

miRNAs as potential markers for breast cancer and regulators of tumorigenesis and progression (Review)

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Abstract. Breast cancer (BC) is one of the most common malignancies affecting women. BC is a heterogeneous disease that involves multiple oncogenic pathways and/or genetic alterations. MicroRNAs (miRNAs or miRs) are a type of small endogenous single-stranded RNA that pairs with the 3'untranslated region of target mRNAs to negatively regulate the gene expression of specific mRNA targets. miRNAs are thus involved in various cellular processes, including proliferation, differentiation, apoptosis, migration, metabolism and the stress response. Over the past decade, a number of studies have demonstrated that the expression levels of miRNAs are dysregulated in a number of types of cancer, including BC.

In the present review, recent research on miRNAs involved in the occurrence and development of BC, as well as the current findings on miRNAs as potential biomarkers for BC are summarized. In addition, the association between miRNA dysregulation and BC development, and the current status of BC treatment and prognosis are discussed. Finally, several signaling pathways involved in the development of BC and the potential roles of miRNAs in these pathways are reviewed. The present review aims to provide insight into the roles of miRNAs in BC.

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Abbreviations: 3'UTR, 3'untranslated region; Ago, argonaute; AKT, v-akt murine thymoma viral oncogene homolog; BC, breast cancer; EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition; ER, estrogen receptor; Exp5, exportin 5; HER2, human epidermal growth factor receptor 2; LA, luminal A; LAPTM4B, lysosomal-associated protein transmembrane 4 beta; LB, luminal B; lncRNA, long non-coding RNA; mRNA, messenger RNA; miRISC, miRNA-induced silencing complex; miRNA/miR, microRNA; mTOR, mechanistic target of rapamycin; NAD, nicotinamide adenine dinucleotide; NAMPT, nicotinamide phosphoribosyltransferase; PARP, poly(adenosine diphosphate-ribose) polymerase; PD-1, programmed death-1; PI3K, phosphoinositide-3-kinase; Pol II, polymerase II; PR, progesterone receptor; pri-miRNA, primary miRNA; RISC, RNA-induced silencing complex; SNHG3, small nucleolar RNA host gene 3; TAM, tamoxifen; TGF- β , transforming growth factor β ; TNBC, triple-negative breast cancer; VEGF, vascular endothelial growth factor; ZEB1, zinc finger E-box binding homeobox 1

Key words: breast cancer, microRNA, biomarker, signaling pathway, treatment and prognosis

1. Introduction

Breast cancer (BC) is one of the most common malignancies affecting women, with approximately 1.5 million new cases diagnosed per year, and accounts for 30% of all cancer types in women. Despite advances in surgery, chemotherapy, radiotherapy, endocrine therapy, molecular-targeted therapy and immunotherapy, BC remains the cause of a vast number of deaths and is the second leading cause of cancer-related mortality among women worldwide (1-3).

BC is a heterogeneous disease, involving the disruption of multiple oncogenic biological pathways and/or genetic alterations. BC can be classified into different subtypes according to gene expression profiling and/or molecular and receptor status. Research has indicated that BC can be categorized into 5 major subtypes as follows: Luminal A (LA), luminal B (LB), human epidermal growth factor receptor 2 (HER2)-enriched, basal-like and normal breast-like cancers (Table I). The LA subtype expresses estrogen receptor (ER) and progesterone receptor (PR), but is negative for HER2. LA is the most common subtype, accounting for approximately 50-60% of all BC cases.

In the LB subtype, ER and PR expression is positive, and HER2 expression can be either positive or negative. HER2-enriched BC expresses HER2, whereas it does not express ER and PR, and this subtype accounts for 5-20% of all BC cases (4-8). The normal-like BC (ER- or PR-positive, HER2-negative) accounts for approximately 5-10% of all BC cases (9). Basal-like subtype BC (ER-negative, PR-negative, HER2-negative), also known as triple-negative breast cancer (TNBC), is the most aggressive subtype of BC and accounts for 15-20% of all BC cases. TNBC lacks the expression of all hormone receptors, rendering it insensitive to the currently available targeted and hormone therapies. Patients with TNBC thus undergo earlier relapse and have higher mortality rates than patients with other BC subtypes (10-12). No clearly defined TNBC-specific therapeutic targets or markers have yet been identified, and therefore, effective treatment methods have become major clinical challenges for the treatment of patients with TNBC.

MicroRNAs (miRNAs or miRs) are a class of small endogenous single-stranded RNA molecules that are 19-25 nucleotides in length. miRNAs interact with the 3'untranslated region (UTR) of the target messenger RNAs (mRNAs) to negatively regulate the gene expression of specific mRNA targets. While the majority of miRNAs are located in endonuclear noncoding regions, some studies have reported miRNAs in the exons of genes (13-15). Each miRNA can regulate hundreds of mRNAs and >60% of human mRNAs contain at least one miRNA binding site (16).

