Neoplasma 2022; 69(5): 1019–1028

doi:10.4149/neo_2022_220611N619

Circular RNAs: novel regulators of resistance to systemic treatments in breast cancer

Minireview

Xiao-Qiang GUO, Yu-Ming HUA*

Department of General Surgery, Affiliated Hospital of Jiangnan University, Wuxi, China

**Correspondence: jndxhym@163.com*

Received June 11, 2022 / Accepted July 19, 2022

Systematic treatments including chemotherapy, endocrine therapy, and HER2-targeted therapy are important therapeutic approaches to breast cancer. However, drug resistance is a major barrier to achieving a cure in breast cancer (BC) patients. Hence, it is urgent to gain insight into the drug-resistance mechanisms in order to improve the prognosis of BC patients. Genetic alternations, epigenetic alternations, and other non-genetic mechanisms such as BC stem-like cells, metabolic reprogramming, and tumor microenvironment contribute to drug resistance of BC. With the development of single-cell sequencing of circulating tumor cell and next-generation sequencing of matched pre- and post- progression tumor biopsies or ctDNA from BC patients with drug resistance, new mechanisms of resistance are being discovered. An increasing number of microRNAs and long non-coding RNAs have been found to be associated with the drug resistance of BC. However, there are few reports on the role of circular RNAs (circRNAs) as master regulators of drug resistance. Therefore, there is still much to say in the field of drug resistance-related circRNAs. In this review, we mainly focus on literature evidence for the detailed mechanisms associated with systematic treatments' resistance of BC and how circRNAs intensify or weaken drug resistance. Exogenous expression of tumor suppressive circRNAs or knockdown of oncogenic circRNAs has been verified to reverse drug resistance of BC cells, which highlights that circRNAs may function as potential biomarkers and/or therapeutic targets of BC. Treatment targeting abnormally expressed circRNAs alone or combined with other systemic treatments may be a promising approach to conquering drug resistance.

Key words: circular RNA, breast cancer, endocrine resistance, chemoresistance, HER2-targeted therapy resistance

It is well known that breast cancer (BC) is the most common malignant tumor among women, which seriously threatens the health of females worldwide. According to data from Global Cancer Statistics 2020, female breast cancer has surpassed lung cancer as the most commonly diagnosed cancer, with an estimated 2.3 million new cases worldwide in 2020 [1]. In the past, surgery was generally the first choice for breast cancer treatment in most cases. In 2000, Perou and his colleagues first reported that BC could be classified into different molecular subtypes by differences in their gene expression patterns [2]. Depending on the expression states of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67, BC can be classified into four molecular subtypes: luminal A subtype, luminal B subtype, HER2-enriched subtype, and basal-like subtype (triple-negative subtype). Each subtype has a different treatment and response. Nowadays, according to different molecular subtypes of BC, different systematic treatment strategies (including conventional chemotherapy, endocrine therapy, and HER2-targeted therapy) are developed for BC patients. With the improvements in early diagnosis and treatment strategies, BC-associated death has been decreasing. However, the prognosis of BC patients is still unsatisfactory, especially locally advanced and advanced BC patients. Drug resistances including endocrine resistance, chemoresistance, and HER2-targeted therapy resistance are the main causes of recurrence and poor prognosis in BC patients. Hence, it is extremely urgent to explore the internal mechanisms of drug resistance in order to develop new strategies to reverse drug resistance and prolong the survival time of BC patients.

Circular RNAs (circRNAs) are the new stars of the noncoding RNA (ncRNA) family featured by covalently closed loops, which render them more stable than liner RNAs and resistant to RNase R. CircRNAs used to be mistaken for products of splicing errors [3]. Nevertheless, with the development of high-throughput RNA sequencing (RNA-seq) and bioinformatic analysis, multiple circRNAs have been discovered and verified to play critical roles in cancer development and progression through modulation of various biological processes [4, 5]. Due to stable structure and crucial biological functions, circRNAs have attracted more and more attention from researchers in recent years. Although the functions of circRNAs need to be further investigated, emerging evidence reveals that circRNAs participate in different biological processes by multiple mechanisms including functioning as sponges for microRNAs or RNA-binding proteins [6, 7], affecting the transcription and splicing of host genes [8, 9], acting as scaffolds in the assembly of protein complexes [10], translating proteins [11], and regulating epigenetic alterations [12]. Among them, the most well-known mechanism for circRNAs is serving as competing endogenous RNA (ceRNAs), thus reducing the inhibition of genes targeted by certain microRNAs. What's more, accumulated evidence has shown that circRNAs play critical roles in drug resistance of human cancers. For example, circCUL2 could regulate cisplatin sensitivity in gastric cancer cell lines through miR-142-3p/ROCK2-mediated autophagy activation. In BC, certain circRNAs were also verified to be associated with drug resistance, such as circ_0025202 and circWAC [13, 14].

In this review, we summarize the detailed mechanisms associated with BC drug resistance and how circRNAs intensify or weaken drug resistance, highlighting that circRNAs may function as potential biomarkers and/or therapeutic targets of BC.

Mechanisms of BC drug resistance

A proportion of BC patients may recurrence and metastasis owing to drug resistance, so it is of great urgency to have a deep understanding of drug resistance mechanisms. With the development of single-cell sequencing of circulating tumor cell (CTC) and next-generation sequencing of matched pre- and post- progression tumor biopsies or circulating tumor DNA (ctDNA) from BC patients with drug resistance, some new mechanisms of resistance are being discovered (Figure 1).

Mechanisms of endocrine resistance. Genetic mutation of endocrine therapy targets may be one of the crucial resistance mechanisms. ESR1, the gene encoding ERα, was found

Figure 1. A summary diagram of mechanisms involved in resistance to systemic treatments in breast cancer.

mutated in metastatic BC (MBC) by Zhang and his colleagues in 1997 [15]. Recent data showed that the ligand-binding domain (LBD) point mutations (most commonly at Y537 and D538) in ESR1 occurred in ~20% of ER+ MBC following long-term endocrine therapy, such as tamoxifen or aromatase inhibitors (AIs) [16]. These point mutations in ESR1 allow hormone-independent ER transcriptional activity, resulting in resistance to endocrine therapy [17]. Magnani et al. [18] found that CYP19A1, the gene encoding aromatase, amplified in 21.5% of AI-resistant breast tumors. Acquired CYP19A1 amplification in ER+ BC patients could increase the aromatase activity and lead to estrogen-independent ERα binding to target genes, thus resulting in resistance to AIs.

