported this finding [86]. They hypothesized that hsa_circ_0087378 may act as a miRNA sponge for miR-1260b and upregulate the expression of secreted frizzled related protein 1 (SFRP1), thus performing a tumor suppressor function in BC invasion. However, *in vivo* and *in vitro* tests are required to confirm these findings. The targeting of Toll-like receptors (TLRs), as well as SOCS, would be beneficial for cancer treatment [87] as would the targeting of the *CTLA4* gene and the tumor suppressor *RASSF1A* and the possible mediating role of the STAT4 gene or protein [88].

Table (2) showed examples of circRNAs involved in BC invasion in different manners.

5.3.1. CircRNA in relation to the mitochondria

CircRNAs are present in body fluids and urine extruded from cells in exosomes [89]. Similarly, circRNAs can be located in any subcellular compartment of the body, such as the mitochondria, where mitochondrial mRNA is circularized [90]

The Warburg effect refers to the phenomenon of increased absorption of glucose and its fermentation to lactate, which is characteristic of altered metabolism in cancer cells, even when the mitochondria are fully functional [91].

Cao et al. studied the association between the Warburg effect and certain circRNAs, such as circRNA ring finger protein 20 (circRNF20). Compared to the blank control, circRNF20 knockdown decreased glucose absorption, lactate generation, and ATP levels in a study correlated with the Warburg effect. CircRNF20 knockdown was shown to reduce tumor growth in an *in vivo* heterograft mouse model. These findings demonstrated how circRNF20 aids in BC development and glycolysis [92]. Interestingly, circRNA Erb-B2 receptor tyrosine kinase 2 (circ-ERBB2) knockdown limits both the Warburg effect and the *in vivo* proliferation of TNBC cells [43]

Knockdown of circRNA DENN domain containing 4 C (circ-DENND4C/hsa_circ_0005684) was found to inhibit glycolysis in BC cells under hypoxia [93] and increase glucose consumption and lactate generation, while silencing circDENND4C significantly decreased these events. Additionally, Huang et al. demonstrated that by modulating the miR-599/E2F3 axis, circRNA WW domain-containing adapter protein with coiled-coil (circWAC) induces glycolysis in BC cells, revealing new potential targets for BC treatment [94].

Furthermore, inhibiting BC proliferation, metastasis, and glycolysis via the miR-1236–3p/6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3) axis was achieved by targeting circ_0102273 [95].

5.4. CircRNAs and BC treatment resistance

Many studies have shown that knocking down certain circRNAs increases BC treatment sensitivity, while the opposite is true for other circRNAs.

A CT on circRNAs in BC patients at the Faculty of Medicine, Assiut University, Egypt, is still ongoing to explore the diagnostic potential of hsa_circ_0001785 (Circ-ELP3) and hsa_circ_100219 (Circ-FAF1) in the serum samples of 80 patients with BC. The goal of this study was to determine whether these circRNAs can serve as diagnostic and prognostic biomarkers for evaluating human breast cancer [96]. The standard of care for BC after breast-conserving surgery is adjuvant radiation. After radiotherapy, tumor recurrence caused by acquired radioresistance has become a perplexing and unsolvable issue. As a result, preventing tumor recurrence is essential for increasing survival. Recent research indicates that circRNAs may play a role in controlling radioresistance in different malignancies, including BC [97]. The ability of breast cancer cells to proliferate, migrate, and invade was inhibited when the expression of circRNA A disintegrin and metalloprotease 9 (circ-ADAM9) was inhibited; nevertheless, radiosensitivity and apoptosis were increased. Additionally, radiation combined with circ-ADAM9 inhibition significantly slowed tumor growth [98].

Compared to the equivalent parental BC cells, radioresistant BC cells were observed to have a considerably greater level of circRNA ATP binding cassette subfamily C member 1 (circ-ABCC1). Mechanistically, circ-ABCC1 acted as a miR-627–5p decoy, enhancing the expression of ABCC1. Rescue tests showed that miR-627–5p inhibition or ABCC1 upregulation neutralized the suppressive effect of circ-ABCC1 silencing on BC cell radioresistance [97]. On the other hand, breast cancer cell radiosensitivity was decreased, and BC cell proliferation was improved by the overexpression of the circRNA nuclear receptor CO-Repressor 1 (circNCOR1). Furthermore, *in vivo* overexpression of circNCOR1 increased tumor cell proliferation and partially reversed radiation-induced loosening of tumor structures [99].

With respect to chemotherapy, tamoxifen (Tam) sensitivity in BC cells was increased, and the half maximal inhibitory concentration (IC50) of tamoxifen was decreased by circRNA cyclin-dependent kinase 1 (circCDK1) knockdown. Through the release of miR-489–3p, CircCDK1 knockdown was shown to improve tamoxifen sensitivity in animal models [100]. In estrogen receptor-positive (ER^+) breast cancer, biologically increased expression of the circRNA Scm-like with four MBT domain 2 (circRNA-SFMBT2) increased cell proliferation and tamoxifen resistance [101].

By altering pyrimidine production, the anticancer drug 5-fluorouracil (5-FU) is used to treat solid tumors, including breast cancer [102]. The effectiveness of this medication is nevertheless constrained by 5-FU resistance. CircRNA F-Box and leucine-rich repeat protein 5 (circFBXL5) were significantly elevated in 5-FU-resistant breast cancer cells and were abundantly expressed in breast cancer tissues and cells [103]. Functional studies demonstrated that circFBXL5 knockdown prevented breast cancer cells from becoming resistant to 5-FU by reducing cell invasion and migration and encouraging apoptosis.

Moreover, miR-873–5p is sponged by Circ_0085495 to effectively control the expression of Integrin β1 [104]. Similarly, adriamycin (ADM) resistance was decreased by integrin β1 knockdown. Furthermore, *in vivo* tumor growth was prevented by circ_0085495 knockdown. circ_0085495 is a promising target for overcoming ADM resistance in breast cancer patients, and circ_0085495 knockdown decreased ADM resistance in ADM-resistant cells by altering the miR-873–5p/integrin β1 axis. Finally, through miR-145, CircRNA_0044556 reduced TNBC cell susceptibility to ADM according to an observational study performed by Chen et al. [105].

Additionally, in terms of function, Liang et al. showed that circRNA lysine demethylase 4 C (circKDM4C) dramatically suppressed doxorubicin resistance, metastasis, and breast cancer growth both *in vitro* and *in vivo* [106]. CircRNA-CREIT was found to overcome doxorubicin resistance in TNBC by destabilizing protein kinase R (PKR), as stated by Wang and his colleagues [107]. It was also established by a recent study that by modulating the miR-149–5p/homeobox A11 (HOXA11) axis, interference with the circRNA ataxin 7 (circATXN7) decreased breast cancer progression and doxorubicin resistance, suggesting that it is a potential biomarker for breast cancer therapy [108]. Finally, the circRNA La-related RNA-binding protein 4 (circLARP4) increases doxorubicin chemosensitivity [109].

When circ_0069094 was silenced, tumor growth, cell proliferation, and invasion were reduced, while paclitaxel (PTX) sensitivity and cell death were increased in PTX-resistant cells. Circ_0069094 is overexpressed in PTX-resistant breast cancer tissues and cells [110]. Moreover, miR-153–3p can be inhibited by circRNA ATP binding cassette subfamily B member 1 (CircABCB1). Therefore, perhaps through this miR-153–3p, CircABCB1 contributes to the resistance of breast cancer to docetaxel [111]. Additionally, circ-RNF111 enhances PTX resistance, colony formation, invasion, glycolysis, and cell survival [40].

One of the most efficient cancer treatments currently available is monastrol, a prototype anti-kinesin medication that specifically targets the mitotic spindle [112]. According to mechanistic studies, upregulating circRNA mitochondrial TRNA translation optimization 1 (circRNA_MTO1/hsa-circRNA-007874) decreased cell survival, accelerated monastrol-induced cell cytotoxicity, and reversed monastrol resistance [113].

The first human epidermal growth factor receptor 2 (HER2)-targeted monoclonal antibody medication, trastuzumab, is essential for treating HER2-positive breast cancer. However, recurrent medication resistance prevents it from being clinically effective [114]. CircRNA profiling was used to identify a novel circRNA called the circRNA biglycan (circ-BGN), which is a major factor in trastuzumab resistance. Trastuzumab-resistant breast cancer cells and tissues clearly had increased levels of Circ-BGN, which was associated with poor overall survival. The viability of breast cancer cells was reduced, and their susceptibility to trastuzumab was dramatically restored when circ-BGN was knocked down [114]. Furthermore, trastuzumab resistance is mostly a result of HER2 signaling, which is maintained by the circRNA Chromodomain Y Like (circCDYL2) [115]. This circRNA was found to be a possible biomarker for trastuzumab resistance in $HER2^{+}$ BC patients.

5.5. CircRNAs and BC patients survival

Upregulation or downregulation of circRNAs may affect the survival of BC patients. For example, hsa_circ_0000519 overexpression is associated with better overall survival (OS) in BC patients [116]. Like hsa_circ_0000519, circCDYL expression is inversely associated with OS [117]. In cancer tissues, the expression of the circular RNA Serine/Threonine Kinase 1 (circ-VRK1/hsa_circ_0141206) is downregulated, which is linked to a lower tumor stage and improved survival [42].

circRAD18 expression is associated with shorter OS in TNBC patients [118], as are hsa_circ_0004771 and hsa_circ_0000375 in BC patients [116,119], circKIF4A in TNBC patients [68], circ_0005230 in ER^{+-}, human epidermal growth factor receptor 2 (HER-2)-positive and progesterone receptor (PR)-positive BC patients [38], circ-UBAP2 in TNBC patients [47] and circRNA epithelial stromal interaction 1 (circEPSTI1/hsa circ-0000479) in TNBC patients [119].

5.6. CircRNAs involved in evading immune destruction in BC

Maintenance of internal homeostasis and defense against exogenous invaders are the responsibilities of the host immune system. Evolving studies on circRNAs have suggested that they are involved in the modification of immunocytes and immune responses [120] and may be related to natural killer cells (NKs).[3]

For example, circRNA100783 plays a key role in the aging and immune senescence of CD8(+) T cells, and circRNA003780 and circRNA010056 function in macrophage differentiation and polarization [121]. Moreover, a study of 422 circRNAs recognized in healthy human saliva divided them into groups, including T-cell polarity establishment, inflammatory response, and chemotaxis, revealing that circRNAs could be considered participants in immune responses [122]. As an immune checkpoint, blocking the programmed cell death protein (PD)-1/PD-1 ligand (PD-L1) signaling pathway restores patients' T-cell immunity. In other words, the PD-1/PD-L1 axis is responsible for tumor immune escape. Therefore, checkpoint blockade therapy, together with the emerging role of circRNAs, has attracted increasing research interest in the quest to elucidate the relationship between them [123]. hsa_circ_0000190 increases PD-L1 mRNA-mediated soluble PD-L1 (sPD-L1) expression, consequently interfering with the efficacy of anti-PD-L1 antibodies and T-cell activation, which may result in immunotherapy resistance and poor outcomes in non-small cell lung carcinoma (NSCLC) [123] and HCC [124].

The circRNA hsa_circ_0067842 was highly expressed in BC tissues. It affects the metastasis and immune escape of BC through the PD-L1 axis [125]. In addition, significant improvements in overall survival were observed in PD-L1-positive patients with advanced TNBC treated with immune checkpoint inhibitors (ICIs). This improvement was observed either with ICIs alone or ICIs combined with nab-paclitaxel [126].

During cancer development, cytokines are usually derived from tumor cells or immunosuppressive cells. In the process of tumor inflammatory microenvironment formation, caspase-1 activates proinflammatory cytokines such as interleukin-1β (IL-1β) and IL-18, inducing a downstream inflammatory response [127]. It was reported that the overexpression of hsa_circRNA_002178 could sponge miR-328–3p, leading to BC progression. However, hsa_circRNA_002178 silencing could decrease IL-6 and tumor necrosis factor-α (TNF-α) levels, leading to precluding tumor inflammation and tumor growth [128].