Through the regulation of gene expression, miRNAs are involved in various cellular processes, including proliferation, differentiation, apoptosis, migration, metabolism and the stress response (17-19). Over the past decade, a number of studies have demonstrated that miRNA expression is dysregulated in a number of types of cancer, including BC. The dysregulation of miRNAs influences various processes that contribute to tumor development, such as inflammation, the stress response, the cell cycle, proliferation, differentiation, invasion, apoptosis and the tumor microenvironment, promoting tumor development, morphogenesis, development and metastasis (20-23). In cancer, miRNAs can act as tumor suppressors or oncogenes and play important roles in resistance to treatment (24-26).

Studies have demonstrated that the tumor cell response to treatment can be consolidated using basic molecular features explored by molecular technology (27,28). Two-thirds of BCs have similar characteristics, depending on the interaction of estrogen with nuclear ER α protein (29,30). In addition, the disorders of a number of oncogenes or tumor suppressors are related to BC (31-33).

A better understanding of the specific functions of the molecules involved in BC progression and the regulatory mechanisms is critical in order to identify effective treatment strategies for BC. In addition, the identification of specific biomarkers will help improve early diagnosis and establish individualized treatments, as well predict recurrence and the clinical efficacy of treatment in patients with BC to improve patient prognosis.

2. Potential biomarkers in BC

Early diagnosis of BC is usually made by screening or symptoms that prompt a diagnostic test (such as the detection of a

palpable mass). The prognosis of BC depends on the tumor characteristics, patient factors and response to treatment. Despite significant advances in the early detection, diagnosis and treatment of BC, the overall survival rates for patients with BC remain low due to acquired drug resistance, heterogeneity, relapse and metastases (34-36). Metastasis and relapse following treatment are the major factors that contribute to morbidity and mortality in patients with BC, and approximately 30% of patients still have a poor prognosis (37).

The early diagnosis and detection of BC can reduce the rates of mortality. Currently, serum-based tumor markers are the most effective screening method for the diagnosis of BC and relapse detection in patients with BC. However, these biomarkers are associated with a low specificity, low sensitivity, high false-positive rates and complications, which limit their use in diagnosis, and in monitoring disease progression and recurrence (38). For example, carcinoembryonic antigen and cancer antigen 15-3 have yielded false-positive results and low sensitivity, limiting their clinical application in detecting early-stage BC (39). Additionally, while some circulating tumor biomarkers, such as tissue peptide-specific antigens, have been used in clinical diagnosis, their diagnostic specificity and sensitivity are low (40). Currently available serum markers are unable to accurately diagnose early-stage BC due to a lack of sensitivity and specificity (41). In addition, the hormone receptors, ER, PR and HER2, have been established as markers for routine analysis; however, their application is limited to specific BC subtypes (42). For example, TNBC lacks the expression of all 3 hormone receptors; thus, hormone receptor-based biomarkers cannot be used to detect TNBC. Therefore, the identification of highly specific and sensitive biomarkers is essential for the early diagnosis and treatment of BC.

As key regulators in tumor progression, miRNAs have been shown to act as potential biomarkers for clinical diagnosis and as novel anticancer drugs (43-45). Over the past few decades, numerous studies have focused on assessing the clinical utility of miRNAs as potential biomarkers in BC. Several tumor-associated circulating miRNAs in BC have been identified as promising biomarkers, such as several circulating miRNAs that are significantly elevated in early BC patients (46,47). Circulating miRNAs, including serum and plasma miRNAs, are not only easy to access and measure, but have also been shown to effectively distinguish cancer patients from healthy individuals (48,49).

Plasma miR-21 can be used as a biomarker for detecting primary and relapsed BC. In a previous study, a significantly increased plasma miR-21 level was detected in patients with primary ($P<0.001$) and recurrent ($P<0.001$) BC compared with the levels in healthy subjects; miR-21 plays an important role in the tumorigenesis, drug resistance and BC recurrence (50). Another study demonstrated that the expression of miR-34a was decreased in the serum of patients with BC, and miRNA-34a can be used as a potential non-invasive molecular marker for the early diagnosis of BC (51). miR-891a-5p negatively regulates the expression of ADAM10 by directly binding to its 3'UTR, resulting in the inhibition of proliferation and migration of BC cells. miR-891a-5p is an important prognostic indicator for hormone receptor-positive BC (52). miR-15b-5p promotes BC cell proliferation, migration, and invasion by directly targeting HPSE2. miR-15b-5p can be used

Table I. Subtypes of BC and their histopathological features.

Subtype	ER	PR	HER2	Other features	(Refs.)
LA	Positive	Positive	Negative	Approximately 50-60%	(4,5)
LB	Positive	Positive	Positive or negative	Approximately 10-20%	(4,5)
HER2-enriched	Negative	Negative	Positive	Approximately 5-20%	(4,5)
Basal-like	Negative	Negative	Negative	Short relapse-free and low survival rate; approximately 15-20%	(4,5,10)
Normal-like	Positive	Positive	Negative	The rarest BC sub-type; approximately 5-10%	(4,7,9)

LA, luminal A; LB, luminal B; HER2, human epidermal growth factor receptor 2.

as a prognostic tool and therapeutic target for patients with BC (53) (Table II).

