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

HONGXIANG MU*, WENMAO ZHANG*, YE QIU*, TING TAO, HONGLIANG WU, ZHUO CHEN and GAOSHENG XU

Yueyang Maternal and Child Health Hospital, Yueyang, Hunan 414000, P.R. China

Received May 29, 2020; Accepted February 10, 2021

DOI: 10.3892/ijo.2021.5196

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.

Correspondence to: Professor Gaosheng Xu or Professor Zhuo Chen, Yueyang Maternal and Child Health Hospital, 693 Baling Road, Yueyang, Hunan 414000, P.R. China
E-mail: xugaosheng0414@163.com
E-mail: 1327978014@qq.com

*Contributed equally

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

Contents

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 ERα 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). NAMP 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

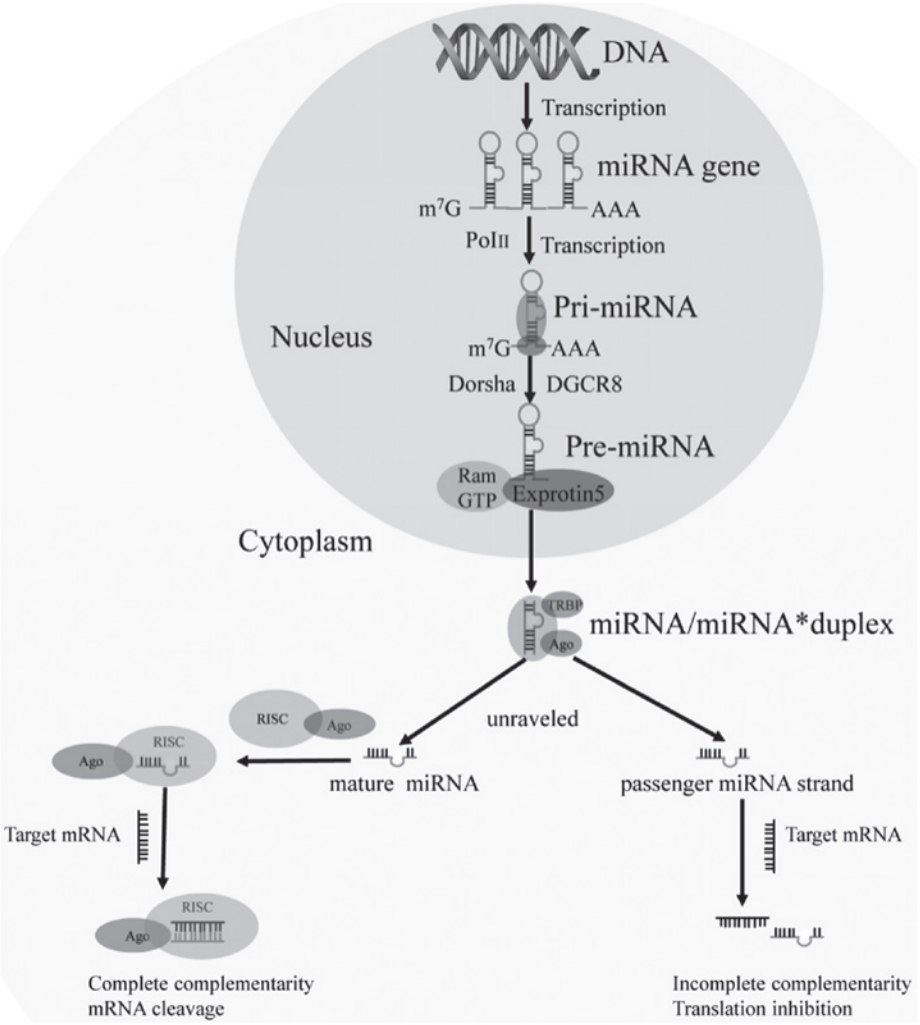

Figure 1. Biogenesis of miRNAs. miRNAs are transcribed as pri-miRNA by RNA pol II and cleaved by Drosha and its cofactor DGCR8 to yield the pre-miRNA in the nucleus. The processed pre-miRNA interacts with the receptor of Exportin 5 and is exported into the cytoplasm in a Ran-GTP-dependent manner, where 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 β4 (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 *in vivo*.	(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)-κB (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 TGFβR1, 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 δ1-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 α/β/γ/δ, 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 TGFβ/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-κB and miRNAs in BC. The NF-κB family consists of 5 members: NF-κB1 (p105/p50), NF-κB2 (p100/p52), RelA (p65), RelB and c-Rel. The NF-κB family consists of 5 members, including NF-κB1 (p105/p50), NF-κB2 (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-κB members, including NF-κB1 (p105/p50), NF-κB2 (p100/p52) and RelA (p65). The miR-132/-212-PTEN-AKT/NF-κB-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-κB 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-κB 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.

Acknowledgements

Not applicable.

Funding

The present study was supported by Hunan Natural Science Foundation (C2019143).

Availability of data and materials

Not applicable.

