SPANDIDOS PUBLICATIONS

ONCOLOGY LETTERS 28: 431, 2024

Role of microRNAs in triple-negative breast cancer and new therapeutic concepts (Review)

SHAOFENG YANG* and DONGHAI LI*

Department of Thyroid and Breast Surgery, Affiliated Hospital of Inner Mongolia Medical University, Inner Mongolia Medical University, Hohhot, Inner Mongolia Autonomous Region 010050, P.R. China

Received March 12, 2024; Accepted June 27, 2024

DOI: 10.3892/ol.2024.14565

Abstract. Breast cancer has surpassed lung cancer as the most prevalent malignancy affecting women worldwide. Triple-negative breast cancer (TNBC) is the type of breast cancer with the worst prognosis. As a heterogeneous disease, TNBC has a pathogenesis that involves multiple oncogenic pathways, including involvement of gene mutations and alterations in signaling pathways. MicroRNAs (miRNAs) are small endogenous, single-stranded non-coding RNAs that bind to the 3' untranslated region of target cell mRNAs to negatively regulate the gene expression of these specific mRNAs. Therefore, miRNAs are involved in cell growth, development, division and differentiation stages. miRNAs are also involved in gene targeting in tumorigenesis, tumor growth and the regulation of metastasis, including in breast cancer. Meanwhile, miRNAs also regulate components of signaling pathways. In this review, the role of miRNAs in the TNBC signaling pathway discovered in recent years is described in detail. The new concept of bi-targeted therapy for breast cancer using miRNA and artificial intelligence is also discussed.

Contents

1. Introduction
2. miRNAs
3. Signal regulation in breast cancer
4. Role of miRNAs in different signaling pathways
5. New ideas for bi-directional treatment of breast cancer with miRNA and artificial intelligence (AI)
6. Summary and outlook

Correspondence to: Dr Donghai Li, Department of Thyroid and Breast Surgery, Affiliated Hospital of Inner Mongolia Medical University, Inner Mongolia Medical University, 5 Xinhua Street, Huimin, Hohhot, Inner Mongolia Autonomous Region 010050, P.R. China
E-mail: 41031510@qq.com

*Contributed equally

Key words: microRNA, signaling pathways, triple-negative breast cancer, artificial intelligence, treatment methods

1. Introduction

Breast cancer is the most common malignant tumor in women worldwide, and the incidence of breast cancer is increasing in all countries. In China, the incidence and mortality rates of breast cancer are the highest of all tumors affecting women (1-3). Annually, ~1 million cases of triple-negative breast cancer (TNBC) are considered to be diagnosed worldwide (4). TNBC is characterized by decreased estrogen receptor (ER), progesterone receptor (PR) and human epidermal receptor (HER2) expression. According to previousa previous study, most patients with TNBC harbor a chromosomal 5q deletion (5). Breast cancer can be categorized into four subtypes (luminal A, luminal B, HER2$^+$ and TNBC) based on the expression of the ER, PR and HER2, and the different subtypes can be treated accordingly (6,7). There are four main signaling pathways related to TNBC, namely, the JAK/STAT, PI3K/AKT/mTOR, TGF-β and INF-γ pathways (8).

MicroRNAs (miRNAs) can regulate parts of the phosphatidylinositol 3-kinase (PI3K) signaling pathway (9). Complex interactions between the PI3K/AKT/mammalian target of rapamycin (mTOR) pathway and several interacting cellular signaling cascades can promote breast cancer progression (10). PI3K is an important protein in the AKT signaling pathway, which is involved in cell survival, differentiation, growth, glucose transport and glucose utilization (11). Insulin-like growth factor (IGF-1) is a self-phosphorylating ligand that stimulates downstream responses, transforming growth factor β (TGF-β) alters cell growth and metabolism by entering the nucleus through cross-linking complexes, and the kinase transcription factor is an autophosphorylated ligand that stimulates downstream responses. The pregnancy-associated plasma protein-A/IGF binding protein/IGF axis plays an important role in TNBC motility and epithelial-mesenchymal transition (EMT). This pathway influences TNBC cell migration and motility (12). Janus kinase (JAK)/STAT, is inextricably linked to TNBC progression, and has a role in breast cell genesis and pathology. miRNAs are circulating non-coding RNA molecules, 17-27 nucleotides in length, that regulate the

post-transcriptional expression of genes (such as oncogenes) in oncogenic pathways (13). Depending on the progression- or inhibition-promoting function of miRNAs, they can be used as oncogenes or tumor suppressors, respectively (14). Different signaling pathways promote different cell growth modes, and miRNAs, as common components, play a role in promoting or inhibiting cell growth.

In the present review, literature from the past 5 years was collected for examination In contrast to the previous single study of a signaling pathway, the present review examines four different signaling pathways and compares the microRNAs that play a role in the signaling pathways, and describes the co-expression of miR-21. Therefore, the aim of the present review was to examine the specific role of miRNAs in four key signaling pathways in breast cancer, and to understand the crosstalk and influence of the signaling pathways with miRNA.

2. miRNAs

miRNAs are short-stranded non-coding RNAs consisting of 17-27 nucleotides that are found in animals, plants and viruses, and which can negatively regulate the gene expression of mRNA (15,16). Gene expression relies on an effector ribonucleoprotein complex termed the RNA-induced silencing complex (RISC), for which mRNAs act as target recognizers. The Ago family of proteins and their array of auxiliary components work together to assemble RISCs (17). The complex has an intrinsic ability to bind to typical 3' untranslated regions (3'UTRs) that are specific to its cytoplasmic mRNA targets. The binding to the mRNA is based on the complementarity between the base pairing at the 5' end of the mature miRNA or open reading frame and the cytoplasmic mRNA molecule. The binding site, termed the seed region, is 6-8 bp from the 5' end of the miRNA. The short length of the binding site allows the miRNA to target and bind to a large number of different mRNAs (18-20). The combination of RISC and other genes is in turn the combination of miRNA and other genes, and therefore both play a role in the degradation, extension or activation of mRNA. If the composition of RISC is modified, or the composition of Ago protein is changed, the role of RISC will be changed. As such, the mechanism of specific miRNAs in the regulation of genes becomes controllable, which can be utilized to understand the role of miRNA in the expression of different genes. The role of miRNAs in breast cancer is partly via signaling pathways. There are four major signaling pathways in breast cancer, and miRNAs are differentially expressed in different signaling pathways and thus play different roles. Ultimately, all miRNAs have an excitatory or inhibitory effect on tumor development. Although different miRNAs play different roles in different signaling pathways, the final effects are the same or similar.

3. Signal regulation in breast cancer

JAK/STAT pathway. Breast cancer has different onset and progression processes according to the different subtypes, which can be linked to different signaling pathways. JAK/STAT is a signaling pathway that has an impact on both breast cancer development and metastasis. It has been demonstrated that the expression and active form of STAT3 is detected in >50% of breast cancer cases, and JAK/STAT signaling has become an emerging therapeutic target in a wide range of malignant tumors (21-23). STAT family members not only transduce signals used for transcription, but also regulate mitochondrial synthesis and metabolism, and have a role in compartmentalization of the nucleus and genome integrity (24). Numerous reports suggest that the acquisition of mutations that alter the function of STAT proteins underlies tumor cell genesis (25-28). STAT proteins do not accomplish tasks independently and function alongside cytokines, inducible factor expression or phosphorylation modifications (29). When JAK/STAT ligand and receptor binding is activated, JAK binds non-covalently to the receptor structure, after which the kinase activity of JAK is activated and phosphorylates the tyrosine residues in the receptor region. Next, the phosphorylated receptor residues recruit STAT through the SH2 structure, and the two combine to form a heterodimer, which translocates to the nucleus to carry out a variety of biological responses in the pathway and the occurrence of disease (30).