Studies have demonstrated that miRNAs are very stable in formalin-fixed paraffin-embedded tissue, suggesting their presence in body fluids (54). Due to the very high stability of miRNAs in tissues and body fluids, such as serum, plasma, saliva, sweat and urine, miRNAs have been considered promising markers for early detection, diagnosis, and prognosis and targets for cancer treatment (55).

3. miRNA dysregulation in BC

In animals, miRNAs are coded as monocistronic (as a single gene), polycistronic (as a cluster), or introns (56). To date, >900 human miRNAs have been identified and are transcribed as a single unit or in polycistronic clusters or synergistically transcribed with host protein-encoding genes (57,58). Mature miRNAs are derived from long primary transcripts (59). miRNAs are transcribed by RNA polymerase II (Pol II) to produce primary miRNAs (pri-miRNA). After pri-miRNAs are transcribed in the nucleus, they are cleaved by nuclear III Drosha to produce a stem-loop intermediate known as precursor miRNAs (60,61). This process requires a series of microprocessors, including RNase III Drosha, DiGeorge Critical Region 8, DDX5 and DDX17 (62). The processed pre-miRNAs interact with the receptor of exportin 5 (Exp5) and are exported into the cytoplasm, where they are subsequently truncated by RNase III Dicer in the cytoplasm to generate a miRNA duplex intermediate containing 20-25 nucleotides (63-66). The duplex is then unraveled and the mature single-stand miRNA is incorporated into the RNA-induced silencing complex (RISC) to form a miRNA-induced silencing complex (miRISC) with argonaute (Ago) family proteins (67). The miRISC complex pairs by complementary target recognition to the 3'UTR of target mRNAs, thereby silencing the expression of the target mRNAs through mRNA cleavage or translation inhibition (68-72) (Fig. 1). Specific sequences in mature miRNAs known as 'seed sequences' are necessary for target site recognition. The binding of a fully complementary mature miRNA to a target site results in the cleavage of the target mRNA, while binding with incomplete complementarity results in translational inhibition. The main function of miRNAs is to downregulate the expression of target genes through mechanisms, such as RNA degradation, the induction of capping, induction of adenylation, change in cap

protein binding, decreased ribosome occupancy and mRNA chelation (73). Generally, the seed sequence of a miRNA is base-paired to the 3'UTR of the mRNA. The seed sequence usually consists of 2-8 nucleotides, beginning at the second nucleotide of the 5'end of the miRNA and ending at the eighth nucleotide (74,75). The seed sequence plays an important role in identifying the target mRNA and provides an important basis for miRNA target prediction. A single miRNA usually targets a number of mRNAs, and a single transcript may be targeted by multiple miRNAs due to shared seed sequences (76).

miRNAs play a key role in human cancer. The underlying mechanisms of abnormal miRNA expression in cancer include chromosomal aberrations, defects in transcriptional control, dysregulated epigenetic regulation and irregularities in miRNA biogenesis. miRNAs can function as tumor suppressors by negatively regulating molecules that are involved in the formation of malignant tumors (77-80). miRNA dysregulation can disrupt intracellular RNA networks in cancer cells, and a number of researchers have focused on exploring the mechanisms of action of miRNA-dependent molecular networks in cancer.

miRNA dysregulation is directly related to the emergence of various aspects of tumorigenesis. miRNAs are involved in tumorigenesis, tumor development, proliferation, metastasis, epithelial-mesenchymal transition (EMT), stemness maintenance and therapeutic resistance by downregulating target oncogenes or tumor suppressor genes (81). Therefore, these dysregulated miRNAs may serve as biomarkers for cancer diagnosis and prognosis, and may be used as potential targets for cancer treatment.

Researchers have performed RNA sequencing on BC clinical specimens to identify potential tumor suppressor miRNAs in BC. In a previous study, 64 miRNAs were identified as candidate tumor suppressor miRNAs in BC cells. The expression levels of miR-99a-5p/-3p, miR-101-5p/-3p, miR-126-5p/-3p, miR-143-5p/-3p and miR-144-5p/-3p were downregulated in BC (82). That study demonstrated that the low expression of miR-101-5p predicts a poor prognosis of patients with BC (82). As previously demonstrated, miR-302b was significantly downregulated in BC tissues and cell lines compared with the controls. Patients with BC with a lower miR-302b expression were found to have shorter survival times than patients with a higher miR-302b expression. miR-302b overexpression inhibited BC cell proliferation, migration and invasion, while miR-302b silencing exerted the

Table II. miRNAs as potential biomarkers for BC.