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

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Ding L, Li J, Wu C, Yan F, Li X and Zhang S: A self-assembled RNA-triple helix hydrogel drug delivery system targeting triple-negative breast cancer. J Mater Chem B 8: 3527-3533, 2020.
2. Siegel RL, Miller KD and Jemal A: Cancer statistics, 2015. CA Cancer J Clin 65: 5-29, 2015.
3. Li Y, Song Y, Wang Z, Zhang Z, Lu M and Wang Y: Long Non-coding RNA LINC01787 drives breast cancer progression via disrupting miR-125b generation. Front Oncol 9: 1140, 2019.
4. Ding L, Gu H, Xiong X, Ao H, Cao J, Lin W, Yu M, Lin J and Cui Q: MicroRNAs involved in carcinogenesis, prognosis, therapeutic resistance and applications in human triple-negative breast cancer. Cells 8: 1492, 2019.
5. Denkiewicz M, Saha I, Rakshit S, Sarkar JP and Plewczynski D: Identification of breast cancer subtype specific MicroRNAs using survival analysis to find their role in transcriptomic regulation. Front Genet 10: 1047, 2019.
6. Xiao Y, Humphries B, Yang C and Wang Z: MiR-205 Dysregulations in breast cancer: The complexity and opportunities. Noncoding RNA 5: 53, 2019.
7. Ediriweera MK and Cho SK: Targeting miRNAs by histone deacetylase inhibitors (HDACi): Rationalizing epigenetics-based therapies for breast cancer. Pharmacol Ther 206: 107437, 2020.
8. Perou CM, Sørlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, Pollack JR, Ross DT, Johnsen H, Akslen LA, *et al*: Molecular portraits of human breast tumours. Nature 406: 747-752, 2000.
9. Dai X, Li T, Bai Z, Yang Y, Liu X, Zhan J and Shi B: Breast cancer intrinsic subtype classification, clinical use and future trends. Am J Cancer Res 5: 2929-2943, 2015.

