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A SYSTEMIC REVIEW OF MicroRNAs AS THERAPEUTIC TARGETS IN BREAST CANCER AND THEIR POTENTIAL APPLICATION IN CANCER THERAPY

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ABSTRACT: Breast cancer, a multifaceted and heterogeneous disease, continues to pose challenges in both oncology research and clinical practice. This review delves into the intricate roles of microRNAs (miRNAs) in breast cancer, focusing on three pivotal dimensions: regulatory mechanisms, drug resistance, and diagnostic potential.As a regulator, miRNAs emerge as key players orchestrating breast cancer progression. Specifically, miR-205, the miR-200 family, and let-7 family play crucial roles in suppressing oncogenic processes, providing essential insights for comprehending and potentially mitigating breast cancer advancement.Drug resistance being a formidable challenge, a comprehensive exploration of how miRNAs contribute to chemotherapy ineffectiveness is required, particularly against widely used breast cancer drugs like tamoxifen, paclitaxel, and doxorubicin. The intricate interplay between miRNAs and drug resistance-associated genes underscores the urgency to explore innovative treatment modalities.From a diagnostic perspective, miRNAs exhibit remarkable promise as biomarkers for early-stage detection and prognostic assessment. Their expression patterns, linked with specific breast cancer subtypes, not only offer insights into disease outcomes but also provide valuable information about patient responses to treatment. Notably, miRNAs are detectable in bodily fluids such as serum, saliva, and urine, emphasizing their potential for non-invasive diagnostic applications.In summary, this review comprehensively underscores the profound impact of miRNAs in breast cancer, elucidating their intricate regulatory roles, addressing challenges related to drug resistance, and highlighting their promise as diagnostic tools. By unravelling the complexities of miRNA involvement in breast cancer, this work sets the stage for new horizons in therapeutic intervention and early disease management.

Keywords: Breast Cancer, tumor, biomarker, microRNA (miRNA), early-stage detection

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1. INTRODUCTION

MicroRNAs are a group of small, endogenous, highly-conserved, non-coding RNAs approximately 19-25 nucleotide long that plays a pivotal role in controlling gene expression precisely at the post-transcriptional level[1]. It was reported that the first miRNA *lin4* was discovered in 1993 which was transcribed as a small RNA from the *lin4* locus of the *Caenorhabditis elegans* [2]. The human genome is comprised of approximately 2654 mature miRNA sequences as per the data given in the miRBase miRNA sequence database (release 22.0, March 2018) (http://www.mirbase.org/). MiRNA is the key regulator of post-transcriptional gene expression through different developmental stages which requires the involvement of highly precise interactions and the interplay between different complex regulatory networks [3]. In most cases, miRNAs execute their function by interacting with the 3′ UTR region of target mRNAs and eventually suppressing their expression [4]. However, it has also been shown that miRNAs interact with other regions such as 5′ UTR, gene promoters, and coding sequences [5]. Recent studies have suggested that miRNAs control the rate of translation and even in a few cases transcription by shuttling between different subcellular compartments [6].Biogenesis or mechanism of synthesis of miRNA requires several critical steps (Fig: 1) starting from the nucleus where miRNA is transcribed and in the cytoplasm where miRNAs are further processed and matured. MiRNA genes can be divided into two categories intergenic or intragenic depending on their genomic location. Intergenic miRNAs can be transcribed independently which includes promoters, sequences of transcripts, and terminator units [7, 8]. However, intronic and exonic regions of the host gene constitute the intragenic genes that share common transcriptional units with those host genes. Intronic miRNAs are mostly present in the non-coding regions of RNA or the protein-coding genes, whereas the exonic miRNAs are present in the region where the intron and exon overlaps with each other [9]. Formation of mitrons occurred when the intronic sequence of the host gene is indistinguishable from precursor miRNA (pre-miRNA), having splice site at either end [9, 10]. Therefore, Drosha processing is not necessary for the maturation of mitrons[11]. Biogenesis of miRNA initiates by Drosha processing which helps in the formation of pre-miRNA from primary miRNA, it is the first of miRNA synthesis. Drosha is an RNA-III endonuclease which has recently been implicated in miRNA biosynthesis(Fig: 1). Drosha cleaves pri-miRNA from primary miRNA, those pri-miRNAs have then undergone processing by a microprocessor complex, Drosha-DiGeorge syndrome critical region 8 (DGCR8) into the precursor miRNA transcript [12, 13].DGCR8 is a protein subunit of the microprocessor complex which ensures the accuracy of splicing by Drosha by acting as a molecular anchor [13].Synthesis of mature miRNA involves two-step cleavage of primary miRNA by incorporating it into the effector complex known as RNA-induced silencing complex (RISC)(Fig: 1). In most cases, miRNA acts as a guide and negatively controls the expression of mRNA by base-pairing with the target mRNA. The type of silencing mechanism is employed based on the complementarity between the guide and the mRNA target [14].Degradation of mRNA is mostly induced by perfect complementary between miRNA and their respective target of mRNA [15].However, the most observed phenomenon is partial complementary base-pairing between miRNA and the target of mRNA which eventually inhibits protein translation [15]. Owing to their shortened miRNA- mRNA binding site, a single miRNA can employ multiple regulatory pathways by which a single miRNA can bind to myriad targeted mRNAs [16, 17].MiRNA regulates approximately one-third of protein-coding genes as per

estimation[18]. Therefore, proper identification of validated targets of miRNA requires great attention.

Multiple cellular and signalling pathways are regulated by miRNAs because of their diverse activity. Significant consequences can happen in cell signalling due to the deregulation of a single miRNA or small subset of miRNAs that can lead to various diseases process even malignancy such as breast cancer [19]. Breast cancer is one of the most prevalently diagnosed malignancy in women across the world accounting for more than 2.3 million new cases each year as per the statistics stated in GLOBECAN 2020 data [20]. Female sex, older age, family history, and most importantly gene mutation accelerate the risk of developing breast cancer. Two major genes have been identified BRCA1 and BRCA2 located on chromosome 17 and chromosome 13 respectively which are directly linked to breast malignancy [21].Cancer associated with BRCA2 is more aggressive as it retains the ability to repair DNA double-strand break by communicating with RAD51 and DMC1 [22, 23].A tumor in the breast usually starts from the ducts of the mammary glands and the microenvironment of the tumor plays an important role in the initiation and progression of ductal carcinoma. In most cases, macrophages help cancer cells to escape immune rejection by generating a mutagenic inflammatory microenvironment resulting in more invasive malignancy [24].Another major contributor to carcinogenesis is a different pattern of DNA methylation resulting in changes in the epigenetic modifications in the tumor microenvironment [25, 26].HER2 (Human epidermal growth factor receptor 2) is also an important oncogene located on the long arm of chromosome 17 (17q12). HER2 protein belongs to the family of EGFR (Epidermal growth factor receptor) of tyrosine kinase that forms a heterodimer with other EGFR family members such as Her3 and Her4, thus stimulating the downstream signal transduction pathways [27].MicroRNAs are gradually emerging as a prospective field in the therapy of breast cancer because of their regulatory involvement in breastcarcinogenesis [28].Recent studies have also established that aberrant expression of miRNA is predominant in several breasts malignant conditions whereas it is absent in its benign counterpart [29]. Cancer-linked regions or fragile chromosomal sites house about 50% of human miRNA coding genes [17]. Numerous studies have shown the altered miRNA expression in breast neoplasm after the first reported study in 2005 [30].MiRNAs associated with breast cancer can be categorized into oncogenic miRNAs (oncomiRs) and tumor suppressor miRNAs (tsmiRs). Upregulation of oncomiRscontributes to the development of breast cancer malignancy by suppressing the expression of potential tumor suppressor genes [31].On the contrary, breasttumorigenesis can be inhibited by tsmiRs which inhibit the expression of oncogenes [32].Therefore, the downregulation of tsmiRs results in breast malignancy [31]. The therapeutic potential of miRNAs in breast cancer emerges as a new aspect of cancer therapeutics due to their small molecular size and role in regulating gene expression [33].The mechanism of silencing the expression of oncogenic miRNAs by employing miRNA inhibitors or bringing back the expression of tumor suppressor miRNAs tsmiRs via miRNA mimetics is the basis of potential miRNA-based cancer therapeutics.This review explores the role of miRNAs associated with breast cancer and the way miRNAs altered signalling pathways involved in breast neoplasm by shedding light on the potential prospects of miRNA-based breast cancer therapeutics.