The upregulation of circ_002172 and CXCL12 and the downregulation of miR-296–5p occur in BC tissues and cells. circ_002172 promoted the oncogenic phenotypes of BC cells *in vitro* and the growth of tumors *in vivo*, and these effects were reversed by knockdown of CXCL12 expression. Circ_002172, a miR-296–5p sponge, was observed to upregulate the expression of CXCL12. Moreover, ectopic expression of circ_002172 inhibited cytotoxic T lymphocyte (CTL) infiltration, promoting immune escape in BC. In conclusion, the tumor-promoting role of circ_002172 in BC was achieved by inducing immune escape via the miR-296–5p/CXCL12 axis [129].

5.7. CircRNA in BC drug resistance

Drug resistance is one of the key difficulties in treating BC and leads to treatment failure and a high mortality rate. Various drugs used for BC treatment, such as doxorubicin, tamoxifen, paclitaxel and even targeted therapy, could cause the development of drug resistance. Although multidrug resistance (MDR) is a major disadvantage in the treatment of BC, the molecular pathways involved remain to be studied. Several mechanisms of MDR have been identified [130]. CircRNAs are involved in the molecular mechanisms that lead to drug resistance in cancer therapy. The first mechanism is drug efflux from cancer cells, which is associated with drug or multidrug resistance [131]. The adenosine triphosphate (ATP)-binding cassette (ABC) is a class of transmembrane transporters that includes breast cancer resistance protein (BCRP) and multidrug resistance protein 1 (MRP1). They play functional roles in drug efflux mechanisms and are responsible for BC chemoresistance [132]. They are responsible for regulating and altering the intracellular

[3] research gap #3

distribution of drugs mediating drug resistance through glutathione-dependent drug efflux, so drugs cannot reach their targets [133]. Most ABC transporters are overexpressed in chemoresistant cancers. The function of some circRNAs in the drug resistance of cancers associated with ABC efflux transporters was reported to be a leading cause of tamoxifen resistance in BC cells [134].

A second mechanism is the inhibition of cell apoptosis. CircRNAs are known to act on and modify pro- or antiapoptotic proteins, thereby regulating the apoptosis of drug-resistant cancer cells. For example, circAMOTL1 was reported to control the expression of the AKT-related pro-apoptotic protein BAX and the anti-apoptotic protein BCL-2 in BC, thus modulating paclitaxel (PAX) resistance [135]. Moreover, circRNA_0006528 was effective in tamoxifen (TAM)-resistant BC cells. On the other hand, knockdown of circRNA_0006528 reduced the IC50 of PAX-resistant BC cells by reducing proliferation, migration, and autophagy and inducing apoptosis [136]. Additionally, the knockdown of circ-ABCB10 and DUSP7 activates let-7a, leading to increased PAX sensitivity in BC cells [137]. A third mechanism is autophagy regulation. Emerging evidence indicates that circRNAs also control autophagy, which could promote drug resistance in various tumors. hsa_circ_0092276 promotes chemoresistance by modulating doxorubicin-induced autophagy in BC cells [138]. A fourth mechanism is the association of several circRNAs with the DNA damage response and the regulation of DNA repair. In MCF-7 and T47D cells, circMET expression was considerably greater in tamoxifen-resistant cells than in tamoxifen-sensitive cells. This process is related to TAM resistance via the targeting of miR-204–5p, which increases aryl hydrocarbon receptor (AHR), an inhibitor of DNA double-strand break repair, leading to increased cell viability and decreased sensitivity to TAM [139]. A fifth mechanism is controlling epithelial–mesenchymal transition (EMT). An increasing number of reports indicate that circRNAs are involved in drug resistance by promoting EMT and stemness in many types of cancer. circUBE2D2 enhances EMT progression and TAM resistance in tamoxifen-resistant BC cells [140].

5.8. CircRNA in relation to metastatic primary or secondary BC

The majority of BC mortality is due to complications from recurrence or tumor metastasis in distant organs such as bone and brain. Notably, the most common site of BC metastasis is the bone, which occurs in 70% of metastatic BC patients [141].

Abnormal expression of circRNAs contributes to both the carcinogenesis and metastasis of BC. These genes may serve as potential diagnostic and prognostic biomarkers and therapeutic targets for BC metastasis. For bone metastasis, circIKBKB (hsa_circ_0084100), which is derived from the IKBKB gene (encoding an inhibitor of nuclear factor kappa B (NF-κB) kinase subunit beta), was shown to play a vital role in the promotion of osteoclastogenesis and BC-bone metastasis via the stimulation of bone premetastatic niche formation through the upregulation of several bone remodeling factors. Notably, treatment with an inhibitor of eukaryotic translation initiation factor 4A3 (EIF4A3) reduced circIKBKB expression and successfully inhibited BC-BM [142].

For brain metastasis, 406 differentially expressed circRNAs were identified between brain metastatic 231-BR cells and parental nonspecific metastatic MDA-MB-231 cells [50]. Among these circRNAs, hsa_circ_0001944 (known as circBCBM1) was one of the most significantly upregulated in breast cancer brain metastases. circBCBM1 strongly promoted the proliferation and migration of 231-BR cells *in vitro* and brain metastasis *in vivo*. Notably, circBCBM1 was upregulated in the *in vitro* cultured BC brain metastasis cells and in clinical tissue and plasma samples.

In addition, the overexpression of circBCBM1 in primary cancerous tissues was correlated with shorter brain metastasis-free survival in BC patients [51].

5.9. CircRNAs as BC vaccines

Cancer vaccines can be designed to specifically target tumor-associated antigens (TAAs), such as growth-associated factors or antigens that are specific to malignant cells, as a result of somatic mutations [143]. Cancer vaccines trigger immune reactions against tumors by expressing tumor antigens, which help antigen-presenting cells (APCs) activate tumor antigen-specific T cells [144,145]. One of the methods for the development of vaccines is via multiepitope vaccine design against viruses via reverse vaccinology methods exploiting immunoinformatic and bioinformatic approaches [146].

There are four types of cancer vaccines: vaccines based on tumor or immune cells, vaccines based on peptides, vaccines using viral vectors, and nucleic acid-based vaccines [147]. RNA-based cancer vaccines are the most promising type of vaccine because they can quickly express antigens in the cytoplasm, leading to a strong immune response. This type of vaccine also avoids the risks associated with genome integration and T-cell tolerance [148,149]. The benefits of using mRNA over DNA in cancer vaccine strategies include the following: first, mRNA can be translated in both dividing and nondividing cells, while RNA only needs to be internalized into the cytoplasm via one-step translation into the selected antigen(s). Second, mRNA vaccines are devoid of insertional mutagenesis because they cannot integrate into the genome sequence, in contrast to DNA vaccines [149].

Recent research suggests that specific circRNAs can be converted into biologically functional proteins through cap-independent mechanisms. Protein expression can be initiated by protein-coding circRNAs, which generate a cap-independent translation initiation structure, the internal ribosome entry site (IRES), in the circRNA sequence in eukaryotic cells [150,151]. Hongjian et al. in 2022 [152] reported the first trial assessing the effectiveness of cancer vaccines based on circRNAs in treating malignancies through the use of lipid nanoparticles (LNPs) to efficiently package and deliver circRNA molecules, facilitating endosome escape and achieving robust circRNA translation *in vivo*. Additionally, they concluded that circRNA-LNPs trigger an appropriate innate immune response and strong activation of antigen-specific cytotoxic T cells, which eradicate difficult-to-treat tumors in mouse models. Interestingly, this vaccination system can also be combined with adoptive cell transfer therapies to deliver enhanced antitumor effectiveness in a late-stage mouse tumor model. These findings serve as a proof-of-concept for the effectiveness of the circRNA-LNP vaccine in cancer treatment.

With regard to clinical application, the circRNA-LNP vaccine shows immense potential for use as both a primary and adjuvant therapy for various malignancies.

Table 4 **addressing strategies targeting circRNAs in BC (drugs known to target circRNAs)**. CircDnmt1 is significantly upregulated in breast cancer and facilitates the nuclear translocation of the p53 and AUF1 proteins, resulting in cellular autophagy and tumor growth [153]. Delivery of circDnmt1-targeting short interfering RNA (siRNA) coupled to gold nanoparticles (PEG-AuNPs) in mice attenuated these effects.

The expression of another circRNA, CircSka3, is substantially increased in breast cancer patients. This circRNA promotes tumor invasion and metastasis by binding to Tks5 and Integrin β1. These effects were reversed by silencing circSka3 with siRNA or disrupting its interactions with Tks5 and Integrin β1. As a result, circSka3 may be a promising target for inhibiting the progression of breast cancer [154].

In triple-negative breast cancer (TNBC) tissues, CircAGFG1 was upregulated and had oncogenic effects through miR-195–5p sponging. *In vitro*, short hairpin RNA (shRNA) targeting circAGFG1 inhibited cell proliferation, migration, and invasion while increasing apoptosis. In addition, tumor development, angiogenesis, and metastasis are inhibited *in vivo* [155].

On the other hand, circTADA2A-E6 was downregulated in TNBC tissues and behaved as a miR-203a-3p sponge [156]. *In vitro*, circTADA2A-E6 overexpression inhibited cell proliferation, migration,

Table 4
Targeting either oncogenic or anticancer (tumor suppressor) circRNAs in breast cancer.

Oncogenic CircRNAs	Treatment	Mechanism	Exerts	Ref.
circDnmt1	polyethylene glycol gold nanoparticles conjugated siRNA	attenuated p53 nuclear translocation & AUF1	dec. cellular autophagy & tumor growth	[153, 159]
circSka3	CTs with siRNA for silencing	disrupting circSka3 interactions with Tks5, integrin β1	inhibit tumor invasion & metastasis	[154]
circAGFG1	short hairpin RNA	-	-	[155]
circHER2	Pertuzumab	decreased circHER2 & HER2–103 expressing cells	decreased tumorigenicity	[158]
Anticancer CircRNAs	**Treatment**	**Mechanism**	**Exerts**	**Ref.**
circTADA2A-E6	-	overexpressed	inhibits proliferation, migration, invasion	[156]
hsa_circ_0025202	Tamoxifen	overexpression	increased BC cells susceptibility to Tam *in vitro* & *in vivo*	[157]

There is a lack of sufficient data concerning all circRNA-potential axes[4] and various new cancer hallmark aspects in BC clinical cases.

and invasion. Hsa_circ_0025202 was likewise downregulated in breast cancer and served as a sponge for miR-182–5p. Its overexpression not only has anticancer effects but also increases the susceptibility of breast cancer cells to tamoxifen both *in vitro* and *in vivo*. [157]. Recently, Zhang et al., 2020 [158] discovered that circHER2 was significantly expressed in TNBC cells, encoded a unique 103 aa peptide, HER2–103, and had a role in carcinogenesis. They proved that the majority of the amino acid sequence of this peptide was shared with the HER2 CR1 domain, which can be inhibited by pertuzumab. *In vivo*, pertuzumab dramatically decreased the tumorigenicity of circHER2- and HER2–103-expressing cells.

6. CircRNA research gaps[5] in BC according to expert opinions

There was a discrepancy in the differential expression of 1155 circRNAs in BC tissues; 715 were upregulated, while 440 were downregulated [12].

The exact functions of these differentially expressed circRNAs in BC remain to be fully elucidated. Researchers have shown that knockdown of ciRNAs, which are located in the nucleus and have minimal enrichment for microRNA target sites, leads to a decrease in the expression of their parent genes. However, the specific functions and processes of ciRNAs in BC still need to be clarified.

CircRNAs as Registered Biomarkers: One study identified three circRNAs, namely, hsa_circ_0000091, hsa_circ_0067772, and hsa_circ_00005123, that are differentially expressed in tumor cells. These circRNAs could serve as circulating biomarkers for diagnosing BC [11]. However, these findings need further research for validation.

These gaps pave the way for future studies to enhance our comprehensive understanding of the role of circRNAs in BC.