TGF-β pathway. TGF-β is known to reprogram the tumor microenvironment in TNBC; it suppresses the immune system by increasing collagen production in cancer-associated fibroblasts (31). The TGF-β pathway has different roles in different stages of tumors. In the early stage of tumors, the TGF-β pathway induces apoptosis and never curbs the development of tumor cells, but in the late stage of the disease, it promotes cell secretion and infiltration, and accelerates disease progression (32). TGF-β binds to two receptors to exert cellular effects, namely, TGFβ-type RI (TGFβRI) and TGF-β type RII (TGFβRII). Initially, TGF-β binds to TGFβRII, and then TGFβRII phosphorylates and activates TGFβRI. The three form a heterodimeric complex to bind an intracellular effector molecule termed SMAD, after which the receptor-regulated-SMAD-common mediator-SMAD complex enters the nucleus and recruits additional co-transcriptional activators, repressors and/or cofactors (32-35).

IGF1 receptor (IGF-1R) pathway. IGF-1R is a cell-surface transmembrane tyrosine kinase receptor consisting of two α and two β subunits, the β subunits of which contain a tyrosine catalytic structural domain. IGF-1R promotes a cascade reaction through ligand binding, the basis of which is that IGF-1R autophosphorylates to activate a variety of downstream signaling pathways, including the PI3K and AKT signaling pathways (36). It is possible that this pathway influences breast cancer development by acting as an upstream signal, activated by autophosphorylation, and then activating downstream signaling pathways for cell proliferation, division and differentiation. This approach may intersect with other signaling pathways in a one-to-many signaling activation process.

PI3K/AKT/mTOR signaling pathway. PI3Ks are a class of lipid kinases that are classified as classes I, II or III in mammals (37). The present review focuses on class I, which has been shown to be strongly associated with the development of cancer (38). The target of PI3K downstream signaling is AKT, a serine/threonine kinase with three isoforms, and this kinase acts in the biological oxidation of glucose and in

Table I. Expression and role of miRNAs in different signaling pathways in breast cancer.

Signaling pathway	miRNA	Role
PI3K/AKT/mTOR	miR-21	Alteration of PTEN expression by different miR-21 to distinguish benign and malignant tumors
	miR-10b	Maintains stem cell self-renewal
	miR-221	Control of tumor progression
	miR-222	Control of tumor progression
	miR-99a	Inhibits tumor cell migration
	miR-100	Control of the cell cycle
JAK/STAT	miR-221/222	Regulation of angiogenesis, lymph node metastasis
	miR-30d	Direct targeting of SOX4 to exert its tumor suppressor effect
	miR-205	Inhibits tumor progression
	miR-31	Promotes breast stem cell and epithelial cell value enhancement
	miR-124	Inhibits breast cancer cell proliferation and invasion
	miR-21	Auxiliary pathway enhancement
	miR-1207-5P/505/148a	Inhibits cancer metastasis
TGF-β	miR-133b	Associated with the initiation of signaling pathways
	miR-133b	Inhibits breast cancer cell invasion
	miR-21	Promotes breast cancer progression
IGF-1R	miR-148a-3p	Promotes breast cancer development and synergizes with other signaling pathways

miR/miRNA, microRNA; PI3K, phosphatidylinositol 3-kinase; mTOR, mammalian target of rapamycin; JAK, Janus kinase; TGF-β, transforming growth factor β; IGF-1R, insulin-like growth factor receptor 1.

cell growth, reproduction and survival (39). The next target is also a serine/threonine kinase, mTOR, which consists of two complex proteins that are important in the regulation of cell cycle progression and growth factors (40). In total, 30-40% of patients with breast cancer have mutations in the PI3K gene, which leads to hyperactivation of PI3K isoforms (41), and this pathway is common to multiple downstream target cells. The cascade reaction resulting from hyperactivation of PI3K may underlie cellular carcinogenesis. PI3Ks promote phosphatidylinositol (3,4,5)-trisphosphate (PIP3) production through phosphorylation of phosphatidylinositol, and docking of AKT to the N region of PIP3 facilitates translocation to the cell membrane and promotes AKT activation, resulting in phosphorylation of serine or threonine residues of AKT (41). The pathways of various signaling pathways may be different, but most pathogenesis caused by signaling pathways is in the form of one-to-many, in which a cascade reaction leads to 'explosive' growth. Therefore, in the cases of mutations in breast cancer genes caused by alterations in signaling pathways, it may be more optimal to treat the downstream signaling targets and upstream trigger points, to curb the subsequent cascade of changes (42,43). miRNAs play different roles in different signaling pathways, and there are connections between different signaling pathways, as shown in Figure 1.

4. Role of miRNAs in different signaling pathways

Different miRNAs are associated with different signaling pathways. In this section, the miRNAs in the signaling pathways of TNBC are summarized. TNBC is currently the most invasive and the most poorly treated type of breast cancer due to a lack of hormone receptors to target. However, the emergence of miRNAs as new biomarkers has brought new light to the treatment of TNBC. The roles of different miRNAs in different signaling pathways are summarized in Table I.

Role of miRNAs in the PI3K/AKT/mTOR pathway. The PI3K/AKT/mTOR signaling pathway plays a key role in causing cancer and promoting tumor growth and survival, and it is typically activated in TNBC (44). Previous studies have shown that miRNA expression is involved in carcinogenesis and is also a notable regulator of PI3K/AKT (45,46). PI3K can be activated by kinases, cells, receptors and other factors to complete autophosphorylation to PIP3, after which PIP3 binds to and activates AKT. PTEN can also dephosphorylate PIP3 to form PIP2, which inactivates downstream AKT by preventing it from covalently binding to PIP3 (46).

miR-21/10b/221/222 (Table I) and others have a notable influence on this pathway. miRNA-21 has been shown to bind to the 3'UTR of PTEN to reduce PTEN levels. miRNA overexpression or PTEN inhibition interferes with cell replication by regulating cell cycle proteins to prolong cell division (47). Serum levels of miR-21 can be used as a PTEN regulator to differentiate between benign and malignant tumors (low expression) and healthy cells (high expression). miR-21 levels decline after surgery, are elevated in advanced stages of tumors and may be associated with lymph node metastasis (48). In addition, PTEN levels decline by as much as 80% after upregulation of miR-21 (42). miR-221/222 act as negative regulators of PTEN in breast cancer and appear

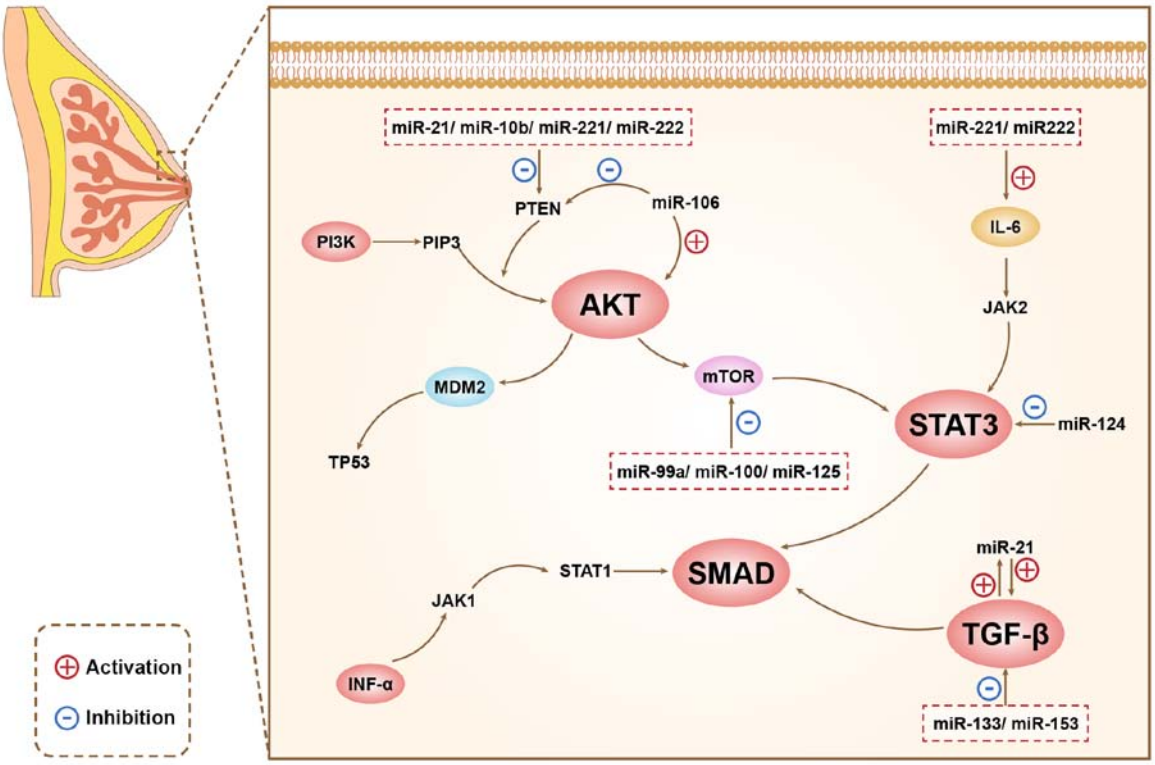

Figure 1. Linkages and roles of miRNAs in different signaling pathways. miR/miRNA, microRNA; PTEN, phosphatase and tensin homolog; IL-6, interleukin 6; mTOR, mammalian target of rapamycin; JAK1, Janus kinase 1; MDM2, E3 ubiquitin-protein ligase Mdm2; PIP3, phosphatidylinositol (3,4,5)-trisphosphate; PI3K, phosphatidylinositol 3-kinase; TGF-β, transforming growth factor β.