Aberrant activation of the downstream signaling pathways such as PI3K/AKT/mTOR (PAM) pathway, CDK4/6/RB pathway, and MAPK pathway can also lead to endocrine resistance in BC. The PTEN/PI3K/AKT/mTOR pathway members are frequently mutated in ER+ HER2– breast tumors, and aberrant activation of the PAM pathway is implicated in acquired resistance to hormonal therapy [19]. Clinical trials' results have shown that the PAM pathway antagonists can improve the prognosis of MBC patients. For example, the BOLERO-2 trial showed that mTORC1 inhibitor everolimus combined with steroidal AI exemestane could prolong the progression-free survival (PFS) of patients with ER+ HER2– MBC previously treated with non-steroidal AI [20]. Based on the data of the SOLAR-1 trial, alpelisib (a specific inhibitor of the PIK3CA product PI3Kα) plus fulvestrant improved PFS of patients with PIK3CA-mutated HR+ HER2– MBC previously treated with AI when compared to fulvestrant alone. Moreover, there was a 7.9-month improvement in median OS for the alpelisib-fulvestrant group, although the analysis did not cross the prespecified boundary for statistical significance [21]. Razavi et al. [22] identified an increased number of genetic alterations involved in components of the MAPK pathway. In particular, loss-of-function NF1 alterations occurred more frequently in endocrine-resistant tumors compared with the other MAPK pathway genes. NF1 loss-of-function mutations are implicated in both acquired and intrinsic endocrine resistance [23]. Cyclin D and cyclin-dependent kinases 4 and 6 (CDK4/6) induce phosphorylation of retinoblastoma (Rb) protein, which is a well-known G1/S-checkpoint regulator. Acquired resistance in ER+ BC is associated with genetic alteration of the cyclin D1-CDK4/6-Rb signaling pathway. Aberrant amplification of both cyclin D1 and CDK4 occurs in the luminal B subtype (58% and 25%, respectively) and HER2-enriched subtype (38% and 24%, respectively) [24]. Nowadays, CDK4/6 inhibitions (palbociclib, ribociclib, and abemaciclib) have been widely used in the treatment of ER+ HER2– MBC patients.

There are several other genetic alternations associated with endocrine resistance. Razavi et al. [22] reported that alterations in ER transcriptional regulators (MYC, CTCF, FOXA1, and TBX3) were enriched in endocrine-resistant MBC and correlated with a poorer response to subsequent endocrine therapies. Some studies suggested that HER2 amplification or HER2-activating mutations could reduce the response to hormonal therapies [25, 26]. Moreover, the crosstalk of ER pathway and HER-2 pathway may result in resistance to ER-directed treatment. Haricharan et al. [27] found that somatic mutations in DNA damage repair genes were involved in endocrine resistance and poor outcomes of ER+ BC patients.

In addition to genetic alternations, epigenetic and other non-genetic mechanisms also contribute to drug resistance to ER-directed therapies. Aberrant activation of histone deacetylase (HDAC) has been found in breast tumors. Loss-of-function of the four ERα corepressors (silencing mediator for retinoid or thyroid hormone receptors (SMRT), COUP-TF II, nuclear corepressor (NCoR), and SPEN) may lead to aberrant recruitment of HDACs to ERα-target genes and decrease endocrine sensitivity in BC [28]. Recently, a randomized, double-blind, placebo-controlled, phase 3 trial showed that a combination of an oral subtype-selective HDAC inhibitor, tucidinostat, with AI could be used for the treatment of postmenopausal patients with HR+ advanced BC [29]. Furthermore, BC stem-like cells (BCSCs), metabolic reprogramming, ncRNAs, and tumor microenvironment (TME) are also implicated in endocrine resistance [30].

Mechanisms of chemoresistance. The phenomenon of multiple drug resistance (MDR) is a critical mechanism of chemotherapy resistance. The emergence of MDR is closely correlated with the expression of a class of ATP binding cassette (ABC) transporters, which can transport anti-neoplastic drugs out of cancer cells via energy from ATP hydrolysis and decrease intracellular drug uptake [31]. Emerging evidence has shown that overexpression of ABC transporters is associated with chemoresistance of BC [32]. Among these ABC transporters, ABCB1, ABCC1, and ABCG2 are extensively studied. ABCB1, also known as P-glycoprotein (P-gp) or multidrug resistance protein 1 (MDR1), is the first identified and the most well-studied ABC transporter owing to its profound impact on the pharmacokinetic profiles of various anticancer drugs. ABCC1, also known as MDR-associated protein 1 (MRP1), has been reported to induce drug resistance by extruding non-ionic lipophilic drugs and amphipathic anions conjugated with sulfate, glucuronic acid, or glutathione and altering intracellular drug redistribution [33]. ABCG2, also known as breast cancer resistance protein (BCRP), is initially cloned from a multidrug-resistant BC cell line where it is found to confer resistance to chemotherapeutic agents such as mitoxantrone and topotecan. ABCG2 can recognize and transport conventional chemotherapeutic drugs and targeted small therapeutic molecules by active efflux of anticancer drugs [34]. Based on the important role of ABC transporters in MDR, the ABC transporter inhibitors have been explored for overcoming cancer MDR. However, the clinical results of ABC transporter inhibitors are far from satisfactory.

Accumulating evidence suggests that multiple signaling pathways are implicated in resistance to chemotherapeutic drugs in BC, such as the PAM pathway, JAK/STAT pathway, and NF-kB pathway. The PAM signaling pathway plays a crucial role in a variety of oncogenic processes in BC. The loss of PTEN and activation of the PAM pathway contribute to poor prognosis and chemoresistance of BC [35]. Currently, PAM inhibitors combined with other drugs are being developed for the treatment of MBC. NF-kB, a pro-inflammatory transcription factor, is widely involved in the initiation and progression of BC. Moreover, data has shown that the NF-kB signaling pathway is a crucial regulator of triple-negative BC (TNBC) and is associated with chemoresistance and metastasis of BC as well as other cancers [36]. BCSCs also play important roles in the chemoresistance in BC [37]. Certain pathways play critical roles in the self-renewal and survival of BCSCs, including the Notch, Wnt/β-catenin, Hedgehog, JAK/STAT, TGF-β, and HIPPO pathways [35, 37]. Therefore, targeting these pathways may be a promising approach to eliminating chemoresistance in BC.