6.1. Expert recommendations and future perspectives for the sustainable use of circRNAs in BC for precision treatment

Several hsa-circRNA-miRs-downstream signaling target proteins or genes, such as TLRs, SOCSs, adipokines, adiponectin, leptin and apelin, and chemokines, lipocalins or apoptosis-related molecules, such as granzymes and perforin, and fractalkine, as well as autophagic molecules [160], growth factors and adhesion molecules to be retrieved and further studied in BC to prove their utility there [87,161–174].

The influence of supplementation with antioxidant anti-inflammatory vitamins such as A, E, and C [175,176], as well as vitamins and their receptor SNPs, on treatment outcomes has been studied [177], as have the influence of drug gating receptors that influence multidrug resistance in various cancer types [178].

Moreover, the trend of identifying peripheral blood B-cell subset frequency and distribution and the inflammatory-to-anti-inflammatory cytokine(s) ratio(s) as severity-associated signatures in various cancers should be studied in BS in relation to oncogenic or tumor suppressor circRNAs [179,180] or circRNA ratios in cancer for diagnosis [181] or in relation to NK- and leukocyte-associated immunoglobulin-like receptor (LAIR) [182]. Moreover, platelet activation [183], DNA damage in cancer [184] or genetic or nongenetic factors influence treatment outcomes in cancer [185] through mediators other than downstream genes or proteins.

To improve current and future treatment options for BC, more studies on differential signaling pathways and nano-bio-medicines targeting circRNAs as nc-epigenetics are needed [186].

Hitting the hsa-circRNA-miR-downstream signaling pathway target axis [187,188] using drug repurposing by molecular docking (MD) followed by experimentally proving the chosen drug utility, as well as being targeted in nanoformulas or carried on exosomes, is the basis for ncRNA treatment inventions for better precision health[6] [189].

CircRNAs involved in the TIME as promoters of BC and the role of exosomes in communicating cells as well as inflammation and in experimentally loaded exosomes with specified circRNAs found in databases are strongly related to BC. This combination of loading for *in vitro* and *in vivo* testing could be used as a promising potential treatment option for BC, which is a step toward ncRNA precision [190].

7. Summary and conclusion(s)

In this comprehensive review, we highlighted, via *in silico* databases, bioinformatics analysis, and extensive literature searches, the following:

- The importance of "circular-RNA in cancer or circular-RNA in disease" as an epigenetic ncRNA influencing the "better health Sustainable Development Goal number 3 (SDG#3) initiative". It's worth noting that SDG#3 is concerned with ensuring healthy lives and promoting well-being for all at all ages.
- CircRNAs eligibility as biomarkers for cancer detection or prognosis because of their exceptional stability like circHIPK3 & circLARP4 in the diagnosis/prognosis of BC while hsa_circ_0006743 in the early diagnosis of BC for example.
- Comprehensive circRNA-disease information is now available, especially related to the biological functions of circRNAs in breast diseases such as BC subtypes, the molecular mechanisms by which circRNAs participate in BC as cancer hallmarks, and the ability of their target miRs to act as sponges as well as the final downstream signaling pathway. And finally, how circRNAs play active roles in the progression of BC, including carcinogenesis, metastasis, and chemoresistance.
- Gaining insight into circRNA interaction/axis dysregulation could aid in pinpointing effective therapeutic targets. As a future

[5] research gap #5

[6] research gap #7

prospective, we recommend using the mentioned circRNAs/exosomal circRNAs in combating drug resistance while improving treatment options for better patient outcomes.
- The future need for mechanistic studies to clarify more ncRNA axes that could be targeted in BC treatment.

Ethical considerations and approvals

None Applicable.

Abbreviations

5-FU, 5-fluorouracil; ABC, Adenosine triphosphate (ATP) binding cassette; ABCB, ATP binding cassette subfamily B member; ABCC1, ATP-Binding Cassette Subfamily C Member 1; ACAP2, ArfGAP with Coiled-Coil Ankyrin Repeat and PH Domains 2; ADAM9, A Disintegrin and Metalloprotease 9; ADM, Adriamycin; AGFG1, ArfGAP with FG Repeats 1; AHR, Aryl hydrocarbon receptor; ANKRD12, ANKyrin Repeat Domain 12; ANKS1B, ANKyrin repeat and Sterile Alpha Motif Domain Containing 1B; AR, androgen receptor; ASS1, ArgininoSuccinate Synthase 1; ATXN7, Ataxin 7; AuNPs, gold nanoparticles; BACH2, BTB Domain and CNC Homolog 2; BARD1, BRCA1-associated RING domain 1; BC, Breast Cancer; BCBM, Breast Cancer Brain Metastasis; BGN, Biglycan; BMPR2, Bone Morphogenetic Protein Receptor Type II; BRWD3, bromodomain and WD repeat domain containing 3; CAPG, Capping Actin Protein, Gelsolin Like; CCND1, Cyclin D1; CDK, Cyclin-dependent kinase; CDYL, Chromodomain Y-like; ceRNA, Competing endogenous RNA; CHIPK3, circRNA homeodomain-interacting protein kinase 3; CircRNA, Circular ribonucleic acid; ciRNAs, Circular intronic RNAs; CNOT2, CCR4-NOT Transcription Complex Subunit 2; CTL, Cytotoxic T lymphocyte; CXCL10, Chemokine (C-X-C motif) ligand 10; DCAF6, DDB1 and CUL4-Associated Factor 6; DDX, DEAD-Box Helicase; DENND4C, DENN Domain Containing 4 C; DHDDS, Dehydrodichyl diphosphate synthase; DNAJC11, DNAJ heat shock protein family (Hsp40) member C11; DNMT1, DNA methyltransferase 1; DUSP1, DUal specificity phosphatase 1; EcRNA, Exonic circRNA; EGFR, Endothelial growth factor receptor; EHMT1, Euchromatic Histone Lysine Methyltransferase 1; EIF3M, Eukaryotic Translation Initiation Factor 3 Subunit M; EIF4A3, Eukaryotic translation initiation factor 4A3; EIF6, Eukaryotic Translation Initiation Factor 6; ElciRNAs, Exon–intron circRNAs; ELP3, Elongator acetyltransferase complex subunit 3; EMT, epithelial–mesenchymal transition; EPSTI1, Epithelial Stromal Interaction 1; ER, Estrogen Receptor; ERBB2, Erb-B2 receptor tyrosine kinase 2; FBXL5, F-Box and Leucine Rich Repeat Protein 5; FBXW7, F-Box and WD Repeat Domain Containing 7; FGFR3, Fibroblast growth factor receptor 3; FOX, Forkhead Box; GFRA1, GDNF Family Receptor Alpha1; GNB1, G Protein Subunit Beta 1; HER-2, Human epidermal growth factor receptor 2 (ErbB2)-overexpressing HER2-positive; HIF1A, Hypoxia-inducible factor 1 subunit alpha; HOXA11, Homeobox A11; HR, Hormone Receptor; IC50, Half maximal inhibitory concentration; ICIs, Immune checkpoint inhibitors; IFI30, Interferon Gamma Inducible protein 30; IGF-1, Insulin-like Growth Factor 1; IKBKB, Inhibitor of Nuclear Factor kappa B kinase subunit; IQCH, IQ Motif Containing H; IRAK3, Interleukin 1 receptor-associated kinase 3; IRES, internal ribosome entry site; ITCH, Itchy E3 ubiquitin protein ligase; KDM, lysine demethylase; KIF4A, kinesin family member 4 A; lncRNAs, Long noncoding RNAs; LNPs, lipid nanoparticles; MBL, Muscleblind; MDR, Multidrug resistance; METTL3, MethylTransferase Like-3; microRNAs, MicroRNAs; miRs, MicroRNAs; MMP11, Matrix metalloproteinase-11; mRNAs, Messenger RNAs; MRP1, Breast cancer resistance protein (BCRP) and multidrug resistance protein 1; MTO1, Mitochondrial TRNA Translation Optimization 1; MYO9B, Myosin IXb; NCOR1, Nuclear receptor CO-Repressor 1; ncRNA, Non-coding RNA; NF-κB, Nuclear factor kappa B-cell; NFIC, Nuclear Factor I C; NINL, Ninein Like; NR3C2, Nuclear Receptor Subfamily 3 Group C Member 2; NSCLC, Non-small cell lung carcinoma; OMA1, Overlapping with M-AAA protease 1; OS, overall survival; PAX, Paclitaxel; PD-L1, Programmed cell death protein (PD)-1/PD-1 ligand; PDCD11, Programmed Cell Death 11; PFKFB, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase; PGAP3, Post-GPI Attachment to Phospholipase 3 Proteins; PITX1, Pituitary Homeo Box 1; PKR, Protein kinase R; PLK1, Polo-Like Kinase 1; PR, Progesterone receptor; PSMA1, Proteasome 20S Subunit Alpha 1; PTK2, Protein Tyrosine Kinase 2; QNBC, quadruple-negative breast cancer; qRT—PCR, Quantitative real-time PCR; RAD54L2, RAD54 Like Protein 2; RASSF2, Ras Association Domain Family Member 2; RNA-seq, RNA sequencing; RNF, Ring Finger protein; ROR-P, Risk of Relapse Proliferation; RPPH1, Ribonuclease P RNA Component H1; SDG#3, Sustainable Development Goal number 3; SEMA4B, Semaphorin 4B; SEPT, Septin; SNX25, Sorting Nexin 25; SETD2, SET domain containing 2; SFMBT2, Scm-like with Four MBT Domain 2; SFRP1, Secreted Frizzled Related Protein 1; siRNA, short interfering RNA; SLC8A, solute carrier family 8 member A1; SMARCA5, SWI/SNF Related, Matrix Associated, Actin Dependent Regulator of Chromatin, Subfamily A, Member 5; snRNP, Small nuclear ribonucleoprotein; SOCS3, Suppressor of Cytokine Signaling 3; TADA3, Transcriptional Adaptor 3; TAM, Tamoxifen; TAMs, Tumor-associated macrophages; TBC1D14, TBC1 Domain Family Member 14; TCDD, 2,3,7,8-Tetrachlorodibenzo-p-dioxin; TFCP2L1, Transcription Factor CP2 Like 1; TFF1, Trefoil Factor 1; TLRs, Toll Like Receptors; TN, Triple negative; TNBC, Triple-negative breast cancer; TNF-α, Tumor necrosis factor-α; TP63, Tumor protein p63; TPGS2, Tubulin PolyGlutamylase Complex Subunit 2; tricRNAs, tRNA intronic circular RNAs; UBE2D2, Ubiquitin Conjugating Enzyme E2 D2; UBR1, Ubiquitin Protein Ligase E3 Component N-Recognin 1; USF1, Upstream Transcription Factor 1; USP42, Ubiquitin-Specific Peptidase 42; VRK1, serine/threonine kinase 1; WAC, WW domain-containing adapter protein with a coiled coil; WHSC1, Wolf-Hirschhorn syndrome candidate 1; WSB1, WD Repeat and SOCS Box Containing 1; YAP, Yes-associated protein; YY1, Yin Yang 1; ZEB1, Zinc finger E-box Binding homeobox 1; ZFAND6, Zinc Finger AN1-Type Containing 6; ZFP36, Zinc Finger Protein 36; ZNF609, Zinc Finger Protein 609

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Declaration of Competing Interest

All authors declare no conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.prp.2024.155651.