10. Kapadia CH, Ioele SA and Day ES: Layer-by-layer assembled PLGA nanoparticles carrying miR-34a cargo inhibit the proliferation and cell cycle progression of triple-negative breast cancer cells. J Biomed Mater Res A 108: 601-613, 2020.
11. Tian Y, Xia S, Ma M and Zuo Y: LINC00096 promotes the proliferation and invasion by sponging miR-383-5p and regulating RBM3 expression in triple-negative breast cancer. Onco Targets Ther 12: 10569-10578, 2019.
12. Zheng S, Li M, Miao K and Xu H: lncRNA GAS5-promoted apoptosis in triple-negative breast cancer by targeting miR-378a-5p/SUFU signaling. J Cell Biochem 121: 2225-2235, 2020.
13. Umeh-Garcia M, Simion C, Ho PY, Batra N, Berg AL, Carraway KL, Yu A and Sweeney C: A novel bioengineered miR-127 prodrug suppresses the growth and metastatic potential of triple-negative breast cancer cells. Cancer Res 80: 418-429, 2020.
14. Das PK, Siddika MA, Asha SY, Aktar S, Rakib MA, Khanam JA, Pillai S and Islam F: MicroRNAs, a promising target for breast cancer stem cells. Mol Diagn Ther 24: 69-83, 2020.
15. Ge JH, Zhu JW, Fu HY, Shi WB and Zhang CL: An antisense oligonucleotide drug targeting miR-21 induces H1650 apoptosis and caspase activation. Technol Cancer Res Treat 18: 1533033819892263, 2019.
16. Guo H, Ingolia NT, Weissman JS and Bartel DP: Mammalian microRNAs predominantly act to decrease target mRNA levels. Nature 466: 835-840, 2010.
17. Di Leva G, Garofalo M and Croce CM: MicroRNAs in cancer. Ann Rev Pathol 9: 287-314, 2014.
18. Bertoli G, Cava C and Castiglioni I: MicroRNAs: New biomarkers for diagnosis, prognosis, therapy prediction and therapeutic tools for breast cancer. Theranostics 5: 1122-1143, 2015.
19. Abdolvahabi Z, Nourbakhsh M, Hosseinkhani S, Hesari Z, Alipour M, Jafarzadeh M, Ghorbanhosseini SS, Seiri P, Yousefi Z, Yarahmadi S and Golpour P: MicroRNA-590-3P suppresses cell survival and triggers breast cancer cell apoptosis via targeting sirtuin-1 and deacetylation of p53. J Cell Biochem 120: 9356-9368, 2019.
20. Shaffi SK, Galas D, Etheridge A and Argyropoulos C: Role of MicroRNAs in renal parenchymal diseases-a new dimension. Int J Mol Sci 19: 1797, 2018.
21. Chen E, Xu X, Liu R and Liu T: Small but heavy role: MicroRNAs in hepatocellular carcinoma progression. Biomed Res Int 2018: 6784607, 2018.
22. Svoronos AA, Engelman DM and Slack FJ: OncomiR or tumor suppressor? The duplicity of microRNAs in cancer. Cancer Res 76: 3666-3670, 2016.
23. Wu H, Wang Q, Zhong H, Li L, Zhang Q, Huang Q and Yu Z: Differentially expressed microRNAs in exosomes of patients with breast cancer revealed by next-generation sequencing. Oncol Rep 43: 240-250, 2020.
24. Farazi TA, Spitzer JI, Morozov P and Tuschl T: miRNAs in human cancer. J Pathol 223: 102-115, 2011.
25. Lu J, Getz G, Miska EA, Alvarez-Saavedra E, Lamb J, Peck D, Sweet-Cordero A, Ebert BL, Mak RH, Ferrando AA, *et al*: MicroRNA expression profiles classify human cancers. Nature 435: 834-838, 2005.
26. Visone R and Croce CM: MiRNAs and cancer. Am J Pathol 174: 1131-1138, 2009.
27. Reis-Filho JS, Weigelt B, Fumagalli D and Sotiriou C: Molecular profiling: Moving away from tumor philately. Sci Transl Med 2: 47ps43, 2010.
28. Sotiriou C and Pusztai L: Gene-expression signatures in breast cancer. N Engl J Med 360: 790-800, 2009.
29. Liu X, Yu H, Qiao Y, Yang J, Shu J, Zhang J, Zhang Z, He J and Li Z: Salivary Glycopatterns as potential biomarkers for screening of early-stage breast cancer. EBioMedicine 28: 70-79, 2018.
30. Gong C, Tan W, Chen K, You N, Zhu S, Liang G, Xie X, Li Q, Zeng Y, Ouyang N, *et al*: Prognostic value of a BCSC-associated MicroRNA signature in hormone receptor-positive HER2-negative breast cancer. EBioMedicine 11: 199-209, 2016.
31. Do SI, Kim HS, Kim K, Lee H, Do IG, Kim DH, Chae SW and Sohn JH: Predictive and prognostic value of sphingosine kinase 1 expression in patients with invasive ductal carcinoma of the breast. Am J Transl Res 9: 5684-5695, 2017.
32. Phillips SL, Williams CB, Zambrano JN, Williams CJ and Yeh ES: Connexin 43 in the development and progression of breast cancer: What's the connection? (Review). Int J Oncol 51: 1005-1013, 2017.
33. Katoh M: Canonical and non-canonical WNT signaling in cancer stem cells and their niches: Cellular heterogeneity, omics reprogramming, targeted therapy and tumor plasticity (Review). Int J Oncol 51: 1357-1369, 2017.
