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The Role of miRNAs in the Resistance of Anthracyclines in Breast Cancer: A Systematic Review

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Breast cancer has been reported as the most common cancer in women globally, with 2.26 million new cases in 2020. While anthracyclines are the first-line drug for breast cancer, they cause a variety of adverse reactions and drug resistance, especially for triple-negative breast cancer, which can lead to poor prognosis, high relapse, and mortality rate. MicroRNAs (miRNAs) have been shown to be important in the initiation, development and metastasis of malignancies and their abnormal transcription levels may influence the efficacy of anthracyclines by participating in the pathologic mechanisms of breast cancer. Therefore, it is essential to understand the exact role of miRNAs in the treatment of breast cancer with anthracyclines. In this review, we outline the mechanisms and signaling pathways involved in miRNAs in the treatment of breast cancer using anthracyclines. The role of miRNA in the diagnosis, prognosis and treatment of breast cancer patients is discussed, along with the involvement of miRNAs in chemotherapy for breast cancer.

Keywords: breast cancer, miRNAs, anthracyclines, drug resistance, efficacy

INTRODUCTION

Different kinds of treatments are applied to different immunohistological types of breast cancer. Triple-negative breast cancer (TNBC), which is not sensitive to endocrine and targeted therapies, is treated with a combination of anthracyclines in the clinical. As the first-line drug class for TNBC, anthracyclines can influence the development of tumors by inhibiting the synthesis of biological DeoxyriboNucleic Acid(DNA). Studies have shown that anthracyclines can affect the activity of DNA topoisomerase to stabilize the DNA double-strand and prevent DNA replication (1, 2). Since daunorubicin, the first anthracycline drug, was discovered, many other anthracycline drugs have been developed one after another, including adriamycin, epirubicin, clarithromycin, and so on. They have been widely used in the treatment of hematological malignancies and solid tumors. However, the frequent use of anthracyclines can cause drug resistance to develop gradually. As a result, cancer will continue to develop, proliferate, invade and metastasize, and eventually lead to patient death. Meanwhile, many adverse reactions caused by anthracyclines, in particular,

cardiotoxicity, also affect the prognosis of patients. Clinical studies have shown that this adverse reaction is often irreversible and fatal to patients. Even the first use of anthracyclines may cause heart damage (3). In addition, it can also induce liver damage (4) and promote breast cancer metastasis to the lungs (5). Therefore, many researchers are now working on the mechanisms of breast cancer cell resistance to anthracyclines and the mechanisms of anthracycline adverse reactions.

As a non-coding Ribonucleic Acid(RNA), miRNA is composed of approximately 20 nucleotides, and participates in the regulation of RNA transcription by activating or blocking the translation of mRNA targets. More and more studies have found that miRNA plays a significant role in biological processes, such as embryonic development, cell proliferation, differentiation, migration, apoptosis, and signal transduction (6). Therefore, the abnormal expression of miRNA is closely related to the development of tumor cells (7). In recent years, many studies have shown that miRNA is involved in the regulation of the efficacy of anthracyclines in the treatment of breast cancer, and may be used as a specific biomarker for diagnosis, control and prediction of adverse reactions. Through reviewing past research, this article summarizes the effects of various miRNAs in breast cancer treated by anthracyclines, and provides certain guidance for future research. At the same time, we prove the clinical application potential of various miRNAs in risk prediction, diagnosis and treatment.