A large number of studies have shown that the DNA damage repair (DDR) mechanism is implicated in the development, metastasis, and chemoresistance of BC. The DDR pathway can repair both endogenous and exogenous sources of DNA damage and maintain the integrity and stability of the genome. By activation of the DDR mechanism, BC cells, especially BCSCs, can resist the anti-cancer efforts of many chemotherapeutic drugs that function by inducing DNA damage, so a deeper understanding of the DDR mechanism may help to reverse the chemoresistance of BC. Inherited or acquired mutations in certain genes are associated with DDR, the best-known of which are the BC susceptibility genes 1/2 (BRCA1/2) [38]. Specific gene mutations can make BC cells sensitive to specific DDR inhibitors, for instance, BRCA1/2 germline mutation-related BC cells are sensitive to poly (ADP-ribose) polymerase (PARP) inhibitors [39].

There is a growing body of evidence showing that the components of TME can crosstalk with tumor cells, thus promoting the chemoresistance of numerous malignancies including BC. TME involves the cellular and non-cellular components, including stromal cells (such as tumor-associated macrophages (TAMs), cancer-associated fibroblasts (CAFs), mesenchymal cells, and endothelial cells), extracellular matrix, immune cells, etc. Genetic and phenotypic alterations of tumor cells result in uncontrolled growth and dysplasia, which create hypoxia, oxidative stress, and acidosis within the TME, leading to an adjustment of the extracellular matrix (ECM) and response from stromal cells and immune cells. The remodeling of TME in turn contributes to the acquisition of resistant phenotype by activation of certain signaling pathways associated with chemoresistance [40]. In recent years, some effort has been made to d evelop the targeting TME components alone or in combination with conventional drugs as new therapeutic strategies [41, 42].

Mechanisms of HER2-targeted therapy resistance. Previously, HER2+ BC tends to be more aggressive than HR+ BC and has a worse prognosis. Fortunately, the rapid development of HER2-targeted therapies has significantly improved the prognosis of HER2+ BC patients. However, there is still a significant number of patients with HER2+ BC suffering from recurrence and metastasis owing to drug resistance to HER2-targeted therapy. Hence, it is of great importance to explore the mechanisms underlying resistance to HER2-targeted therapy. Some mechanisms have been reported to be concerned with resistance to HER2-targeted therapy. Studies have shown that aberrant activation of downstream Raf/MEK/ERK signaling pathway and PAM signaling pathway, induced by a loss of PTEN or PIK3CA mutations, may be correlated with trastuzumab resistance [43–45]. Furthermore, increased HER signaling through compensatory mechanisms within other HER family members (such as HER1 and HER3) and activation of receptor tyrosine kinases (RTKs) or other membrane receptors beyond the HER family (such as vascular endothelial growth factor receptor (VEGFR), insulin-like growth factor 1 receptor (IGF-1R), and mesenchymal epithelial transition factor (MET)) may also contribute to resistance to HER2-targeted therapy [46]. In addition, overexpression of heat shock protein 90 (HSP90) or the p95 isoform of HER2 (p95HER2) can modulate HER2 kinase activity, which confers resistance to trastuzumab [47]. Of note, sensitivity to anti-HER2 therapy is dependent on the host immune system, so failure to elicit an appropriate immune response due to disrupted antibody-receptor interaction may be another mechanism of trastuzumab resistance [48]. What's more, the crosstalk of the ER pathway and the HER-2 pathway may result in resistance not only to endocrine therapy but also to anti-HER2 therapy. Nowadays, some novel anti-HER2 drugs including tyrosine kinase inhibitors (TKIs), pertuzumab, trastuzumab-DM1, and trastuzumab deruxtecan have been used in the treatment of HER2+ MBC patients following treatment with trastuzumab. However, resistance to other anti-HER2 therapies is also an issue to be faced in the therapeutic process.

The dysregulation of circRNAs is related to drug resistance in BC

Though a large number of studies have been done to reveal the mechanisms of drug resistance, a complete understanding of the molecular mechanisms of drug resistance in BC remains a great challenge. It is crucial to overcome drug resistance and improve patient outcomes. Significantly differential circRNA expression profiles have been identified between drug-resistant and drug-sensitive BC cells by high-throughput sequencing, indicating that circRNAs participate in BC drug resistance. The involvement of circRNAs in BC resistance to endocrine drugs, chemotherapy drugs, and anti-HER2 drugs is summarized below (Table 1).

Table 1. CircRNAs associated with resistance to systemic treatments in breast cancer.

circRNA	Expression	Genes and Pathways	Drug resistance	References
circ_UBE2D2	↑	miR-200q-3p/ERα	tamoxifen	[50]
circBMPR2	↓	miR-553/ USP4	tamoxifen	[51]
circ_0025202	↓	miR-182-5p/ FOXO3a; miR-197-3p/HIPK3	tamoxifen	[13, 52]
circGFRA1	↑	miR-361-5p/TLR4	Paclitaxel	[53]
circAMOTL1	↑	AKT pathway	Paclitaxel	[54]
circ-RNF11	↑	miR-140-5p/E2F3	Paclitaxel	[55]
circWAC	↑	miR-142/MMP1/ PTEN/PAM pathway	Paclitaxel	[14]
circ_0006528	↑	miR-1299/CDK8	Paclitaxel	[62]
circ_0000199	↑	miR206/612/ PAM pathway	Docetaxel; Cisplatin; Adriamycin; Gemcitabine	[57]
circABCB1	↑	PI3K-AKT and AGE-RAGE pathways	Docetaxel	[58]
circEPHA3.1/3.2	↓	PI3K-AKT and AGE-RAGE pathways	Docetaxel	[58]
circ_0006528	↑	miR-7-5p/Raf1/ MAPK/ERK pathway; miR-1236-3p/CHD4	Adriamycin	[59-61]
circKDM4C	↓	miR-548p/ PBLD	Adriamycin	[63]
circ_0001667	↑	miR-4458/ NCOA3	Adriamycin	[64]
circ_0085495	↑	miR-873-5p/integrin β1	Adriamycin	[64]
circ-LARP4	↓	–	Adriamycin	[66]
circATXN7	↑	miR-149-5p/HOXA11	Adriamycin	[67]
CDR1as	↑	miR-7/CCNE1	5-FU	[69]
circSMARCA5	↓	SMARCA5	Cisplatin	[71]
circUBAP2	↑	microRNA-300/anti-silencing function 1B/ PAM pathway	Cisplatin	[72]
circ_0001598	↑	miR-1184/PD-L1	Trastuzumab	[73]
circCDYL2	↑	GRB7/ FAK/ AKT and ERK1/2 pathway	Trastuzumab	[74]
circ-BGN	↑	OTUB1/SLC7A11	Trastuzumab	[75]
circ-MMP11	↑	miR-153-3p/ANLN	Lapatinib	[76]