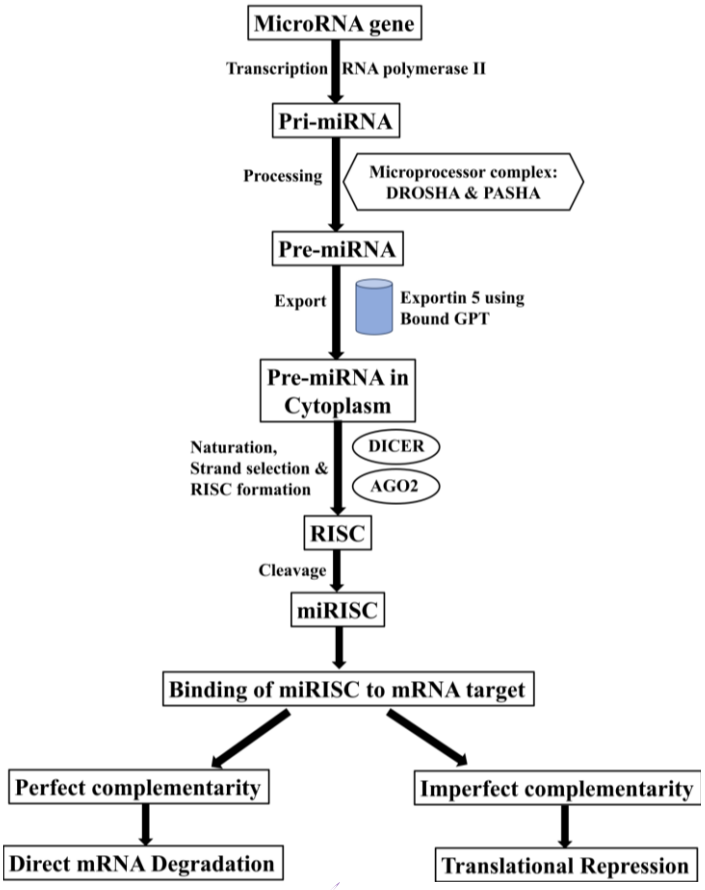

Figure 1: The process of microRNA (miRNA) biogenesis and regulation involves several key steps. Initially, miRNA genes undergo transcription by RNA polymerase II, generating primary miRNA transcripts (pri-miRNA). The Drosha–DGCR8 complex then cleaves the pri-miRNA, forming a precursor miRNA transcript (pre-miRNA). Subsequently, the pre-miRNA is transported from the nucleus to the cytoplasm through the nuclear pore via exportin 5. Within the cytoplasm, the pre-miRNA undergoes further modifications facilitated by the DICER and TRBP complex, resulting in the formation of a mature miRNA duplex. This duplex is integrated into an Argonaute (Ago) within the RNA-induced silencing complex (RISC). Helicase unwinds the duplex into two single-stranded miRNAs. The mature single-stranded miRNA can then bind to target mRNA, exerting its inhibitory function through translational blockage or mRNA degradation, depending on the degree of nucleotide complementarity [34].

2. ASSOCIATION OF miRNAS IN SIGNALING PATHWAYS OF BREAST CANCER

2.1 PI3K/AKT/mTOR pathway

Proliferation and progression of cancer cell is frequently accelerated by a central intracellular signalling axis, called PI3K/AKT/mTOR pathway that incorporates different signal in order to proceed towards tumorigenesis [35]. This signalling pathway is comprised of three main components PI3K (PhosphatidyInositol-3-Kinase), AKT (Protein Kinase B; PKB), and mTOR (mammalian target of rapamycin). PI3K heterodimer plays an important role in initiation and progression of this pathway that belongs to the ClassIA PI3Ks. Activation of the catalytic subunit (p110) depends upon presence or absence of the growth factor receptor tyrosine kinase which initiate upstream stimulation by a regulatory subunit (p85) [36]. AkT, a serine/ threonine kinase, has an important impact on cancer cell cycle, proliferation and survival. Phosphatidylnositol 4,5 bisphosphate or PIP_2 is phosphorylated by the PI3Ks and forms phosphatidyInositol 3,4-4 triphosphate, which in turn phosphorylates AkT [37]. Another important tumour suppressor is phosphatise and tensin which are identified on chromosome 10 (PTEN). PTEN plays a reverse

action and dephosphorylates PIP3 into PIP2 [38]. Mutation of PTEN and PI3K, frequently involve exon 9 and 10, most common occurrence in breast tumorigenesis[39, 40].mTOR signalling is comprised of two subunit mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC 2). Different multiprotein complex is also present in mTORC1 such as raptor a regulatory protein present in mTOR, mammalian lethal with Sec 13 protein 8 (mLST8) and mTORC2 is composed of three core component mTOR, rapamycin insensitive companion of mTOR (Rictor), and mLST8. MicroRNA has direct influence on mTOR signalling pathway by targeting multiple genes. PTEN a vital anti-oncogene of mTOR signalling pathway is downregulated by miR-10a and eventually accelerates progression of malignancy [41]. miR-100 has the ability to impede cell cycle progression and promotes apoptosis by inhibiting mTOR signalling pathway in breast malignancy [42, 43]. The miR-100 is generally downregulated in breast carcinogenesis as per the bioinformatics analysis of GSE45666, GSE48088, GSE44124, GSE44899 breast cancer related datasets which was obtained from the Gene Expression Omnibus Database. mTOR pathway also initiates downstream signalling by miR100 which regulates the expression of proliferation-and survival-promoting oncogene insulin like growth factor 2(IGF2) [44].A recent study demonstrated that three miRs (miR-147, miR-124, and miR-193a-3p) can arrest cell cycle progression by directly interfering with EGFR (Epidermal Growth Factor Receptor) –driven cell-cycle network protein in breast tumorigenesis [45]. EGFR is one of the key activators of AkT/mTOR signallingpathway. Members of the EGFR family share a common domain which houses a ligand-binding region which in turn connects with cytoplasmic region through a hydrophobic transmembrane domain. This cytoplasmic region consist both a tyrosine-kinase domain and C terminal tail [46]. After binding with ligand, EGFR goes through receptor dimerization that results in tyrosine kinase activation and transphosphorylation of the receptor dimmers in the cytoplasmic tail [46, 47]. The class Ia phosphoinositide 3-kinases(PI3K) are stimulated in response to EGFR signalling and converts plasma membrane phosphatydinositol- 4,5- bisphosphate [PI $(4,5)P_2$] to phosphatidyinositol- 3,4,5-triphosphate [PI $(3,4,5)P_3$] [36].