MIRNAS AND ANTHRACYCLINES RESISTANCE

An important problem to overcome in the application of anthracyclines is drug resistance. The emergence of drug resistance makes tumor cells more aggressive and metastatic and leads to failure in clinical treatments, eventually leading to patient death (8). Therefore, in hopes of overcoming the resistance of anthracyclines through miRNA regulation, scientists have been studying the mechanism of drug resistance. To modify sensitization, transformation, and metastasis, miRNAs regulate their downstream signaling pathways or associated proteins by modulating their target genes. Increased drug efflux *via* altering cell membrane transporters is one of the mechanisms of drug resistance generated by anthracyclines, according to Li, X.J. et al.The key factor is the ATP-bindingcassette transporter (ABC) family and its derivatives, P-glycoprotein (P-gp), Multidrug Resistance-associated Protein (MRP) and topoisomerase II. The other potential mechanism of drug resistance is the inhibition of tumor cell apoptosis. Anthracycline reduces tumor cell apoptosis and increases cell survival and causes cell cycle arrest, then activates the epithelial-mesenchymal transition (EMT) by activating or inhibiting cell signaling transduction pathways (9). In addition, the drug resistance of tumors depends on some tumor proteins, which can affect the metabolic function of tumor cells and control their microenvironment.

Wang, Y.D. et al. reported that the target genes of miRNAs can be divided into four types: oncogenes, tumor suppressor genes, signaling pathway genes, and cell cycle regulatory genes (10). The upstream or downstream of these pathways are also interspersed with various apoptotic proteins, oncogenes, and tumor suppressor genes to affect cell apoptosis, changes in EMT processes, and cell cycle arrest. Accumulating studies have found that one miRNA may be able to regulate multiple genes, and these genes can cooperate to influence each other, and even produce feedback loops.

MIRNAS AND MEMBRANE TRANSPORT

The factors that cause changes in cell membrane transport mainly include the ABC family, P-gp protein, MRP protein, topoisomerase, etc. MiRNAs participate in their regulation cells to anthracycline drugs. Xie, M.X. et al. demonstrated that the expression of miR-132 and miR-212 inhibits the expression of nuclear factor kappa-β (NF-κβ), which leads to an increase in the expression of breast cancer resistance protein (BCRP), a member of ABC family, and reduces the sensitivity of tumor cells to anthracyclines (11). Some studies have reported that miR-128 exerts its function of reducing drug resistance of tumor cells by inhibiting the B-cell- specific Moloney murine leukemia virusintegration site-1 (Bmi-1) and ABCC5 (9, 12, 13). The relationship between miR-760 and ABCA1 has also been studied. The high expression of miR-760 can mediate the decline of tumor cell resistance to drugs by reducing the expression of ABCA1 (13). There was a negative correlation between miR-134 and ABCC1, the high expression of miR-134 resulting in reduced tumor cell proliferation and increased apoptosis, which reflects its potential to reduce drug resistance (14). miR-145, miR-451, miR-326, and miR-199a are also implicated in MRP1 (ABCC1) (15–18). Di, H. et al. reported that miR-124-3p enhanced the sensitivity of tumor cells to drugs by reducing the expression of ABCC4 (19).

P-gp is a molecular pump located on the cell membrane to protect cells from harmful exogenous molecules (20). However, this protective mechanism on tumor cells can hinder the entry of anticancer drugs, thereby inducing drug resistance. P-gp genes can be downstream targets of many oncogenes and tumor suppressor genes. MiRNAs affect the number of transcription and synthesis of P-gp through modulating related signaling pathways. Research showed that miR-302s can cause cancer cells susceptible to anthracyclines by down-regulating the expression of P-gp through the MAP/ERK kinase 1 (MAKK1) pathway (21). The overexpression of miR-195 can inhibit the expression of P-gp through the Raf-1 signaling pathway, making more breast cancer cells susceptible to apoptosis and increasing their sensitivity to anthracyclines (22).