References

[1] N. Harbeck, F. Penault-Llorca, J. Cortes, M. Gnant, N. Houssami, P. Poortmans, R. Kathryn, J. Tsang, F. Cardoso, Breast cancer, Nat. Rev. Dis. Prim. 5 (1) (2019 Sep 23) 66, https://doi.org/10.1038/s41572-019-0111-2.
[2] K. Won, C. Spruck, Triple-negative breast cancer therapy: Current and future perspectives (Review) (Epub), Int J. Oncol. 2020 Dec. 57 (6) (2020 Oct 16) 1245–1261, https://doi.org/10.3892/ijo.2020.5135.
[3] L. Mulrane, S.F. McGee, W.M. Gallagher, D.P. O'Connor, miRNA dysregulation in breast cancer, Cancer Res 73 (22) (2013 Nov 15) 6554–6562, https://doi.org/10.1158/0008-5472.CAN-13-1841.
[4] M.M. Mahmoud, E.F. Sanad, N.M. Hamdy, MicroRNAs role in the environment-related non-communicable diseases and link to multidrug resistance, regulation or alteration, Environ. Sci. Pollut. Res. 28 (2021) 36984–37000, https://doi.org/10.1007/s11356-021-14550-w.
[5] H.L. Sanger, G. Klotz, D. Riesner, H.J. Gross, A.K. Kleinschmidt, Viroids are single-stranded covalently closed circular RNA molecules existing as highly base-paired rod-like structures, Proc. Natl. Acad. Sci. USA 73 (11) (1976 Nov) 3852–3856, https://doi.org/10.1073/pnas.73.11.3852.
[6] M.T. Hsu, M. Coca-Prados, Electron microscopic evidence for the circular form of RNA in the cytoplasm of eukaryotic cells, Nature 280 (5720) (1979 Jul 26) 339–340, https://doi.org/10.1038/280339a0.

[7] J.U. Guo, V. Agarwal, H. Guo, D.P. Bartel, Expanded identification and characterization of mammalian circular RNAs, Genome Biol. 15 (2014) 409.

[8] S. Memczak, P. Papavasileiou, O. Peters, N. Rajewsky, Identification and characterization of circular RNAs as a new class of putative biomarkers in human blood (eCollection), PLoS One 2015 Oct. 20 10 (10) (2015) e0141214, https://doi.org/10.1371/journal.pone.0141214.

[9] L. Tang, B. Jiang, H. Zhu, T. Gao, Y. Zhou, F. Gong, R. He, L. Xie, Y. Li, The biogenesis and functions of circRNAs and their roles in breast cancer, Front Oncol. 11 (2021 Feb 25) 605988, https://doi.org/10.3389/fonc.2021.605988. PMID: 33718157; PMCID: PMC7947672.

[10] X.Y. Feng, S.X. Zhu, K.J. Pu, H.J. Huang, Y.Q. Chen, W.T. Wang, New insight into circRNAs: characterization, strategies, and biomedical applications, Exp. Hematol. Oncol. 12 (1) (2023 Oct 12) 91, https://doi.org/10.1186/s40164-023-00451-w. PMID: 37828589; PMCID: PMC10568798.

[11] Y. Yu, W. Zheng, C. Ji, X. Wang, M. Chen, K. Hua, X. Deng, L. Fang, Tumor-derived circRNAs as circulating biomarkers for breast cancer, Front Pharm. 13 (2022 Feb 15) 811856, https://doi.org/10.3389/fphar.2022.811856. PMID: 35242035; PMCID: PMC8886293.

[12] X. Wang, L. Fang, Advances in circular RNAs and their roles in breast Cancer, J. Exp. Clin. Cancer Res 37 (1) (2018 Aug 29) 206, https://doi.org/10.1186/s13046-018-0870-8. PMID: 30157902; PMCID: PMC6116371.

[13] L. Chen, C. Huang, X. Wang, G. Shan, Circular RNAs in eukaryotic cells, Curr. Genom. 16 (5) (2015 Oct) 312–318, https://doi.org/10.2174/1389202916666150707161554.

[14] Y. Zhang, X.O. Zhang, T. Chen, J.F. Xiang, Q.F. Yin, Y.H. Xing, et al., Circular intronic long noncoding RNAs, Mol. Cell 51 (2013) 792–806.

[15] Y. Zhang, W. Xue, X. Li, J. Zhang, S. Chen, J. Zhang, L. Yang, L. Chen, The biogenesis of nascent circular RNAs (Epub), Cell Rep. 2016 Apr 19 15 (3) (2016 Apr 7) 611–624, https://doi.org/10.1016/j.celrep.2016.03.058.

[16] C.A. Schmidt, J.J. Noto, G.S. Filonov, A.G. Matera, A method for expressing and imaging abundant, stable, circular RNAs in vivo using tRNA splicing (Epub), Methods Enzymol. 2016 572 (2016 Mar 25) 215–236, https://doi.org/10.1016/bs.mie.2016.02.018.

[17] Z. Lu, G.S. Filonov, J.J. Noto, C.A. Schmidt, T.L. Hatkevich, Y. Wen, S.R. Jaffrey, A.G. Matera, Metazoan tRNA introns generate stable circular RNAs in vivo, RNA 21 (9) (2015 Sep) 1554–1565, https://doi.org/10.1261/rna.052944.115. . Epub 2015 Jul 20.

[18] J.O. Westholm, P. Miura, S. Olson, S. Shenker, B. Joseph, P. Sanfilippo, S. E. Celniker, B.R. Graveley, E.C. Lai, Genome-wide analysis of drosophila circular RNAs reveals their structural and sequence properties and age-dependent neural accumulation, Cell Rep. 9 (5) (2014 Dec 11) 1966–1980, https://doi.org/10.1016/j.celrep.2014.10.062. Epub 2014 Nov 26.

[19] W.B. Yin, M.G. Yan, X. Fang, J.J. Guo, W. Xiong, R.P. Zhang, Circulating circular RNA hsa_circ_0001785 acts as a diagnostic biomarker for breast cancer detection, Clin. Chim. Acta 487 (2018 Dec) 363–368, https://doi.org/10.1016/j.cca.2017.10.011. Epub 2017 Oct 16.

[20] L. Lü, J. Sun, P. Shi, W. Kong, K. Xu, B. He, S. Zhang, J. Wang, Identification of circular RNAs as a promising new class of diagnostic biomarkers for human breast cancer, Oncotarget 8 (2017) 44096–44107.

[21] A.A. Nair, N. Niu, X. Tang, K.J. Thompson, L. Wang, J.P. Kocher, S. Subramanian, K.R. Kalari, Circular RNAs and their associations with breast cancer subtypes, Oncotarget 7 (49) (2016 Dec 6) 80967–80979, https://doi.org/10.18632/oncotarget.13134.

[22] Y.Y. Tang, P. Zhao, T.N. Zou, J.J. Duan, R. Zhi, S.Y. Yang, D.C. Yang, X.L. Wang, Circular RNA hsa_circ_0001982 promotes breast cancer cell carcinogenesis through decreasing miR-143, DNA Cell Biol. 36 (11) (2017) 901–908.

[23] C.L. Zhang, H. Wu, Y.H. Wang, Y.L. Zhao, X.T. Fang, C.F. Chen, H. Chen, Expression patterns of circular RNAs from primary kinase transcripts in the mammary glands of lactating rats, J. Breast Cancer 18 (3) (2015 Sep) 235–241, https://doi.org/10.4048/jbc.2015.18.3.235. Epub 2015 Sep 24.

[24] Z. Zhao, K. Wang, F. Wu, W. Wang, K. Zhang, H. Hu, Y. Liu, T. Jiang, circRNA disease: a manually curated database of experimentally supported circRNA-disease associations, Cell Death Dis. 9 (2018) 475.

[25] M.M. Mahmoud, E.F. Sanad, A.A.R. El-Shemy, N.M. Hamdy, Competitive endogenous role of LINC00511/miR-185-3p axis and miR-301a-3p from liquid biopsy as molecular markers for breast cancer diagnosis, Front. Oncol. 11 (749753) (2021) 1–17, https://doi.org/10.3389/fonc.2021.749753.

[26] U. Ala, Competing endogenous RNAs, non-coding RNAs and diseases: an intertwined story, Cells 9 (7) (2020 Jun 28) 1574, https://doi.org/10.3390/cells9071574.

[27] O. Emam, E.F. Wasfey, N.M. Hamdy, Notch-associated lncRNAs profiling circuiting epigenetic modification in colorectal cancer, Cancer Cell Int. 22 (2022) 316, https://doi.org/10.1186/s12935-022-02736-2.

[28] Q. Zheng, C. Bao, W. Weijie Guo, S. Li, J. Chen, B. Chen, Y. Luo, D. Lyu, Y. Li, G. Shi, L. Liang, J. JGu, X. He, S. Huang, Circular RNA profiling reveals an abundant circHIPK3 that regulates cell growth by sponging multiple miRNAs, Nat. Commun. 7 (2016 Apr 6) 11215, https://doi.org/10.1038/ncomms11215.

[29] H.F. Liang, X.Z. Zhang, B.G. Liu, G.T. Jia, W.L. Li, Circular RNA circ-ABCB10 promotes breast cancer proliferation and progression through sponging miR-1271, Am. J. Cancer Res 7 (7) (2017) 1566–1576.

[30] Y.C. Xin, R. Bradbury, V. Flamini, B. Wu, N. Jordan, W.G. Jiang, MicroRNA-7 suppresses the homing and migration potential of human endothelial cells to highly metastatic human breast cancer cells (Epub), Br. J. Cancer 2017 Jun. 27 117 (1) (2017 Jun 1) 89–101, https://doi.org/10.1038/bjc.2017.156.

[31] X. Kong, G. Li, Y. Yuan, Y. He, X. Wu, W. Zhang, Z. Wu, T. Chen, W. Wu, P. E. Lobie, T. Zhu, MicroRNA-7 inhibits epithelial-to-mesenchymal transition and metastasis of breast cancer cells via targeting FAK expression, PLoS One 7 (8) (2012) e41523, https://doi.org/10.1371/journal.pone.0041523. Epub 2012 Aug 2.

[32] H. Zhang, K. Cai, J. Wang, X. Wang, K. Cheng, F. Shi, L. Jiang, Z. Zhang, J. Dou, MiR-7, inhibited indirectly by lincRNA HOTAIR, directly inhibits SETDB1 and reverses the EMT of breast cancer stem cells by downregulating the STAT3 pathway, Stem Cells 32 (11) (2014 Nov) 2858–2868, https://doi.org/10.1002/stem.1795.

[33] H. Zhang, K. Cai, J. Wang, X. Wang, K. Cheng, F. Shi, L. Jiang, Z. Zhang, J. Dou, MiR-7, inhibited indirectly by lincRNA HOTAIR, directly inhibits SETDB1 and reverses the EMT of breast cancer stem cells by downregulating the STAT3 pathway, Stem Cells 32 (11) (2014 Nov) 2858–2868, https://doi.org/10.1002/stem.1795.

[34] L. Smit, K. Berns, K. Spence, W.D. Ryder, N. Zeps, M. Madiredjo, R. Beijersbergen, R. Bernards, R.B. Clarke, An integrated genomic approach identifies that the PI3K/AKT/FOXO pathway is involved in breast cancer tumor initiation, Oncotarget 7 (3) (2016 Jan 19) 2596–2610, https://doi.org/10.18632/oncotarget.6354.

[35] W.W. Du, L. Fang, W. Yang, N. Wu, F.M. Awan, Z. Yang, B.B. Yang, Induction of tumor apoptosis through a circular RNA enhancing Foxo3 activity. Induction of tumor apoptosis through a circular RNA enhancing Foxo3 activity, Cell Death Differ. 24 (2) (2017 Feb) 357–370, https://doi.org/10.1038/cdd.2016.133. Epub 2016 Nov 25.

[36] C. Zhao, L. Li, Z. Li, J. Xu, Q. Yang, P. Shi, K. Zhang, R. Jiang, A Novel Circular RNA Hsa_circRPPH1_015 Exerts an Oncogenic Role in Breast Cancer by Impairing MiRNA-326-Mediated ELK1 Inhibition, Front. Oncol. 10 (2020) 906.

[37] M. Ameli-Mojarad, M. Ameli-Mojarad, M. Nourbakhsh, E. Nazemalhosseini-Mojarad, Circular RNA Hsa_circ_0005046 and Hsa_circ_0001791 May Become Diagnostic Biomarkers for Breast Cancer Early Detection, J. Oncol. 2021 (2021) 2303946.