miRNAs	Type of biomarker	Biological sample	Features	(Refs.)
miR-21	Diagnosis	Plasma	Plasma miR-21 can be used as a biomarker for detecting primary and relapsed BC. miR-21 is closely related to tumorigenesis, drug resistance and BC recurrence.	(50)
miRNA-34a	Diagnosis	Serum	miRNA-34a can be used as a potential non-invasive molecular marker for the early diagnosis of BC.	(51)
miR-891a-5p	Prognosis	Tissues	miR-891a-5p prevents the expression of ADAM10 by directly binding to its 3'UTR, thereby inhibiting the proliferation and migration of BC cells. miR-891a-5p is an important prognostic indicator for hormone receptor-positive BC.	(52)
miR-15b-5p	Prognosis	Tissues	miR-15b-5p promotes BC cell proliferation, migration and invasion by directly targeting HPSE2. miR-15b-5p can be used as a prognostic tool and therapeutic target for patients with BC.	(53)

BC, breast cancer; miR/miRNA, microRNA; 3'UTR, 3'untranslated region.

opposite effects (83). miR-302b expression was shown to be an independent prognostic factor for BC.

A previous study demonstrated that the expression level of miR-9 in BC tissues was significantly decreased compared with the controls; however, the expression level of miR-9 in serum samples was not significantly altered (84). In another study, a decreased miR-296 expression was associated with malignant phenotypes and a poorer prognosis of patients with BC. The upregulation of miR-296 inhibited the proliferation, invasion and migration ability of BC cells *in vivo* (85). Another study also demonstrated that miR-539 expression was downregulated in BC tissues and cell lines. The decreased expression of miR-539 was closely related to lymph node metastasis in patients with BC. The overexpression of miR-539 inhibited the proliferation and promoted the apoptosis of BC cells (86). miR-124 was significantly reduced in metastatic bone tissues from BC. The downregulation of miR-124 was found to be associated with aggressive clinical characteristics and a shorter bone metastasis-free survival and overall survival (87). miRNA-221-5p has been shown to be upregulated in BC tissues, and its increased expression is associated with lymph node metastasis, distant metastasis and a poor prognosis of BC (88). miR-34a has been found to be significantly downregulated in BC tissues, and miR-34a can be used as a biomarker for the diagnosis of BC in healthy women (89). A previous study found that miRNA-663b was upregulated in BC with tamoxifen (TAM) resistance. The downregulation of miRNA-663b inhibited cell proliferative ability and promoted cell apoptosis, resulting in an enhanced TAM sensitivity (90) (Table III).

4. miRNAs as therapeutic targets of BC

Treatment of BC is mainly determined based on tumor subtype, disease stage, the mutation status of the BC gene and several genomic markers, and the health status and age of the patient.

Conventional treatments for BC include radiotherapy, chemotherapy, molecular-targeted therapies, endocrine treatments and surgical resection (91,92). Endocrine therapies (such as TAM and aromatase inhibitors) are used for the treatment of hormone receptor-positive BC tumors, while the monoclonal antibody, trastuzumab, is widely used for the treatment of HER2-positive tumors. TNBC does not respond to endocrine therapy as this subtype lacks hormone receptors (7). TNBC is the most aggressive and metastatic subtype of BC with poor treatment outcomes (93), and chemotherapy is currently the only treatment option for TNBC (94).

The treatment of BC remains a clinical challenge. Chemotherapy, hormone therapy and targeted therapy are traditionally used in the treatment of BC. However, BC is a heterogeneous disease, and patients often develop drug resistance. Although substantial progress has been made in the treatment of BC, novel therapeutic targets are still required to overcome the current obstacles to BC treatment. Studies have demonstrated that the abnormal expression of specific miRNAs has been associated with resistance to chemotherapy, radiation therapy and hormone therapy. The dysregulation of miRNAs can affect target protein expression in cells, the ability for anticancer drugs to reach their targets within cells and apoptotic pathways (95).

In recent years, the inhibition of cellular and molecular mechanisms that interfere with the development of BC is one of the critical diagnostic and therapeutic strategies (96,97). The upregulation of nicotinamide phosphoribosyltransferase (NAMPT) in patients with BC has been associated with the increased adverse effects of doxorubicin. Thus, inhibiting NAMPT is a strategy for the treatment of BC (98). NAMPT is a rate-limiting enzyme of rescues the biosynthetic pathway of nicotinamide adenine dinucleotide (NAD) (99,100). NAD disorders may be related to the progression of BC. NAMPT is a target of miR-154, and the expression level of miR-154 has been found to be inversely related to the mRNA and protein levels