MiRNAs and Cell Apoptosis

Most of the miRNAs achieve their aims by regulating signaling pathways. The most important and widely studied pathways are the Phosphatase and tensin homolog deleted on chromosome

ten- phosphatidylinositol 3 kinase- AKT (PTEN-PI3K-AKT) signaling pathway, Notch signaling pathway, Ras signaling p–athway, etc (23). The antiapoptotic protein, B cell leukemia oncogene (Bcl) protein family is the most important link in cell apoptosis, including Bcl-2, Bcl-Xl, Mcl-1, Bcl-w, and so on (24). Many studies have shown that various signaling pathways related to apoptosis have a common junction, which is regulated by the Bcl family. Therefore, Bcl family proteins can inhibit cell death caused by a variety of cytotoxic factors. This phenomenon is even more prominent in tumor cells. Many researchers are trying to link miRNAs with the expression of Bcl family proteins to find a therapeutic strategy to reduce the resistance of tumor cells to anthracyclines. miR-181a is a well recognized miRNA at present. Ying, Z. et al. found that Bcl-2 was decreased by increasing the expression of miR-181a and induced the apoptosis of mitochondria, thereby increasing the apoptosis induced by doxorubicin drugs (25). There is evidence that the overexpression of miR-192-5p will also reduce the expression of Bcl-2, which makes the Bcl-2-Asociated Agonist of Cell Death (BAD) gene competitively increases. As a result, the expression of Peptidylprolyl Isomerase A (PPIA) is inhibited and the resistance of tumor cells to anthracyclines reduced (26). Furthermore, miR-122-5p, miR-195, miR-125b, miR-193b, miR-34a, and miR-200c are negatively related to the regulation of Bcl-2 or Myeloid cell leukemia sequence (Mcl) family and other Bcl family proteins (24, 27–31). Other studies showed that some miRNAs, such as miR-222, miR-19a, and miR-21, are positively correlated with the expression of the Bcl family (32, 33).

The Bcl activating gene proteins are tumor suppressors. Their mutations can affect the process of cell proliferation, transcription and apoptosis. The relationship between the mutation of P53 and miRNA is attractive to researchers. miR-214 has been shown to down-regulate RFWD2-p53 cascade, causing tumor cells sensitive to anthracyclines (34). Yuan, Y. et al. identified that miR-133a improves sensitization of tumor cells by suppressing the expression of the uncoupling protein-2 (UCP-2) (35). This mechanism is considered to be related to P53 mutation (36). Furthermore, it is interesting to note that miR-191-5p declines the expression of P53, which binds to the promoter of miR-191-5p, forming a negative feedback regulation chain by downregulating the expression of SOX4 (37). Not only can miRNAs change drug resistance by regulating the mutation of P53, recent studies demonstrated that some miRNAs can also be regulated by P53. Lin, S. et al. found that the expression level of miR-30c is controlled by P53 mutation, which could contribute to tumor cell sensitivity to doxorubicin by regulating the Fanconi anemia complementation group F protein (FANCY) and REV1 protein (38). In addition, miR-127, miR-34a, and miR-542-3p are all mentioned to be related to P53 network in other studies (16, 39).

PI3K-AKT is also a classic signaling pathway that can induce the apoptosis of cells. The abnormal expression of PTEN protein is enough to antagonize PI3K-AKT *via* dephosphorylating the Phosphatidylinositol (3–5) Trisphosphate (PIP3) on the cell membrane to produce phosphati-dylinositol-4,5-bisphosphate (PIP2), which plays a role in the growth, apoptosis, adhesion (40), infiltration and migration of cancer cells (41). Once the PI3K-AKT signaling pathway is inhibited or damaged, it will promote the activation of tumor cell apoptosis and reduce the occurrence of drug resistance. It was reported that the expression of miR-222 (42, 43) and miR-29a (44) were decreased after treatment with anthracyclines. As a result, it led to anthracycline resistance because of the decreased of PTEN. In addition, miR-221 has been shown to make the PI3K-AKT pathway more active by targeting the PTEN protein, which strengthens the tolerance of tumor cells to anthracyclines. Many miRNAs, such as miR-21 (45, 46), miR-19a (47), miR-132 (11), and miR-212 (11), are negatively correlated with PTEN expression to promote anthracycline resistance in breast cancer. In contrast, miR-200c raised the expression of PTEN, contributing to reverse drug resistance (48). Not only can the PTEN protein affect the PI3K-AKT pathway, but this pathway also accepts other regulations. For example, insulin-like growth factor-1 receptor (IGF-1R) is a tyrosine kinase receptor that can activate the expression of PI3K-AKT and prevent cell apoptosis. Zhang, H. et al. found that the downregulation of miR-520b expression can increase the expression of PI3K-AKT by activating IGF-1R so that tumor cells can acquire drug resistance (49). Similarly, the downregulation of miR-452 can also induce drug resistance through the IGF-1 signaling pathway (50). Other studies have shown that miR-7 can restrain the expression of epidermal growth factor receptor (EGFR), thereby regulating the PI3K-AKT pathway to enhance the sensitivity of cells to anthracycline drugs (51). miR-200c can enhance tumor cell resistance to anthracyclines by decreasing the expression of Friend of GATA2 (FOG2) protein (52). In addition to the above pathways, vascular endothelial growth factor A (VEGFA) and fibroblast growth factor 2 (FGF2) also target the PI3K-AKT pathway. miR-205 has also been shown to inhibit the synthesis of VEGFA and FGF2, causing damage to the pathway and tumor cell apoptosis (53).