34. Javadian M, Shekari N, Soltani-Zangbar MS, Mohammadi A, Mansoori B, Maralbashi S, Shanehbandi D, Baradaran B, Darabi M and Kazemi T: Docosahexaenoic acid suppresses migration of triple-negative breast cancer cell through targeting metastasis-related genes and microRNA under normoxic and hypoxic conditions. J Cell Biochem 121: 2416-2427, 2020.
35. Zhao CH, Qu L, Zhang H and Qu R: Identification of breast cancer-related circRNAs by analysis of microarray and RNA-sequencing data: An observational study. Medicine 98: e18042, 2019.
36. Tang W, Li GS, Li JD, Pan WY, Shi Q, Xiong DD, Mo CH, Zeng JJ, Chen G, Feng ZB, *et al*: The role of upregulated miR-375 expression in breast cancer: An in vitro and in silico study. Pathol Res Pract 216: 152754, 2020.
37. Tungsukruthai S, Petpiroon N and Chanvorachote P: Molecular mechanisms of breast cancer metastasis and potential Anti-metastatic compounds. Anticancer Res 38: 2607-2618, 2018.
38. Li X, Dai D, Chen B, Tang H, Xie X and Wei W: Determination of the prognostic value of preoperative CA15-3 and CEA in predicting the prognosis of young patients with breast cancer. Oncol Lett 16: 4679-4688, 2018.
39. Duffy MJ, Evoy D and McDermott EW: CA 15-3: Uses and limitation as a biomarker for breast cancer. Clin Chim Acta 411: 1869-1874, 2010.
40. Xie S, Ding X, Mo W and Chen J: Serum tissue polypeptide-specific antigen is an independent predictor in breast cancer. Acta Histochem 116: 372-376, 2014.
41. Duffy MJ: Serum tumor markers in breast cancer: Are they of clinical value? Clin Chem 52: 345-351, 2006.
42. Weigel MT and Dowsett M: Current and emerging biomarkers in breast cancer: Prognosis and prediction. Endocr Relat Cancer 17: R245-R262, 2010.
43. Guo S, Zhang J, Wang B, Zhang B, Wang X, Huang L, Liu H and Jia B: A 5-serum miRNA panel for the early detection of colorectal cancer. Onco Targets Ther 11: 2603-2614, 2018.
44. Adams BD, Arem H, Hubal MJ, Cartmel B, Li F, Harrigan M, Sanft T, Cheng CJ, Pusztai L and Irwin ML: Exercise and weight loss interventions and miRNA expression in women with breast cancer. Breast Cancer Res Treat 170: 55-67, 2018.
45. Paszek S, Gabło N, Barnaś E, Szybka M, Morawiec J, Kołacińska A and Zawlik I: Dysregulation of microRNAs in triple-negative breast cancer. Ginekol Pol 88: 530-536, 2017.
46. Heneghan HM, Miller N, Lowery AJ, Sweeney KJ, Newell J and Kerin MJ: Circulating microRNAs as novel minimally invasive biomarkers for breast cancer. Ann Surg 251: 499-505, 2010.
47. Zhao H, Shen J, Medico L, Wang D, Ambrosone CB and Liu S: A pilot study of circulating miRNAs as potential biomarkers of early stage breast cancer. PLoS One 5: e13735, 2010.
48. Wang N, Wang L, Yang Y, Gong L, Xiao B and Liu X: A serum exosomal microRNA panel as a potential biomarker test for gastric cancer. Biochem Biophys Res Commun 493: 1322-1328, 2017.
49. Zhou X, Wen W, Zhu J, Huang Z, Zhang L, Zhang H, Qi LW, Shan X, Wang T, Cheng W, *et al*: A six-microRNA signature in plasma was identified as a potential biomarker in diagnosis of esophageal squamous cell carcinoma. Oncotarget 8: 34468-34480, 2017.
50. Motamedi M, Hashemzadeh Chaleshtori M, Ghasemi S and Mokarian F: Plasma level of miR-21 and miR-451 in primary and recurrent breast cancer patients. Breast Cancer (Dove Med Press) 11: 293-301, 2019.
51. Raheem AR, Abdul-Rasheed OF and Al-Naqqash MA: The diagnostic power of circulating micro ribonucleic acid 34a in combination with cancer antigen 15-3 as a potential biomarker of breast cancer. Saudi Med J 40: 1218-1226, 2019.
52. Zhang Z, Xu L, He L, Wang J, Shi X, Li Z, Shi S, Hou K, Teng Y and Qu X: MiR-891a-5p as a prognostic marker and therapeutic target for hormone receptor-positive breast cancer. J Cancer 11: 3771-3782, 2020.
53. Wu B, Liu G, Jin Y, Yang T, Zhang D, Ding L, Zhou F, Pan Y and Wei Y: miR-15b-5p promotes growth and metastasis in breast cancer by targeting HPSE2. Front Oncol 10: 108, 2020.
54. Xi Y, Nakajima G, Gavin E, Morris CG, Kudo K, Hayashi K and Ju J: Systematic analysis of microRNA expression of RNA extracted from fresh frozen and formalin-fixed paraffin-embedded samples. RNA 13: 1668-1674, 2007.