circRNAs regulate endocrine resistance of BC. The potential of circRNAs in the resistance of BC has begun to be recognized. A number of oncogenic as well as tumor suppressive circRNAs have been proven to be implicated in the endocrine resistance of BC by regulation of their target genes. In recent reports, circRNAs play their roles mainly by severing as sponges for miRNAs and forming a ceRNA network. For instance, Gao et al. [49] delineated a circRNA-microRNA-mRNA regulatory network in tamoxifen and fulvestrant resistant BC cells by microarray analysis. Another study showed that circ_UBE2D2 was upregulated in tamoxifen-resistant BC tissues and cell lines, indicating the potential role of circ_UBE2D2 in tamoxifen resistance of BC [50]. Moreover, exosomes-mediated transfer of circ_UBE2D2 could interact with miR-200q-3p to reinforce tamoxifen resistance of BC by regulation of cell viability, metastasis, and ERα level. In addition, several tumor suppressive circRNAs have been identified to be associated with tamoxifen resistance. Liang et al. [51] found that downregulation of circBMPR2 resulted in tamoxifen resistance of BC cells via inhibition of tamoxifen-induced apoptosis, which could be reversed by restoration of its expression. Mechanistically circBMPR2 could serve as a sponge for miR-553 and further lead to the upregulation of ubiquitin-specific protease 4 (USP4), which inhibited tamoxifen resistance by regulation of ER protein expression levels. Another circRNA, circ_0025202, was significantly downregulated in tamoxifen-resistant BC tissues and cells, and the upregulation of circ_0025202 suppressed cell proliferation, invasion, and migration, and increased apoptosis and sensitivity to tamoxifen [52]. Mechanistically, circ_0025202 could act as a sponge for miR-182-5p and then indirectly regulate the expression of FOXO3a. Functional studies showed that silencing of FOXO3a might diminish tamoxifen-induced apoptosis and promote tamoxifen resistance. A recent similar study reported that circ_0025202 could regulate tamoxifen sensitivity via miR-197-3p/HIPK3 axis in BC [13]. Hence, targeting the circRNA-microRNA-mRNA network may be a potent therapeutic approach for the endocrine resistance in BC patients.

circRNAs regulate the chemoresistance of BC. Chemotherapy can effectively reduce the risk of BC recurrence and improve the prognosis of patients, especially for patients with TNBC and HER2+ BC. Nevertheless, acquired resistance to chemotherapy drugs is one of the main causes of tumor recurrence. Recently, several oncogenic and tumor suppressive circRNAs have been proven to play key roles in the chemoresistance of BC.

Taxanes are commonly used as first-line chemotherapy drugs for the treatment of BC patients. Paclitaxel (PTX), also called taxol, is one of the taxane family members and functions by stabilizing microtubules and preventing mitosis (M)-phase entry, thus resulting in cell death. Several

oncogenic circRNAs have been reported to contribute to PTX resistance. For instance, circGFRA1 could enhance PTX resistance of TNBC by the miR-361-5p/TLR4 pathway [53]. Another study showed that the overexpression of circular RNA angiomotin-like 1 (circAMOTL1) induced the PTX resistance of MDA-MB-231 BC cells via posttranscriptional regulation of the AKT pathway [54]. Recently, Zang et al. [55] reported that the expression of circ-RNF11 was increased in PTX-resistant BC tissues and cells, and silencing of circ-RNF11 could enhance the PTX sensitivity of BC cells by the miR-140-5p/E2F3 axis. What's more, circWAC was demonstrated to be upregulated in PTX-resistant TNBC cells and induced PTX resistance by serving as a sponge of miR-142 and indirectly regulating the expression of MMP1, which has been confirmed to activate the PI3K/AKT pathway by regulating PTEN polyubiquitination and play an oncogenic role [14, 56]. Similarly, inhibition of circ_0000199 could increase the chemosensitivity of TNBC cells to PTX as well as other agents (such as cisplatin, adriamycin, and gemcitabine) by interfering with miR206/612 and attenuating the PI3K/AKT/mTOR signaling pathway [57]. Docetaxel is regarded as a second-generation taxoid anticancer agent, which is a semisynthetic derivative of paclitaxel. A recent comprehensive RNA research found that circABCB1 was upregulated in docetaxel-resistant BC cell lines, while circEPHA3.1 and cirEPHA3.2 were downregulated, indicating their potential roles in docetaxel resistance. Mechanistically, the above three circRNAs may contribute to docetaxel resistance by crosstalk with eight abnormally expressed miRNAs and indirectly regulate the PI3K-AKT and AGE-RAGE pathways [58].

Adriamycin (ADM), also called doxorubicin, is another important first-line chemotherapy drug for BC therapy. Multiple circRNAs have been verified to be involved in ADM resistance in BC. By next-generation sequencing and bioinformatics analysis, Gao et al. [59, 60] found that circ_0006528 expression was significantly upregulated in ADM-resistant BC cells and tissues, and the overexpression of circ_0006528 could contribute to ADM resistance via the miR-7-5p/Raf1 axis and indirect activation of the MAPK/ERK signaling pathway. Another study also verified that circ_0006528 could contribute to ADM resistance in BC cells via modulating the miR-1236-3p/CHD4 axis [61]. Interestingly, circ_0006528 was also found to be involved in PTX resistance in BC cells by modulating the miR-1299/CDK8 axis [62]. Another circRNA, circKDM4C, has been shown to act as a ceRNA of miR-548p and, thus, attenuate the ADM resistance of BC cells via blocking miR-548p-dependent suppression of PBLD [63]. In addition, circ-LARP4, circ_0001667, circATXN7, and circ_0085495 have also been found to be associated with ADM resistance of BC and function mainly by a ceRNA network [64–67].