The Notch gene, as a highly conserved gene, regulates cell proliferation, differentiation, and apoptosis (54, 55). It also plays an important role in the interaction of adjacent cells, which makes the Notch pathway a possible target for tumor treatment. Among published studies, miR-34a is closely related to the Notch pathway (56). The expression of homolog 1 declined after downregulating miR-34a. Cell drug resistance is reduced because of the inhibition of the Notch pathway, after upregulating miR-34a (57). Moreover, it has been reported that miR-34a can suppress tumor cell migration effectively through the Notch pathway (28).

Beyond the above pathways, the mitogen-activated protein kinase/the extracellular signal-related kinases (MAPK/ERK) pathway is also a potential direction that countributes to regulate the resistance to anthracyclines (58). The MAPK family are highly conserved serine/threonine protein kinases, a group of major signaling molecules in the process of signal transduction. Thus, it plays an important role in cancer development and disease occurrence (59). It has been reported that miR-302s inhibited the transcription of P-gp glycoprotein and resensitized the resistance of breast cancer cells to

Adriamycin (ADR) to death by reducing the expression of mitogen-activated protein kinase/ERK kinase 1 (MEKK1) (21). Furthermore, P38 is an another important member of the MAPK family. miR-381 executes its function by inhibiting the expression of Fyn, a Src-family kinase (60) and cutting down the synthesis of P38 (61). This means that it may become a potential target for overcoming the resistance of anthracyclines in the future. Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein zeta (YWHAZ), an antiapoptotic gene located downstream of miR-30c, can inhibit the expression of the P38 pathway (62). Other pathways have also been mentioned. For example, miR-140-5p was found to suppress the Wnt1 pathway, resulting in decline of anthracyclines resistance (63). Another miRNA, miR-148a, plays a role in tumor migration and erosion by inhibiting the expression of the Wnt-1 pathway (64). Lastly, miR-129-5p induced apoptosis of cancer cells by disrupting SOX2 expression (65).