55. Hayes J, Peruzzi PP and Lawler S: MicroRNAs in cancer: Biomarkers, functions and therapy. Trends Mol Med 20: 460-469, 2014.
56. Treiber T, Treiber N and Meister G: Regulation of microRNA biogenesis and its crosstalk with other cellular pathways. Nat Rev Mol Cell Biol 20: 5-20, 2019.
57. Griffiths-Jones S, Saini HK, van Dongen S and Enright AJ: miRBase: Tools for microRNA genomics. Nucleic Acids Res 36: D154-D158, 2008.
58. Altuvia Y, Landgraf P, Lithwick G, Elefant N, Pfeffer S, Aravin A, Brownstein MJ, Tuschl T and Margalit H: Clustering and conservation patterns of human microRNAs. Nucleic Acids Res 33: 2697-2706, 2005.
59. Lee Y, Kim M, Han J, Yeom KH, Lee S, Baek SH and Kim VN: MicroRNA genes are transcribed by RNA polymerase II. EMBO J 23: 4051-4060, 2004.
60. Kim VN: MicroRNA precursors in motion: Exportin-5 mediates their nuclear export. Trends Cell Biol 14: 156-159, 2004.
61. Lee Y, Ahn C, Han J, Choi H, Kim J, Yim J, Lee J, Provost P, Rådmark O, Kim S and Kim VN: The nuclear RNase III Drosha initiates microRNA processing. Nature 425: 415-419, 2003.
62. Gregory RI, Yan KP, Amuthan G, Chendrimada T, Doratotaj B, Cooch N and Shiekhattar R: The Microprocessor complex mediates the genesis of microRNAs. Nature 432: 235-240, 2004.
63. Lund E, Güttinger S, Calado A, Dahlberg JE and Kutay U: Nuclear export of microRNA precursors. Science 303: 95-98, 2004.
64. Grishok A, Pasquinelli AE, Conte D, Li N, Parrish S, Ha I, Baillie DL, Fire A, Ruvkun G and Mello CC: Genes and mechanisms related to RNA interference regulate expression of the small temporal RNAs that control C. elegans developmental timing. Cell 106: 23-34, 2001.
65. Bernstein E, Caudy AA, Hammond SM and Hannon GJ: Role for a bidentate ribonuclease in the initiation step of RNA interference. Nature 409: 363-366, 2001.
66. Hutvágner G, McLachlan J, Pasquinelli AE, Bálint E, Tuschl T and Zamore PD: A cellular function for the RNA-interference enzyme Dicer in the maturation of the let-7 small temporal RNA. Science 293: 834-838, 2001.
67. Ha M and Kim VN: Regulation of microRNA biogenesis. Nat Rev Mol Cell Biol 15: 509-524, 2014.
68. Valencia-Sanchez MA, Liu J, Hannon GJ and Parker R: Control of translation and mRNA degradation by miRNAs and siRNAs. Genes Dev 20: 515-524, 2006.
69. Parker R and Song H: The enzymes and control of eukaryotic mRNA turnover. Nat Struct Mol Biol 11: 121-127, 2004.
70. Mathe A, Scott RJ and Avery-Kiejda KA: MiRNAs and other epigenetic changes as biomarkers in triple negative breast cancer. Int J Mol Sci 16: 28347-28376, 2015.
71. Petersen CP, Bordeleau ME, Pelletier J and Sharp PA: Short RNAs repress translation after initiation in mammalian cells. Mol Cell 21: 533-542, 2006.
72. Sharma S and Lu HC: microRNAs in Neurodegeneration: Current findings and potential impacts. J Alzheimers Dis Parkinsonism 8: 420, 2018.
73. Mohr AM and Mott JL: Overview of microRNA biology. Semin Liver Dis 35: 3-11, 2015.
74. Lewis BP, Burge CB and Bartel DP: Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets. Cell 120: 15-20, 2005.
75. Ma F, Liu X, Li D, Wang P, Li N, Lu L and Cao X: MicroRNA-466l upregulates IL-10 expression in TLR-triggered macrophages by antagonizing RNA-binding protein tristetraprolin-mediated IL-10 mRNA degradation. J Immunol 184: 6053-6059, 2010.
76. Abolghasemi M, Tehrani SS, Yousefi T, Karimian A, Mahmoodpoor A, Ghamari A, Jadidi-Niaragh F, Yousefi M, Kafil HS, Bastami M, *et al*: MicroRNAs in breast cancer: Roles, functions, and mechanism of actions. J Cell Physiol 235: 5008-5029, 2020.
77. Tavakolian S, Goudarzi H, Eslami G and Faghihloo E: Transcriptional regulation of epithelial to mesenchymal transition related genes by lipopolysaccharide in human cervical cancer cell line HeLa. Asian Pac J Cancer Prev 20: 2455-2461, 2019.
78. Calin GA, Ferracin M, Cimmino A, Di Leva G, Shimizu M, Wojcik SE, Iorio MV, Visone R, Sever NI, Fabbri M, *et al*: A MicroRNA signature associated with prognosis and progression in chronic lymphocytic leukemia. N Engl J Med 353: 1793-1801, 2005.
79. Brennecke J, Hipfner DR, Stark A, Russell RB and Cohen SM: Bantam encodes a developmentally regulated microRNA that controls cell proliferation and regulates the proapoptotic gene hid in Drosophila. Cell 113: 25-36, 2003.
80. Pourbagheri-Sigaroodi A, Bashash D, Safaroghli-Azar A, Farshi-Paraasghari M, Momeny M, Mansoor FN and Ghaffari SH: Contributory role of microRNAs in anti-cancer effects of small molecule inhibitor of telomerase (BIBR1532) on acute promyelocytic leukemia cell line. Eur J Pharmacol 846: 49-62, 2019.
81. Wang W and Luo YP: MicroRNAs in breast cancer: Oncogene and tumor suppressors with clinical potential. J Zhejiang Univ Sci B 16: 18-31, 2015.
82. Toda H, Seki N, Kurozumi S, Shinden Y, Yamada Y, Nohata N, Moriya S, Idichi T, Maemura K, Fujii T, *et al*: RNA-sequence-based microRNA expression signature in breast cancer: Tumor-suppressive miR-101-5p regulates molecular pathogenesis. Mol Oncol 14: 426-446, 2020.
83. Ma J and Zhou Z: Downregulation of miR-302b is associated with poor prognosis and tumor progression of breast cancer. Breast Cancer 27: 291-298, 2020.
84. Tavakolian S, Goudarzi H, Torfi F and Faghihloo E: Evaluation of microRNA-9 and -192 expression levels as biomarkers in patients suffering from breast cancer. Biomed Rep 12: 30-34, 2020.
85. Sun WM, Tao W, Li JC, Zhu DM and Miao Y: MicroRNA-296 functions as a tumor suppressor in breast cancer by targeting FGFR1 and regulating the Wnt/β-catenin signaling pathway. Eur Rev Med Pharmacol Sci 23: 10422-10432, 2019.
86. Cai F, Chen L, Sun Y, He C, Fu D and Tang J: MiR-539 inhibited the malignant behaviors of breast cancer cells by targeting SP1. Biochem Cell Biol 98: 426-433, 2020.
87. Cai WL, Huang WD, Li B, Chen TR, Li ZX, Zhao CL, Li HY, Wu YM, Yan WJ and Xiao JR: microRNA-124 inhibits bone metastasis of breast cancer by repressing Interleukin-11. Mol Cancer 17: 9, 2018.
88. Niu XY, Zhang ZQ and Ma PL: MiRNA-221-5p promotes breast cancer progression by regulating E-cadherin expression. Eur Rev Med Pharmacol Sci 23: 6983-6990, 2019.
89. Orangi E and Motovali-Bashi M: Evaluation of miRNA-9 and miRNA-34a as potential biomarkers for diagnosis of breast cancer in Iranian women. Gene 687: 272-279, 2019.
90. Jiang H, Cheng L, Hu P and Liu R: MicroRNA-663b mediates TAM resistance in breast cancer by modulating TP73 expression. Mol Med Rep 18: 1120-1126, 2018.
91. Aoki N, Amano S, Ando M, Fukuda A, Ami K, Imai K, Ganno H, Sugita H, Amagasa H, Arai K, *et al*: A study of therapy for locally advanced breast cancer with metastasis. Gan To Kagaku Ryoho 43: 1432-1434, 2016 (In Japanese).
92. Anderson GM: Breast-cancer recurrence after stopping endocrine therapy. N Engl J Med 378: 870, 2018.
93. Neophytou C, Boutsikos P and Papageorgis P: Molecular mechanisms and emerging therapeutic targets of triple-negative breast cancer metastasis. Front Oncol 8: 31, 2018.
94. Huang L, Tang X, Shi X and Su L: miR-532-5p promotes breast cancer proliferation and migration by targeting RERG. Exp Ther Med 19: 400-408, 2020.
95. Robertson NM and Yigit MV: The role of microRNA in resistance to breast cancer therapy. Wiley Interdiscip Rev RNA 5: 823-33, 2014.
96. Vranic S, Palazzo J, Sanati S, Florento E, Contreras E, Xiu J, Swensen J and Gatalica Z: Potential novel therapy targets in neuroendocrine carcinomas of the breast. Clin Breast Cancer 19: 131-136, 2019.
97. Ang D, Ballard M, Beadling C, Warrick A, Schilling A, O'Gara R, Pukay M, Neff TL, West RB, Corless CL and Troxell ML: Novel mutations in neuroendocrine carcinoma of the breast: Possible therapeutic targets. Appl Immunohistochem Mol Morphol 23: 97-103, 2015.
98. Folgueira MA, Carraro DM, Brentani H, Patrão DF, Barbosa EM, Netto MM, Caldeira JR, Katayama ML, Soares FA, Oliveira CT, *et al*: Gene expression profile associated with response to doxorubicin-based therapy in breast cancer. Clin Cancer Res 11: 7434-7443, 2005.
99. Shackelford RE, Mayhall K, Maxwell NM, Kandil E and Coppola D: Nicotinamide phosphoribosyltransferase in malignancy: A review. Genes Cancer 4: 447-456, 2013.
100. Grolla AA, Travelli C, Genazzani AA and Sethi JK: Extracellular nicotinamide phosphoribosyltransferase, a new cancer metabokine. Br J Pharmacol 173: 2182-2194, 2016.

