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Review

MicroRNA-based therapy and breast cancer: A comprehensive review of novel therapeutic strategies from diagnosis to treatment

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ABSTRACT

MicroRNAs (miRNA) are 21–23 nucleotide molecules not translated into proteins that bind and target the 3′ untranslated regions of mRNA. These characteristics make them a possible tool for inhibiting protein translation. Different cellular pathways involved in cancer development, such as cellular proliferation, apoptosis, and migration, are regulated by miRNAs. The objective of this review is to discuss various miRNAs involved in breast cancer in detail as well as different therapeutic strategies from the clinic to industry. A comprehensive discussion is provided on various miRNAs involved in breast cancer development, progression, and metastasis as well as the roles, targets, and related therapeutic strategies of different miRNAs associated with breast cancer. miRNAs known to be clinically useful for the diagnosis and prognosis of breast cancer are also discussed. Different strategies and challenges, including nucleic acid-based (miRNA mimics, antagomiRs, and miRNA sponges) and drug-based (drug resistance, drugs/miRNA interaction, nanodelivery, and sensing systems) approaches to suppress specific oncogenes and/or activate target tumor suppressors are discussed. In contrast to other articles written on the same topic, this review focuses on the therapeutic and clinical value of miRNAs as well as their corresponding targets in order to explore how these strategies can overcome breast cancer, which is the second most frequent type of cancer worldwide. This review focuses on promising and validated miRNAs involved in breast cancer. In particular, two miRNAs, miR-21 and miR-34, are discussed as the most promising targets for RNA-based therapy in non-invasive and invasive breast cancer, respectively. Finally, relevant and commercialized therapeutic strategies are highlighted.

Contents

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1. Introduction

MicroRNAs (miRNAs or miRs) are small (21–23 nucleotides) molecules transcribed by type II and type III RNA polymerases. In general, miRNAs bind the 3′ untranslated regions (UTRs) of mRNAs and suppress mRNA translation [1]. miRNAs play a crucial role in breast cancer development by promoting uncontrolled cell division and blocking apoptosis [2]. Approximately 50% of miRNAs are located at intergenic regions and the remaining 50% of miRNAs have been predicted to be located within intragenic (intronic) regions [3]. It has been estimated that approximately 50% of miRNA genes are located within genomic regions associated with cancer [4], but the exact roles of intronic miRNAs are not well understood. To date, several cancer-associated intronic miRNAs have been discovered in humans, including miR-10b, miR-15b, miR-16-2, miR-17-92, miR-26a1, miR-26-a2, miR-26b, and miR-126 [5]. The intronic miRNAs involved in breast cancer are listed in Tables 1 and 2.

Primary miRNA (pri-miRNA) is transcribed as capped, polyadenylated, and double-stranded stem-loop containing structures. The pri-miRNAs are then processed into 70-100 nucleotide-long hairpin structures by the Drosha RNase complex. The second form of intermediate miRNA is called precursor miRNA (pre-miRNA), which is transported to the cytoplasm via exportin 5. Cytoplasmic processing of pre-miRNAs occurs when Dicer (another RNase) cleaves pre-miRNAs into an approximately 22 nucleotide-long double-stranded miRNA duplex. This miRNA duplex is then incorporated into the miRNA-induced silencing complex (miRISC). The Argonuate protein located in miRISC unwinds double-stranded miRNA, and the mature strand is separated from the passenger [6,7]. According to the currently accepted hypothesis, the passenger strand (miR-XXX*) is then released, and the mature strand (miR-XXX) is activated as part of a powerful cellular regulatory system within miRISC that targets 3′-UTRs of specific mRNAs; however, it is known that the passenger strand also has a functional role in post-transcriptional gene silencing. Therefore, the annotation of miRNA strands has been changed to miR-XXX-5p (former miR-XXX) and miR-XXX-3p (former miR-XXX*) for mature strands released from the 5′-end and 3′-end of mature miRNA hairpin duplex, respectively [8]. miRNAs contain a six to seven nucleotide-long seed sequence that mediates the interaction with targets [9]. Intronic miRNAs, which have mostly been predicted by bioinformatics, are only transcribed by type II RNA polymerase because they bypass the Drosha dependent step [10]. Instead, a spliceosomal complex is required for post-transcriptional processing of intronic miRNAs [11].

It is well-known that miRNAs play a crucial role in cancer progression, but reports showing the role of miRNAs in cancer development are rare. Some miRNAs, such as miR-21, miR-221/222, and miR-182 are known to be involved in cell proliferation (Table 1), but it cannot be unequivocally concluded that they play roles in cancer initiation. However, stem cell-associated miRNAs, such as miR-302 and miR-373-3, may be related to the origin of cancer [12]. It has also been demonstrated that LIN28/let-7, c-MYC-E2F/miR-17-92, and OCT4/SOX2/miR-302-Cyclin D1 networks play a crucial role in the pluripotency and self-renewal of cancer stem cells and embryonic stem cells [13]. During cancer development, progression, and metastasis, miRNAs are subdivided into two main categories: tumor suppressor and oncogenic miRNAs. To date, a number of miRNAs have been found to be associated with breast cancer; these miRNAs and their molecular targets will be highlighted in this review.