2.2JAK / STAT signalling pathway in breast cancer

The JAK/STAT signalling pathway is predominant in breast cancer cell survival, progression and metastasis. The JAK-STAT (Janus kinase - Signal Transducer and Activator of Transcription) signalling pathway plays a significant role in breast cancer [48]. This pathway is a crucial part of the cellular communication network and is responsible for transmitting signals from the cell surface to the nucleus, where it regulates gene expression [49]. In breast cancer, dysregulation of the JAK-STAT pathway can contribute to the development and progression of the disease.

Here's a brief overview of how the JAK-STAT pathway is involved in breast cancer:

The JAK-STAT pathway can be activated in response to various cytokines and growth factors. These signalling molecules are often overproduced in breast cancer and can lead to the activation of JAK and subsequent STAT proteins [50]. When cytokines or growth factors bind to their respective receptors on the cell surface, it triggers the activation of Janus kinases (JAKs), specifically JAK1, JAK2, JAK3, and Tyk2. These activated JAKs then phosphorylate tyrosine residues on the receptor, creating docking sites for STAT proteins [51].Once recruited to the receptor, Signal Transducer and Activator of Transcription (STAT) proteins are phosphorylated by JAKs. This phosphorylation activates STAT proteins, allowing them to form dimers. The phosphorylated STAT dimers then translocate to the cell nucleus, where they bind to specific DNA sequences, called STAT response elements [52]. This binding initiates the transcription of target

genes involved in cell growth, survival, and proliferation.The transcription of target genes regulated by the JAK-STAT pathway can promote cell cycle progression, inhibit apoptosis (programmed cell death), and stimulate angiogenesis (formation of blood vessels) [53]. These processes are critical for tumor growth and metastasis in breast cancer.Dysregulation of the JAK-STAT pathway can also contribute to immune evasion by breast cancer cells. Some immune checkpoint proteins, such as PD-L1, can be regulated by this pathway, allowing cancer cells to evade immune system surveillance.Targeting the JAK-STAT pathway has emerged as a potential therapeutic strategy for breast cancer treatment. Inhibitors of JAK and STAT proteins are being studied in clinical trials to disrupt the pathway's aberrant signalling in cancer cells. Additionally, understanding the specific alterations and mutations in the JAK-STAT pathway in breast cancer can help in developing more targeted and personalized treatment approaches for patients.Janus kinase (JAK), often humorously referred to as "Just another kinase," comprises a group of intracellular protein tyrosine kinases (PTKs) that do not act as receptor proteins. This family includes JAK1, JAK2, JAK3, and TYK2, and they have a specific affinity for the cytoplasmic portions of various cytokine receptors [54, 55]. JAK2 is a crucial mediator within cells for cytokine and hormone signalling. When cytokines bind to a receptor on the cell's surface, this causes the receptor to pair up and initiate the phosphorylation and activation of JAK tyrosine kinases. These JAK kinases, in turn, phosphorylate the receptor, allowing it to bind and phosphorylate cytoplasmic STAT proteins. These STAT proteins then form pairs and move into the cell nucleus, where they control the transcription of various target genes [56, 57]. Growing evidence suggests that abnormal JAK2 signalling is associated with a wide range of tumors and plays a vital role in processes like cell proliferation, differentiation, and apoptosis [58, 59]. STAT3 is the primary target downstream of phosphorylated JAK2 and remains active in various human tumors, exhibiting oncogenic and anti-apoptotic capabilities [60, 61]. Recent findings have shown that JAK2 functions as an oncogene in breast cancer, and alterations in the JAK/STAT pathway are especially prominent in this context [62, 63].JAK2, a non-receptor tyrosine kinase, plays a role in promoting the growth, development of blood vessels, escape from the immune system, and prevention of cell death in cancer cells [57]. Persistent activation of the JAK signalling pathway is detected in multiple cancer types [64], and this includes cases of human breast cancer [62, 65].Signal transducer and activator of transcription (STAT) proteins constitute a family of transcription factors involved in a wide range of biological processes, including cell growth, cell death, and the progression of tumors[48, 66]. Among these STAT proteins, STAT3 is often found to be persistently active in approximately 60% of breast cancer cases [67]. Since STAT3 is influenced by JAK2, which phosphorylates STAT3, causing it to form pairs and enter the cell nucleus, where it regulates the transcription of various oncogenes such as BCl-2 and surviving [68-70]. BCl-2 and survivin are known for their roles as genes that prevent cell death and promote the spread of cancer in different human cancer types [70-72].In these studies, an investigation was conducted to assess the influence of miR-204 on the expression of STAT3, BCl-2, and survivin in the context of breast cancer. Western blotting analysis was employed, revealing that pre-treatment with miR-204 mimics yielded reductions in the levels of BCl-2 and survivin within the breast cancer cell environment. These findings provide evidence for the involvement of miR-204 in the modulation of cell death pathways in breast cancer, specifically through the BCl-2/survivin signalling pathway.

3. ONCOGENIC AND TUMOR SUPPRESSIVE microRNAs IN BREAST CANCER

It is noted that expression of some miRNAs are interrupted in different kinds of diseases as well as breast cancer (Fig 2). Aberrant expression of microRNA establishes the basis of exploring its functionality in breast neoplasm. MicroRNAs that are located in the cancer-associated genomic region or fragile site, plays a vital role in cancer progression as oncogene [73].Oncogenic miRNAs are also known as "oncomirs" whose expression is usually stimulated in different cancers. Oncomirs accelerates cancer progression by impeding the expression of tumor suppressor genes in different biological procedures [74].

3.1 Oncogenic MicroRNAs in breast cancer

3.1.1 miR-21

miR-21 is one of the prominent tumor-causing miRNA in various cancers, and notably its expression is highly increased in breast oncogenesis (Table-1). It is demonstrated in numerous studies that miR-21 is associated with cancer cell proliferation, tumor metastasis, and poor prognosis in breast cancer. Various tumor suppressor genes such as tumor suppressor tropomycin 1 (TPM1), programmed cell death 4 (PDCD4), TIMP metallopeptidase inhibitor 3 (TIMP3), and phosphatise and tensin homologue (PTEN) are suppressed by the over expression of miR-21 in breasttumor cells [75-78]. MiR-21 exerts its action on tumor suppressor genes by inhibiting apoptosis that aids in cancer cell progression. Recent studies have shown that Leucine zipper transcription factor-like 1 (LZTFL1) is another key gene which is also targeted by miR-21 in advanced breast cancer and is associated with poor prognosis [79, 80]. It has also been reported that LZTFL1 is tended to decline its expression in gastric and lung cancer by directly exerting its action on beta-catenin pathway [79]. Though the mode of action of miR21/LZTFL1 is still needed further investigation, but some recent research sheds light on the role LZTFL1 in regulation Epithelial-Mesenchymal Transmission (EMT) in several malignancies. It stabilizes E-cadherin - mediated adherens junction synthesis by impeding the nuclear translocation of beta-catenin and downstream transcription factor snail and slug [79-81]. Therefore, knocking down the effect of miR-21/LZTFL1 could find new insights in cancer therapeutics.