Several other agents are also commonly used for the treatment of BC patients in clinical settings, such as 5-fluorouracil (5-FU) and cisplatin. 5-FU is an antimetabolite drug, which functions by suppressing thymidylate synthase and incorporating its metabolites into RNA and DNA [68]. It has been found that several circRNAs are related to 5-FU chemoresistance in cancers, including BC. For example, circRNA CDR1as expression was increased while the miR-7 expression was decreased in 5-FU-resistant BC cells, and silencing of CDR1as enhanced the chemosensitivity of 5-FU-resistant BC cells via upregulation of miR-7 expression and downregulation of CCNE1 expression [69]. Cisplatin exerts anticancer activity via interfering with DNA repair mechanisms, causing DNA damage, and finally leading to apoptosis [70]. Cisplatin is often used for neoadjuvant and palliative treatment of TNBC in clinical practice. Recently, overexpression of circSMARCA5 has been verified to increase the chemosensitivity of BC cells to cisplatin by interacting with host gene SMARCA5 and inhibiting DNA damage repair [71]. More recently, circUBAP2 has been verified to induce the cisplatin resistance of TNBC via the microRNA-300/antisilencing function 1B histone chaperone axis, which further triggered the PAM signaling [72].

circRNAs regulate HER2-targeted therapy resistance of BC. There are numerous reports focused on analyzing the roles of miRNAs or lncRNAs in resistance to HER2-targeted therapy. However, few reports explore the expression and function of circRNAs in resistance to HER2-targeted therapy of BC. A recent study showed that circ_0001598 was upregulated in trastuzumab-resistant BC tissues, and its overexpression could induce programmed death-ligand-1 (PD-L1) mediated immune escape and trastuzumab resistance by the circ_0001598/miR-1184/PD-L1 axis [73]. More recently, Ling et al. [74] found that circCDYL2 was upregulated in trastuzumab-resistant BC tissues and cells, indicating its potential role in trastuzumab resistance. Mechanistically, circCDYL2 inhibited the ubiquitination degradation of GRB7, thus sustaining its expression and enhancing its interaction with FAK, which subsequently sustained HER2 downstream AKT and ERK1/2 signaling. In addition, Wang et al. [75] found that a new circRNA, circ-BGN, upregulated in trastuzumab-resistant BC tissues and cells, which could contribute to trastuzumab resistance by directly binding to OTUB1 and SLC7A11, enhancing OTUB1-mediated SLC7A11 deubiquitination and thereby inhibiting ferroptosis. Lapatinib is an oral small-molecular TKI inhibitor, which commonly acts as one of the second-line anti-HER2 therapy drugs to treat HER2+ MBC patients. A recent study reported that circ-MMP11 could contribute to lapatinib resistance of BC cells via the miR-153-3p/ANLN axis [76].

Conclusions and future perspectives

In the treatment of BC, systematic therapies including chemotherapy, endocrine therapy, and HER2-targeted therapy are important therapeutic approaches. However, drug resistance is a major barrier to achieving a cure in BC patients. Hence, it is urgent to gain insight into the drug-resistance mechanisms in order to improve the prognosis of BC

patients. Genetic alternations, epigenetic alternations, and other non-genetic mechanisms such as BCSCs, metabolic reprogramming, and TME contribute to drug resistance of BC. With the development of single-cell sequencing of CTC and next-generation sequencing of matched pre- and post-progression tumor biopsies or ctDNA from BC patients with drug resistance, new mechanisms of resistance are being discovered. Recently, an increasing number of miRNAs and lncRNAs have been found to be associated with drug resistance of BC. However, there are few reports on the role of circRNAs as master regulators of drug resistance. Therefore, there is still much to say in the field of drug resistance-related circRNAs. In this review, we summarize the underlying mechanisms of how circRNAs intensify or weaken drug resistance, highlighting that circRNAs may function as potential systemic treatment-resistance biomarkers and/or therapeutic targets in BC. Current reports have shown that circRNAs contribute to drug resistance in BC mainly by acting as sponges of miRNAs, which, thus, regulate several signaling pathways involved in drug resistance. Nevertheless, there may be many other unknown physiological processes by which circRNAs lead to drug resistance. Hence, further studies are needed regarding the precise mechanisms of drug resistance-related circRNAs. Exogenous expression of tumor suppressive circRNAs or knockdown of oncogenic circRNAs have been verified to reverse drug resistance of BC cells, so treatment targeting abnormally expressed circRNAs alone or combined with other systemic treatments may be a promising approach to conquer drug resistance. However, circRNAs are far from being used in clinical applications. More clinical and translational studies are needed before circRNA-based treatment can be recommended in clinical application. We believe that our understanding of their role in drug resistance will broaden in the foreseeable future.

Acknowledgments: This work was supported by grants from the health bureau of Wuxi (Q202023).

References

[1] SUNG H, FERLAY J, SIEGEL RL, LAVERSANNE M, SOERJOMATARAM I et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021; 71: 209–249. https://doi.org/10.3322/caac.21660

[2] PEROU CM, S RLIE T, EISEN MB, VAN DE RIJN M, JEFFREY SS et al. Molecular portraits of human breast tumours. Nature 2000; 406: 747–752. https://doi.org/10.1038/35021093

[3] COCQUERELLE C, MASCREZ B, H TUIN D, BAILLEUL B. Mis-splicing yields circular RNA molecules. FASEB J 1993; 7: 155–160. https://doi.org/10.1096/fasebj.7.1.7678559

[4] KRISTENSEN LS, JAKOBSEN T, HAGER H, KJEMS J. The emerging roles of circRNAs in cancer and oncology. Nat Rev Clin Oncol 2022; 19: 188–206. https://doi.org/10.1038/s41571-021-00585-y

[5] CHEN LL. The biogenesis and emerging roles of circular RNAs. Nat Rev Mol Cell Biol 2016; 17: 205–211. https://doi.org/10.1038/nrm.2015.32

[6] ZENG Z, XIA L, FAN S, ZHENG J, QIN J et al. Circular RNA CircMAP3K5 Acts as a MicroRNA-22-3p Sponge to Promote Resolution of Intimal Hyperplasia Via TET2-Mediated Smooth Muscle Cell Differentiation. Circulation 2021; 143: 354–371. https://doi.org/10.1161/circulationaha.120.049715

[7] CHEN Q, WANG H, LI Z, LI F, LIANG L et al. Circular RNA ACTN4 promotes intrahepatic cholangiocarcinoma progression by recruiting YBX1 to initiate FZD7 transcription. J Hepatol 2022; 76: 135–147. https://doi.org/10.1016/j.jhep.2021.08.027

[8] LI Z, HUANG C, BAO C, CHEN L, LIN M et al. Exon-intron circular RNAs regulate transcription in the nucleus. Nat Struct Mol Biol 2015; 22: 256–264. https://doi.org/10.1038/nsmb.2959