According to GLOBACAN 2013, breast cancer is the most frequently diagnosed cancer in women and the second most common cancer worldwide. In 2012, Twenty-five percent (1.67 million) of all new cancer cases and 15% (522,000) of all cancer deaths in women were due to breast cancer [14]. Therefore, advanced therapeutic strategies are urgently needed for effectively treating breast cancer patients. However, only a limited number of literature reviews on the molecular properties and anti-breast cancer effects of miRNAs with special focus on therapeutic strategies have been published to date. In addition to our recent review (2014) published on the role of the natural product, berberine (PubChem CID: 2353), in breast cancer treatment that briefly focused on miRNA/berberine interactions [15], two other reviews have been recently published on the role of miRNA in breast cancer. Goh et al. [16] reconstructed and listed miRNAs involved in breast cancer based on the hallmarks of cancer, but the review does not discuss the therapeutic importance of miRNAs in detail. The other review focused on the impact of miRNAs on drug resistance in breast cancer with a short discussion on miRNA targets [17]. Therefore, a comprehensive review discussing the role of miRNAs in breast cancer development, progression, and migration as well as miRNA targets and therapeutic strategies has not been published to date. This review aims to provide an extensive analysis of miRNA effects on various molecular targets (e.g., tumor suppressor genes, oncogenes, and other regulators) involved in breast cancer development as well as miRNA-based therapeutic opportunities for overcoming breast cancer.

Table 1
Oncogenic miRNAs (oncomiRs) reported to be upregulated in breast cancer cells.

OncomiRs	Targets	Oncogenic pathway	Oncogenic behavior	Tested treatment (s)	References
miR-9[a]	Cyclin D1 E-cadherin	Wnt/β-catenin	Metastasis	AntagomiR-9 MiR-9 sponges	[25,41,42,70,71]
miR-10b[b]	Hoxd10 Syndecan-1	Wnt/β-catenin	Metastasis	AntagomiR-10b MiR-10b LNA Nano-delivery	[50,72,73]
miR-17/92[b]	PTEN	Wnt/β-catenin PI3K/AKT/mTOR	Metastasis	Unknown	[63,74]
miR-20b	PTEN	PI3K/AKT/mTOR	Metastasis Proliferation	Unknown	[75]
miR-21	PTEN Cdc25,MSH2 Mespin	PI3K/AKT/mTOR DNA repair	Metastasis Proliferation	AntagomiR-21 MiR-21 sponges Mimics MiR-21 LNA Curcumin Glyceolin 3,6-dihydroflavon Nano-delivery	[25,29,30,58,59,70,72,73,76–79]
miR-93	LATS2	Microtubule formation	Metastasis Angiogenesis	Unknown	[74,80]
miR-103/107	Dicer DAPK, KLF4	miR processing	Metastasis Global microRNA biogenesis	Unknown	[74]
miR-142	APC	Wnt/β-catenin	Self-renewal Metastasis	Unknown	[81]
miR-146	BRCA1	DNA repair NFκB MAP kinase	Proliferation Anti-apoptotic	Unknown	[66]
miR-155 [a]	CXCR4, FOXO3, TRF1, SHIP, TP53INPI	JAK/STAT MAP kinase	Telomere synthesis Metastasis Proliferation	Unknown	[22,34,42,69,82–84]
miR-181	ATM	DNA repair	Anti-apoptotic	Unknown	[85]
miR-181b-1	Smad3	Wnt/β-catenin	Metastasis	Unknown	[23]
miR-182	BRCA1	DNA repair	Proliferation Anti-apoptotic	Unknown	[65,66,86]
miR-221/222	ERα, P27kip1, KIT, P57, PTEN	PI3K/AKT/mTOR	Proliferation Anti-apoptotic	Unknown	[36,87,88]
miR-301a	PTEN	Wnt/β-catenin PI3K/AKT/mTOR	Metastasis Proliferation	Unknown	[89]
miR-373	CD44	Wnt/β-catenin	Metastasis	Unknown	[43,45,47,74,90]
miR-489	E-Cadherin Smad3	Wnt/β-catenin	Metastasis	Unknown	[32]
miR-495	E-Cadherin REDD1	Wnt/β-catenin	Metastasis	Unknown	[85]
miR-520c	CD44	Wnt/β-catenin	Metastasis	Unknown	[43,45,47,74,90]
miR-888	E-Cadherin Actin-γ1 Cdc42	Wnt/β-catenin	Metastasis	Unknown	[91]

[a] These miRNAs have dual actions and opposing effects in breast cancer (function as both oncomiRs and tumor suppressor miRNA in different stages and/or cancers).
[b] Intronic miRNAs.

2. Breast cancer-linked miRNAs

Breast cancer-linked miRNAs can be subdivided into oncogenic miRNAs (oncomiRs) and tumor suppressor miRNAs (tsmiRs; Tables 1 and 2). In various cases of cancer, oncomiRs were found to be overexpressed or upregulated, and inversely, tsmiRs were down-regulated [18]. To treat breast cancer, we first need to understand the oncogenic or tumor suppressive role of miRNAs and how their regulation may affect breast cancer development and progression. Blocking and down-regulating oncomiRs may play an important role in the treatment of breast cancer, while the overexpression of tsmiRs may provide anti-cancer therapeutic effects [19–27].