MiRNAs and the Cell Cycle

In addition to the function of apoptosis and the EMT process in the formation of drug resistance, abnormal cell cycle is also an important factor to consider. As we all know, cancer cells can produce infinite proliferation, so uncontrollable proliferation is a manifestation of cancer drug resistance. The cell cycle includes the division phase and the interphase. When the cell cycle is in the G0 phase, the cells stop dividing. Therefore, restraining the cancer cell cycle in the G0 phase is a potential way to overcome cancer drug resistance. Cyclin-dependent kinase (CDK), a regulator of the cell cycle, are divided into two categories based on their positive and negative effects (66). The positive regulation is *via* cyclin and the negative regulation is *via* cyclin-dependent protein kinase inhibitor (CKI) (67). The reduced expression of p27kip, a CKI regulated by miR-222, causing proliferation of tumor cells and reducing apoptosis. Based on the view of Wang, D.D. et al., the IC50 of tumor cells was increased after upregulating miR-222, which indicated that the increased resistance to anthracyclines (68). Additionly, miR-24 inhibited expression of p27kip (69, 70). It changed the chemosensitivity by regulating autophagy and tumor vascular survival. miR-574 has also been found to inhibit the expression of Smad4. It accelerates the G1-S phase of the cell cycle through regulating the Transforming Growth Factor-β (TGF-β), inducing cell growth and reducing the sensitivity of cells to anthracyclines (71). Other studies have discovered a negative feedback regulation of CDKs. miR-449 could inhibit cell cycle gene expression against drug resistance by reducing the synthesis of CDK2, E2F transcription factor 1 (E2F1), E2F transcription factor 3 (E2F3). Surprisingly, E2F1 regulates the expression of miR-449, forming a negative feedback loop (72). Furthermore, the aforementioned miR-122-5p can reduce the expression of drug resistance by targeting CDKs (27). A mircoRNA targeting cyclin was rarely discovered. The downregulation of miR-135b-5p was confirmed to promote the synthesis of Anterior Gradient 2 (AGR2), an enzyme that functions as a folding protein on the endoplasmic reticulum of tumor cells. It can mediate the expression of cyclin D1 and make cells sensitive to anthracyclines (73).

MiRNAs and Epithelial-Mesenchymal Transition

EMT ensures the cells with the ability of transformation and invasion, therefore against cell senescence and apoptosis (74). EMT regulates the process of cell development, as well as participates in the process of tissue healing, cancer occurrence, and metastasis. So EMT is critical to the development of drug resistance in the treatment of breast cancer with anthracyclines (75). miR-93 was found to strengthen cell proliferation and reduce the sensitivity of tumor cells to the drug by inhibiting the PTEN pathway and promoting the occurrence of EMT (76). Du, F.Y. and his colleagues showed that the overexpression of miR-137 would be detrimental to the synthesis of dual-specifificity phosphatase 4 (DUSP4), which blocked the EMT process. Therefore, it implied that miR-137 has a great potential for sensitivity enhancement against anthracyclines resistance (77). In addition, studies have validated that miR-124 targets the expression of t signal transducer and activator of transcription 3 (STAT3), suppressing the activity of the hypoxia-inducible factor-1(HIF-1) pathway, resulting in the reversal of drug resistance (78). An intriguing discovery is the miR-448 positive feedback. It has been reported that the downregulation of miR-448 can promote the high expression of special AT-rich sequence-binding protein-1 (SATB1) sequence binding protein, sequentially activating the EMT process and the nuclear factor NF-κβ (79). Moreover, NF-κβ, when bonded to miR-448, inhibits the transcription of miR-448. This positive feedback phenomenon enhances the drug resistance of tumor cells. Vimentin and cadherin are important protein targets in the EMT process and are closely related to miRNAs. Zhou, Y. et al. found that miR-25 played a major role in the miR106b-25 cluster, which can reduce the expression of EP300, a transcriptional activator of E-cadherin. This change obstructed the occurrence of EMT and restored the chemosensitivity of tumor cells (80). Similarly, miR-181c renders tumor cells to regain sensitivity to anthracyclines by suppressing vimentin and N-cadherin (81). miR-489 performed its function of improving drug resistance of tumor cells by losing vimentin, but increasing the synthesis of E-cadherin, through reducing the synthesis of Smad3 (82, 83). Because there are many potential targets for a miRNA, a miRNA can also be regulated in many ways. As previously mentioned, it affects drug resistance through the PTEN-PI3K-AKT pathway and also can inhibit the EMT process by reducing the synthesis of E-calcein (48).