to have a regulatory effect on breast cancer progenitor cells, achieving control of tumor progression by downregulating PTEN levels (49). However, miR-10b is known to maintain self-renewal of cancer stem cells by downregulating PTEN and activating AKT (50,51). mTOR is a downstream member of the AKT pathway and can also phosphorylate AKT at ser473 to fully activate it (52). miR-99a is an inhibitor of downstream signaling by inhibiting mTOR expression *in vivo* to control cell migration and invasion (53). miR-204 also targets mTOR as an anti-oncogene in breast cancer (54). In addition, miR-100 controls the progression of breast cancer by blocking the cell cycle and downregulating mTOR expression, which reduces the effect of the entire pathway. miR-125 directly reduces the expression of mTOR, which differs from miR-100, as miR-100 indirectly reduces mTOR expression (55). In addition, miR-15 and miR-16 have also been shown to have an inhibitory effect on breast cancer (55-59).

Role of miRNAs in the JAK/STAT pathway. miRNAs can also regulate the JAK/STAT pathway. JAK is a tyrosine kinase, and the JAK/STAT signaling pathway is activated when JAK binds to and interacts with receptors such as cytokines (60). These transduction and transcriptional activators ultimately enter the nucleus to participate in cellular replication and transcription, apoptosis and metastasis, and miRNAs are involved in these regulatory processes. miR-221/222 can activate interleukin (IL)-6-dependent-NF-κB and STAT3 via lipocalin receptor 1, activation of STAT3 is important for breast cancer survival and tumorigenesis, with important implications (61,62). In addition to its oncogenic and tumor-suppressive effects, miR-205 has also been shown to have a notable role in the maintenance of TNBC stem cell characteristics by SUM159PT (preventing downstream cell renewal by blocking STAT downstream signaling), which has a high probability of inhibiting breast cancer through blocking STAT signaling, thus restricting cancer cell division and migration (63). High expression of miR-31 in mammary stem cells promotes mammary epithelial cell proliferation and stem cell expansion, which also reduces tumor growth through various signaling pathways such as the STAT pathway (64). miR-124, as an inhibitory factor, directly targets STAT3 in breast cancer, an interaction which can inhibit the growth and invasion of breast cancer cells. When miR-124 is upregulated, it will reduce the level of STAT3 and related proteins in breast cancer cells, and reduce the expansion of breast cancer (65). In addition to positive regulation, miRNAs also negatively regulate STAT. miR-1207-5P and miR-505/148a can inhibit STAT expression to activate the corresponding EMT/Wnt signaling molecule to inhibit cancer metastasis (66,67).

Role of miRNAs in the TGF-β pathway. A total of 33 members of the human TGF-β family bind both TGFβRI and TGFβRII receptors. These receptors are serine/threonine kinases that can be considered as intracellular signaling pathways that initiate SMAD intracellular effectors in the form of heterodimers. Compared with that in normal breast tissues, the transcriptional expression of TGFβRI was higher in breast cancer tissues, the expression of miR-133b was negatively correlated with TGFβRI and miR-133b expression was lower in tumor tissues (68). Similarly, TGFβRII expression was higher

in breast cancer tissues than in normal breast tissues, but the expression of TGFβRII was negatively correlated with the expression of miR-153, which was decreased in breast cancer tissues (69). Furthermore, overexpression of miR-133b significantly inhibited the function of TGFβRI transduction in the TGF-β signaling pathway and also inhibited TGFβ-induced endometrial stromal transformation and breast cancer cell invasion (68). It was found that miRNAs can not only affect the function of TGF-β, but can also be affected by TGF-β signaling. Compared with its role in normal breast tissues, TGFβI upregulated the expression of miR-21 and downregulated the expression of miR-196a-3p, both of which were significantly associated with breast cancer progression (70,71). In TNBC, miR-21 is upregulated through TGF-β1 and then through interaction with oncogenes. Therefore, in TNBC, miR-21 upregulation or downregulation provides a further explanation for tumor promotion or inhibition.

In the relationship between TGF-β and miRNAs, it is difficult to say which influences the other, but it is more akin to a mutually constraining relationship or fundamentally a crosstalk between short-stranded non-coding RNAs and the signaling pathway as a whole. Unlike other signaling pathways, this signaling pathway is more of an initiator, as TGF-β can influence the transduction of mTOR and EGFR, and in short, it is an alteration in TGF-β that first leads to the subsequent signaling crosstalk (72).

Role of miRNAs in the IGF-1R pathway. In the 46% of patients with TNBC and IGF-1R alterations, there is an association with poor survival (73). IGF-1R interacts with other pathways to upregulate tumor stem cells in TNBC (74). As such, when the level of IGF-1 is reduced, the number of tumor stem cells is also reduced. It has also been shown that there is a significant relationship between IGF-1 expression and drug resistance in TNBC (75). IGFs are categorized into two types, IGF1 and IGF2, which are both classes of polypeptides with effects on growth (76). IGF1 is a major target gene of growth hormone, its post-transcriptional product has a major role in growth and development, and high circulating levels of IGF1 are present in human cancer (77). Moreover, IGF-1R is not mutated in most cancer types, therefore expression levels are assessed to predict the cancer outcome (77). IGF1 promotes breast cancer progression by forming an insulin-like substrate complex that preferentially activates the PI3K/AKT pathway thereby altering survival genes (78). miR-148a-3p targets the mRNA of DNA transmethylase 1, thereby enhancing target gene IGF1 expression (79). In addition, miR-148a-3p attenuates the expression of p53, which is a negative transcriptional regulator of IGFR, and thus elevated levels of miR-148a-3p are positively associated with breast cancer (80,81). However, miR-21-5p is strongly associated with PI3K/AKT. miR-21-5p inhibits PTEN expression thereby enhancing PI3K/AKT/mTOR signaling (82).

Role of miRNAs in the breast cancer microenvironment. In addition to crosstalk within and between signaling pathways, miRNAs also influence cell chemotaxis and are enriched in the tumor microenvironment (83). During tumorigenesis, tumor cells produce non-coding RNAs that regulate monocyte recruitment and differentiation to the tumor site by affecting the expression of inflammatory factors or macrophages (84). miR-149 directly targets colony stimulating factor 1 mRNA in breast cancer cells, resulting in a significant reduction in macrophage levels in primary tumors (85). In addition, miR-19 targets PTEN to enhance the polarization of IL-17-producing T cells, and miR-15/16 is targeted to induce the expression of FOXP3, thus affecting the expression of $CD4^+$ T cells (86-88). In the tumor microenvironment, miRNAs not only affect increase or decrease the number of tumor cells, but also have other mechanisms that effect tumor cells. For instance, the production of miR-146a-5p by breast cancer cells forms a crosstalk with tumor cells and macrophages, thus altering the whole tumor microenvironment. Specifically, miR-146a-5p inhibits macrophages, which leads to the escape of tumor cells from the microenvironment (89). Finally, in the tumor microenvironment, the number of infiltrating lymphocytes indicates the antitumor immune efficiency. miR-155 is able to activate the immune system to infiltrate tumor cells, thus an increase in miR-155 levels is beneficial to increase the fight against tumors (90). Therefore, miRNAs play a role in signaling pathways, as well as in the tumor microenvironment where the signaling pathways are located.