101. Bolandghamat Pour Z, Nourbakhsh M, Mousavizadeh K, Madjd Z, Ghorbanhosseini SS, Abdolvahabi Z, Hesari Z and Ezzati Mobasser S: Suppression of nicotinamide phosphoribosyltransferase expression by miR-154 reduces the viability of breast cancer cells and increases their susceptibility to doxorubicin. BMC Cancer 19: 1027, 2019.
102. Liu J, Yang L, Guo X, Jin G, Wang Q, Lv D, Liu J, Chen Q, Song Q and Li B: Sevoflurane suppresses proliferation by upregulating microRNA-203 in breast cancer cells. Mol Med Rep 18: 455-460, 2018.
103. Valadi H, Ekström K, Bossios A, Sjöstrand M, Lee JJ and Lötvall JO: Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. Nat Cell Biol 9: 654-659, 2007.
104. Nie H, Xie X, Zhang D, Zhou Y, Li B, Li F, Li F, Cheng Y, Mei H, Meng H and Jia L: Use of lung-specific exosomes for miRNA-126 delivery in non-small cell lung cancer. Nanoscale 12: 877-887, 2020.
105. Li XJ, Ren ZJ, Tang JH and Yu Q: Exosomal MicroRNA MiR-1246 promotes cell proliferation, invasion and drug resistance by targeting CCNG2 in breast cancer. Cell Physiol Biochem 44: 1741-1748, 2017.
106. Li Y, Dai Y, Zhang X and Chen J: Three-layered polyplex as a microRNA targeted delivery system for breast cancer gene therapy. Nanotechnology 28: 285101, 2017.
107. Jafari SH, Saadatpour Z, Salmaninejad A, Momeni F, Mokhtari M, Nahand JS, Rahmati M, Mirzaei H and Kianmehr M: Breast cancer diagnosis: Imaging techniques and biochemical markers. J Cell Physiol 233: 5200-5213, 2018.
108. Zarredar H, Ansarin K, Baradaran B, Shekari N, Eyvazi S, Safari F and Farajnia S: Critical microRNAs in lung cancer: Recent advances and potential applications. Anticancer Agents Med Chem 18: 1991-2005, 2018.
109. Hu J, Markowitz GJ and Wang X: Noncoding RNAs regulating cancer signaling network. Adv Exp Med Biol 927: 297-315, 2016.
110. Chen W, Zhou S, Mao L, Zhang H, Sun D, Zhang J, Li J and Tang JH: Crosstalk between TGF-beta signaling and miRNAs in breast cancer metastasis. Tumour Biol 37: 10011-10019, 2016.
111. Smith B, Agarwal P and Bhowmick NA: MicroRNA applications for prostate, ovarian and breast cancer in the era of precision medicine. Endocr Relat Cancer 24: R157-R172, 2017.
112. Kia V, Sharif Beigli M, Hosseini V, Koochaki A, Paryan M and Mohammadi-Yeganeh S: Is miR-144 an effective inhibitor of PTEN mRNA: A controversy in breast cancer. In vitro Cell Dev Biol Anim 54: 621-628, 2018.
113. Yue D and Qin X: miR-182 regulates trastuzumab resistance by targeting MET in breast cancer cells. Cancer Gene Ther 26: 1-10, 2019.
114. Zhang Y, Zhao Z, Li S, Dong L, Li Y, Mao Y, Liang Y, Tao Y and Ma J: Inhibition of miR-214 attenuates the migration and invasion of triple-negative breast cancer cells. Mol Med Rep 19: 4035-4042, 2019.
115. Samadi P, Saki S, Dermani FK, Pourjafar M and Saidijam M: Emerging ways to treat breast cancer: Will promises be met? Cell Oncol (Dordr) 41: 605-621, 2018.
116. Xu C, Sun X, Qin S, Wang H, Zheng Z, Xu S, Luo G, Liu P, Liu J, Du N, *et al*: Let-7a regulates mammosphere formation capacity through Ras/NF-κB and Ras/MAPK/ERK pathway in breast cancer stem cells. Cell Cycle 14: 1686-1697, 2015.
117. Zhao Y, Yang F, Li W, Xu C, Li L, Chen L, Liu Y and Sun P: miR-29a suppresses MCF-7 cell growth by downregulating tumor necrosis factor receptor 1. Tumour Biol 39: 1010428317692264, 2017.
118. Wang R and Nakshatri H: Systemic actions of breast cancer facilitate functional limitations. Cancers 12: 194, 2020.
119. Ruan L and Qian X: MiR-16-5p inhibits breast cancer by reducing AKT3 to restrain NF-κB pathway. Biosci Rep 39: BSR20191611, 2019.
120. D'Souza LC, Mishra S, Chakraborty A, Shekher A, Sharma A and Gupta SC: Oxidative stress and cancer development: Are noncoding RNAs the missing links? Antioxid Redox Signal 33: 1209-1229, 2020.
121. Mohammady M, Ghetmiri SI, Baharizade M, Morowvat MH and Torabi S: Expanding the Biotherapeutics realm via miR-34a: 'Potent Clever Little' agent in breast cancer therapy. Curr Pharm Biotechnol 20: 665-673, 2019.
122. Pan JY, Zhang F, Sun CC, Li SJ, Li G, Gong FY, Bo T, He J, Hua RX, Hu WD, *et al*: miR-134: A human cancer suppressor? Mol Ther Nucleic Acids 6: 140-149, 2017.