MiRNAs and Other Mechanisms of Resistance

In addition to the above-mentioned key factors, exosomes have been discovered as having an emerging role. Exosomes encapsulates specific signaling molecules or biologically active molecules and can transmit from one cell to another, ventually, changing the biological activity of recipient cells (84). Tumor cells with anthracyclines resistance can deliver miRNA to sensitive tumor cells through exosomes so that sensitive cells can be transformed into resistant cells. Therefore, the emergence of drug resistance is also closely related to exosomes (85). From the prespective of Chen, W.X. et al., miR-222 and miR-100 are

potential biomarkers that can be used to predic 4t drug resistance and prognosis. Moreover, upregulated miR-222 and miR-29 can be secreted from drug-resistant cells through exosomes and enter sensitive cells to infect them to endure anthracyclines (86). Among them, miR-222 was further studied to show that it can be transported from drug-resistant tumor cells to macrophages through exosomes. Finally, research showed its overall tumor cell resistance by causing inhibition of the PTEN pathway and remodeling of macrophages. Conversely, this mechanism can be used to improve medicinal properties to overcome drug resistance after anthracycline treatment of breast cancer. For example, drug-resistant cells combined with integrin and dvβ3 can deliver miR-159 through exosomes to inhibit tumor cell proliferation (87).

In addition, some miRNAs are associated with the anthracycline resistance of breast cancer cells through their unique effects. For example, miR-548p can elevate the synthesis of phenazine biosynthesis-like domain-containing protein (PBLD),which was identified as a tumor suppressor. Therefore, the overexpression of miR-548p expression restricted tumor growth and proliferation (88). miR-770 proomotes the polarization of macrophages by inhibiting the Stathmin1 (STMN1) protein, indicating that miR-770 controls the tumor microenvironment, which is conducive to reducing the drug resistance of tumor cells (89). miR-548c-3p and miR-1236-3p moderated drug resistance by inhibiting DNA damage and repair (52, 90). The downregulation of miR-149 contributes to the activation of heparinase by increasing the expression of GlcNAc N-deacetylase/N-sulfotransferase-1 (NDST1) and inducing drug resistance (91). In addition, miR-3609 causes tumor cells to become sensitive to anthracyclines through promoting the synthesis of Programmed death-ligand 1 (PDL1) (92). Meanwhile, Drug metabolizing enzymes and transporters can be inhibited by miR-148 and miR-152 to reduce the drug resistance of tumor cells (64). miR-133a plays its role in enhancing cell drug sensitivity by targeting ferritin light chain (FTL) protein (93). It has been shown that the decreasing expression of FBXW7, a tumor suppressor gene regulated by miR-188-5p, leads to the emergence of drug resistance (94).

MiRNAs and Adverse Effects

In the process of applying anthracyclines to treat breast cancer patients, many adverse reactions often emerge. Among them, cardiovascular adverse reactions are the most prominent (95). Studies have shown that when using anthracycline chemotherapy regimens, the occurrence of cardiovascular events increases the risk of patient death (96). Therefore, urgent attention is needed on the occurrence of cardiovascular adverse events clinically. Appropriate stratification of risk factors and early detection is extremely meaningful for the survival and prognosis of breast cancer patients. Thus, a large number of miRNA related research is ongoing. miRNAs clearly show an objective quantitative or expression-intensity correlation with the occurrence of adverse reactions, which may help avoid or reduce the harm caused by adverse reactions to patients. It has guiding significance in improving the prognosis. Furthermore, X-ray photography, a commonly used method in clinical diagnosis, has the unavoidable disadvantage of discomfort, overdiagnosis, and false positives. **Figure 1** shows that the different roles of above mentioned miRNAs plays in anthracyclines resistance. As a detection method of peripheral blood indicators, miRNA is more nontoxic, convenient (97).