3.1.2 miR-155

Ectopic expression of miR-155 influences tumor cell survival, proliferation and also acquires chemosensitivity by down-regulating the expression of forkhead box 03 (FOXO3a)(Table-1). Therefore, knocking down the expression of miR-155 stimulates cell chemosensitivity and helps in mediating apoptosis [82].Expression of miR-155 is generally up regulated in breast cancer patients. The exact cause behind this phenomenon is not well characterized. However, some studies elucidate the role of Transforming Growth Factor- beta (TGF-beta) that in turn increase the expression of miR-155 resulting in epithelial to mesenchymal transition (EMT) in breast cancer [83]. It is well understood that one of the key contributor of EMT is TGF-beta that transforms immobile epithelial cell to motile mesenchymal cells, and consequently promote tumor invasion [84]. A non-transformed mouse mammary gland epithelial cell (NMuMMG) cells shows both growth inhibitory and growth promoting response to TGF-beta. A chief signalling molecule Smad4 in TGF-beta pathway forming a bond with BIC promoter and enhances miR-155 expression that in turn augments EMT process in breast carcinogenesis [83].

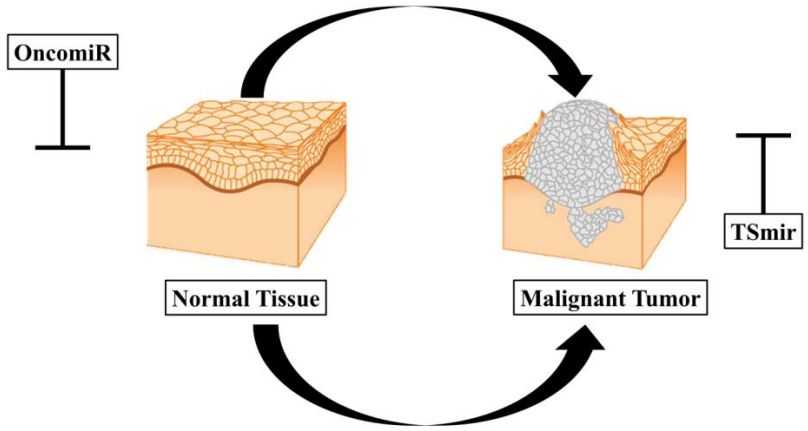

Figure 2: The regulatory mechanisms governing the impact of oncogenic and tumor suppressor microRNAs on tumorigenesis involve intricate processes. Elevated levels of oncogenic miRNAs within cancer cells act to suppress tumor suppressor genes, while diminished levels of tumor suppressor miRNAs may potentially amplify the expression of oncogenes. As a result, both oncogenic and tumor suppressor miRNAs contribute to the progression of tumors by promoting cell proliferation, anti-apoptotic responses, replicative immortality, invasion, metastasis, and angiogenesis [85]

3.1.3 miR-182

The first step in invasive breast cancer is breast tumor-initial cell (BT-IC)-associated metastasis. Upregulation of miR-182 is mediated by beta-catenin one of the key regulators of EMT binds to the promoter of miR-182 that leads to overexpression of miR-182 in breast tumor cells(Table-1). Ectopic expression of miR-182 attenuates the expression of its target gene reversion-rich-cysteine-rich protein with kazal motifs (RECK) that in turn accelerates the expression of matrix metallopeptidase 9 (MMP-9) resulting in invasive breast cancer [86].Forkhead Box (FOX)F2 is a mesenchymal regulator falls under the category of FOX transcription factor superfamily is another target gene of miR-182 which is responsible for maintaining homeostasis between epithelial mesenchymal interactions and also maintains epithelium polarity[87]. FOXF2 acts as a direct and functional target of miR-182 in Triple Negative Breast Cancer (TNBC). Hirata et al.[88]has uncovered that two potential binding site for miR-182-5p is present within 3′ UTR region of FOXF2 mRNA. MMP-1is downregulated by FOXF2 resulting in overexpression of (Tissue Inhibitor of Metalloproteinases-3) TIMP3, is an inhibitor of MMPs [89]. In addition, FOXF2 attenuates the expression of Wnt5a, which is a key component of Wnt non-canonical signalling pathway contributes in developing invasive breast cancer phenotype by inducing angiogenesis[90].Another research has shown that Missing in Metastasis (MIM), is a scaffold protein down-regulated in various metastatic carcinoma. MIM maintains dynamicity of cytoskeleton and actin polymerization. Both MIM and FOXO1 (Forkhead Box Protein 01, a transcription factor acts as a tumor suppressor) activates Ras homologue family member A are the target of miR-182 responsible for cancer cell proliferation and invasive cancer phenotype [91, 92]. Therefore, inhibition of the expression of miR-182 may emerge as a therapeutic benefit by enhancing the expression of tumor suppressor genes RECKS, FOXF2, FOXO1, and MIM etc.

3.1.4 miR-10b

miR-10 is also as “metastasis miR” an important downstream effector of twist-related protein 1 (TWIST1)(Table-1)[93]. Inclined expression of miR-10b is evident in metastatic breast carcinomas makes a significant contribution in cancer cell migration and metastasis. Transcription factor twist directly binds to the promoter region of miR-10b (MIRN10B) resulting in over

expression of miR-10b [93]. Over expression of miR-10b tends to inhibit translation of an mRNA encoding homobox D10 that in turn stimulates a pro-metastatic gene RHOC (Ras Homologue Family member C) belongs to the Ras superfamily of small GTPases. Inhibition of the expression of homobox D10 (HOXD10), a tumor suppressor gene and controlling the expression of T lymphoma invasion and metastasis 1 (Tiam1) oriented Rac activation induces breast cancer cell proliferation, colony formation, and metastasis [94]. One recent study has demonstrated that CCN5 previously known as WISP2 is a 29kda protein that belongs to the connective tissue growth factor/cysteine-rich 61/ nephroblastoma overexpressed family (CCN) family has the potential to suppress the expression of miR-10b [95]. CCN5 exerts its action by inhibiting HIF-1alpha-TWIST1 signalling cascades [96]. Thus, stimulating the expression of CCN5 can open a novel therapeutic approach in invasive breast cancer therapy. Another research has shown that E-cadherin is a cell-adhesion molecule that helps in maintaining breast cancer cell growth and mortality, whose aberrant expression gives rise to invasive breast cancer phenotype[97]. There are lots of underlying molecular mechanisms which are responsible for the loss of E-cadherin. Reduced expression of E-cadherin is associated with higher metastatic risk and poor prognosis. It has been reported that loss of heterozygosity in the 16q region of the chromosome where the E-cad gene is present, contributes to 45%-60% of sporadic breast cancer [98, 99]. Moreover, Matrix Metalloproteinase (MMP) is responsible for regulating E-Cad level, post-transcriptionally. MMP controls the level of E-cad by proteolytic degradation and tyrosine phosphorylation-mediated E3 ligase-targetedproteosomal degradation also takes part in regulating the level of E-cad. This phenomenon is responsible for releasing an extracellular domain of E-Cad as an 80kDa soluble fragment resulting in loss of E-cad availability for the formation of adhesion complex and also accelerates cancer cell invasion and migration by stimulating the expression of ErBb receptor or MMPs [100, 101].