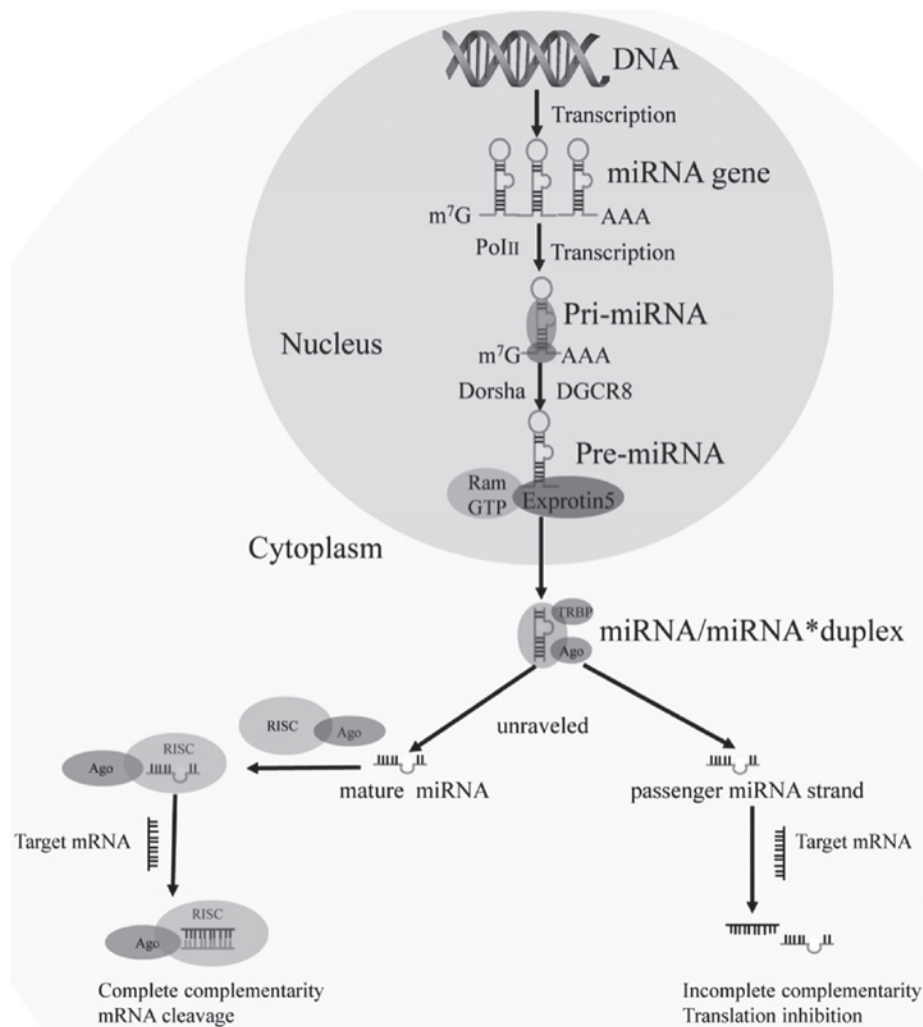


Figure 1. Biogenesis of miRNAs. miRNAs are transcribed as pri-miRNA by RNA pol II and cleaved by Drosha and its cofactor DGCR8 to yield the pre-miRNA in the nucleus. The processed pre-miRNA interacts with the receptor of Exportin 5 and is exported into the cytoplasm in a Ran-GTP-dependent manner, where it is subsequently truncated by RNase III Dicer in the cytoplasm to generate a miRNA duplex intermediate. The duplex is then unraveled and the mature single-stand miRNA is incorporated into the RISC to form a miRISC with Ago family proteins. The miRISC complex pairs by complementary target recognition to the 3'UTR of target mRNAs, thereby silencing the expression of the target mRNA through mRNA cleavage or translation inhibition. pri-miRNA, primary miRNA; pol II, polymerase II enzyme; DGCR8, DiGeorge syndrome critical region in gene 8; pre-miRNA, precursor miRNA; RISC, RNA-induced silencing complex; miRISC, miRNA-induced silencing complex; Ago, argonaute.

of NAMPT in BC cell lines. miR-154 inhibits the NAD rescue pathway, leading to a significant decrease in cell viability and an increase in cell mortality. In BC cells co-treated with doxorubicin and miR-154 mimics, cell viability was markedly reduced compared with cells treated with doxorubicin alone. Therefore, targeting the inhibitory effect of miR-154 on NAD may be an effective strategy to improve the therapeutic effect on BC (101).

TAM is an endocrine therapy that is commonly used in the treatment of patients with BC expressing ER. The downregulation of miRNA-663b has been shown to inhibit the proliferative ability and promote the apoptosis of BC cells, resulting in an enhanced TAM sensitivity. miRNA-663b may therefore be a critical therapeutic target in BC (90). Sevoflurane significantly suppresses BC cell proliferation by arresting the cell cycle at the G1 phase. A previous study demonstrated that sevoflurane inhibits BC cell proliferation by upregulating the expression of miR-203 (102).

Due to the low immune response and low toxicity of miRNAs, miRNAs have become a promising therapeutic

strategy for cancer treatment. At present, the main challenge of miRNA-based cancer therapy is to achieve the specificity of miRNA therapy and the effective and safe delivery of miRNAs to cancer cells. In addition to free miRNAs in patient serum or plasma, miRNAs have also been identified in exosomes (103). Exosomes or microvesicles are small endosomally-derived vesicles that are secreted by a variety of cell types and tissues. Engineered exosomes have become a new drug delivery vehicle for cancer treatment, and exosomes carrying miRNAs can be transferred among different cell lines through direct uptake.