[38] Y. Xu, Y. Yao, K. Leng, D. Ji, L. Qu, Y. Liu, Y. Cui, Increased Expression of Circular RNA Circ_0005230 indicates dismal prognosis in breast cancer and regulates cell proliferation and invasion via MiR-618/CBX8 Signal Pathway, CPB 51 (2018) 1710–1722.

[39] A.K.D.M. Rao, V.R. Arvinden, D. Ramasamy, K. Patel, B. Meenakumari, P. Ramanathan, S. Sundersingh, V. Sridevi, T. Rajkumar, Z. Herceg, et al., Identification of Novel Dysregulated Circular RNAs in Early-Stage Breast Cancer, J. Cell Mol. Med 25 (2021) 3912–3921.

[40] H. Zang, Y. Li, X. Zhang, G. Huang, Circ-RNF111 contributes to paclitaxel resistance in breast cancer by elevating E2F3 expression via miR-140-5p, Thorac. Cancer 11 (7) (2020) 1891–1903.

[41] C.Y. Yang, F.X. Zhang, J.N. He, S.Q. Wang, CircRNA_100876 promote proliferation and metastasis of breast cancer cells through adsorbing microRNA-361-3p in a sponge form, Eur. Rev. Med Pharm. Sci. 23 (16) (2019) 6962–6970.

[42] Y. Li, H. Li, Circular RNA VRK1 Correlates with Favorable Prognosis, Inhibits Cell Proliferation but Promotes Apoptosis in Breast Cancer, J. Clin. Lab. Anal. 34 (2020) e22980.

[43] Q. Huang, Y. He, X. Zhang, L. Guo, Circular RNA hsa_circ_0103552 Promotes Proliferation, Migration, and Invasion of Breast Cancer Cells through Upregulating Cysteine-Rich Angiogenic Inducer 61 (CYR61) Expression via Sponging MicroRNA-515-5p, Tohoku J. Exp. Med 255 (2) (2021) 171–181.

[44] L. Meng, S. Chang, Y. Sang, P. Ding, L. Wang, X. Nan, R. Xu, F. Liu, L. Gu, Y. Zheng, et al., Circular RNA CircCCDC85A Inhibits Breast Cancer Progression via Acting as a MiR-550a-5p Sponge to Enhance MOB1A Expression, Breast Cancer Res 24 (2022) 1.

[45] H. Tang, X. Huang, J. Wang, L. Yang, Y. Kong, G. Gao, L. Zhang, Z.-S. Chen, X. Xie, CircKIF4A Acts as a Prognostic Factor and Mediator to Regulate the Progression of Triple-Negative Breast Cancer, Mol. Cancer 18 (2019) 23.

[46] Z. Xing, R. Wang, X. Wang, J. Liu, M. Zhang, K. Feng, X. Wang, CircRNA Circ-PDCD11 Promotes Triple-Negative Breast Cancer Progression via Enhancing Aerobic Glycolysis, Cell Death Discov. 7 (2021) 218.

[47] S. Wang, Q. Li, Y. Wang, X. Li, R. Wang, Y. Kang, X. Xue, R. Meng, Q. Wei, X. Feng, Upregulation of Circ-UBAP2 Predicts Poor Prognosis and Promotes Triple-Negative Breast Cancer Progression through the MiR-661/MTA1 Pathway, Biochem. Biophys. Res. Commun. 505 (2018) 996–1002.

[48] X. Xu, J. Zhang, Y. Tian, Y. Gao, X. Dong, W. Chen, X. Yuan, W. Yin, J. Xu, K. Chen, C. He, L. Wei, "CircRNA inhibits DNA damage repair by interacting with host gene.", Mol. Cancer 19 (1) (2020) 128.

[49] Y. Zhong, S. Pan, S. Zhi, Y. Li, Z. Xiu, C. Wei, J. Luo, "Construction and Investigation of circRNA-associated ceRNA Regulatory Network in Molecular Subtypes of Breast Cancer.", Curr. Comput. Aided Drug Des. 18 (3) (2022) 185–195.

[50] B. Fu, A. Zhang, M. Li, L. Pan, W. Tang, M. An, W. Liu, J. Zhang, "Circular RNA profile of breast cancer brain metastasis: identification of potential biomarkers and therapeutic targets.", Epigenomics 10 (12) (2018) 1619–1630.

[51] B. Fu, W. Liu, C. Zhu, P. Li, L. Wang, L. Pan, K. Li, P. Cai, M. Meng, Y. Wang, A. Zhang, W. Tang, M. An, "Circular RNA circBCBM1 promotes breast cancer brain metastasis by modulating miR-125a/BRD4 axis.", Int J. Biol. Sci. 17 (12) (2021) 3104–3117.

[52] X. Ma, C. Liu, C. Gao, J. Li, J. Zhuang, L. Liu, H. Li, X. Wang, X. Zhang, S. Dong, C. Zhou, C. Sun, "circRNA-associated ceRNA network construction reveals the circRNAs involved in the progression and prognosis of breast cancer.", J. Cell Physiol. 235 (4) (2020) 3973–3983.

[53] Y. Fan, J. Wang, W. Jin, Y. Sun, Y. Xu, Y. Wang, X. Liang, D. Su, "CircNR3C2 promotes HRD1-mediated tumor-suppressive effect by sponging miR-513a-3p in triple-negative breast cancer.", Mol. Cancer 20 (1) (2021) 1–22.

[54] W. Mao, X. Huang, L. Wang, Z. Zhang, M. Liu, "Circular RNA hsa_circ_0068871 regulates FGFR3 expression and activates STAT3 by targeting miR-181a-5p to promote bladder cancer progression.", J. Exp. Clin. Cancer Res 38 (2019) 169.

[55] H. Wang, Y. Xiao, L. Wu, D. Ma, "Comprehensive circular RNA profiling reveals the regulatory role of the circRNA-000911/miR-449a pathway in breast carcinogenesis.", Int. J. Oncol. 52 (3) (2018) 743–754.

[56] R. Ashwal-Fluss, M. Meyer, N.R. Pamudurti, A. Ivanov, O. Bartok, M. Hanan, N. Evantal, S. Memczak, N. Rajewsky, S. Kadener, "circRNA biogenesis competes with pre-mRNA splicing.", Mol. Cell 56 (1) (2014) 55–66.

[57] U. Paul, S. Banerjee, "The functional significance and cross-talk of noncoding RNAs in triple negative and quadruple negative breast cancer.", Mol. Biol. Rep. 49 (7) (2022) 6899–6918.

[58] J.D. Hon, B. Singh, A. Sahin, G. Du, J. Wang, V.Y. Wang, F.M. Deng, D.Y. Zhang, M.E. Monaco, P. Lee, "Breast cancer molecular subtypes: from TNBC to QNBC.", Am. J. Cancer Res 6 (9) (2016) 1864–1872.

[59] H. Lai, Y. Li, H. Zhang, J. Hu, J. Liao, Y. Su, Q. Li, B. Chen, C. Li, Z. Wang, Y. Li, et al., exoRBase 2.0: an atlas of mRNA, lncRNA and circRNA in extracellular vesicles from human biofluids, 7, Nucleic Acids Res. 50 (D1) (2022) D118–D128, https://doi.org/10.1093/nar/gkab1085.

[60] M. Zhang, X. Bai, X. Zeng, J. Liu, F. Liu, Z. Zhang, "circRNA-miRNA-mRNA in breast cancer.", Clin. Chim. Acta 523 (2021) 120–130.

[61] J. Zhang, S. Ke, W. Zheng, Z. Zhu, Y. Wu, "Hsa-circ-0003645 Promotes Breast Cancer Progression by Regulating miR-139-3p/HMGB1 Axis.", Onco Targets Ther. 13 (2020) 10361–10372.

[62] G. Ye, R. Pan, L. Zhu, D. Zhou, "Circ_DCAF6 potentiates cell stemness and growth in breast cancer through GLI1-Hedgehog pathway.", Exp. Mol. Pathol. 116 (2020) 104492.

[63] F. Cai, W. Fu, L. Tang, J. Tang, J. Sun, G. Fu, G. Ye, "Hsa_circ_0000515 is a novel circular RNA implicated in the development of breast cancer through its regulation of the microRNA-296-5p/CXCL10 axis.", FEBS J. 288 (3) (2021) 861–883.

[64] Y. Mao, M. Lv, W. Cao, X. Liu, J. Cui, Y. Wang, Y. Wang, G. Nie, X. Liu, H. Wang, "Circular RNA 000554 represses epithelial–mesenchymal transition in breast cancer by regulating microRNA-182/ZFP36 axis." The, FASEB J. 34 (9) (2020) 11405–11420.

[65] Y.-J. Chen, C.-M. Hung, N. Kay, C.-C. Chen, Y.-H. Kao, S.-S. Yuan, "Progesterone receptor is involved in 2,3,7,8-tetrachlorodibenzo-p-dioxin-stimulated breast cancer cells proliferation.", Cancer Lett. 319 (2) (2012) 223–231.

[66] B. Zhao, R. Zhou, C. Ji, D. Liu, T. Wu, H. Xu, D. Lan, C. Yao, Y. Xu, L. Fang, "The Function of circRNA-0047604 in Regulating the Tumor Suppressor Gene DACH1 in Breast Cancer.", Biomed. Res Int 2022 (2022) 6589651.

[67] J. Yao, G. Xu, L. Zhu, H. Zheng, "circGFRA1 Enhances NSCLC Progression by Sponging miR-188-3p.", Onco Targets Ther. 13 (2020) 549–558.

[68] Y. Jin, L. Yang, X. Li, F. Liu, "Circular RNA KIF4A promotes cell migration, invasion and inhibits apoptosis through miR-152/ZEB1 axis in breast cancer.", Diagn. Pathol. 15 (1) (2020) 55.

[69] L.W. Huo, Y.F. Wang, X.B. Bai, H.L. Zheng, M.D. Wang, "CircKIF4A promotes tumorogenesis of glioma by targeting miR-139-3p to activate Wnt5a signaling.", Mol. Med. 26 (2020) 1.

[70] S. Sheng, Y. Hu, F. Yu, W. Tong, S. Wang, Y. Cai, J. Zhu, "circKIF4A sponges miR-127 to promote ovarian cancer progression.", Aging (Albany NY) 12 (18) (2020) 17921–17929.

[71] Y. Shi, Y. Liu, J. Huang, Z. Luo, X. Guo, M. Jiang, et al., Optimized mobilization of MHC class I- and II- restricted immunity by dendritic cell vaccine potentiates cancer therapy, Theranostics 12 (2022) 3488–3502.

[72] H. Hartog, H.M. Boezen, M.M. de Jong, M. Schaapveld, J. Wesseling, W.T.A. van der Graaf, "Prognostic value of insulin-like growth factor 1 and insulin-like growth factor binding protein 3 blood levels in breast cancer.", Breast 22 (6) (2013) 1155–1160.

[73] S. Li, H. Mai, Y. Zhu, G. Li, J. Sun, G. Li, B. Liang, S. Chen, "MicroRNA-4500 Inhibits Migration, Invasion, and Angiogenesis of Breast Cancer Cells via RRM2-Dependent MAPK Signaling Pathway.", Mol. Ther. - Nucleic Acids 21 (2020) 278–289.

[74] G. Lin, S. Wang, X. Zhang, D. Wang, "Circular RNA circPLK1 promotes breast cancer cell proliferation, migration and invasion by regulating miR-4500/IGF1 axis.", Cancer Cell Int. 20 (2020) 1.

[75] L. Zhang, D. Sun, J. Zhang, Y. Tian, "Circ-UBR1 facilitates proliferation, metastasis, and inhibits apoptosis in breast cancer by regulating the miR-1299/CCND1 axis.", Life Sci. 266 (2021) 118829.

[76] S. Qie, J.A. Diehl, "Cyclin D1, cancer progression, and opportunities in cancer treatment.", J. Mol. Med. 94 (12) (2016) 1313–1326.

[77] G. Chen, M. Hu, X. Qu, K. Wang, Y. Qu, "MicroRNA-584 directly targets CCND1 and inhibits cell proliferation and invasion in pancreatic cancer.", Mol. Med. Rep. 19 (1) (2019) 719–726.