[9] ASHWAL-FLUSS R, MEYER M, PAMUDURTI NR, IVANOV A, BARTOK O et al. circRNA biogenesis competes with pre-mRNA splicing. Mol Cell 2014; 56: 55–66. https://doi.org/10.1016/j.molcel.2014.08.019

[10] DU WW, YANG W, LIU E, YANG Z, DHALIWAL P et al. Foxo3 circular RNA retards cell cycle progression via forming ternary complexes with p21 and CDK2. Nucleic Acids Res 2016; 44: 2846–2858. https://doi.org/10.1093/nar/gkw027

[11] PAMUDURTI NR, BARTOK O, JENS M, ASHWAL-FLUSS R, STOTTMEISTER C et al. Translation of CircRNAs. Mol Cell 2017; 66: 9–21e27. https://doi.org/10.1016/j.molcel.2017.02.021

[12] CHEN N, ZHAO G, YAN X, LV Z, YIN H et al. A novel FLI1 exonic circular RNA promotes metastasis in breast cancer by coordinately regulating TET1 and DNMT1. Genome Biol 2018; 19: 218. https://doi.org/10.1186/s13059-018-1594-y

[13] LI H, LI Q, HE S. Hsa_circ_0025202 suppresses cell tumorigenesis and tamoxifen resistance via miR-197-3p/HIPK3 axis in breast cancer. World J Surg Oncol 2021; 19: 39. https://doi.org/10.1186/s12957-021-02149-x

[14] WANG L, ZHOU Y, JIANG L, LU L, DAI T et al. CircWAC induces chemotherapeutic resistance in triple-negative breast cancer by targeting miR-142, upregulating WWP1 and activating the PI3K/AKT pathway. Mol Cancer 2021; 20: 43. https://doi.org/10.1186/s12943-021-01332-8

[15] ZHANG QX, BORG A, WOLF DM, OESTERREICH S, FUQUA SA. An estrogen receptor mutant with strong hormone-independent activity from a metastatic breast cancer. Cancer Res 1997; 57: 1244–1249

[16] JESELSOHN R, YELENSKY R, BUCHWALTER G, FRAMPTON G, MERIC-BERNSTAM F et al. Emergence of constitutively active estrogen receptor-α mutations in pretreated advanced estrogen receptor-positive breast cancer. Clin Cancer Res 2014; 20: 1757–1767. https://doi.org/10.1158/1078-0432.ccr-13-2332

[17] JESELSOHN R, BUCHWALTER G, DE ANGELIS C, BROWN M, SCHIFF R. ESR1 mutations—a mechanism for acquired endocrine resistance in breast cancer. Nat Rev Clin Oncol 2015; 12: 573–583. https://doi.org/10.1038/nrclinonc.2015.117

[18] MAGNANI L, FRIGE G, GADALETA RM, CORLEONE G, FABRIS S et al. Acquired CYP19A1 amplification is an early specific mechanism of aromatase inhibitor resistance in ERα metastatic breast cancer. Nat Genet 2017; 49: 444–450. https://doi.org/10.1038/ng.3773

[19] ARAKI K, MIYOSHI Y. Mechanism of resistance to endocrine therapy in breast cancer: the important role of PI3K/Akt/mTOR in estrogen receptor-positive, HER2-negative breast cancer. Breast Cancer 2018; 25: 392–401. https://doi.org/10.1007/s12282-017-0812-x

[20] BASELGA J, CAMPONE M, PICCART M, BURRIS HA, 3RD, RUGO HS et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med 2012; 366: 520–529. https://doi.org/10.1056/NEJMoa1109653

[21] ANDR F, CIRUELOS EM, JURIC D, LOIBL S, CAMPONE M et al. Alpelisib plus fulvestrant for PIK3CA-mutated, hormone receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: final overall survival results from SOLAR-1. Ann Oncol 2021; 32: 208–217. https://doi.org/10.1016/j.annonc.2020.11.011

[22] RAZAVI P, CHANG MT, XU G, BANDLAMUDI C, ROSS DS et al. The Genomic Landscape of Endocrine-Resistant Advanced Breast Cancers. Cancer Cell 2018; 34: 427–438 e426. https://doi.org/10.1016/j.ccell.2018.08.008

[23] PEARSON A, PROSZEK P, PASCUAL J, FRIBBENS C, SHAMSHER MK et al. Inactivating NF1 Mutations Are Enriched in Advanced Breast Cancer and Contribute to Endocrine Therapy Resistance. Clin Cancer Res 2020; 26: 608–622. https://doi.org/10.1158/1078-0432.ccr-18-4044

[24] Comprehensive molecular portraits of human breast tumours. Nature 2012; 490: 61–70. https://doi.org/10.1038/nature11412

[25] ALQAISI A, CHEN L, ROMOND E, CHAMBERS M, STEVENS M et al. Impact of estrogen receptor (ER) and human epidermal growth factor receptor-2 (HER2) co-expression on breast cancer disease characteristics: implications for tumor biology and research. Breast Cancer Res Treat 2014; 148: 437–444. https://doi.org/10.1007/s10549-014-3145-x

[26] NAYAR U, COHEN O, KAPSTAD C, CUOCO MS, WAKS AG et al. Acquired HER2 mutations in ER(+) metastatic breast cancer confer resistance to estrogen receptor-directed therapies. Nat Genet 2019; 51: 207–216. https://doi.org/10.1038/s41588-018-0287-5

[27] HARICHARAN S, BAINBRIDGE MN, SCHEET P, BROWN PH. Somatic mutation load of estrogen receptor-positive breast tumors predicts overall survival: an analysis of genome sequence data. Breast Cancer Res Treat 2014; 146: 211–220. https://doi.org/10.1007/s10549-014-2991-x

[28] LEGARE S, BASIK M. Minireview: The Link Between ERα Corepressors and Histone Deacetylases in Tamoxifen Resistance in Breast Cancer. Mol Endocrinol 2016; 30: 965–976. https://doi.org/10.1210/me.2016-1072

[29] JIANG Z, LI W, HU X, ZHANG Q, SUN T et al. Tucidinostat plus exemestane for postmenopausal patients with advanced, hormone receptor-positive breast cancer (ACE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2019; 20: 806–815. https://doi.org/10.1016/s1470-2045(19)30164-0

[30] HANKER AB, SUDHAN DR, ARTEAGA CL. Overcoming Endocrine Resistance in Breast Cancer. Cancer Cell 2020; 37: 496–513. https://doi.org/10.1016/j.ccell.2020.03.009