Researchers have indicated that MDA-MB-231 BC cell-derived exosomes (231-Exo) can be specifically internalized by non-small cell lung cancer cells through specific interactions between overexpressed integrin $\beta 4$ (on exosomes) and surfactant protein C (SPC) on cancer cells. miRNA-231-Exo (miRNA-126 loaded in 231-Exo) has been shown to significantly inhibit the proliferation and migration of A549 lung cancer cells by interrupting the phosphatase

Table III. Dysregulation of miRNAs in BC.

miRNA	Type of deregulation	Samples type	Features	(Refs.)
miR-101-5p, miR-126-5p/-3p, miR-143-5p/-3p, miR-144-5p/-3p	Downregulated	Tissues	Low expression of miR-101-5p predicts a poor prognosis for patients with BC.	(82)
miR-302b	Downregulated	Tissues	miR-302b expression is an independent prognostic factor for BC. miR-302b overexpression inhibits BC cell proliferation, migration and invasion.	(83)
miR-9	Downregulated	Tissues	The expression level of miR-9 in serum samples is not significantly altered.	(84)
miR-296	Downregulated	Tissues	A decreased expression of miR-296 is associated with the malignant phenotypes and poorer prognosis in patients with BC. The upregulation of miR-296 inhibits the proliferative, invasive and migratory ability of BC cells <i>in vivo</i> .	(85)
miR-539	Downregulated	Tissues	The decreased expression of miR-539 is closely related to lymph node metastasis in patients with BC. The overexpression of miR-539 inhibits the proliferation and promotes the apoptosis of BC cells.	(86)
miR-124	Downregulated	Tissues	Downregulation of miR-124 is associated with aggressive clinical characteristics and a shorter bone metastasis-free survival and overall survival.	(87)
miRNA-221-5p	Upregulated	Tissues	miRNA-221-5p is associated with lymph node metastasis, distant metastasis, and a poor prognosis of BC.	(88)
miR-34a	Downregulated	Tissues	miR-34a can be used as a biomarker for the diagnosis of BC in healthy women.	(89)
miRNA-663b	Upregulated	Tissues	miRNA-663b may be a critical therapeutic target in BC.	(90)

BC, breast cancer; miR/miRNA, microRNA.

and tensin homolog (PTEN)/PI3K/AKT signaling pathway. In addition, miRNA-231-Exo also inhibits the formation of lung metastases (104). A previous study demonstrated that treatment with exosomes derived from MDA-MB-231 cells enhanced the viability, migration and chemotherapy resistance of non-malignant HMLE cells (105). Some researchers used three-layered polyplex with folic acid as a targeting group to deliver miR-210 systemically to BC cells, thereby inhibiting the growth of BC (106). miRNAs and exosomes also have been shown to function as novel diagnostic and therapeutic biomarkers for monitoring patients with BC (107).

5. miRNAs and various signaling pathways, and therapeutic targets involved in BC

miRNAs can positively or negatively regulate signaling pathways, promoting or preventing signal transmission to downstream effectors. Multiple studies have demonstrated that miRNAs play key functions in tumorigenesis by regulating tumor suppressors or oncogenes (108,109). Over the past decade, research on the pathogenesis of BC has led to the discovery of a number of signaling pathways and corresponding therapeutic targets involved in BC, such as transforming growth factor

β (110,111), phosphoinositide-3-kinase (PI3K), v-akt murine thymoma viral oncogene homolog (AKT), mechanistic target of rapamycin (mTOR) (112-114), Ras/mitogen-activated protein kinase (MAPK) (115,116), nuclear factor (NF)- κ B (117-120), Notch (121-123), Wnt/ β (124,125), HER2 (126), vascular endothelial growth factor (VEGF) (127,128), epidermal growth factor receptor (EGFR) (129,130), cyclin-dependent kinase 4/6 (CDK4/6) (131), poly(adenosine diphosphate-ribose) polymerase (PARP) (132,133) and programmed death-1 (PD-1) (134). Below, several key signaling pathways in BC and the involvements of miRNAs in BC are reviewed.

TGF- β signaling pathway and miRNAs in BC. TGF- β is a polypeptide growth factor. The TGF- β signaling pathway is involved in hindering the growth and proliferation of early-stage cancer cells, and increasing the metastasis and invasion of late-stage tumor cells. TGF- β plays a key role in EMT in cells and cancer metastasis, and promotes EMT in BC (135). EMT is the conversion of epithelial phenotype to a highly active fibroblast or mesenchymal phenotype (136). EMT is generally considered to be one of the most important steps which triggers migration, thus also promoting tumor invasion and metastasis (137-139).