5. New ideas for bi-directional treatment of breast cancer with miRNA and artificial intelligence (AI)

New AI technologies for breast cancer detection. The high incidence and mortality rates of breast cancer, and its late detection, have indicated that early and accurate screening of breast cancer is particularly important. Diagnostic imaging has been widely used for breast cancer detection and staging, but a high workload and the clarity of the images greatly mislead clinicians when making accurate judgments (91). Image-based AI technology optimizes the role of computer-aided diagnosis (CAD) in the clinic, improving accuracy (92). Deep-learning algorithms used for image recognition analysis mainly include convolutional neural networks (CNNs), deep CNNs, fully convolutional networks, recurrent neural networks and generative adversarial networks (93). The final target is decomposed into a number of visible layers and the data input is used for multiple image extraction in these visible layers. Next, a representative feature image is output from the subsequent analysis of the extracted layers. The main part of breast cancer AI examination includes image segmentation and identification of benign and malignant tumors (94,95). Mammography is the mainstay of early breast cancer screening (96). Obtaining high-resolution images allows the images to be preserved and further used regardless of age and size. Full-field mammography has the capability of inputting raw images and outputting processed images, where AI analyzes the images and analyzes the breast mass, mass segmentation, tissue density and risk assessment. The breast mass is the most common manifestation of breast cancer assessment and therefore CAD becomes one of the most important steps (97). Another method to assess the risk of breast cancer is calcification. Calcification foci in X-rays are classified as microcalcifications or macrocalcifications, and while it is difficult to identify microcalcifications via manual visualization, the CAD system is able to detect these

foci (98). This allows for timely detection and intervention for patients with early stage breast cancer. In addition, the use of AI can automate the process of differentiating breast lumps from normal tissues in mammograms, which was theorized to greatly improve the prognosis of patients with early stage disease (99). However, the reality is not as optimistic. CAD became part of mammography screening 20 years ago, but the data so far have shown that it does not necessarily have an advantage over a single reading by a radiologist. The combination of the two methods has, however, been reported to have an improved success rate in determining the early stage of breast cancer in patients (100). AI for the detection of breast cancer still has a greater outlook and development space, as the performance of the algorithm, the identification of different breast tissues and algorithm judgment still need to be updated. We consider that, if the algorithms can be updated for differentiating benign and malignant pathology, this method will be a more convenient and efficient way for diagnosing breast cancer compared with puncture or intraoperative pathology.

Changes in miRNA expression in early breast cancer. miRNAs contribute to *de novo* markers of early breast cancer, particularly in patients who are too young to be screened by mammography according to guidelines, and in whom AI is therefore not particularly useful. miRNAs are involved in oncogenic or oncostatic gene signaling pathways through the silencing or degradation of mRNA molecules to regulate post-transcriptional expression (101). The stability and ease of detection of miRNAs has led to the detection of new biomarkers for patients with early stage breast cancer (102). The relative expression of miR-21, miR-155, miR-23a, miR-130a, miR-145, miR-425-5p and miR-139-5p is significantly upregulated in plasma samples from patients with early stage breast cancer (103). Therefore, the combination of the early detection of miRNA expression and AI technology may be of great help for the identification of early stage breast cancer in patients. Furthermore, early stage patients often do not exhibit obvious clinical symptoms, and clinical doctors rarely perform needle biopsy pathology diagnostics on patients with early stage breast cancer. Due to the lack of clear symptoms, clinical doctors mostly opt for observation or follow-up, potentially delaying the optimal treatment timing for patients.

miRNA for breast cancer treatment. It is known that miR-21 is expressed at elevated levels in patients with breast cancer, and miR-21 inhibitors have been tested for their ability to reduce cell metastasis, suggesting that inhibition of miR-21 could lead to a reduction in metastasis and enhanced breast cancer treatment. This means that miR-21 inhibitor treatment brings the hope of new therapeutic approaches for patients (104). In addition, miR-21 also has a significant role in drug resistance. Specifically, miR-21 regulates the resistance of breast cancer cells to azithromycin by targeting phosphatases and PTEN (105). It has been reported that miR-21 also targets TGF-β, which can increase the rapid cell growth and transformation of cancer cells. Therefore, knockdown of this specific miRNA could be targeted to treat breast cancer (105,106). miR-155 is also a notable marker. miR-155 is involved in the regulation of breast cancer growth and is an oncogenic miRNA. It has been demonstrated that miR-155 leads to telomere destabilization and that this mechanism is mediated by telomeric repeat binding factor 1 (TRF1) expression (107,108). In addition, miR-125b has a targeting effect on human invasive breast cancer. miR-125b downregulated in breast cancer reduces the expression of mucin 1 (MUC1), an oncoprotein, and the silencing of MUC1 leads to DNA damage-induced apoptosis in cancer cells (109). Jang *et al* (75) investigated the effect of miR-125 deregulation on the formation of metastasis and found that miR-125b can cause metastasis by targeting MCF1, which is a TRF1. miR-125b also induces metastasis by targeting StAR-related lipid transfer domain containing 13 mRNA in MCF-7 and MDA-MB-231 breast cancer cells (110). miR-17, as a potential regulator, can directly negatively regulate c-Jun activation domain binding protein-1 (JAB1) *in vitro*. In tissue samples from patients with TNBC, both the JAB1 gene and protein were highly expressed, while miR-21 expression was low. It has been suggested that miR-17 inhibits JAB1 cell division through E2F amplification, thus suppressing tumors (111). miR-21 is known to be expressed at elevated levels in patients with breast cancer, and miR-21 inhibitors have been tested for their ability to reduce cellular migration, suggesting that inhibition of miR-21 could lead to a reduction in metastasis and cell division in breast cancer. Therefore, miR-21 inhibitor therapy offers patients the hope of new treatments (104,112). In addition, miR-21 also has a major role in drug resistance. Specifically, miR-21 regulates azithromycin resistance in breast cancer cells, which is mediated by targeting phosphatases and PTEN. It has been reported that miR-21 can also target TGF-β, which can increase the exponential growth and transformation of cancer cells. Therefore, the knockdown of this specific miRNA may be a targeted therapy for breast cancer (105,106,113). miR-155 is also an important marker that is involved in the growth regulation of breast cancer and is an oncogenic miRNA that has been shown to cause telomere destabilization through the expression of TRF1 (107,108). The therapeutic approach of miRNA functions more like a source, paving the way for new strategies in breast cancer drug therapy. Building upon the earlier discussion, investigating the positive and negative regulatory mechanisms of miR-21 and miR-155, and researching corresponding targeted drugs, can either stimulate or inhibit the concentration of a specific biomarker, thereby achieving treatment for breast cancer.

Co-expressed miRNAs in the four key signaling pathways. It has been shown that inflammatory factors and other substances in the body are controlled by high levels of miR-21, which in turn activates the expression of STAT3 (114). When miR-21 expression is knocked down, the expression of STAT3 is suppressed *in vivo* (115). Moreover, STAT3 in turn affects the expression of miR-21 (116). When the expression level of STAT3 is changed, the oncogenic signaling pathway of breast cancer will be altered, meaning that miR-21 influences STAT3 and thus affects the development of breast cancer. Similarly, miR-21 is not only involved in the expression of STAT3 pathway in breast cancer, but also in the expression of other signaling pathways. miR-21 acts as an oncogenic marker by targeting PTEN, which is an inhibitor of the PI3K/AKT pathway. Therefore, miR-21 enhances the action of the PI3K/AKT pathway (117-119). A study has shown that the levels of

miR-21 and TGF-β increase with breast cancer stage (120). With in-depth research, it was found that miR-21 upregulation in breast cancer tissues was closely related to TGF-β and mediated the effects of TGF-β on cell invasion and chemotherapy through direct downregulation of PTEN and phosphatase (70). In other words, miR-21 indirectly affected the expression of TGF-β and thus the treatment of breast cancer. Finally, miR-21 downregulation also affects the expression of IGF-1 (121).