[78] F. Afzali, M. Salimi, "Unearthing Regulatory Axes of Breast Cancer circRNAs Networks to Find Novel Targets and Fathom Pivotal Mechanisms.", Interdiscip. Sci.: Comput. Life Sci. 11 (4) (2019) 711–722.

[79] Y. Shen, M. Zhang, L. Da, W. Huang, C. Zhang, "Circular RNA circ_SETD2 represses breast cancer progression by modulating the miR-155-5p/SCUBE2 axis. Open Med. 15 (1) (2020) 940–953.

[80] L.H. Liu, Q.Q. Tian, J. Liu, Y. Zhou, H. Yong, "Upregulation of hsa_circ_0136666 contributes to breast cancer progression by sponging miR-1299 and targeting CDK6.", J. Cell Biochem 120 (8) (2019) 12684–12693.

[81] H.-D. Zhang, L.-H. Jiang, J.-C. Hou, S.-Y. Zhou, S.-L. Zhong, L.-P. Zhu, D.-D. Wang, S.-J. Yang, Y.-J. He, C.-F. Mao, Y. Yang, J.-Y. Wang, Q. Zhang, H.-Z. Xu, D.-D. Yu, J.-H. Zhao, J.-H. Tang, Z.-L. Ji, "Circular RNA hsa_circ_0072995 promotes breast cancer cell migration and invasion through sponge for miR-30c-2-3p.", Epigenomics 10 (9) (2018) 1229–1242.

[82] J. Ding, Q. Wang, N. Guo, H. Wang, H. Chen, G. Ni, P. Li, "CircRNA circ_0072995 promotes the progression of epithelial ovarian cancer by modulating miR-147a/CDK6 axis.", Aging (Albany NY) 12 (17) (2020) 17209–17223.

[83] K. Zeng, B. He, B.B. Yang, T. Xu, X. Chen, M. Xu, X. Liu, H. Sun, Y. Pan, S. Wang, "The pro-metastasis effect of circANKS1B in breast cancer.", Mol. Cancer 17 (2018) 1.

[84] W.-B. Yin, M.-G. Yan, X. Fang, J.-J. Guo, W. Xiong, R.-P. Zhang, "Circulating circular RNA hsa_circ_0001785 acts as a diagnostic biomarker for breast cancer detection.", Clin. Chim. Acta 487 (2018) 363–368.

[85] Y. Li, P. Shi, T. Zheng, Z. Ying, D. Jiang, "Circular RNA hsa_circ_0131242 Promotes Triple-Negative Breast Cancer Progression by Sponging hsa-miR-2682.", Onco Targets Ther. 13 (2020) 4791–4798.

[86] C. Yuan, L. Zhou, L. Zhang, K. Yin, J. Peng, R. Sha, S. Zhang, Y. Xu, X. Sheng, Y. Wang, Y. Lin, S. Xu, W. Yin, J. Lu, "Identification and integrated analysis of key differentially expressed circular RNAs in ER-positive subtype breast cancer.", Epigenomics 11 (3) (2019) 297–321.

[87] S.S. Youssef, N.M. Hamdy, Suppressor of Cytokine Signaling 1 (rs243327), Toll-Like Receptor-9 (rs352140) and Retinoic Acid Inducible Gene-I (rs669260) SNPs Haplotype Novel Association in Egyptian Fibrotic/Cirrhotic Patients from HCV Genotype 4, Arch. Virol. 162 (11) (2017) 3347–3354, https://doi.org/10.1007/s00705-017-3498-7.

[88] N.A. Ali, M.Hamdy Nadia, et al., Investigation of the relationship between CTLA4 and the tumor suppressor RASSF1A and the possible mediating role of STAT4 in a cohort of Egyptian patients infected with HCV with and without HCC, Arch. Virol. 166 (2021) 1643–1651, https://doi.org/10.1007/s00705-021-04981-8.

[89] H. Zhou, G. Tang, M. Zhao, L. Xie, Y. Xie, Z. Zhang, X. He, "circFBXL5 promotes breast cancer progression by sponging miR-660.", J. Cell Mol. Med 24 (1) (2020) 356–361.

[90] C.M. Smoniewski, P. Mirzavand Borujeni, A. Petersen, et al., Circular mitochondrial-encoded mRNAs are a distinct subpopulation of mitochondrial mRNA in Trypanosoma brucei, Sci. Rep. 13 (2023) 7825, https://doi.org/10.1038/s41598-023-34255-z.

[91] M.V. Liberti, J.W. Locasale, "The Warburg Effect: How Does it Benefit Cancer Cells?", Trends Biochem Sci. 41 (3) (2016) 211–218.

[92] L. Cao, M. Wang, Y. Dong, B. Xu, J. Chen, Y. Ding, S. Qiu, L. Li, E. Karamfilova Zaharieva, X. Zhou, Y. Xu, "Circular RNA circRNF20 promotes breast cancer tumorigenesis and Warburg effect through miR-487a/HIF-1α/HK2.", Cell Death Dis. 11 (2) (2020) 145.

[93] S. Ren, J. Liu, Y. Feng, Z. Li, L. He, L. Li, X. Cao, Z. Wang, Y. Zhang, "Knockdown of circDENND4C inhibits glycolysis, migration and invasion by upregulating miR-200b/c in breast cancer under hypoxia.", J. Exp. Clin. Cancer Res 38 (1) (2019) 388.

[94] W.H. Huang, Q. Yang, C. Zhang, "eIF4A3-induced circWAC promotes breast cancer progression through mediating miR-599/E2F3 axis, Kaohsiung J. Med Sci. 38 (4) (2022) 321–335.

[95] H. Yu, H. Luo, X. Liu, "Knockdown of circ_0102273 inhibits the proliferation, metastasis and glycolysis of breast cancer through miR-1236-3p/PFKFB3 axis.", Anticancer Drugs 33 (4) (2022) 323–334.

[96] Shokrey, S.N.S. (2023). Circular RNA and Chemerin in Breast Cancer Patient (NCT05771337). ClinicalTrials.gov. Retrieved from [ClinicalTrials.gov].

[97] C. Zhang, J. Wang, H. Wang, J. Li, "Circ-ABCC1 enhances radioresistance of breast cancer cells via miR-627-5p/ABCC1 axis.", Cell Mol. Biol. (Noisy-Le. -Gd.) 68 (10) (2022) 187–192.

[98] P. Song, J. Wu, J. Chen, F. Wang, J. Chen, G. Wang, "Knockdown of circ-ADAM9 inhibits malignant phenotype and enhances radiosensitivity in breast cancer cells by acting as a sponge for miR-383-5p.", Strahl. Onkol. 199 (1) (2023) 78–89.

[99] Z.Y. He, R.G. Zhuo, S.P. Yang, P. Zhou, J.Y. Xu, J. Zhou, S.G. Wu, "CircNCOR1 regulates breast cancer radiotherapy efficacy by regulating CDK2 via hsa-miR-638 binding.", Cell Signal 109 (2023) 110787.

[100] D. Liu, Z. Zhou, Y. Guo, Q. Du, L. Li, "CircCDK1 knockdown reduces CDK1 expression by targeting miR-489-3p to suppress the development of breast cancer and strengthen the sensitivity of Tamoxifen.", Anticancer Drugs 33 (3) (2022) 286–299.

[101] Z. Li, Y. Li, D. Han, X. Wang, C. Li, T. Chen, W. Li, Y. Liang, D. Luo, B. Chen, L. Wang, W. Zhao, Q. Yang, "circRNA-SFMBT2 orchestrates ERα activation to drive tamoxifen resistance in breast cancer cells.", Cell Death Dis. 14 (7) (2023) 482.

[102] M. Garcia-Cortes, M. Robles-Diaz, C. Stephens, A. Ortega-Alonso, M.I. Lucena, R. J. Andrade, "Drug induced liver injury: an update.", Arch. Toxicol. 94 (2020) 3381–3407.

[103] M. Zhu, Y. Wang, F. Wang, L. Li, X. Qiu, "CircFBXL5 promotes the 5-FU resistance of breast cancer by modulating miR-216b/HMGA2 axis.", Cancer Cell Int 21 (1) (2021) 384.

[104] H. Xie, R. Zheng, "Circ_0085495 knockdown reduces adriamycin resistance in breast cancer through miR-873-5p/integrin β1 axis.", Anticancer Drugs 33 (1) (2022) e166–e177.

[105] J. Chen, P. Shi, J. Zhang, Y. Li, J. Ma, Y. Zhang, H. Liu, "CircRNA_0044556 diminishes the sensitivity of triple-negative breast cancer cells to adriamycin by sponging miR-145 and regulating NRAS.", Mol. Med Rep. 25 (2022) 2.

[106] Y. Liang, X. Song, Y. Li, P. Su, D. Han, T. Ma, R. Guo, B. Chen, W. Zhao, Y. Sang, N. Zhang, X. Li, H. Zhang, Y. Liu, Y. Duan, L. Wang, Q. Yang, "circKDM4C suppresses tumor progression and attenuates doxorubicin resistance by regulating miR-548p/PBLD axis in breast cancer.", Oncogene 38 (42) (2019) 6850–6866.