Qin, X. et al. (98). showed that anthracyclines induce myocardium damage in three possible ways: Firstly, it increased free radicals can cause tissue lipid oxidation leading to destruction of sarcomeres and causing autophagy and

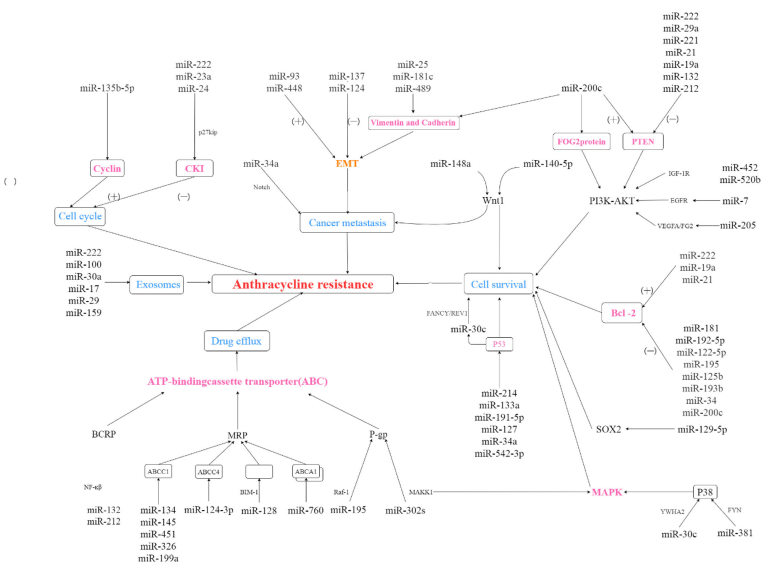

FIGURE 1 | The role of miRNAs in anthracyclines resistance. (+): microRNA promotes expression of dowmstream protein; (-): microRNA suppresses expression of dowmstream protein.

apoptosis of cardiomyocytes. The second mechanism is that it renders the death of cardiomyocytes by influencing topoisomerase II and opening the double strands of DNA of cardiomyocytes. Lastly, anthracyclines can damage myocardial fibers by inhibiting the ErbB-2 pathway (99). Anthacyclines induce early toxicity particularly in the left ventricle. The process of reconstruction is closely related to the reactivation of embryonic genes (100). miRNA can contribute to the cardiotoxicity occurrence (101).

The lethal-7 (let-7) family, a member of miRNAs, is mentioned extensivly. Upregulation of let-7a can predict the occurrence of cardiotoxicity (102). The downregulation of the expression of let-7f, a family member of let-7, signified the appearance of cardiac dysfunction because of its good correlation with N-terminal pro-B type natriuretic peptide (NT-proBNP) (98, 103). In addition to the let-7 family, miR-1 is another important biomarker, and has also been used as a clinical indicator. Expression of miR-1 implies the occurrence of arrhythmia to heart failure through a good response with left ventricular ejection fraction (LVEF) (98). Rigaud. et al. further explored its mechanism by demonstrating that miR-1 has a direct connection with the inhibition of antioxidant genes, leading to oxidative stress, promoting cardiomyocyte apoptosis, and myocardial damage (104). In another study, it was also found that miR-1 expression was increased in patients with adverse cardiotoxic reactions, possibly indicating that miR-1 was released by necrotic cardiomyocytes. miR-20a, miR-210, miR-34a, miR-126, and miR-130a are also have great potential. There is evidence that miR-20a is a dependable predictor of the occurrence of cardiotoxicity *via* the mechanism of activating angiogenesis and abnormal tumor vascular development. Another miRNA that plays a role in the development of chemoresistance, metastasis, proliferation, and self-renewal of tumor cells from hypoxic conditions is miR-210 (103). miR-34a-5p was also significantly increased after treatment with anthracyclines, which induces DNA breakage and P53 activation (105). MiR-126 also has the potential to be used to predict cardiotoxicity because it was validated to protect cardiomyocyte from apoptosis with its elevated expression (106–108). Recent findings have suggested that β-adrenergic pathway can modulate the contractile function in the heart by stimulating guanylyl nucleotide binding proteins, including adenylyl cyclase,cyclic adenosine monophosphate (cAMP), and so on (109–111). miR-30 affects the activation of the elements of the contraction coupling system by targeting the expression of β-adrenergic receptors. It was also concluded that miR-30 is a cardioprotective biomarker to monitor calcium overload and myocardial damage (112, 113).