3.1.5 miR-9

Loss of contact inhibition and invasiveness are two important characteristics of metastatic breast carcinomas(Table-1). miR-9 is highly expressed in metastatic breast cancer and promotes cancer cell proliferation by attenuating the expression of E-Cadherin. MYC and MYCN are two oncoproteins which act on mir-9-3 locus leads to activation of miR-9 in mammary gland tumor cells that in turn down regulates the expression of E-cadherin, thus promotes cancer cell motility and invasiveness. miR-9 also activates beta-catenin which induces tumor-associated angiogenesis by activating VEGFA (Vascular Endothelial Growth Factor A) release. Therefore, down regulation of E-cadherin and up regulation of beta-catenin appears to be significant in promoting miR-9 mediated VEGF activation [102].Leukemia inhibitory factor receptor (LIFR) has been shown to down regulate the expression of miR-9 by stimulating Hippo-oriented cascades. The initiation of this cascade leads to phosphorylation, cytoplasm retentiveness and numbing the expression of YES- associated proteins (YAP) [103]. Hence, activating the expression of LIFR can unfold a novel therapeutic prospect in metastatic breast carcinomas.

Table 1: Oncogenic miRNAs associated with breast cancer.

Associated event	MicroRNA (family)	Target Gene	Reference
Cell proliferation, cell survival and apoptosis	miR-155	*FOXO3a*, *SOCS1*, *caspase-3*, *TP53INP1*	[82, 104-106]
Cell invasion, colony formation	miR-182	*RECK*, *MIM*, *FOXO1*	[86, 91, 92]
Cell invasion, migration	miR-10b	*HOXD10*, *Tiam1*	[94, 96]
Cell motility and invasiveness, angiogenesis	miR-9	*E-cadherin*	[102]
EMT	miR-22	*TET* family	[107]
EMT, cancer metastasis	miR-181a	*Bim*	[108]
Cell migration and invasion	miR-373, miR-520c	*CD44*	[109]
Cell proliferation	miR-375	*RASD1*	[110]
Metastatic cancer, tumor growth, EMT	miR-221/222	*TRPS1*, *ADIPOR1*, *p27Kip1*	[111-113]
Cancer metastasis	miR-632	*DNAJB6*	[114]
Cell cycle, colony formation	miR-7, miR-218	*HoxB3*	[115]
Cancer metastasis	miR-374a	*WIF1*, *PTEN*, *WNT5A*	[116]
Cell viability, angiogenesis	miR-27a	*HOXO1*, *ZBTB10*	[91, 117, 118]
Cancer metastasis	miR-21	*TPM1*, *PDCD4*, *TIMP3*, *PTEN*	[75, 76, 78, 119]

3.2Tumor Suppressive miRNAs in breast cancer

3.2.1 miR-145

miR-145 retains its tumor suppressive ability by numbing the effect of different target genes in stage-specific events (Table-2). miR-145 directly targetsinsulin receptor substrate- 1 (IRS1), which is necessary for BT-IC differentiation [120]. It has been found that IRS-1 initially binds to the SV40 –T antigen leading to oncogenic transformation of mammary gland epithelial cells. Activation of IRS-1 in fibroblast cells leads to increased phosphorylation of IRS-1 resulting in further stimulation of ERK1/2 (Extracellular signal related kinase 1/2) [121].miR-145also significantly reduces the expression of Rhotekin protein resulting in inhibition of cell growth and activation of apoptotic pathways [122]. Rhotekin generally interacts with the scaffold RhoA and RhoC belongs to scaffold family proteins [123].Vinexin, Lin7b, PIST and septin has shown direct coupling with Rhotekin, which is necessary for maintaining cell polarity, cell adhesion, and septin arrangements [124, 125]. Overexpression of Rhotekin can also activate nuclear kappa B(NF-kB) pathway and causes delay in apoptosis. Some anti-apoptotic genes such as c1AP-2, BCL-xL, A20 and A1 are regulated through NF-kB and exert their anti-apoptotic effect resulting in invasive cancer phenotype and worse prognosis [126].An important metastasis inducing gene mucin 1(MUC 1) can also be directly targeted by miR-145 resulting in a reduction of beta-catenin and cadherin 11 secretion, thereby inhibiting cancer cell migration and metastasis [127]. Inhibiting the expression of Octamer binding transcription factor 4 (Oct 4) miR-145 is also able to arrest EMT in breast metastasis. During the progress of breast tumorigenesis, a significant decrease in the level

of miR-145 is notable which promoted the expression of Oct4 that in turn activates three key EMT regulators, Snail, ZEB1 and ZEB2 by controlling the release of beta-catenin. As a result, cancer cells are transformed from polarized epithelial cells to migratory mesenchymal cells, providing a suitable environment for invasive breast carcinoma [128].

3.2.2 miR-335

Deletion and epigenetic silencing of miR-335 is a prevalent scenario of metastatic breast cancer (Table-2). Previous study revealed that expression of miR-335 was significantly reduced in those breast cancer patients who went on metastasis. miRNA product of miR-335 arises from the second intron of the mesoderm-specific transcript (Mest gene) which resides on miR-335 locus [129]. Mest is a maternally imprinted gene whose expression is highly dictating the expression of miR-335[129, 130]. One recent analysis has uncovered that Mest/miR-335 locus usually undergoes hypermethylation in metastatic breast cancer [131]. Invasiveness of breast tumorigenesis can also be arrested by targeting SRY-related HMG box 4 (SOX4) and tenascin C [132]. Tenascin C (TNC) is a glycoprotein, an important component of extra cellular matrix that takes significant part in cancer development [133, 134].Human TNC gene is localized on chromosome 9q33 and consists of 30 exons. TNC helps in the formation of new blood vessel; known as angiogenesis is one of the well characterized hallmarks of cancer progression [135]. Newly formed blood vessels provide route for dissemination of cancer cells to distant organ and initiates metastatic progression. Moreover, connection to the new blood vessels provide sufficient oxygen and nutrients that aids in cancer cell survival and also help leukocytes to enter into the tumor, making cancer cells defensive against therapy [136].miR-335 also shows its tumor suppressive effect by regulating familiar Breast Cancer 1*(BRCA1)* activators, *ER-alpha, IGF1, Sp1,* and repressor *ID4* by inhibiting cell proliferation and colonization [137]. miR-335 is able to suppress the expression of tumor-promoting signal transducers *ER-alphA, IGF1,Sp1,*and *ID4.*The mechanism of action of miR-335 is happened in two-ways; it exerts its tumor suppressive role by acting anti-mitogenically on *BRCA1* activators ER-*alpha, IGFI,* and*Sp1.*On the other hand, it acts pro-apoptically by regulating Jagged-1 and SOX4. In addition, miR-335 ensures genomic stability by exhibiting its repressive role on key repressor molecule ID4 [137].