6. Summary and outlook

As a simple and detectable marker, miRNAs are notably expressed in the early stages of tumors, which provides a convenient method for subsequent analysis. Moreover, different miRNAs have different roles among the four signaling pathways and cannot be replaced. By decreasing or increasing the expression of genes, miRNA expression leads to the alteration of gene expression direction, which leads to the development of cancer. Moreover, the miRNAs that play a role are different based on the type of breast cancer and signaling pathway, raising the question of whether the same miRNAs can also form a crosstalk between different signaling pathways. Aberrant expression of miRNAs is closely related to the development and progression of breast cancer and can be used as a potential therapeutic target. Combining AI with miRNA therapy may lead to more comprehensive and precise breast cancer treatment programs. Furthermore, understanding the role of miRNAs in breast cancer can be improved through big data analysis via AI, which can optimize treatment strategies for individualized and efficient treatment. However, numerous challenges remain to be faced in both fields, including issues such as validation in clinical practice and regulatory approval. With the deepening of research and the continuous development of technology, more breakthroughs are expected in the future.

The innovation of the present review lies in the fact that miRNA, as a new biomarker for breast cancer diagnosis, treatment and prognosis, has a profound future research prospect. In addition, miRNA also targets downstream target genes and proteins, which is a new research direction for breast cancer treatment. miRNAs also link a variety of different signaling pathways, which can be used to form a non-coding RNA network for the treatment of breast cancer. It is also evident that miRNA levels are significantly changed in the blood of patients with breast cancer and are relatively easy indicators to extract and obtain.

The roles of miRNAs, IGF-1 and IGF-1R have been established in breast cancer, related receptors and related signaling pathways. miRNA has been found to participate in a number of signaling pathways, including PI3K/AKT and other pathways. The present review mainly discussed the association and role of miR-21 and other related factors in four key signaling pathways, as miR-21 is expressed in all four of these pathways. miR-21 plays a similar role in inhibiting tumor development in different breast cancer signaling pathways; therefore, the present review also linked the crosstalk between the four signaling pathways in breast cancer. The present review supplements the previous shortcomings of the influence of a single upstream target gene or signal on breast cancer, and provides a new direction for future breast cancer research. In addition, miR-21 is a key regulator of various oncogenic pathways and can interact with circular RNA and long non-coding RNA to regulate tumorigenesis. The present review focused on the relationship between miRNA and signaling pathways, which plays an important role in tumor formation and development, and in diagnostic markers.

Acknowledgements

Not applicable.

Funding

This review was supported by The Natural Science Foundation of Inner Mongolia Autonomous Region (grant no. 2022MS08010) and The Graduate Student Excellence Program (grant no. YKDD2023ZY001).

Availability of data and materials

Not applicable.

Authors' contributions

SY was responsible for drafting the manuscript, building the logical framework, literature collection, retrieval, reading, and embellishment of the manuscript's description and typographical layout. DL was responsible for manuscript review and revision, and communication with reviewers. Both authors have read and approved the final version of the manuscript. Data authentication is not applicable.

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. DeSantis CE, Ma J, Gaudet MM, Newman LA, Miller KD, Goding Sauer A, Jemal A and Siegel RL: Breast cancer statistics, 2019.CA Cancer J Clin 69: 438-451, 2019.
2. Global Burden of Disease Cancer Collaboration; Fitzmaurice C, Akinyemiju TF, Al Lami FH, Alam T, Alizadeh-Navaei R, Allen C, Alsharif U, Alvis-Guzman N, Amini E, *et al*: Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2016: A systematic analysis for the global burden of disease study. JAMA Oncol 4: 1553-1568, 2018.
3. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, Yu XQ and He J: Cancer statistics in China, 2015.CA Cancer J Clin 66: 115-132, 2016.
4. Elizabeth MS, Cristina SBJ and Christian CG: Immunotherapy in combination with chemotherapy for triple-negative breast cancer. Mini Rev Med Chem 24: 431-439, 2024.
5. Herschkowitz JI, Simin K, Weigman VJ, Mikaelian I, Usary J, Hu Z, Rasmussen KE, Jones LP, Assefnia S, Chandrasekharan S, *et al*: Identification of conserved gene expression features between murine mammary carcinoma models and human breast tumors. Genome Biol 8: R76, 2007.