[107] X. Wang, T. Chen, C. Li, W. Li, X. Zhou, Y. Li, D. Luo, N. Zhang, B. Chen, L. Wang, W. Zhao, S. Fu, Q. Yang, "CircRNA-CREIT inhibits stress granule assembly and overcomes doxorubicin resistance in TNBC by destabilizing PKR.", J. Hematol. Oncol. 15 (1) (2022) 122.
[108] H. Wang, S. Shan, H. Wang, X. Wang, CircATXN7 contributes to the progression and doxorubicin resistance of breast cancer by modulating miR-149-5p/HOXA11 pathway, Anticancer Drugs 33 (1) (2022) e700–e710.
[109] X. Zhang, X. Su, Z. Guo, X. Jiang, X. Li, Circular RNA La-Related RNA-Binding Protein 4 Correlates with Reduced Tumor Stage, as Well as Better Prognosis, and Promotes Chemosensitivity to Doxorubicin in Breast Cancer, J. Clin. Lab. Anal. 34 (2020) e23272.
[110] Z. Kong, Q. Han, B. Zhu, L. Wan, E. Feng, Circ_0069094 regulates malignant phenotype and paclitaxel resistance in breast cancer cells by targeting the miR-136-5p/YWHAZ axis, Thorac. Cancer 14 (19) (2023) 1831–1842.
[111] J. Liu, L. Kong, W. Bian, X. Lin, F. Wei, J. Chu, CircRNA CircABCB1 Diminishes the Sensitivity of Breast Cancer Cells to Docetaxel by Sponging MiR-153-3p, Tohoku J. Exp. Med 261 (1) (2023) 25–33.
[112] S. Quasthoff, H.P. Hartung, Chemotherapy-induced peripheral neuropathy, J. Neurol. 249 (2002) 9–17.
[113] Y. Liu, Y. Dong, L. Zhao, L. Su, J. Luo, Circular RNA-MTO1 suppresses breast cancer cell viability and reverses monastrol resistance through regulating the TRAF4/Eg5 axis, Int. J. Oncol. 53 (4) (2018) 1752–1762.
[114] S. Wang, Y. Wang, Q. Li, X. Li, X. Feng, A novel circular RNA confers trastuzumab resistance in human epidermal growth factor receptor 2-positive breast cancer through regulating ferroptosis, Environ. Toxicol. 37 (7) (2022) 1597–1607.
[115] Y. Ling, G. Liang, Q. Lin, X. Fang, Q. Luo, Y. Cen, M. Mehrpour, A. Hamai, Z. Liu, Y. Shi, J. Li, W. Lin, S. Jia, W. Yang, Q. Liu, E. Song, J. Li, C. Gong, circCDYL2 promotes trastuzumab resistance by sustaining HER2 downstream signaling in breast cancer, Mol. Cancer 21 (1) (2022) 8.
[116] C.-H. Zhao, L. Qu, H. Zhang, R. Qu, Identification of breast cancer-related circRNAs by analysis of microarray and RNA-sequencing data: an observational study, Medicine 98 (2019) 46.
[117] S. Wang, F. Liu, H. Ma, X. Cui, S. Yang, R. Qin, circCDYL Acts as a Tumor Suppressor in Triple Negative Breast Cancer by Sponging miR-190a-3p and Upregulating TP53INP1, Clin. Breast Cancer 20 (5) (2020) 422–430.
[118] Y. Zou, S. Zheng, W. Xiao, X. Xie, A. Yang, G. Gao, Z. Xiong, Z. Xue, H. Tang, X. Xie, circRAD18 sponges miR-208a/3164 to promote triple-negative breast cancer progression through regulating IGF1 and FGF2 expression, Carcinogenesis 40 (12) (2019) 1469–1479.
[119] R. Xie, J. Tang, X. Zhu, H. Jiang, Silencing of hsa_circ_0004771 inhibits proliferation and induces apoptosis in breast cancer through activation of miR-653 by targeting ZEB2 signaling pathway, Biosci. Rep. 39 (5) (2019). BSR20181919.
[120] H. Li, W. Xu, Z. Xia, W. Liu, G. Pan, J. Ding, J. Li, J. Wang, X. Xie, D. Jiang, "Hsa_circ_0000199 facilitates chemo-tolerance of triple-negative breast cancer by interfering with miR-206/613-led PI3K/Akt/mTOR signaling.", Aging (Albany NY) 13 (3) (2021) 4522–4551.
[121] Y. Zhang, Y. Zhang, X. Li, M. Zhang, K. Lv, Microarray analysis of circular RNA expression patterns in polarized macrophages (Epub), Int J. Mol. Med. 2017 Feb 39 (2) (2017 Jan 11) 373–379, https://doi.org/10.3892/ijmm.2017.2852.
[122] W. Li, J.-Q. Liu, M. Chen, J. Xu, D. Zhu, Circular RNA in cancer development and immune regulation, J. Cell Mol. Med 26 (2022) 1785–1798, https://doi.org/10.1111/jcmm.16102.
[123] W. Jiang, S. Pan, X. Chen, Z.W. Wang, X. Zhu, The role of lncRNAs and circRNAs in the PD-1/PD-L1 pathway in cancer immunotherapy, Mol. Cancer 20 (1) (2021 Sep 8) 116, https://doi.org/10.1186/s12943-021-01406-7.
[124] T. Abaza, N.M. Hamdy, C.K. Kontos, R.A. Younes, Emerging Role of Circular RNAs in Hepatocellular Carcinoma Immunotherapy, Int. J. Mol. Sci. 24 (22) (2023) 16484, https://doi.org/10.3390/ijms242216484.
[125] J. Li, X. Dong, X. Kong, Y. Wang, Y. Li, Y. Tong, W. Zhao, W. Duan, P. Li, Y. Wang, C. Wang, "Circular RNA hsa_circ_0067842 facilitates tumor metastasis and immune escape in breast cancer through HuR/CMTM6/PD-L1 axis.", Biol. Direct 18 (1) (2023) 48.
[126] X. Gao, Y. Zhu, P. Wang, L. Yu, S. Ruan, M. Shen, K. Zhang, Addition of immune checkpoint inhibitors to chemotherapy versus chemotherapy alone in patients with triple-negative breast cancer: A systematic review and meta-analysis, Cancer Med 12 (24) (2023 Dec) 21873–21884.
[127] M.D. Molla, Y. Akalu, Z. Geto, B. Dagnew, B. Ayelign, T. Shibabaw, Role of Caspase-1 in the Pathogenesis of Inflammatory-Associated Chronic Noncommunicable Diseases, J. Inflamm. Res 13 (2020) 749–764.
[128] T. Liu, P. Ye, Y. Ye, S. Lu, B. Han, Circular RNA hsa_circRNA_002178 silencing retards breast cancer progression via microRNA-328-3p-mediated inhibition of COL1A1, J. Cell. Mol. Med. 24 (3) (2020) 2189–2201.
[129] P. Li, X. Ren, Y. Zheng, J. Sun, G. Ye, Tumor promoting effect of circ_002172 associates with induced immune escape in breast cancer via the miR-296-5p/CXCL12 axis, Int Immunopharmacol. 106 (2022) 108530.
[130] M.H. Ghazimoradi, S. Babashah, The role of CircRNA/miRNA/mRNA axis in breast cancer drug resistance, Front. Oncol. 12 (2022) 966083.
[131] J. Gong, R. Jaiswal, J.M. Mathys, V. Combes, G.E. Grau, M. Bebawy, Microparticles and their emerging role in cancer multidrug resistance, Cancer Treat. Rev. 38 (3) (2012 May) 226–234, https://doi.org/10.1016/j.ctrv.2011.06.005. Epub 2011 Jul 14.
[132] A. Modi, D. Roy, Vishnoi Sharma Jeewan, J.R. Pareek, P. Elhence, P. Sharma, P. Purohit, ABC transporters in breast cancer: their roles in multidrug resistance and beyond (Epub), J. Drug Target. 2022 Nov. 30 (9) (2022 Jun 26) 927–947, https://doi.org/10.1080/1061186X.2022.2091578.
[133] A. Domenichini, A. Adamska, M. Falasca, ABC transporters as cancer drivers: Potential functions in cancer development, Biochim Biophys. Acta Gen. Subj. 1863 (1) (2019 Jan) 52–60, https://doi.org/10.1016/j.bbagen.2018.09.019. Epub 2018.
[134] J.Q. Wang, Z.X. Wu, Y. Yang, Q.X. Teng, Y.D. Li, Z.N. Lei, K.A. Jani, N. Kaushal, Z. S. Chen, ATP-binding cassette (ABC) transporters in cancer: A review of recent updates, J. Evid. Based Med 14 (3) (2021 Sep) 232–256, https://doi.org/10.1111/jebm.12434.
[135] J. Ma, L. Fang, Q. Yang, S. Hibberd, W.W. Du, N. Wu, B.B. Yang, Posttranscriptional regulation of AKT by circular RNA angiomotin- like 1 mediates chemoresistance against paclitaxel in breast cancer cells, Aging (Albany NY) 11 (23) (2019 Dec 9) 11369–11381, https://doi.org/10.18632/aging.102535. Epub 2019 Dec 9.
[136] J. Hao, X. Du, F. Lv, Q. Shi, Knockdown of circ_0006528 Suppresses Cell Proliferation, Migration, Invasion, and Adriamycin Chemoresistance via Regulating the miR-1236-3p/CHD4 Axis in Breast Cancer, J. Surg. Res 260 (2021 Apr) 104–115, https://doi.org/10.1016/j.jss.2020.10.031. Epub 2020 Dec 14.
[137] W. Yang, P. Gong, Y. Yang, C. Yang, B. Yang, L. Ren, Circ-ABCB10 Contributes to Paclitaxel Resistance in Breast Cancer Through Let-7a-5p/DUSP7 Axis (eCollection), Cancer Manag Res. 2020 Mar. 27 12 (2020) 2327–2337, https://doi.org/10.2147/CMAR.S238513.
[138] Q. Wang, D. Liang, P. Shen, Y. Yu, Y. Yan, W. You, Hsa_circ_0092276 promotes doxorubicin resistance in breast cancer cells by regulating autophagy via miR-348/ATG7 axis, Transl. Oncol. 14 (2021) 101045, https://doi.org/10.1016/j.tranon.2021.101045.
[139] Y. Huang, S. Zheng, Y. Lin, L. Ke, Circular RNA circ-ERBB2 Elevates the Warburg Effect and Facilitates Triple-Negative Breast Cancer Growth by the MicroRNA 136-5p/Pyruvate Dehydrogenase Kinase 4 Axis, Mol. Cell Biol. 41 (10) (2021) e0060920.
[140] K. Hu, X. Liu, Y. Li, Q. Li, Y. Xu, et al., Exosomes mediated transfer of Circ-UBE2D2 enhances the resistance of breast cancer to tamoxifen by binding to MiR-200a-3p, Med. Sci. Monit. 26 (2020) e922253, https://doi.org/10.12659/MSM.922253.
[141] B. Huang, F.C. Wu, W.D. Wang, B.Q. Shao, X.M. Wang, Y.M. Lin, G.X. Zheng, M. M. Dong, C.T. Liu, Y.W. Xu, X.J. Wang, The prognosis of breast cancer patients with bone metastasis could be potentially estimated based on blood routine test and biochemical examination at admission. Randomized Controlled Trial, Ann. Med 55 (1) (2023 Dec) 2231342.
[142] Y. Xu, S. Zhang, X. Liao, M. Li, S. Chen, X. Li, X. Wu, M. Yang, M. Tang, Y. Hu, Z. Li, R. Yu, M. Huang, L. Song, J. Li, "Circular RNA circIKBKB promotes breast cancer bone metastasis through sustaining NF-κB/bone remodeling factors signaling.", Mol. Cancer 20 (1) (2021) 98.
[143] N. Vigneron, Human Tumor Antigens and Cancer Immunotherapy, Biomed. Res Int 2015 (2015) 948501, https://doi.org/10.1155/2015/948501.
[144] H. Fritah, R. Rovelli, C.L. Chiang, L.E. Kandalaft, The current clinical landscape of personalized cancer vaccines, Cancer Treat. Rev. 106 (2022) 102383.
[145] J. Liu, M. Fu, M. Wang, D. Wan, Y. Wei, X. Wei, Cancer vaccines as promising immuno-therapeutics: platforms and current progress, J. Hematol. Oncol. 15 (1) (2022 Mar 18) 28, https://doi.org/10.1186/s13045-022-01247-x.
[146] K. Bhattacharya, I.M. Shamkh, M.S. Khan, M.M. Lotfy, J.B. Nzeyimana, R. F. Abutayeh, N.M. Hamdy, D. Hamza, N.R. Chanu, P. Khanal, et al., Multi-Epitope Vaccine Design against Monkeypox Virus via Reverse Vaccinology Method Exploiting Immunoinformatic and Bioinformatic Approaches, Vaccines 10 (2022) 2010, https://doi.org/10.3390/vaccines10122010.
[147] E. Faghfuri, F. Pourfarzi, A.H. Faghfouri, M. Abdoli Shadbad, K. Hajiasgharzadeh, B. Baradaran, Recent developments of RNA-based, Vaccin. Cancer Immunother. Expert Opin. Biol. Ther. (2020) 1–8.
[148] J.D. Beck, D. Reidenbach, N. Salomon, U. Sahin, Ö. Türeci, M. Vormehr, et al., mRNA therapeutics in cancer immunotherapy, Mol. Cancer 20 (2021) 69.
[149] L. Miao, Y. Zhang, L. Huang, mRNA vaccine for cancer immunotherapy, Mol. Cancer 20 (1) (2021 Feb 25) 41, https://doi.org/10.1186/s12943-021-01335-5. PMID: 33632261; PMCID: PMC7905014.
[150] R.A. Wesselhoeft, P.S. Kowalski, D.G. Anderson, Engineering circular RNA for potent and stable translation in eukaryotic cells, Nat. Commun. 9 (2018) 2629.
[151] R.A. Wesselhoeft, P.S. Kowalski, F.C. Parker-Hale, Y. Huang, N. Bisaria, D. G. Anderson, RNA Circularization Diminishes Immunogenicity and Can Extend Translation Duration In vivo, Mol. Cell 74 (2019) 508–520.
[152] H. Li, K. Peng, K. Yang, W. Ma, S. Qi, X. Yu, J. He, X. Lin, G. Yu, Circular RNA cancer vaccines drive immunity in hard-to-treat malignancies, Theranostics 12 (14) (2022 Aug 29) 6422–6436, https://doi.org/10.7150/thno.77350.
[153] W.W. Du, et al., A circular RNA circ-DNMT1 enhances breast cancer progression by activating autophagy, Oncogene 37 (2018) 5829–5842, https://doi.org/10.1038/s41388-018-0369-y.
[154] W.W. Du, et al., The circular RNA circSKA3 binds integrin beta1 to induce invadopodium formation enhancing breast cancer invasion, Mol. Ther. 28 (2020) 1287–1298, https://doi.org/10.1016/j.ymthe.2020.03.002.
[155] R. Yang, L. Xing, X. Zheng, Y. Sun, X. Wang, J. Chen, The CircRNA CircAGFG1 Acts as a Sponge of MiR-195-5p to Promote Triple-Negative Breast Cancer Progression through Regulating CCNE1 Expression, Mol. Cancer 18 (2019) 4, https://doi.org/10.1186/s12943-018-0930-x.
[156] J.-Z. Xu, et al., circTADA2As suppress breast cancer progression and metastasis by targeting miR-203a-3p/SOCS3 axis, Cell Death Dis. 10 (2019) 1–16, https://doi.org/10.1038/s41419-018-1236-z.
[157] Y. Sang, B. Chen, X. Song, Y. Li, Y. Liang, D. Han, N. Zhang, H. Zhang, Y. Liu, T. Chen, C. Li, L. Wang, W. Zhao, Q. Yang, circRNA_0025202 Regulates