3.2.3 miR-19a

Tumor microenvironment is one of the predominant factors in cancer progression. Tumor-associated macrophages (TAMs) comprising 40% of TME is major regulator of cancer cell survival (Table-2). A major transition is seen in TAMs phenotypic expression. TAMs are converted from a pro-immune (M1-like) phenotype to an immune-suppressive phenotype is one of the prominent hallmarks of tumorigenesis. TAMs form clusters specifically in vascular, necrotic/hypoxic areas of tumor. They are involved in clearing necrotic debris from those sites [138]. TAMs which are present in these sites usually interact with the surrounding TMEs with an altered expression of genes that eventually leads to the development of a malignant phenotype [139].Many human and mouse epithelial tumor cells show over expression of Fos-related antigen-1 *(Fra-1)*belonging to the AP1 family is involved in metastatic progression to lymph nodes [140]. Previous studies have demonstrated that *Fra-1* plays a pivotal role in macrophage (TAMs) polarization from M1 to M2 phenotype [141, 142].*Fra-1* usually acts a transcription factor during the transformation of TAMs from M1 to invasive M2 phenotype. Numerous studies have reported that *Fra-1* also act as a proto-oncogene and stimulates IL-6/JAK/STAT-3 signalling pathway

[139]. Thereby, in breast tumor cells a malignant switch has occurred resulting in increased release of pro-angiogenic factors such as VEGF, matrix metalloproteinase-9 (MMP-9), and transforming growth factor beta (TGF-beta) from the surrounding tumor microenvironment that contributes in malignant transformation [141]. On the other hand, miR-19a arrests cancer progression by signalling pathways that activates M2 macrophage transition, precisely the glucocorticoid pathways. Glucocorticoid pathway promotes therecruitment and polarization of M2 macrophage by stimulating STAT-3 pathway and NEAT pathway that is also responsible for secretion of M2 cytokines such as IL-4 and IL-6 in Th2 cells [143, 144]. In this regard, it can be said that silencing the expression of Fra-*1* can provide a novel therapeutic strategy in breast tumorigenesis.

3.2.4 miR-205

Structure of miR-205 is a highly conserved and it is located on chromosome 1q32.2, and it has been mainly illustrated for its onco-suppressive role in breast carcinoma [145] (Table-2). Previous study has reported that miR-205 shows tumor suppressive function by directly targeting on E2F transcription factor 1 (E2F1) and Laminin Subunit Gamma 1 (LAMC1) [146]. E2F1 is mainly associated with cell-cycle regulation, whereas LAMC1 is usually involved in cell proliferation, survival, and metastasis[147]. It is well known that $_{p}^{53}$is a vital transcription factor for miRNAs [146]. $P^{53}$is able to transactivate miR-205 and eventually this P^{53}/miR-205 axis can arrest cell cycle progression and breast carcinoma. More recently, it has been uncovered that Kruppel-like factor 12 (KLF-12) can also be targeted by miR-205 resulting in decreasing the progression of breast cancer basal-like malignancies [148]. KLF-12 is a transcription factor that plays an important role in tumor progression by regulation epithelial-mesenchymal transition which is a key step in cancer metastasis. miR-205 is also capable of downregulating the action of Nuclear factor 1/B (NF1B) in Estrogen receptor positive (ER+) breast cancer [149]. In vitro experiments have shown that NF1B induce MCF-7 cell cycle progression and it is overexpressed in ER+ cancer and promotes metastasis [150]. Angiomotin (AMOT), an adaptor protein of tight junction, stimulates ERK1/2 signalling pathway to promote cell proliferation in ER+ breast tumorigenesis. miR-205 directs interrupts this underlying mechanism by targeting AMOT in MCF7 cells [151, 152]. Role of miR-205 is also implicated in the process of angiogenesis by repressing the expression of VEGF-A. Suppressed expression of VEGF-A and fibroblast growth factor 2 (FGF2) cumulatively cause better response to neo-adjuvant chemotherapy [153]. miR-205 can downregulate VEGF-A and FGF2 expression by interfering with PI3K/AKT pathway and thus inducing apoptosis [154]. miR-205 can also be secreted from the tumor stroma and can be associated with the formation of a cancer stem cell-like phenotype. Therefore, miR-205 can have a therapeutic potential that needs further investigation [155].

3.2.5 miR-200 family

miR-200 family miRNAs act as tumor suppressors and their expression is commonly downregulated in cancer(Table-2). miR-200 families have the potential to be regarded as diagnostic and prognostic markers. miR-200 family is comprised of miR-200a, miR-200b, miR-200c, miR-141, and miR-429. miR-200a, miR-200b and mir-429 and are clustered on chromosome 1 and miR-200c and miR-141 are clustered on chromosome 12. A potential binding site for P^{53} is present in the promoter region of miR-200a/-b/-c. P^{53} is responsible for increasing the expression of miR-200 family [156]. Epithelial-mesenchymal transition is inhibited by P^{53}- binding protein 1 (53BP1) that directly binds to the promoter sequence of miR-200 family by maintaining the

expression level of miR-200b and miR-429 [157]. miR-200a/-b/-c also contains a potential binding site for paired box-5 (Pax5). Pax5 has the ability to suppress breast cancer cell proliferation and invasion by arresting EMT [158]. Pax5 helps in increasing the tumor suppressive phenotype of miR-200 family. A prospective binding site for nuclear receptors such as Glucocorticoid receptor alpha (GR-alpha) is also present at the promoter sequences of miR-200a/-b/-c. It has the ability to suppress pancreatic tumorigenesis. Therefore, it might inhibit the breast cancer cell growth by increasing the expression of miR-200 family [159]. Expression of miR-200c is higher in ER-positive breast cancer than triple negative breast cancer (TNBC).miR-200c usually targetsand suppresses the expression of genes that are associated with metastasis [160]. This miRNA family regulates cancer cell progression by binding with Zinc Finger E-Box Binding Homobox1 and 2 and different transcriptional suppressors such as E-cadherin[161, 162]. Therefore, loss or silencing of miR-200 family in TNBC might enhance the process of metastasis and make cancer cells chemotherapy-resistant. On the other hand, miR-200 family inhibits *ZEB2* (Zinc finger E-box-binding homobox 2) expression which induces mesenchymal-to-epithelial cell transition (MET), it is also responsible for macroscopic metastasis of breast cancer cell lines [163]. Therefore, the role of miR-200 family needs further evaluation.