6. Pernas S and Tolaney SM: HER2-positive breast cancer: New therapeutic frontiers and overcoming resistance.Ther Adv Med Oncol 11: 1758835919833519, 2019.
7. Ferrari P, Scatena C, Ghilli M, Bargagna I, Lorenzini G and Nicolini A: Molecular mechanisms, biomarkers and emerging therapies for chemotherapy resistant TNBC. Int J Mol Sci 23: 1665, 2022.
8. Guo XQ and Hua YM: Circular RNAs: novel regulators of resistance to systemic treatments in breast cancer. Neoplasma 69: 1019-1028, 2022.
9. Majidinia M and Yousefi B: DNA damage response regulation by microRNAs as a therapeutic target in cancer.DNA Repair (Amst) 47: 1-11, 2016.
10. Abu-Alghayth MH, Khan FR, Belali TM, Abalkhail A, Alshaghdali K, Nassar SA, Almoammar NE, Almasoudi HH, Hessien KBG, Aldossari MS and Binshaya AS: The emerging role of noncoding RNAs in the PI3K/AKT/mTOR signalling pathway in breast cancer. Pathol Res Pract 255: 155180, 2024.
11. Elfaki I, Mir R, Abu-Duhier FM, Khan R and Sakran M: Phosphatidylinositol 3-kinase Glu545Lys and His1047Tyr Mutations are not Associated with T2D. Curr Diabetes Rev 16: 881-888, 2020.
12. Poddar A, Ahmady F, Rao SR, Sharma R, Kannourakis G, Prithviraj P and Jayachandran A: The role of pregnancy associated plasma protein-A in triple negative breast cancer: A promising target for achieving clinical benefits. J Biomed Sci 31: 23, 2024.
13. 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.
14. Calin GA, Dumitru CD, Shimizu M, Bichi R, Zupo S, Noch E, Aldler H, Rattan S, Keating M, Rai K, *et al*: Frequent deletions and down-regulation of micro-RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia. Proc Natl Acad Sci USA 99: 15524-15529, 2002.
15. Abdelfattah AM, Park C and Choi MY: Update on non-canonical microRNAs. Biomol Concepts 5: 275-287, 2014.
16. O'Brien J, Hayder H, Zayed Y and Peng C: Overview of MicroRNA biogenesis, mechanisms of actions, and circulation. Front Endocrinol (Lausanne) 9: 402, 2018.
17. Kawamata T and Tomari Y: Making RISC.Trends Biochem Sci 35: 368-376, 2010.
18. Krol J, Loedige I and Filipowicz W: The widespread regulation of microRNA biogenesis, function and decay. Nat Rev Genet 11: 597-610, 2010.
19. Qin W, Shi Y, Zhao B, Yao C, Jin L, Ma J and Jin Y: miR-24 regulates apoptosis by targeting the open reading frame (ORF) region of FAF1 in cancer cells. PLoS One 5: e9429, 2010.
20. Ørom UA, Nielsen FC and Lund AH: MicroRNA-10a binds the 5'UTR of ribosomal protein mRNAs and enhances their translation. Mol Cell 30: 460-471, 2008.
21. Banerjee K and Resat H: Constitutive activation of STAT3 in breast cancer cells: A review. Int J Cancer 138: 2570-2578, 2016.
22. Chung SS, Giehl N, Wu Y and Vadgama JV: STAT3 activation in HER2-overexpressing breast cancer promotes epithelial-mesenchymal transition and cancer stem cell traits. Int J Oncol 44: 403-411, 2014.
23. Küçük C, Jiang B, Hu X, Zhang W, Chan JK, Xiao W, Lack N, Alkan C, Williams JC, Avery KN, *et al*: Activating mutations of STAT5B and STAT3 in lymphomas derived from γδ-T or NK cells. Nat Commun 6: 6025, 2015.
24. Heppler LN and Frank DA: Rare mutations provide unique insight into oncogenic potential of STAT transcription factors. J Clin Invest 128: 113-115, 2018.
25. Rajala HL, Eldfors S, Kuusanmäki H, van Adrichem AJ, Olson T, Lagström S, Andersson EI, Jerez A, Clemente MJ, Yan Y, *et al*: Discovery of somatic STAT5b mutations in large granular lymphocytic leukemia. Blood 121: 4541-4550, 2013.
26. de Araujo ED, Keserű GM, Gunning PT and Moriggl R: Targeting STAT3 and STAT5 in Cancer. Cancers (Basel) 12: 2002, 2020.
27. Owen KL, Brockwell NK and Parker BS: JAK-STAT Signaling: A double-edged sword of immune regulation and cancer progression. Cancers (Basel) 11: 2002, 2019.
28. Zhao L, Pang A and Li Y: Function of GCN5 in the TGF-β1-induced epithelial-to-mesenchymal transition in breast cancer. Oncol Lett 16: 3955-3963, 2018.
29. López-Mejía JA, Mantilla-Ollarves JC and Rocha-Zavaleta L: Modulation of JAK-STAT Signaling by LNK: A forgotten oncogenic pathway in hormone receptor-positive breast cancer. Int J Mol Sci 24: 14777, 2023.
30. Budi EH, Duan D and Derynck R: Transforming Growth Factor-β Receptors and Smads: Regulatory complexity and functional versatility. Trends Cell Biol 27: 658-672, 2017.
31. Said SS and Ibrahim WN: Breaking Barriers: The promise and challenges of immune checkpoint inhibitors in triple-negative breast cancer. Biomedicines 12: 369, 2024.
32. Heldin CH and Moustakas A: Signaling Receptors for TGF-β Family Members. Cold Spring Harb Perspect Biol 8: a022053, 2016.
33. Wrana JL, Attisano L, Wieser R, Ventura F and Massagué J: Mechanism of activation of the TGF-beta receptor. Nature 370: 341-347, 1994.
34. Moustakas A, Souchelnytskyi S and Heldin CH: Smad regulation in TGF-beta signal transduction. J Cell Sci 114 (Pt 24): 4359-4369, 2001.
35. Christodoulou C, Oikonomopoulos G, Koliou GA, Kostopoulos I, Kotoula V, Bobos M, Pentheroudakis G, Lazaridis G, Skondra M, Chrisafi S, *et al*: Evaluation of the insulin-like growth factor receptor pathway in patients with advanced breast cancer treated with trastuzumab. Cancer Genomics Proteomics 15: 461-471, 2018.
36. Lee JS, Tocheny CE and Shaw LM: The insulin-like growth factor signaling pathway in breast cancer: An elusive therapeutic target. Life (Basel) 12: 1992, 2022.
37. Bilanges B, Posor Y and Vanhaesebroeck B: PI3K isoforms in cell signalling and vesicle trafficking. Nat Rev Mol Cell Biol 20: 515-534, 2019.
38. Vanhaesebroeck B, Perry MWD, Brown JR, André F and Okkenhaug K: PI3K inhibitors are finally coming of age. Nat Rev Drug Discov 20: 741-769, 2021.
39. Engelman JA: Targeting PI3K signalling in cancer: Opportunities, challenges and limitations. Nat Rev Cancer 9: 550-562, 2009.
40. Mayer IA and Arteaga CL: The PI3K/AKT pathway as a target for cancer treatment. Annu Rev Med 67: 11-28, 2016.
41. Tariq K and Luikart BW: Striking a balance: PIP(2) and PIP(3) signaling in neuronal health and disease. Explor Neuroprotective Ther 1: 86-100, 2021.
42. Hu M, Zhu S, Xiong S, Xue X and Zhou X: MicroRNAs and the PTEN/PI3K/Akt pathway in gastric cancer (Review). Oncol Rep 41: 1439-1454, 2019.
43. Li YJ, Li XF, Yang EH and Shi M: Reaserch Advances on the Role of PI3K/AKT Signaling Pathway and MiRNA in Acute T-Cell Lymphocytic Leukemia-Review. Zhongguo Shi Yan Xue Ye Xue Za Zhi 27: 1344-1347, 2019 (In Chinese).
44. Pereira B, Chin SF, Rueda OM, Vollan HK, Provenzano E, Bardwell HA, Pugh M, Jones L, Russell R, Sammut SJ, *et al*: The somatic mutation profiles of 2,433 breast cancers refines their genomic and transcriptomic landscapes. Nat Commun 7: 11479, 2016.
45. Huang J, Wang X, Wen G and Ren Y: miRNA-205-5p functions as a tumor suppressor by negatively regulating VEGFA and PI3K/Akt/mTOR signaling in renal carcinoma cells. Oncol Rep 42: 1677-1688, 2019.
46. Hoxhaj G and Manning BD: The PI3K-AKT network at the interface of oncogenic signalling and cancer metabolism. Nat Rev Cancer 20: 74-88, 2020.
47. Walter BA, Gómez-Macias G, Valera VA, Sobel M and Merino MJ: miR-21 expression in pregnancy-associated breast cancer: A possible marker of poor prognosis. J Cancer 2: 67-75, 2011.
48. Gimm O, Perren A, Weng LP, Marsh DJ, Yeh JJ, Ziebold U, Gil E, Hinze R, Delbridge L, Lees JA, *et al*: Differential nuclear and cytoplasmic expression of PTEN in normal thyroid tissue, and benign and malignant epithelial thyroid tumors. Am J Pathol 156: 1693-1700, 2000.
49. Li B, Lu Y, Wang H, Han X, Mao J, Li J, Yu L, Wang B, Fan S, Yu X and Song B: RETRACTED: miR-221/222 enhance the tumorigenicity of human breast cancer stem cells via modulation of PTEN/Akt pathway. Biomed Pharmacother 79: 93-101, 2016.
50. Li B, Lu Y, Wang H, Han X, Mao J, Li J, Yu L, Wang B, Fan S, Yu X and Song B: miR-221/222 enhance the tumorigenicity of human breast cancer stem cells via modulation of PTEN/Akt pathway. Biomed Pharmacother 79: 93-101, 2016.
51. Bahena-Ocampo I, Espinosa M, Ceballos-Cancino G, Lizarraga F, Campos-Arroyo D, Schwarz A, Maldonado V, Melendez-Zajgla J and Garcia-Lopez P: miR-10b expression in breast cancer stem cells supports self-renewal through negative PTEN regulation and sustained AKT activation. EMBO Rep 17: 648-658, 2016.