[31] FRUCI D, CHO WC, NOBILI V, LOCATELLI F, ALISI A. Drug Transporters and Multiple Drug Resistance in Pediatric Solid Tumors. Curr Drug Metab 2016; 17: 308–316. https://doi.org/10.2174/1567205010666131212110948

[32] HE J, FORTUNATI E, LIU DX, LI Y. Pleiotropic Roles of ABC Transporters in Breast Cancer. Int J Mol Sci 2021; 22: 3199. https://doi.org/10.3390/ijms22063199

[33] MOHAMMAD IS, HE W, YIN L. Understanding of human ATP binding cassette superfamily and novel multidrug resistance modulators to overcome MDR. Biomed Pharmacother 2018; 100: 335–348. https://doi.org/10.1016/j.biopha.2018.02.038

[34] NAKANISHI T, ROSS DD. Breast cancer resistance protein (BCRP/ABCG2): its role in multidrug resistance and regulation of its gene expression. Chin J Cancer 2012; 31: 73–99. https://doi.org/10.5732/cjc.011.10320

[35] NEDELJKOVIĆ M, DAMJANOVIĆ A. Mechanisms of Chemotherapy Resistance in Triple-Negative Breast Cancer-How We Can Rise to the Challenge. Cells 2019; 8: 957. https://doi.org/10.3390/cells8090957

[36] FAN Y, DUTTA J, GUPTA N, FAN G, G LINAS C. Regulation of programmed cell death by NF-kappaB and its role in tumorigenesis and therapy. Adv Exp Med Biol 2008; 615: 223–250. https://doi.org/10.1007/978-1-4020-6554-5_11

[37] QAYOOM H, WANI NA, ALSHEHRI B, MIR MA. An insight into the cancer stem cell survival pathways involved in chemoresistance in triple-negative breast cancer. Future Oncol 2021; 17: 4185–4206. https://doi.org/10.2217/fon-2021-0172

[38] ALI R, RAKHA EA, MADHUSUDAN S, BRYANT HE. DNA damage repair in breast cancer and its therapeutic implications. Pathology 2017; 49: 156–165. https://doi.org/10.1016/j.pathol.2016.11.002

[39] FARAONI I, GRAZIANI G. Role of BRCA Mutations in Cancer Treatment with Poly(ADP-ribose) Polymerase (PARP) Inhibitors. Cancers (Basel) 2018; 10: 487. https://doi.org/10.3390/cancers10120487

[40] MEHRAJ U, DAR AH, WANI NA, MIR MA. Tumor microenvironment promotes breast cancer chemoresistance. Cancer Chemother Pharmacol 2021; 87: 147–158. https://doi.org/10.1007/s00280-020-04222-w

[41] CASSETTA L, POLLARD JW. Targeting macrophages: therapeutic approaches in cancer. Nat Rev Drug Discov 2018; 17: 887–904. https://doi.org/10.1038/nrd.2018.169

[42] ROMA-RODRIGUES C, MENDES R, BAPTISTA PV, FERNANDES AR. Targeting Tumor Microenvironment for Cancer Therapy. Int J Mol Sci 2019; 20. https://doi.org/10.3390/ijms20040840

[43] SAINI KS, LOI S, DE AZAMBUJA E, METZGER-FILHO O, SAINI ML et al. Targeting the PI3K/AKT/mTOR and Raf/MEK/ERK pathways in the treatment of breast cancer. Cancer Treat Rev 2013; 39: 935–946. https://doi.org/10.1016/j.ctrv.2013.03.009

[44] DAVE B, MIGLIACCIO I, GUTIERREZ MC, WU MF, CHAMNESS GC et al. Loss of phosphatase and tensin homolog or phosphoinositol-3 kinase activation and response to trastuzumab or lapatinib in human epidermal growth factor receptor 2-overexpressing locally advanced breast cancers. J Clin Oncol 2011; 29: 166–173. https://doi.org/10.1200/jco.2009.27.7814

[45] RIMAWI MF, DE ANGELIS C, CONTRERAS A, PAREJA F, GEYER FC et al. Low PTEN levels and PIK3CA mutations predict resistance to neoadjuvant lapatinib and trastuzumab without chemotherapy in patients with HER2 over-expressing breast cancer. Breast Cancer Res Treat 2018; 167: 731–740. https://doi.org/10.1007/s10549-017-4533-9

[46] PERNAS S, TOLANEY SM. HER2-positive breast cancer: new therapeutic frontiers and overcoming resistance. Ther Adv Med Oncol 2019; 11: 1758835919833519. https://doi.org/10.1177/1758835919833519

[47] PARK JM, KIM YJ, PARK S, PARK M, FARRAND L et al. A novel HSP90 inhibitor targeting the C-terminal domain attenuates trastuzumab resistance in HER2-positive breast cancer. Mol Cancer 2020; 19: 161. https://doi.org/10.1186/s12943-020-01283-6

[48] MOHD SHARIAL MSN, CROWN J, HENNESSY BT. Overcoming resistance and restoring sensitivity to HER2-targeted therapies in breast cancer. Ann Oncol 2012; 23: 3007–3016. https://doi.org/10.1093/annonc/mds200

[49] GAO L, SHEN K, YIN N, JIANG M. Comprehensive Transcriptomic Analysis Reveals Dysregulated Competing Endogenous RNA Network in Endocrine Resistant Breast Cancer Cells. Front Oncol 2020; 10: 600487. https://doi.org/10.3389/fonc.2020.600487

[50] HU K, LIU X, LI Y, LI Q, XU Y 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 2020; 26: e922253. https://doi.org/10.12659/msm.922253

[51] LIANG Y, SONG X, LI Y, MA T, SU P et al. Targeting the circBMPR2/miR-553/USP4 Axis as a Potent Therapeutic Approach for Breast Cancer. Mol Ther Nucleic Acids 2019; 17: 347–361. https://doi.org/10.1016/j.omtn.2019.05.005

[52] SANG Y, CHEN B, SONG X, LI Y, LIANG Y et al. circRNA_0025202 Regulates Tamoxifen Sensitivity and Tumor Progression via Regulating the miR-182-5p/FOXO3a Axis in Breast Cancer. Mol Ther 2019; 27: 1638–1652. https://doi.org/10.1016/j.ymthe.2019.05.011

[53] ZHENG SR, HUANG QD, ZHENG ZH, ZHANG ZT, GUO GL. circGFRA1 affects the sensitivity of triple-negative breast cancer cells to paclitaxel via the miR-361-5p/TLR4 pathway. J Biochem 2021; 169: 601–611. https://doi.org/10.1093/jb/mvaa148