123. Majumder M, Dunn L, Liu L, Hasan A, Vincent K, Brackstone M, Hess D and Lala PK: COX-2 induces oncogenic micro RNA miR655 in human breast cancer. Sci Rep 8: 327, 2018.
124. Zou Y, Lin X, Bu J, Lin Z, Chen Y, Qiu Y, Mo H, Tang Y, Fang W and Wu Z: Timeless-Stimulated miR-5188-FOXO1/β-Catenin-c-Jun feedback loop promotes stemness via Ubiquitination of β-catenin in breast cancer. Mol Ther 28: 313-327, 2020.
125. Han B, Peng X, Cheng D, Zhu Y, Du J, Li J and Yu X: Delphinidin suppresses breast carcinogenesis through the HOTAIR/microRNA-34a axis. Cancer Sci 110: 3089-3097, 2019.
126. Ju J, Zhu AJ and Yuan P: Progress in targeted therapy for breast cancer. Chronic Dis Transl Med 4: 164-175, 2018.
127. Liu H, Li A, Sun Z, Zhang J and Xu H: Long non-coding RNA NEAT1 promotes colorectal cancer progression by regulating miR-205-5p/VEGFA axis. Hum Cell 33: 386-396, 2020.
128. Kaban K, Salva E and Akbuga J: Modulation of the dual-faced effects of miR-141 with chitosan/miR-141 nanoplexes in breast cancer cells. J Gene Med 21: e3116, 2019.
129. Han M, Wang F, Gu Y, Pei X, Guo G, Yu C, Li L, Zhu M, Xiong Y and Wang Y: MicroRNA-21 induces breast cancer cell invasion and migration by suppressing smad7 via EGF and TGF-β pathways. Oncol Rep 35: 73-80, 2016.
130. Qian B, Katsaros D, Lu L, Preti M, Durando A, Arisio R, Mu L and Yu H: High miR-21 expression in breast cancer associated with poor disease-free survival in early stage disease and high TGF-beta1. Breast Cancer Res Treat 117: 131-140, 2009.
131. Citron F, Segatto I, Vinciguerra GLR, Musco L, Russo F, Mungo G, D'Andrea S, Mattevi MC, Perin T, Schiappacassi M, *et al*: Downregulation of miR-223 expression is an early event during mammary transformation and confers resistance to CDK4/6 inhibitors in luminal breast cancer. Cancer Res 80: 1064-1077, 2020.
132. Lee A, Moon BI and Kim TH: BRCA1/BRCA2 pathogenic variant breast cancer: Treatment and prevention strategies. Ann Lab Med 40: 114-121, 2020.
133. Vinayak S, Tolaney SM, Schwartzberg L, Mita M, McCann G, Tan AR, Wahner-Hendrickson AE, Forero A, Anders C, Wulf GM, *et al*: Open-label clinical trial of Niraparib combined with pembrolizumab for treatment of advanced or metastatic triple-negative breast cancer. JAMA Oncol 5: 1132-1140, 2019.
134. Wang X and Liu Y: PD-L1 expression in tumor infiltrated lymphocytes predicts survival in triple-negative breast cancer. Pathol Res Pract 216: 152802, 2020.
135. Yahya SM and Elsayed GH: A summary for molecular regulations of miRNAs in breast cancer. Clin Biochem 48: 388-396, 2015.
136. Grelet S and Howe PH: hnRNP E1 at the crossroads of translational regulation of epithelial-mesenchymal transition. J Cancer Metastasis Treat 5: 16, 2019.
137. Campbell K and Casanova J: A common framework for EMT and collective cell migration. Development 143: 4291-4300, 2016.
138. Schaeffer D, Somarelli JA, Hanna G, Palmer GM and Garcia-Blanco MA: Cellular migration and invasion uncoupled: Increased migration is not an inexorable consequence of epithelial-to-mesenchymal transition. Mol Cell Biol 34: 3486-3499, 2014.
139. Son H and Moon A: Epithelial-mesenchymal transition and cell invasion. Toxicol Res 26: 245-252, 2010.
140. Gregory PA, Bert AG, Paterson EL, Barry SC, Tsykin A, Farshid G, Vadas MA, Khew-Goodall Y and Goodall GJ: The miR-200 family and miR-205 regulate epithelial to mesenchymal transition by targeting ZEB1 and SIP1. Nat Cell Biol 10: 593-601, 2008.
141. Wardhani BW, Puteri MU, Watanabe Y, Louisa M, Setiabudy R and Kato M: TGF-β-induced TMEPAI attenuates the response of triple-negative breast cancer cells to doxorubicin and paclitaxel. J Exp Pharmacol 12: 17-26, 2020.
142. Wang S, Huang M, Wang Z, Wang W, Zhang Z, Qu S and Liu C: MicroRNA-133b targets TGFβ receptor I to inhibit TGF-β-induced epithelial-to-mesenchymal transition and metastasis by suppressing the TGF-β/SMAD pathway in breast cancer. Int J Oncol 55: 1097-1109, 2019.
143. Zeng Y, Gao T, Huang W, Yang Y, Qiu R, Hou Y, Yu W, Leng S, Feng D, Liu W, *et al*: MicroRNA-455-3p mediates GATA3 tumor suppression in mammary epithelial cells by inhibiting TGF-β signaling. J Biol Chem 294: 15808-15825, 2019.