52. Sarbassov DD, Guertin DA, Ali SM and Sabatini DM: Phosphorylation and regulation of Akt/PKB by the rictor-mTOR complex. Science 307: 1098-1101, 2005.
53. Yang Z, Han Y, Cheng K, Zhang G and Wang X: miR-99a directly targets the mTOR signalling pathway in breast cancer side population cells. Cell Prolif 47: 587-595, 2014.
54. Imam JS, Plyler JR, Bansal H, Prajapati S, Bansal S, Rebeles J, Chen HI, Chang YF, Panneerdoss S, Zoghi B, *et al*: Genomic loss of tumor suppressor miRNA-204 promotes cancer cell migration and invasion by activating AKT/mTOR/Rac1 signaling and actin reorganization. PLoS One 7: e52397, 2012.
55. Zhang B, Zhao R, He Y, Fu X, Fu L, Zhu Z, Fu L and Dong JT: MicroRNA 100 sensitizes luminal A breast cancer cells to paclitaxel treatment in part by targeting mTOR. Oncotarget 7: 5702-5714, 2016.
56. Pakravan K, Babashah S, Sadeghizadeh M, Mowla SJ, Mossahebi-Mohammadi M, Ataei F, Dana N and Javan M: MicroRNA-100 shuttled by mesenchymal stem cell-derived exosomes suppresses in vitro angiogenesis through modulating the mTOR/HIF-1α/VEGF signaling axis in breast cancer cells. Cell Oncol (Dordr) 40: 457-470, 2017.
57. Janaki Ramaiah M, Lavanya A, Honarpisheh M, Zarea M, Bhadra U and Bhadra MP: MiR-15/16 complex targets p70S6 kinase 1 and controls cell proliferation in MDA-MB-231 breast cancer cells. Gene 552: 255-264, 2014.
58. Hu Y, Zhu Q and Tang L: MiR-99a antitumor activity in human breast cancer cells through targeting of mTOR expression. PLoS One 9: e92099, 2014.
59. Zhang ZW, Guo RW, Lv JL, Wang XM, Ye JS, Lu NH, Liang X and Yang LX: MicroRNA-99a inhibits insulin-induced proliferation, migration, dedifferentiation, and rapamycin resistance of vascular smooth muscle cells by inhibiting insulin-like growth factor-1 receptor and mammalian target of rapamycin. Biochem Biophys Res Commun 486: 414-422, 2017.
60. Banerjee S, Biehl A, Gadina M, Hasni S and Schwartz DM: JAK-STAT signaling as a target for inflammatory and autoimmune diseases: Current and Future Prospects. Drugs 77: 521-546, 2017.
61. Liang YK, Lin HY, Dou XW, Chen M, Wei XL, Zhang YQ, Wu Y, Chen CF, Bai JW, Xiao YS, *et al*: MiR-221/222 promote epithelial-mesenchymal transition by targeting Notch3 in breast cancer cell lines. NPJ Breast Cancer 4: 20, 2018.
62. Han M, Wang Y, Guo G, Li L, Dou D, Ge X, Lv P, Wang F and Gu Y: microRNA-30d mediated breast cancer invasion, migration, and EMT by targeting KLF11 and activating STAT3 pathway. J Cell Biochem 119: 8138-8145, 2018.
63. Mayoral-Varo V, Calcabrini A, Sánchez-Bailón MP and Martín-Pérez J: miR205 inhibits stem cell renewal in SUM159PT breast cancer cells. PLoS One 12: e0188637, 2017.
64. Lv C, Li F, Li X, Tian Y, Zhang Y, Sheng X, Song Y, Meng Q, Yuan S, Luan L, *et al*: MiR-31 promotes mammary stem cell expansion and breast tumorigenesis by suppressing Wnt signaling antagonists. Nat Commun 8: 1036, 2017.
65. Shi P, Chen C, Li X, Wei Z, Liu Z and Liu Y: MicroRNA-124 suppresses cell proliferation and invasion of triple negative breast cancer cells by targeting STAT3. Mol Med Rep 19: 3667-3675, 2019.
66. Qin Z, He W, Tang J, Ye Q, Dang W, Lu Y, Wang J, Li G, Yan Q and Ma J: MicroRNAs Provide Feedback Regulation of Epithelial-Mesenchymal Transition Induced by Growth Factors. J Cell Physiol 231: 120-129, 2016.
67. Tang Y, Wu B, Huang S, Peng X, Li X, Huang X, Zhou W, Xie P and He P: Downregulation of miR-505-3p predicts poor bone metastasis-free survival in prostate cancer. Oncol Rep 41: 57-66, 2019.
68. 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.
69. Wang J, Liang S and Duan X: Molecular mechanism of miR-153 inhibiting migration, invasion and epithelial-mesenchymal transition of breast cancer by regulating transforming growth factor beta (TGF-β) signaling pathway. J Cell Biochem 120: 9539-9546, 2019.
70. Dai X, Fang M, Li S, Yan Y, Zhong Y and Du B: miR-21 is involved in transforming growth factor β1-induced chemoresistance and invasion by targeting PTEN in breast cancer. Oncol Lett 14: 6929-6936, 2017.
71. Chen Y, Huang S, Wu B, Fang J, Zhu M, Sun L, Zhang L, Zhang Y, Sun M, Guo L and Wang S: Transforming growth factor-β1 promotes breast cancer metastasis by downregulating miR-196a-3p expression. Oncotarget 8: 49110-49122, 2017.
72. Yang Y, Hong M, Lian WW and Chen Z: Review of the pharmacological effects of astragaloside IV and its autophagic mechanism in association with inflammation. World J Clin Cases 10: 10004-10016, 2022.
73. Zhang GN, Zhang YK, Wang YJ, Gupta P, Ashby CR Jr, Alqahtani S, Deng T, Bates SE, Kaddoumi A, Wurpel JND, *et al*: Epidermal growth factor receptor (EGFR) inhibitor PD153035 reverses ABCG2-mediated multidrug resistance in non-small cell lung cancer: In vitro and in vivo. Cancer Lett 424: 19-29, 2018.
74. Farabaugh SM, Boone DN and Lee AV: Role of IGF1R in breast cancer subtypes, stemness, and lineage differentiation. Front Endocrinol (Lausanne) 6: 59, 2015.
75. Jang GB, Hong IS, Kim RJ, Lee SY, Park SJ, Lee ES, Park JH, Yun CH, Chung JU, Lee KJ, *et al*: Wnt/β-Catenin Small-Molecule Inhibitor CWP232228 preferentially inhibits the growth of breast cancer stem-like cells. Cancer Res 75: 1691-1702, 2015.
76. Clemmons DR: Modifying IGF1 activity: An approach to treat endocrine disorders, atherosclerosis and cancer. Nat Rev Drug Discov 6: 821-833, 2007.
77. Cao J and Yee D: Disrupting Insulin and IGF receptor function in cancer. Int J Mol Sci 22: 555, 2021.
78. Bowers LW, Cavazos DA, Maximo IX, Brenner AJ, Hursting SD and deGraffenried LA: Obesity enhances nongenomic estrogen receptor crosstalk with the PI3K/Akt and MAPK pathways to promote in vitro measures of breast cancer progression. Breast Cancer Res 15: R59, 2013.
79. Xu Y, Chao L, Wang J and Sun Y: miRNA-148a regulates the expression of the estrogen receptor through DNMT1-mediated DNA methylation in breast cancer cells. Oncol Lett 14: 4736-4740, 2017.
80. Melnik BC: Milk disrupts p53 and DNMT1, the guardians of the genome: Implications for acne vulgaris and prostate cancer. Nutr Metab (Lond) 14: 55, 2017.
81. Li X, Tang X, Li K and Lu L: Evaluation of Serum MicroRNAs (miR-9-5p, miR-17-5p, and miR-148a-3p) as potential biomarkers of breast cancer. Biomed Res Int 2022: 9961412, 2022.
82. Chawra HS, Agarwal M, Mishra A, Chandel SS, Singh RP, Dubey G, Kukreti N and Singh M: MicroRNA-21's role in PTEN suppression and PI3K/AKT activation: Implications for cancer biology. Pathol Res Pract 254: 155091, 2024.
83. Ruskovska T, Budić-Leto I, Corral-Jara KF, Ajdžanović V, Arola-Arnal A, Bravo FI, Deligiannidou GE, Havlik J, Janeva M, Kistanova E, *et al*: Systematic analysis of nutrigenomic effects of polyphenols related to cardiometabolic health in humans-Evidence from untargeted mRNA and miRNA studies. Ageing Res Rev 79: 101649, 2022.
84. Curtale G, Rubino M and Locati M: MicroRNAs as molecular switches in macrophage activation. Front Immunol 10: 799, 2019.
85. Sánchez-González I, Bobien A, Molnar C, Schmid S, Strotbek M, Boerries M, Busch H and Olayioye MA: miR-149 suppresses breast cancer metastasis by blocking paracrine interactions with macrophages. Cancer Res 80: 1330-1341, 2020.
86. Zou X, Xia T, Li M, Wang T, Liu P, Zhou X, Huang Z and Zhu W: MicroRNA profiling in serum: Potential signatures for breast cancer diagnosis. Cancer Biomark 30: 41-53, 2021.
87. Warth SC, Hoefig KP, Hiekel A, Schallenberg S, Jovanovic K, Klein L, Kretschmer K, Ansel KM and Heissmeyer V: Induced miR-99a expression represses Mtor cooperatively with miR-150 to promote regulatory T-cell differentiation. EMBO J 34: 1195-1213, 2015.
88. Singh Y, Garden OA, Lang F and Cobb BS: MicroRNA-15b/16 enhances the induction of regulatory T cells by regulating the expression of rictor and mTOR. J Immunol 195: 5667-5677, 2015.
89. Simanovich E, Brod V, Rahat MM and Rahat MA: Function of miR-146a-5p in tumor cells as a regulatory switch between cell death and angiogenesis: Macrophage therapy revisited. Front Immunol 8: 1931, 2018.
90. Zarogoulidis P, Petanidis S, Domvri K, Kioseoglou E, Anestakis D, Freitag L, Zarogoulidis K, Hohenforst-Schmidt W and Eberhardt W: Autophagy inhibition upregulates CD4(+) tumor infiltrating lymphocyte expression via miR-155 regulation and TRAIL activation. Mol Oncol 10: 1516-1531, 2016.
91. Giger ML: Update on the potential of computer-aided diagnosis for breast cancer. Future Oncol 6: 1-4, 2010.
92. Bilska-Wolak AO, Floyd CE Jr, Lo JY and Baker JA: Computer aid for decision to biopsy breast masses on mammography: Validation on new cases. Acad Radiol 12: 671-680, 2005.