3.2.6 let-7 family

let-7 families of miRNAs were first observed in *Caenorhabditis elegans*, andare considered as most ancient and highly conserved miRNAs(Table-2)[164]. They are mainly regarded as tumor suppressive miRNAs and follow a heterochronic pathway which is required for cancer including breast tumorigenesis, to initiate cell proliferation, differentiation, and migration at the appropriate time [165].During initiation of breast cancer let-7 family is usually associated with BT-IC stem cell like activities by numbing the expression of its target gene *H-Ras* (transforming protein 21) and *HMGA2* (high- mobility group AT-hook 2). On the other hand, it has been observed that the onset of the development of breast carcinoma is effectively delayed by the overexpression of let-7 [166]. Another recent study has claimed that low expression of let-7b/c in breast cancer stem cellsresults in the loss of its ability to hold and impede the expression of Ras mRNA eventually leading to the stimulation of p-Ras and p-Erk [167]. Thus, let-7 plays an important role in sustaining stemness of breast cancer cells. Migration and invasion of breast cancer cell can also be hindered by nullifying the effect of four important target genes of let-7 family which are associated with actin cytoskeleton pathway, *PAK1* (Serine-Threonine protein kinase 1), *DIAPH2* (known as protein diaphanous homolog 2), *RDX* (Radixin), *ITGB8* (integrin beta-8) [168].The excessive presence of kinase defective *PAK1*is able to reduce the disease invasiveness by forming numerous focal adhesion points[169].*PAK1* is regarded as an important regulator of cell motility, and remodeling of cytoskeleton. *PAK1*-deprived cellsexhibit inhibited lamellipodial protrusion and are unable to synthesize mature focal adhesions [170].Another target gene of let-7 is *DIAPH2* which belongs to the diaphanous subfamily of formin homology family. *DIAPH2* along with Cdc42 is also able to maintain the attachment of microtubule to kinetochore [171]. RDX comes under ezrin-RDX-moesin (ERM) family which retains the ability to organize membrane domains through the interaction with transmembrane proteins and the cytoskeleton [172].

4. THE ROLE AND MECHANISM OF ACTION OF microRNAs IN DRUG RESISTANCE OF BREAST CANCER

One of the most important properties of cancer cell is that it becomes resistant to cancer chemotherapy. Recent statistical analysis has revealed that 90% of death due to cancer is related to cancer drug resistance [173]. Drug resistance in cancer can be caused by various underlying mechanisms such as modification of drug targets, decreased antitumor drug uptake, alteration in cell cycle check point, increased DNA damage repair etc. In recent years, numerous studies have uncovered that microRNAs play a crucial role in breast cancer drug resistance by targeting different drug-resistance-related genes or promoting gene which enhancecell cycle and apoptosis. Breast cancer is the most prevalent malignant tumor among women, constituting 31% of all female cancers. In 2012, the number of new cases recorded reached 1.68 million [174]. Chemotherapy drugs, such as paclitaxel (PTX), 5-fluorouracil(5-FU), and doxorubicin/adrinamycin (DOX) are commonly employed in breast cancer treatment. However, the majority of these drugs can eventually lead to chemoresistance and treatment failure. In the MCF-7 breast cancer cell line, both upregulation and downregulation of miRNA-21 affected their susceptibility to DOX [175]. Increased miRNA-21 expression coincided with decreased expression of phosphatase and tensin homolog (PTEN) Overexpression of PTEN mimicked the effects of miRNA-21 and reduced the resistance of MCF-7 cells to DOX. This finding indicates that miR-21 promotes DOX resistance in breast cancer cells by downregulating PTEN [176]. Similar resistance can be observed with trastuzumab, an antibody commonly used in the treatment of breast cancer that targets the epidermal growth factor receptor 2 (HER2). In the MDA-MB- 453 breast cancer cell line, miRNA-21 also conferred resistance to trastuzumab by silencing PTEN. Restoring trastuzumab sensitivity in the drug resistant breast cancer xenografts was achieved by administering miRNA-21 antisense oligonucleotides, which induced PTEN expression. In contrast to miRNA-21, miRNA-137 was found to reduce drug resistance to DOX in MCF-7 cells [177]. This effect was mediated through the targeting of Y-box-binding- protein 1(YB-1), leading to downregulation of p-glycoprotein (p-gp) by miRNA-137.Additionally, miRNA-149, miRNA-195, miRNA-452, miRNA-489, miRNA-181a, and miRNA-320a also decreased the sensitivity of breast cancer to DOX [178].

Table 2: Tumor suppressive miRNAs associated with breast cancer

Associated event	MicroRNA (family)	Identified target	Reference
Tumor initiation, cell differentiation and metastasis, cell stemness maintenance	let-7 family	*H-Ras*, *HMGA2*, *PAK1*, *DIAPH2*, *RDX*, *ITGB8*	[165-168]
EMT, tumor growth and metastasis	miR-200 family	*ZEB1*, *ZEB2*, *HER3*, *Sec23a*, *SIRT1*	[119, 163, 179-182]
Tumor migration and invasion, cell viability and apoptosis	miR-335	*SOX4*, *tenascin C*, *ER-α*, *IGF1*, *RSP1*, *ID4*	[131, 132, 137]
Metastatic angiogenesis	miR-126	*IGFBP2*, *MERTK*, *PITPNC1*	[183]
CSC self-renewal, cell apoptosis, EMT	miR-30 family	*Ubc9*, *TWF1*, *Vimentin*, *KRAS*, *MTDH*	[184-187]
Cancer metastasis	miR-146a/b	*IL-1-RSK*, *NFRSF-6*	[188]
Cell proliferation	miR17-20 cluster	*Cyclin D1*	[189]
Cell apoptosis	miR-26b	*SLC7A11*	[190]
Cell apoptosis	miR-290	*Arid4b*	[188]
Tumor growth	miR-27b	*CYP1B1*	[191]
Cancer metastasis, cell apoptosis	miR-31	*Integrin-α5*, *radixin*, *RhoA*, *WAVE3*, *PRKCE*	[181, 192, 193]
Cell invasion	miR-125a/b	*HER2*, *HER3*	[194]
EMT, cell invasion	miR-203	*SNAI2*	[195]
Cancer metastasis	miR-224	*CDC42*, *CXCR4*	[196]
Angiogenesis	miR-20b	*HIF-1*, *STAT3*	[197]
Cell proliferation	miR-206	*Cyclin D2*	[198]
Cell apoptosis	miR-342	*HER2*	[199]
Angiogenesis	miR-519c	*HIF-1α*	[200]
Tumor growth	miR-16	*Cyclin E*	[201]
Tumor growth, cell apoptosis	miR-290	*Arid4b*	[202]
Cell proliferation and invasion	miR-497	*Cyclin E1*	[203]
Cell cycle and proliferation	miR-133a	*EGFR*	[204]
Cell proliferation and apoptosis	miR-26a	*MCL-1*	[205]
Cell invasion and migration	miR-720	*TWIST1*	[206]
Cancer metastasis	miR-7	*KLF4*	[207]
Angiogenesis	miR-98	*MMP1*, *ALK4*	[208]
Angiogenesis	miR-542-3p	*Angiopoietin-2*	[209]
Angiogenesis	miR-148a/152	*IGF-IR*, *IRS1*	[210]
EMT, cell proliferation and invasion, CSC stemness promotion	miR-205	*ZEB1*, *ZEB2*, *HER3*, *VEGF-A*	[153, 155, 161, 194, 211]
Tumor growth, cell differentiation, invasion and metastasis, angiogenesis	miR-145	*IRS-1*, *ER-α*, *RTKN*, *MUC1*, *OCT4*, *N-Ras*, *VEGF-A*	[122, 127, 128, 208, 212]

Clinical studies indicate that over two-thirds of breast cancer patients with estrogen receptor positive (ER) tumors are treated with tamoxifen (TAM), an ER inhibitor, resulting in generally favourable outcomes. However, a significant proportion of these patients eventually develop resistance to TAM[213]. Recent research has unveiled the involvement of certain miRNAs in this regulatory process. Zhao et. al.,[213]conducted a comparative analysis of miRNA expression profiles in ER alpha-positive and ER alpha-negative breast cancer cell lines and primary tumors. They discovered elevated levels of miR-222 and miR-221 expression in ER alpha-negative cells.