In addition, another common adverse effect is liver metastasis. Studies have shown that miR-1-3p can mediate the occurrence of liver injury during the application of anthracyclines (4). Meanwhile, miRNA also plays a role in regulating the metastasis of breast cancer. miR-222 can promote the EMT process through the the mitogen-activated protein kinase (RAS-RAF-MEK-ERK) pathway, inducing breast cancer to be more aggressive and metastatic (68). Moreover, Deng, Z. et al. found that myelosuppressive cells (MDSC) can release miR-126a through exosomes to generate T helper 2 (Th2) cells with Interleukin-13 (IL-13) positive after Dox treatment. It promoted tumor angiogenesis, and ultimately led to breast cancer metastasis to the lungs (5). This also shows that miR-126a has the potential to predict breast cancer metastasis. **Table 1** presents the link of several miRNAs involved in response to adverse effects of anthracyclines treatment in breast cancer.

CONCLUSIONS AND OUTLOOK

There are many mechanisms and signaling pathways involved in the miRNA implications in breast cancer patients being treated with anthracyclines, and there is an abundance of possible miRNAs involved in the diagnosis, prognosis, and treatment of breast cancer patients. The study of microRNAs in regulating the resistance of anthracyclines in the treatment of breast cancer signifies that people may be able to control various types of microRNAs to overcome the shortcomings of anthracyclines application. MicroRNAs may be the key to the selection and development of personalized and safe anticancer drugs in the future. Moreover, as mentioned above, microRNAs can be used as a more accurate and safe early prediction tool, and has the potential as prognostic markers to be used in the clinic. Therefore, to overcome the challenge of providing individualized medicine in a complex disease, especially breast cancer, it is essential that more understanding of the biological effects of the various miRNAs will guide the possible direction of future academic interests.

TABLE 1 | MicroRNAs involved in response to adverse effects linked to anthracyclines treatment in breast cancer.

microRNA expression	Adverse effect	Reference
let-7a(↑)	cardiotoxicity	(102)
let-7f(↓)	cardiac dysfunction	(98, 103)
miR-1(↑)	Arrhythmia, heart failure	(98, 103, 104)
miR-20a(↑)	cardiotoxicity	(103)
miR-210(↑)	tumor metastasis	(98, 103)
miR-34a-5p(↑)	P53 activation,	(105)
	cardiotoxicity	(98)
miR-130a(↓)	myocardial damage	(98)
miR-1-3p(↑)	liver injury	(4)
miR-222(↑)	tumor metastasis	(117)
miR-126a(↑)	lung metastasis	(5)

↑, *microRNA expression increasing;* ↓, *microRNA expression decline.*

Moreover, there are many challenges in current researches. Firstly, many groups of miRNAs involving breast cancer were found by metabonomics methods (9, 114, 115). To a certain extent, these results only found a simple quantitative relationship between them. But do not provide adequate epidemiological information, such as age, the course of disease, the breast cancer type and stage, complications, the dosage and dosing interval of anthracyclines administration and so on. More importantly, most studies do not consider whether drug interactions, especially some cardioprotective drugs, have influence on the outcomes. Whether this relationship could be used as a reliable early detection indicator for the clinic is doubtful. Therefore, more effort should be invested into a more deeper study. Lastly, not only are the traditional techniques of miRNA detection complex and require special laboratory skills, but they can also generate false-positives during the amplification process (116). The optimization of methods for quantification and visualization of abnormal miRNA expression are needed for early clinical diagnosis. A more accurate and economical detection method is an absolutely need in the future.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

ZS and WZ: conceptualization, interpretation of data, and writing original draft. SL and YW: review, interpretation of data, and editing. WZ, GZ and YZ: conceptualization, writing original draft, review, editing, and supervision. All authors contributed to the article and approved the submitted version.

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