93. Nassif AB, Talib MA, Nasir Q, Afadar Y and Elgendy O: Breast cancer detection using artificial intelligence techniques: A systematic literature review. Artif Intell Med 127: 102276, 2022.
94. Yanagawa M, Niioka H, Hata A, Kikuchi N, Honda O, Kurakami H, Morii E, Noguchi M, Watanabe Y, Miyake J and Tomiyama N: Application of deep learning (3-dimensional convolutional neural network) for the prediction of pathological invasiveness in lung adenocarcinoma: A preliminary study. Medicine (Baltimore) 98: e16119, 2019.
95. Tran WT, Sadeghi-Naini A, Lu FI, Gandhi S, Meti N, Brackstone M, Rakovitch E and Curpen B: Computational radiology in breast cancer screening and diagnosis using artificial intelligence. Can Assoc Radiol J 72: 98-108, 2021.
96. Welch HG, Prorok PC, O'Malley AJ and Kramer BS: Breast-Cancer tumor size, overdiagnosis, and mammography screening effectiveness. N Engl J Med 375: 1438-1447, 2016.
97. S P, N KV and S S: Breast cancer detection using crow search optimization based intuitionistic fuzzy clustering with neighborhood attraction. Asian Pac J Cancer Prev 20: 157-165, 2019.
98. Cruz-Bernal A, Flores-Barranco MM, Almanza-Ojeda DL, Ledesma S and Ibarra-Manzano MA: Analysis of the Cluster Prominence Feature for Detecting Calcifications in Mammograms. J Healthc Eng 2018: 2849567, 2018.
99. Hmida M, Hamrouni K, Solaiman B and Boussetta S: Mammographic mass segmentation using fuzzy contours. Comput Methods Programs Biomed 164: 131-142, 2018.
100. Lei YM, Yin M, Yu MH, Yu J, Zeng SE, Lv WZ, Li J, Ye HR, Cui XW and Dietrich CF: Artificial intelligence in medical imaging of the breast. Front Oncol 11: 600557, 2021.
101. Herranz H and Cohen SM: MicroRNAs and gene regulatory networks: Managing the impact of noise in biological systems. Genes Dev 24: 1339-1344, 2010.
102. Nassar FJ, Nasr R and Talhouk R: MicroRNAs as biomarkers for early breast cancer diagnosis, prognosis and therapy prediction. Pharmacol Ther 172: 34-49, 2017.
103. Itani MM, Nassar FJ, Tfayli AH, Talhouk RS, Chamandi GK, Itani ARS, Makoukji J, Boustany RN, Hou L, Zgheib NK and Nasr RR: A signature of four circulating microRNAs as potential biomarkers for diagnosing early-stage breast cancer. Int J Mol Sci 22: 6121, 2021.
104. Wang H, Tan Z, Hu H, Liu H, Wu T, Zheng C, Wang X, Luo Z, Wang J, Liu S, *et al*: microRNA-21 promotes breast cancer proliferation and metastasis by targeting LZTFL1. BMC Cancer 19: 738, 2019.
105. Najjary S, Mohammadzadeh R, Mokhtarzadeh A, Mohammadi A, Kojabad AB and Baradaran B: Role of miR-21 as an authentic oncogene in mediating drug resistance in breast cancer. Gene 738: 144453, 2020.
106. Shi Y, Ye P and Long X: Differential expression profiles of the transcriptome in breast cancer cell lines revealed by next generation sequencing. Cell Physiol Biochem 44: 804-816, 2017.
107. Dinami R, Ercolani C, Petti E, Piazza S, Ciani Y, Sestito R, Sacconi A, Biagioni F, le Sage C, Agami R, *et al*: miR-155 drives telomere fragility in human breast cancer by targeting TRF1. Cancer Res 74: 4145-4156, 2014.
108. 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.
109. Rajabi H, Jin C, Ahmad R, McClary C, Joshi MD and Kufe D: MUCIN 1 ONCOPROTEIN EXPRESSION IS SUPPRESSED BY THE miR-125b ONCOMIR. Genes Cancer 1: 62-68, 2010.
110. Tang F, Zhang R, He Y, Zou M, Guo L and Xi T: MicroRNA-125b induces metastasis by targeting STARD13 in MCF-7 and MDA-MB-231 breast cancer cells. PLoS One 7: e35435, 2012.
111. Wang S, Oh DY, Leventaki V, Drakos E, Zhang R, Sahin AA, Resetkova E, Edgerton ME, Wu W and Claret FX: MicroRNA-17 acts as a tumor chemosensitizer by targeting JAB1/CSN5 in triple-negative breast cancer. Cancer Lett 465: 12-23, 2019.
112. Teichgraeber DC, Guirguis MS and Whitman GJ: Breast cancer staging: Updates in the AJCC cancer staging manual, 8th edition, and current challenges for radiologists, from the AJR special series on cancer staging. AJR Am J Roentgenol 217: 278-290, 2021.
113. Wang ZX, Lu BB, Wang H, Cheng ZX and Yin YM: MicroRNA-21 modulates chemosensitivity of breast cancer cells to doxorubicin by targeting PTEN. Arch Med Res 42: 281-290, 2011.
114. Filková M, Jüngel A, Gay RE and Gay S: MicroRNAs in rheumatoid arthritis: Potential role in diagnosis and therapy. BioDrugs 26: 131-141, 2012.
115. Zhou Q, Haupt S, Kreuzer JT, Hammitzsch A, Proft F, Neumann C, Leipe J, Witt M, Schulze-Koops H and Skapenko A: Decreased expression of miR-146a and miR-155 contributes to an abnormal Treg phenotype in patients with rheumatoid arthritis. Ann Rheum Dis 74: 1265-1274, 2015.
116. Sun SS, Zhou X, Huang YY, Kong LP, Mei M, Guo WY, Zhao MH, Ren Y, Shen Q and Zhang L: Targeting STAT3/miR-21 axis inhibits epithelial-mesenchymal transition via regulating CDK5 in head and neck squamous cell carcinoma. Mol Cancer 14: 213, 2015.
117. Carbognin L, Miglietta F, Paris I and Dieci MV: Prognostic and predictive implications of PTEN in breast cancer: Unfulfilled promises but intriguing perspectives. Cancers (Basel) 11: 1401, 2019.
118. 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.
119. Yan LX, Wu QN, Zhang Y, Li YY, Liao DZ, Hou JH, Fu J, Zeng MS, Yun JP, Wu QL, *et al*: Knockdown of miR-21 in human breast cancer cell lines inhibits proliferation, in vitro migration and in vivo tumor growth. Breast Cancer Res 13: R2, 2011.
120. Wu X: Expressions of miR-21 and miR-210 in breast cancer and their predictive values for prognosis. Iran J Public Health 49: 21-29, 2020.
121. Nivetha R, Arvindh S, Baba AB, Gade DR, Gopal G, K C, Reddy KP, Reddy GB and Nagini S: Nimbolide, a neem limonoid, inhibits angiogenesis in breast cancer by abrogating aldose reductase mediated IGF-1/PI3K/Akt signalling. Anticancer Agents Med Chem 22: 2619-2636, 2022.

Copyright © 2024 Yang and Li. This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.