[54] MA J, FANG L, YANG Q, HIBBERD S, DU WW et al. Post-transcriptional regulation of AKT by circular RNA angiomotin- like 1 mediates chemoresistance against paclitaxel in breast cancer cells. Aging (Albany NY) 2019; 11: 11369–11381. https://doi.org/10.18632/aging.102535

[55] ZANG H, LI Y, ZHANG X, HUANG G. Circ-RNF111 contributes to paclitaxel resistance in breast cancer by elevating E2F3 expression via miR-140-5p. Thorac Cancer 2020; 11: 1891–1903. https://doi.org/10.1111/1759-7714.13475

[56] LEE YR, CHEN M, LEE JD, ZHANG J, LIN SY et al. Reactivation of PTEN tumor suppressor for cancer treatment through inhibition of a MYC-WWP1 inhibitory pathway. Science 2019; 364: eaau0159. https://doi.org/10.1126/science.aau0159

[57] LI H, XU W, XIA Z, LIU W, PAN G et al. 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) 2021; 13: 4522–4551. https://doi.org/10.18632/aging.202415

[58] HUANG P, LI F, MO Z, GENG C, WEN F et al. A Comprehensive RNA Study to Identify circRNA and miRNA Biomarkers for Docetaxel Resistance in Breast Cancer. Front Oncol 2021; 11: 669270. https://doi.org/10.3389/fonc.2021.669270

[59] GAO D, QI X, ZHANG X, FANG K, GUO Z et al. hsa_circRNA_0006528 as a competing endogenous RNA promotes human breast cancer progression by sponging miR-7-5p and activating the MAPK/ERK signaling pathway. Mol Carcinog 2019; 58: 554–564. https://doi.org/10.1002/mc.22950

[60] GAO D, ZHANG X, LIU B, MENG D, FANG K et al. Screening circular RNA related to chemotherapeutic resistance in breast cancer. Epigenomics 2017; 9: 1175–1188. https://doi.org/10.2217/epi-2017-0055

[61] HAO J, DU X, LV F, SHI Q. 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 2021; 260: 104–115. https://doi.org/10.1016/j.jss.2020.10.031

[62] LIU G, ZHANG Z, SONG Q, GUO Y, BAO P et al. Circ_0006528 Contributes to Paclitaxel Resistance of Breast Cancer Cells by Regulating miR-1299/CDK8 Axis. Onco Targets Ther 2020; 13: 9497–9511. https://doi.org/10.2147/ott.s252886

[63] LIANG Y, SONG X, LI Y, SU P, HAN D et al. circKDM4C suppresses tumor progression and attenuates doxorubicin resistance by regulating miR-548p/PBLD axis in breast cancer. Oncogene 2019; 38: 6850–6866. https://doi.org/10.1038/s41388-019-0926-z

[64] CUI Y, FAN J, SHI W, ZHOU Z. Circ_0001667 knockdown blocks cancer progression and attenuates adriamycin resistance by depleting NCOA3 via releasing miR-4458 in breast cancer. Drug Dev Res 2022; 83: 75–87. https://doi.org/10.1002/ddr.21845

[65] XIE H, ZHENG R. Circ_0085495 knockdown reduces adriamycin resistance in breast cancer through miR-873-5p/integrin β1 axis. Anticancer Drugs 2022; 33: e166–e177. https://doi.org/10.1097/cad.0000000000001174

[66] ZHANG X, SU X, GUO Z, JIANG X, LI X. 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 2020; 34: e23272. https://doi.org/10.1002/jcla.23272

[67] WANG H, SHAN S, WANG H, WANG X. CircATXN7 contributes to the progression and doxorubicin resistance of breast cancer via modulating miR-149-5p/HOXA11 pathway. Anticancer Drugs 2022; 33: e700–e710. https://doi.org/10.1097/cad.0000000000001243

[68] LONGLEY DB, HARKIN DP, JOHNSTON PG. 5-fluorouracil: mechanisms of action and clinical strategies. Nat Rev Cancer 2003; 3: 330–338. https://doi.org/10.1038/nrc1074

[69] YANG W, GU J, WANG X, WANG Y, FENG M et al. Inhibition of circular RNA CDR1as increases chemosensitivity of 5-FU-resistant BC cells through up-regulating miR-7. J Cell Mol Med 2019; 23: 3166–3177. https://doi.org/10.1111/jcmm.14171

[70] GHOSH S. Cisplatin: The first metal based anticancer drug. Bioorg Chem 2019; 88: 102925. https://doi.org/10.1016/j.bioorg.2019.102925

[71] XU X, ZHANG J, TIAN Y, GAO Y, DONG X et al. CircRNA inhibits DNA damage repair by interacting with host gene. Mol Cancer 2020; 19: 128. https://doi.org/10.1186/s12943-020-01246-x

[72] WANG L, YANG X, ZHOU F, SUN X, LI S. Circular RNA UBAP2 facilitates the cisplatin resistance of triple-negative breast cancer via microRNA-300/anti-silencing function 1B histone chaperone/PI3K/AKT/mTOR axis. Bioengineered 2022; 13: 7197–7208. https://doi.org/10.1080/21655979.2022.2036894

[73] HUANG L, MA J, CUI M. Circular RNA hsa_circ_0001598 promotes programmed death-ligand-1-mediated immune escape and trastuzumab resistance via sponging miR-1184 in breast cancer cells. Immunol Res 2021; 69: 558–567. https://doi.org/10.1007/s12026-021-09237-w

[74] LING Y, LIANG G, LIN Q, FANG X, LUO Q et al. circCDYL2 promotes trastuzumab resistance via sustaining HER2 downstream signaling in breast cancer. Mol Cancer 2022; 21: 8. https://doi.org/10.1186/s12943-021-01476-7

[75] WANG S, WANG Y, LI Q, LI X, FENG X. A novel circular RNA confers trastuzumab resistance in human epidermal growth factor receptor 2-positive breast cancer through regulating ferroptosis. Environ Toxicol 2022; 37: 1597–1607. https://doi.org/10.1002/tox.23509

[76] WU X, REN Y, YAO R, ZHOU L, FAN R. Circular RNA circ-MMP11 Contributes to Lapatinib Resistance of Breast Cancer Cells by Regulating the miR-153-3p/ANLN Axis. Front Oncol 2021; 11: 639961. https://doi.org/10.3389/fonc.2021.639961