144. Guerrero-Zotano A, Mayer IA and Arteaga CL: PI3K/AKT/mTOR: Role in breast cancer progression, drug resistance, and treatment. Cancer Metastasis Rev 35: 515-524, 2016.
145. Fruman DA, Chiu H, Hopkins BD, Bagrodia S, Cantley LC and Abraham RT: The PI3K pathway in human disease. Cell 170: 605-635, 2017.
146. Li S, Xu JJ and Zhang QY: MicroRNA-132-3p inhibits tumor malignant progression by regulating lysosomal-associated protein transmembrane 4 beta in breast cancer. Cancer Sci 110: 3098-3109, 2019.
147. Yu X, Li R, Shi W, Jiang T, Wang Y, Li C and Qu X: Silencing of MicroRNA-21 confers the sensitivity to tamoxifen and fulvestrant by enhancing autophagic cell death through inhibition of the PI3K-AKT-mTOR pathway in breast cancer cells. Biomed Pharmacother 77: 37-44, 2016.
148. Wang B, Wang H and Yang Z: MiR-122 inhibits cell proliferation and tumorigenesis of breast cancer by targeting IGF1R. PLoS One 7: e47053, 2012.
149. Thompson KN, Whipple RA, Yoon JR, Lipsky M, Charpentier MS, Boggs AE, Chakrabarti KR, Bhandary L, Hessler LK, Martin SS and Vitolo MI: The combinatorial activation of the PI3K and Ras/MAPK pathways is sufficient for aggressive tumor formation, while individual pathway activation supports cell persistence. Oncotarget 6: 35231-35246, 2015.
150. Carlomagno F and Chiariello M: Growth factor transduction pathways: Paradigm of anti-neoplastic targeted therapy. J Mol Med (Berl) 92: 723-733, 2014.
151. Osaki LH and Gama P: MAPKs and signal transduction in the control of gastrointestinal epithelial cell proliferation and differentiation. Int J Mol Sci 14: 10143-10161, 2013.
152. Johnston SR, Semiglazov VF, Manikhas GM, Spaeth D, Romieu G, Dodwell DJ, Wardley AM, Neven P, Bessems A, Park YC, *et al*: A phase II, randomized, blinded study of the farnesyltransferase inhibitor tipifarnib combined with letrozole in the treatment of advanced breast cancer after antiestrogen therapy. Breast Cancer Res Treat 110: 327-335, 2008.
153. Song C, Liu LZ, Pei XQ, Liu X, Yang L, Ye F, Xie X, Chen J, Tang H and Xie X: miR-200c inhibits breast cancer proliferation by targeting KRAS. Oncotarget 6: 34968-34978, 2015.
154. Chen P, Xu W, Luo Y, Zhang Y, He Y, Yang S and Yuan Z: MicroRNA 543 suppresses breast cancer cell proliferation, blocks cell cycle and induces cell apoptosis via direct targeting of ERK/MAPK. Onco Targets Ther 10: 1423-1431, 2017.
155. Xu Q, Jiang Y, Yin Y, Li Q, He J, Jing Y, Qi YT, Xu Q, Li W, Lu B, *et al*: A regulatory circuit of miR-148a/152 and DNMT1 in modulating cell transformation and tumor angiogenesis through IGF-IR and IRS1. J Mol Cell Biol 5: 3-13, 2013.
156. Wu H, Wang G, Wang Z, An S, Ye P and Luo S: A negative feedback loop between miR-200b and the nuclear factor-κB pathway via IKBKB/IKK-β in breast cancer cells. FEBS J 283: 2259-2271, 2016.
157. Xie M, Fu Z, Cao J, Liu Y, Wu J, Li Q and Chen Y: MicroRNA-132 and microRNA-212 mediate doxorubicin resistance by down-regulating the PTEN-AKT/NF-κB signaling pathway in breast cancer. Biomed Pharmacother 102: 286-294, 2018.
158. Wang L, Wang YX, Chen LP and Ji ML: Upregulation of microRNA-181b inhibits CCL18-induced breast cancer cell metastasis and invasion via the NF-κB signaling pathway. Oncol Lett 12: 4411-4418, 2016.
159. Senthil Kumar KJ, Gokila Vani M, Hsieh HW, Lin CC, Liao JW, Chueh PJ and Wang SY: MicroRNA-708 activation by glucocorticoid receptor agonists regulate breast cancer tumorigenesis and metastasis via downregulation of NF-κB signaling. Carcinogenesis 40: 335-348, 2019.
160. Jiang H, Li X, Wang W and Dong H: Long non-coding RNA SNHG3 promotes breast cancer cell proliferation and metastasis by binding to microRNA-154-3p and activating the notch signaling pathway. BMC Cancer 20: 838, 2020.
161. Sun X, Huang T, Liu Z, Sun M and Luo S: LncRNA SNHG7 contributes to tumorigenesis and progression in breast cancer by interacting with miR-34a through EMT initiation and the Notch-1 pathway. Eur J Pharmacol 856: 172407, 2019.
162. Lan L, Wang Y, Pan Z, Wang B, Yue Z, Jiang Z, Li L, Wang C and Tang H: Rhamnetin induces apoptosis in human breast cancer cells via the miR-34a/Notch-1 signaling pathway. Oncol Lett 17: 676-682, 2019.
163. Kang L, Mao J, Tao Y, Song B, Ma W, Lu Y, Zhao L, Li J, Yang B and Li L: MicroRNA-34a suppresses the breast cancer stem cell-like characteristics by downregulating Notch1 pathway. Cancer Sci 106: 700-708, 2015.
164. Li WJ, Xie XX, Bai J, Wang C, Zhao L and Jiang DQ: Increased expression of miR-1179 inhibits breast cancer cell metastasis by modulating Notch signaling pathway and correlates with favorable prognosis. Eur Rev Med Pharmacol Sci 22: 8374-8382, 2018.
165. Ren L, Chen H, Song J, Chen X, Lin C, Zhang X, Hou N, Pan J, Zhou Z, Wang L, *et al*: MiR-454-3p-Mediated Wnt/β-catenin signaling Antagonists suppression promotes breast cancer metastasis. Theranostics 9: 449-465, 2019.
166. Xie Q, Wang S, Zhao Y, Zhang Z, Qin C and Yang X: MicroRNA-216a suppresses the proliferation and migration of human breast cancer cells via the Wnt/β-catenin signaling pathway. Oncol Rep 41: 2647-2656, 2019.
167. Liu S, Wang Z, Liu Z, Shi S, Zhang Z, Zhang J and Lin H: miR-221/222 activate the Wnt/β-catenin signaling to promote triple-negative breast cancer. J Mol Cell Biol 10: 302-315, 2018.
168. Tan Z, Zheng H, Liu X, Zhang W, Zhu J, Wu G, Cao L, Song J, Wu S, Song L and Li J: MicroRNA-1229 overexpression promotes cell proliferation and tumorigenicity and activates Wnt/β-catenin signaling in breast cancer. Oncotarget 7: 24076-24087, 2016.
169. Liu F, Liu Y, Shen J, Zhang G and Han J: MicroRNA-224 inhibits proliferation and migration of breast cancer cells by down-regulating Fizzled 5 expression. Oncotarget 7: 49130-49142, 2016.