Tamoxifen Sensitivity and Tumor Progression via Regulating the miR-182-5p/FOXO3a Axis in Breast Cancer, Mol. Ther. 27 (9) (2019) 1638–1652.
[158] J. Li, M. Ma, X. Yang, M. Zhang, J. Luo, H. Zhou, N. Huang, F. Xiao, B. Lai, W. Lv, "Circular HER2 RNA positive triple negative breast cancer is sensitive to Pertuzumab.", Mol. Cancer 19 (1) (2020) 1–18.
[159] D. Singh, P. Kesharwani, N.A. Alhakamy, H.R. Siddique, Accentuating CircRNA-miRNA-Transcription Factors Axis: A Conundrum in Cancer Research, Front Pharm. 12 (2022 Jan 11) 784801, https://doi.org/10.3389/fphar.2021.784801. PMID: 35087404; PMCID: PMC8787047.
[160] S.M. Radwan, N.M. Hamdy, et al., Beclin-1 and hypoxia-inducible factor-1alpha genes expression: potential biomarkers in acute leukemia patients, Cancer Biomark. 16 (4) (2016 Mar 18) 619–626, https://doi.org/10.3233/CBM-160603.
[161] E.F. Sanad, N.M. Hamdy, et al., Peripheral leucocytes and tissue gene expression of granzyme B/perforin system and serpinB9: Impact on inflammation and insulin resistance in coronary atherosclerosis, Diabetes Res. Clin. Pract. 131 (2017) 132–141, https://doi.org/10.1016/j.diabres.2017.07.013.
[162] M.S. Khella, N.M. Hamdy, et al., The (FTO) gene polymorphism is associated with metabolic syndrome risk in Egyptian females: a case-control study, BMC Med. Genet. 18 (2017) 101, https://doi.org/10.1186/s12881-017-0461-0.
[163] M.A. Abou-Ouf, N.M. Hamdy, et al., Genotype screening of APLN rs3115757 variant in Egyptian women population reveals an association with obesity and insulin resistance, Diabetes Res. Clin. Pract. 109 (2015) 40–47, https://doi.org/10.1016/j.diabres.2015.05.016.
[164] H.O. El-Mesallamy, E. Farag, N.M. Hamdy, A.K. AL-Etriby, Plasma Granzyme B in ST Elevation Myocardial Infarction versus Non ST Elevaion Acute Coronary Syndrome: Comparisons with IL-18 and Fractalkine, Article ID 343268, 8 pages, Mediat. Inflamm. 2013 (2013), https://doi.org/10.1155/2013/343268.
[165] H.O. El-Mesallamy, N.M. Hamdy, et al., The Serine Protease Granzyme B as an Inflammatory Marker, in Relation to the Insulin Receptor Cleavage in Human Obesity and Type 2 Diabetes Mellitus, J. Interferon Cytokine Res 34 (2013) 179–186, https://doi.org/10.1089/jir.2013.0059.
[166] H.O. El-Mesallamy, N.M. Hamdy, et al., Clinical Value of Circulating Lipocalins and Insulin Like Growth Factor Axis in Pancreatic Cancer Diagnosis, Pancreas 42 (1) (2013) 149–154, https://doi.org/10.1097/MPA.0b013e3182550d9d.
[167] H.O. El-Mesallamy, N.M. Hamdy, et al., Adiponectin and sE-selectin Concentrations in Relation to Inflammation in Obese Type 2 Diabetic Patients With Coronary Heart Disease (Feb), Angiology 63 (2) (2012) 96–102, https://doi.org/10.1177/0003319711408587.
[168] H.O. El-Mesallamy, N.M. Hamdy, et al., Serum retinol binding protein-4 and neutrophil-gelatinase associated lipocalin are interrelated in pancreatic cancer patients, Scand. J. Clin. Lab. Investig. 72 (8) (2012) 602–607, https://doi.org/10.3109/00365513.2012.723135.
[169] M.M. Swellam, N.M. Hamdy, Association of nonalcoholic fatty liver disease with a single nucleotide polymorphism on the gene encoding leptin receptor, IUBMB Life 64 (2) (2012 Feb) 180–186. Epub 2012 Jan 3; https://doi:10.1002/iub.597.
[170] N.M. Hamdy, Relationship between pro-anti-inflammatory cytokines, T-cell activation and CA 125 in obese patients with heart failure, 17(3):CR174-179;, Med Sci. Monit. 25 (2011) https://doi.org/10.12659/MSM.881453.
[171] N.M. Hamdy, L. El-Wakeel, S.M. Suwailem, Involvement of Depressive Catecholamines as Thrombosis Risk/Inflammatory Markers in Non-Smoker, Non-Obese Congestive Heart Failure, Linked to Increased Epidermal Growth Factor-Receptor (EGF-R) Production, Ind. J. Clin. Biochem 26 (2) (2011) 140–145, https://DOI:10.1007/s12291-010-0106-y.
[172] H.O. El-Mesallamy, M.O. El-Derany, N.M. Hamdy, Serum omentin-1 and chemerin levels are interrelated in patients with Type 2 diabetes mellitus with or without ischemic heart disease, Diabet. Med 28 (10) (2011) 1194–1200, https://doi.org/10.1111/j.1464-5491.2011.03353.x.
[173] H.O. El-Mesallamy, M.Hamdy Nadia, et al., Apelin serum level in Egyptian patients with Chronic Hepatitis C, Mediat. Inflamm. (2011), 2011: 703031 (2011) 1-7; https://doi:10.1155/2011/703031.
[174] H. El-Mesalamy, S. Swailem, N.M. Hamdy, Evaluation of C-Reactive Protein, Endothelin-1, Adhesion Molecule(s), and Lipids as Inflammatory Markers in Type 2 D.M Patients (pages), Mediat. Inflamm. ; 2007 7 (2007) 73635, https://doi.org/10.1155/2007/73635.
[175] Y.-C. Chen, Y.-F. Chiang, Y.-J. Lin, K.-C. Huang, H.-Y. Chen, M. Nadia, Hamdy, et al., Effect of Vitamin D supplementation on primary dysmenorrhea; a systematic review and meta-analysis of randomized clinical trials, Nutrients 15 (13) (2023) 2830, https://doi.org/10.3390/nu15132830.
[176] N.M. Hamdy, S. Swailem, et al., Influence of Vitamin E Supplementation on Endothelial Complications in Type 2 Diabetes Mellitus Patients Who Performed Coronary Artery Bypass Graft, J. Diabetes Complicat. 23 (3) (2009) 167–173, https://doi.org/10.1016/j.jdiacomp.2007.10.006.
[177] M.O. El-Derany, M.Hamdy Nadia, et al., Integrative role of vitamin D related and Interleukin-28B genes polymorphism in predicting treatment outcomes of Chronic Hepatitis C, BMC Gastroenterol. 16 (2016) 19, https://doi.org/10.1186/s12876-016-0440-5.
[178] H.O. El-Mesallamy, W. Anwar, N.M. Hamdy, M. Hamdy, High-Dose Methotrexate in Egyptian Pediatric Acute Lymphoblastic Leukemia: the Impact of ABCG2 C421A Genetic Polymorphism on Plasma Levels, what is next? J. Cancer Res. Clin. Oncol. 140 (8) (2014) 1359–1365, 10.1007/s00432-014-1670-y.
[179] E.R. Mokhtar, N.M. Hamdy, et al., Peripheral Blood B-cell subsets Frequency and Distribution and BSF-2(IL-6) to CSIF:TGIF(IL-10) ratio as Severity-Associated Signatures in Primary Open Angle Glaucoma: A Case-controlled Study, Biomedicines 12 (3) (2024) 485, https://doi.org/10.3390/biomedicines12030485.
[180] R. Hammad, N.M. Hamdy, Monocytes Subsets Altered Distribution and Dysregulated Plasma hsa-miR-21-5p and hsa-miR-155-5p in HCV-Linked Liver Cirrhosis Progression to Hepatocellular Carcinoma, J. Cancer Res. Clin. Oncol. 149 (2023) 15349–15364, https://doi.org/10.1007/s00432-023-05313-w.
[181] M.A. Eldosoky, N.M. Hamdy, et al., Diagnostic significance of hsa-miR-21-5p, hsa-miR-192-5p, hsa-miR-155-5p, hsa-miR-199a-5p panel and ratios in hepatocellular carcinoma on top of liver cirrhosis in HCV-infected patients, Int. J. Mol. Sci. 24 (2023) 3157, https://doi.org/10.3390/ijms24043157.
[182] R. Hammad, N.M. Hamdy, T-cytotoxic expression of leukocyte-associated immunoglobulin-like receptor-1 (LAIR-1) in HCV-mediated hepatocellular carcinoma, Int. J. Mol. Sci. 23 (20) (2022) 12541. ⟨https://www.mdpi.com/1422-0067/23/20/12541⟩.
[183] H. El-Mesalamy, N.M. Hamdy, et al., Oxidative stress and platelet activation: markers of myocardial infarction in type 2 diabetes mellitus, Angiology 61 (1) (2010) 14–18, https://doi.org/10.1177/0003319709340891.
[184] A.M. Kamal, N.M. Hamdy, et al., Expression of thioredoxin-1 (TXN) and its relation with oxidative DNA damage and treatment outcome in adult AML and ALL: A comparative study, Hematology (May 2016) 1–9, https://doi.org/10.1080/10245332.2016.1173341.
[185] B.M. Khalil, N.M. Hamdy, et al., Genetic and nongenetic factors affecting clopidogrel response in the Egyptian population, Clin. Transl. Sci. 9 (1) (2016) 23, https://doi.org/10.1111/cts.12383.
[186] D. Sokolov, N.M. Hamdy, A. Banerjee, Differential signaling pathways in medulloblastoma: nano-biomedicine targeting non-coding epigenetics to improve current and future therapeutics, Curr. Pharm. Des. (2024) 30, https://doi.org/10.2174/0113816128277350231219062154.
[187] D.S. Metibemu, O.A. Akinloye, A.J. Akamo, et al., Exploring receptor tyrosine kinases-inhibitors in Cancer treatments, Egypt J. Med Hum. Genet 20 (2019) 35, https://doi.org/10.1186/s43042-019-0035-0.
[188] W. Feroz, A.M.A. Sheikh, Exploring the multiple roles of guardian of the genome: P53, Egypt J. Med Hum. Genet 21 (2020) 49, https://doi.org/10.1186/s43042-020-00089-x.
[189] M.K. Abd El-Aziz, N.M. Hamdy, et al., Decoding Hepatocarcinogenesis from a Non-Coding RNAs Perspective, J. Cell. Physiol. (2023) 1–28, https://doi.org/10.1002/jcp.31076.
[190] M. Elanany, D. Mostafa, N.M. Hamdy, Remodeled Tumor Immune Microenvironment (TIME) Parade via Natural killer cells Reprogramming in Breast Cancer, Life Sci. 330 (2023) 121997, https://doi.org/10.1016/j.lfs.2023.121997.