The TGF- β signaling pathway is controlled by multiple molecules. miR-200b-200a-429 or miR-200c-141 in Madin Darby canine kidney epithelial cells lead to the suppression of TGF- β -stimulated EMT (140). TMEPAI can transform TGF- β from a tumor suppressor to a tumor promoter and can induce the tumorigenic function of EMT (141). The overexpression of miR-133b has been shown to significantly reduce the expression of TGF β R1, an essential receptor of TGF- β /SMAD signaling, and to inhibit TGF- β -induced EMT and BC cell invasion *in vitro* (142). GATA3 has been shown to play a role in inhibiting EMT in BC by activating miR-455-3p expression. The enforced expression of miR-455-3p alone partially prevents EMT induced by TGF- β in cells and tumor xenografts by directly inhibiting key components of TGF- β signaling (143). Zinc finger E-box binding homeobox 1 (ZEB1) is an important member of the zinc finger homeodomain transcription factor family and was originally identified as a binding protein of the lens-specific δ 1-crystalline enhancer. ZEB1 is also a key transcription factor in the EMT process and plays a vital role in the progression of BC.

PI3K/AKT/mTOR and miRNAs in BC. The PI3K/Akt/mTOR pathway is involved in tumor growth, proliferation, survival, motility, metabolism and in the regulation of the immune response. The activation of this pathway is one of the main mechanisms underlying the resistance of cancer cells to antitumor therapy (144,145). Lysosomal-associated protein transmembrane 4 beta (LAPTM4B) is a proto-oncogene and a positive regulator of cancer progression. A previous study demonstrated that miR-132-3p inhibited the migration and invasion of BC cells through LAPTM4B by mediating EMT signals and partially reversed the carcinogenesis induced by LAPTM4B by inhibiting the PI3K/AKT/mTOR signaling pathway (146). miR-21 targets PTEN by inhibiting the PI3K/AKT/mTOR pathway to coordinate the functions of autophagy and apoptosis. The silencing of miR-21 has been shown to enhance the sensitivity of ER(+) BC cells to TAM and fulvestrant by increasing autophagic cell death (147). miR-122 can inhibit cancer by targeting insulin-like growth factor 1 receptor (IGF1R) and regulating the PI3K/Akt/mTOR/p70S6K pathway. miR-122 may thus be a treatment or diagnosis or prognosis target for the treatment of BC (148).

Ras/MAPK and miRNAs in BC. Ras is a signal transduction effector that acts as a second-messenger to initiate intracellular signaling pathways. In BC, Ras may be overactivated by growth factor receptors, such as HER2 and IGF-1, and they may subsequently activate downstream pathways, such as the MAPK and PI3K/AKT pathways through Raf, MEK and extracellular signal-regulated kinase (ERK)1/2, ultimately leading to the survival and proliferation of BC cells (149). The MAPK pathway superfamily involves several members constituting seven groups: ERK1/2, Jun N-terminal kinase (JNK) 1/2/3, ERK3/4, p38 $\alpha/\beta/\gamma/\delta$, ERK5, ERK7/8 and Nemo-like kinases (NLKs). The MAPK pathways do not individually regulate cell functions, but interact with each other, as well as with other signaling pathways such as the TGF β /Smads, PI3K/Akt/mTor, Wnt/ β -catenin and Rho/actin pathways (150,151). A major targeted therapeutic strategy for BC is to block its downstream effectors with specific small molecule inhibitors targeting

the Ras/MAPK pathway (152). miR-200c has been shown to suppress the expression of KRas, and thus, miR-200c hinders the proliferation and survival of breast tumor cells via negative control of Akt and ERK (153). It has been demonstrated that the increased expression of miR-543 inhibits the progression of BC cells by targeting ERK2 and inhibiting the MAPK/ERK pathway (154). An increase in miR-148a/152 has also been shown to prevent the development of BC via the downregulation of the expression levels of IGF1R and IRS-1, and the inactivation of the Akt and MAPK/ERK pathways (155).

NF- κ B and miRNAs in BC. The NF- κ B family consists of 5 members: NF- κ B1 (p105/p50), NF- κ B2 (p100/p52), RelA (p65), RelB and c-Rel. The NF- κ B family consists of 5 members, including NF- κ B1 (p105/p50), NF- κ B2 (p100/p52) and RelA (p65), which are influenced by miRNAs and have major functions in the tumorigenesis of BC (156). A previous study demonstrated that miR-132/-212 were overexpressed in doxorubicin (DOX)-resistant BC, and the silencing of miR-132/-212 expression induced DOX accumulation, while the overexpression of miR-132/-212 led to BC resistance protein (BCRP)-based DOX efflux. The upregulation of miR-132/-212 suppressed the expression of PTEN, a target gene of miR-132/-212, which activated AKT phosphorylation and the NF- κ B members, including NF- κ B1 (p105/p50), NF- κ B2 (p100/p52) and RelA (p65). The miR-132/-212-PTEN-AKT/NF- κ B-BCRP pathway plays an important role in the development of BC drug resistance and provides a potential method to reverse drug resistance (157). The upregulation of miRNA-181b has been shown to suppress BC cell survival and migration via the NF- κ B signaling pathway (158). The therapeutic administration of glucocorticoids is frequently used as an add-on chemotherapy for palliative purposes during the of treatment BC. In a previous study, glucocorticoid receptor agonists induced miR-708 and the downstream suppression of NF- κ B signaling, which may be applicable as a novel therapeutic intervention in the treatment of BC (159).