Subsequent investigations revealed a direct interaction between miRNA-221 and miRNA-222 and 3′- UTR of ER alpha mRNA. The introduction of miRNA-222 and miRNA-221 into MCF-7 and T47D cells resulted in reduced production of ER-alpha protein, without affecting mRNA expression. Notably, MCF-7 and TD7D cells transfected with miRNA-221 and/or miRNA-222 became resistant to TAM compared to cells treated with a controlled vector. Conversely, miRNA-221 and/ or miRNA-222 sensitized MDA-MB-468 cells to TAM, leading to cell growth arrest and apoptosis. In contrast, the let-7 family of miRNAs sensitized MCF-7 cells to TAM by directly targeting ER alpha-36, a variant of ER alpha. It is important to note that ER- alpha and ER- alpha 36 have direct functions in cells, as they regulate different downstream signalling pathways, highlighting the intricate role of ER-alpha in the regulation of chemoresistance [214].

FOXO, a prominent member of the forkhead transcription factor family, can trigger cell death through pro-apoptotic proteins like BIM, p27, and BNIP3. The expression of FOXO3a can be diminished by miRNA-155, resulting in breast cancer cells developing resistance to several chemotherapy drugs such as DOX, VP-16, and PTX [82]. Other miRNAs like miRNA-203, miRNA-125b, miRNA-34a, and miRNA-663 have been observed to be over expressed in drug-resistant cancer cells and silencingthem has shown to restore the sensitivity of cancer cells to drugs like TAM, docetaxel, 5-FU, and CDDP [215-218]. These investigations demonstrate the potential of combining miRNA with chemotherapy for effective anti-tumor treatment.

5. microRNAs AS PROMISING BIOMARKERS FOR THE DIAGNOSIS AND PROGNOSIS OF BREAST CANCER

Due to rapid development in gene microarrays and experimental technologies, an increasing number of studies are providing promising evidence regarding the role of microRNAs in the development and progression of breast cancer. Abnormal patterns of microRNA expression are closely associated with specific stages of tumors, metastasis to lymph nodes, poor survival rates, disease outcomes, and response to particular treatmentsacross various cancer types[219, 220].Besides their traditional intercellular functions, microRNAs have been discovered in various forms over the last decade, including serum, saliva, urine, and milk. These microRNAs are enclosed within micro-vesicles or exosomes or exists as compounds with protective modifications [221-223].

Due to superior correlation between microRNA profiling and biological processes compared to gene expression profiling, the utilization of microRNA profiling has been employed for the early-stage diagnosis of breast cancer and for determining the treatment prognosis in patients withthese types of cancer. In an initial study conducted by Blenkironet. al.,[224], an analysis of microRNA expression and genomic alterations was performed in human breast cancer. The authors employed unique miRNA patterns specific to various molecular subtypes of breast cancer (such as luminal A, luminal B, basal-like, HER2+ and normal-like) to characterize their prognostic implications. Shortly thereafter, Farazi et. al.,[225]carried out an extensive sequencing of microRNA in breast tumor and revealed that the microRNA 17-92 cluster exhibits elevated levels in triple-negative breast carcinomas, distinguishing it from other tumor subtypes. The combination of mRNA and microRNA expression profiling in breast cancer offers us a greater understanding of the microRNAs linked to prognosis. Elevated levels of miR-767-3p, miR-128a, and miR-769-3p, as well as miR-27b, miR-144, and /or miR-210 in ER-negative cases are associated with an unfavourable prognosis [226]. In samples of metastasis lymph nodes or breast cancer with a high

proliferation index, the let-7 family of microRNA is downregulated, implying that a deficiency of let-7 family microRNAs is indicative of poor prognosis [30]. Furthermore, the miR-106b-25 cluster can provide a faster prediction of relapse [227]. Both miR-181a [108]and the miR-221/ miR-222 cluster [228] show promise as diagnostic and prognostic marker due to their positive correlation with tumor development. Overall, these findings highlight the potential of microRNAs as valuable diagnostic and prognostic indicators. Additionally, several microRNAs have been identified as specifically dysregulated in the blood plasma of breast cancer patients compared to healthy individuals [229, 230]. The serum expression of miR-451, miR-21 and miR-16 exhibited amplification in breast cancer patients compared to healthy individuals [231]. Furthermore, aberrant expression of microRNAs has been quantified in the serum of breast cancer patients. Notably miR-21, miR-106a, miR-155 has been significantly overexpressed, whereas the expression of miR-126, miR-199a and miR-335 in tumor specimen showed an opposite pattern to that observed in normal specimen [232]. Interestingly, the previously mentioned elevated levels of these microRNAs demonstrated a significant reduction in postoperative cases compared to preoperative cases. These findings collectively support the proposition that these circulating microRNAs in the serum hold potential as diagnostic markers for breast cancer [230, 232, 233].

2. CONCLUSION

In recent years, significant efforts have been dedicated to understanding the molecular mechanisms underlying breast cancer. The findings of these investigations strongly support the pivotal role played by the dysregulation of specific microRNAs in the progression of this disease. Extensive research has elucidated the molecular mechanisms through which microRNAs contribute to the pathological processes associated with breast cancer. Considering the information presented above, microRNAs hold immense potential for clinical diagnosis and prognosis. Elucidating the functional network that connects microRNAs with their target molecules will enhance their utility as therapeutic targets. However, despite the vast possibilities for utilizing microRNAs in clinical treatments, certain perplexing questions remain unanswered. For example, among the numerous microRNAs that are deregulated in breast cancer, it remains unclear which ones are most representative of each stage of cancer. The origin and primary functions of the microRNAs found at high levels in the serum of breast cancer patients, as well as their release from tumors, are still not fully understood. Moreover, since a single microRNA can target multiple genes and mRNA can bind to different microRNAs, there is a possibility that a single microRNA may be involved in various events related to both cancer progression and normal tissue development. This creates uncertainties in the context of microRNA-based therapy. In the future, addressing underexplored issues, such as utilizing microRNAs as markers for diagnosis and prognosis, and implementing miRNA-based therapies effectively in clinical settings for the treatment of human cancers, will likely pose significant challenges that need to be resolved.

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