Notch and miRNAs in BC. The Notch signaling pathway regulates a number of biological processes, such as cell proliferation, differentiation and apoptosis. The interplay between the Notch pathway and miRNAs is associated with the progression of BC. The long non-coding RNA (lncRNA) small nucleolar RNA host gene 3 (SNHG3) has been found to promote BC cell proliferation and invasion by regulating the miR-101/zinc-finger enhancer binding axis in BC. lncRNA SNHG3 promotes BC cell proliferation and metastasis by activating the Notch signaling pathway (160). The small nucleolar RNA host gene 7 has been shown to promote BC tumorigenesis and progression by sponging miR-34a through the initiation of EMT and the Notch-1 pathway (161). Rhamnetin has been shown to significantly promote the expression of p53 protein and miR-34a and suppresses the expression of Notch1 protein in MCF-7 cells. Rhamnetin induces the apoptosis of human BC cells via the miR-34a/Notch-1 signaling pathway (162). In a previous study, miR-34a inhibited BC stemness and enhanced chemosensitivity to paclitaxel partially by downregulating the Notch1 pathway. Thus, miR-34a is a potential target for the prevention and therapy for BC (163). The overexpression of

miR-1179 has also been shown to significantly inhibit the proliferation, migration and invasion of BC cells. miR-1179, a tumor suppressor, may act as a novel potential prognostic biomarker or molecular therapeutic target for BC (164).

Wnt/ β and miRNAs in BC. The Wnt/ β -catenin pathway is constitutively active in BC and promotes metastasis in BC. miR-454-3p is overexpressed in metastatic BC. The inhibitory effect of miR-454-3p on RPRD1A activates Wnt/ β -catenin signaling, thereby promoting metastasis. miR-454-3p and RPRD1A may be potential diagnostic and therapeutic targets for BC metastasis (165). In a previous study, miRNA-216a overexpression was shown to lead to a decrease in the proliferation and migration of MCF-7 cells, and to inhibit Wnt and β -catenin expression in MCF-7 cells. The anticancer effects of miRNA-216a were reversed by anti-miRNA-216a by promoting the Wnt/ β -catenin signaling pathway. The inactivation of the Wnt pathway enhanced the anticancer effects of miRNA-216a on MCF-7 cells. miRNA-216a suppressed the growth of human BC cells by targeting the Wnt/ β -catenin signaling pathway (166). miR-221/222 activates the Wnt/ β -catenin signaling to promote aggressiveness and TNBC properties of BC (167). The constitutive activation of the Wnt/ β -catenin pathway is inversely associated with the prognosis of patients with BC. The expression of miR-1229 is significantly upregulated in BC and is associated with a poor survival. The overexpression of miR-1229 activates the Wnt/ β -catenin signaling pathway in BC (168). miR-224 downregulates the Wnt/ β -catenin signaling possibly by binding to Frizzled 5 and inhibited proliferation and migration of BC cells (169).

6. Summary and future perspectives

BC is the most frequently diagnosed type of cancer among women worldwide and one of the leading causes of cancer-related mortality in women. miRNAs play an important role in the tumorigenesis and development of BC. In the present review, the recent findings of miRNAs involved in the occurrence and development of BC and the current research on miRNAs as potential biomarkers and therapeutic targets for BC were summarized. In addition, several signaling pathways that function in the development of BC and the roles of miRNAs in these pathways were reviewed.

Multiple studies have demonstrated that miRNAs are involved in cell proliferation, apoptosis and metastasis in BC. Some miRNAs function as oncogenes and activate cancer-related signaling pathways, while others act as tumor suppressors, negatively regulating many biomolecules that are critical for the formation of malignant tumors. Several miRNAs are frequently dysregulated in BC and represent not only potential diagnostic markers, but also precise targets for therapies. Increasing research has been exploring miRNA as therapeutic agents in chemotherapy or combined with anti-cancer therapies. The currently available serum markers exhibit a low diagnostic specificity and sensitivity, thus limiting their applicability for the early diagnosis of BC. The exact molecular mechanisms responsible for BC progression remain unknown. Therefore, future research on BC is required to focus on elucidating the molecular mechanisms of BC in

order to identify effective molecular biomarkers and develop novel treatment strategies.

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Authors' contributions

HMU, WZ and YQ were involved in the writing of the article and critically revised the manuscript. TT and HW were involved in data collection for the purposes of the review. ZC and GX conceived the review and revised the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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