2.1. Oncogenic miRNAs (OncomiRs)

Hanahan and Weinberg [28] described ten hallmarks of cancer, of which four have the most impact in miRNA regulation and breast cancer development [16]. In this review, we focus on the following: cell migration and motility (metastasis), proliferation, vessel formation (angiogenesis), and evasion of apoptosis. In breast cancer, oncomiRs mostly affect metastasis and proliferation of cancer cells, and very few oncomiRs are known to be involved in angiogenesis and evasion of apoptosis (Fig. 1).

2.1.1. Cell motility and metastasis

2.1.1.1. Key oncomiRs. Almost 90% of deaths related to cancer are due to metastasis; thus, finding an effective way to inhibit metastasis may lead to a substantial reduction in the number of deaths reported annually. Current anti-cancer drugs (e.g., bevacizumab) are less effective against metastasis. Several miRNAs have been found to promote the metastasis of breast cancer, such as miR-301a, miR-103/107, miR-21, miR-9, miR-181b-1, miR-17/92, miR-489, miR-495, miR-520c, and miR-373. Finding a therapeutic strategy to reduce the expression of these miRNAs may lead to an effective approach for treating breast cancer (Table 1) [15,29,30].

2.1.1.2. Wnt/β-catenin dependent pathway. Epithelial-mesenchymal transition (EMT) is a process by which breast cells begin to move along tissue. Breast cancer cells may hijack the EMT system, and some miRNAs affect EMT to promote metastasis. β-catenin is a membrane-linked protein involved in cell adhesion

Table 2
Tumor suppressor miRNAs (tsmiRs) reported to be down-regulated in breast cancer cells.

tsmiRs	Targets	Affected pathway	Tumor suppressive behavior	Tested treatment (s)	References
Let-7	HMGA2, H-Ras, KRAS, Myc, Cyclin D2, PBX3	MAP kinase Cell cycle	Anti-metastatic Anti-proliferative	Lentiviral mimics	[19,21,74,98]
miR-7	FAK, IGFR, EGFR, REGγ	MAP kinase PI3K/AKT	Anti-metastatic Anti-proliferative	Unknown	[74,99]
miR-15a[a]	Bcl2, E2F	wnt/β-catenin	Anti-metastatic Pro-apoptotic	Curcumin	[100,101]
miR-16[a]	Wip1, Bcl2, E2F, CDK6, CCND1	wnt/β-catenin	Anti-metastatic Pro-apoptotic	Curcumin EGCG	[43,100–102]
miR-19a-3p	FRA1/STAT3 VEGF	STAT	Anti-metastatic Anti-proliferative Anti-angiogenic	Unknown	[93]
miR-22	CDK6, SIRT1, SP1	Cellular senescence	Anti-metastatic	Glyceolin	[74,103,104]
miR-26[a]	GREB1, CHD, MTDH CCND2, CCNE2	Cell cycle PI3K/AKT	Anti-proliferative Anti-metastatic	Unknown	[21,24,105]
miR-29b	Integrin β1 MMP2, TIAM1	Focal adhesion Cell cycle Epigenetic modification	Anti-proliferative Anti-metastatic Anti-angiogenic	Glyceolin	[74,104]
miR-30a	MTDH, CDK6, Eya2	PI3K/AKT wnt/β-catenin	Anti-proliferative Anti-metastatic	Unknown	[106]
miR-31	RhoA, RDX, ITGA5	Wnt/β-catenin	Anti-metastatic	Unknown	[74]
miR-34 (a,b,c)	Cyclin D1, E2F, FRA1, c-Myc, Notch 1, Eya2, CDK4, CDK6, CCND1, SIRT1, AXL	MAP kinase Gene expression Tyrosine phosphatases Cell cycle P53 network wnt/β-catenin MAP kinase	Anti-metastatic Anti-proliferative Pro-apoptotic	Synthetic mimics liposomal miR-34 mimics Glyceolin 3,6-dihydroflavon	[21,74,104,107–110]
miR-124	Slug, EZH2, ROCK2, CDK4	Snail/slug	Anti-metastatic	Unknown	[74,111]
miR-125a-5p	HDAC4, HDAC5, HER3, HuR	P53 network Cell cycle Epigenetic modification	Anti-proliferative	Prognostic biomarker	[112,113]
miR-125b	HER2, EST1, E2F3	MAP kinase	Anti-metastatic Anti-proliferative	Unknown	[79,114–117]
miR-126[a]	IGFBP2, PITPNC1, MERTK, VEGF	GAS6/MERTK Epigenetic modification	Anti-proliferative Anti-metastatic Anti-angiogenic	MiR mimics	[19,27,29,71,118]
miR-128	BMI1, ABCC5	Cell cycle	Anti-self-renewing	Unknown	[85]
miR-143	HER3	PI3K/AKT	Anti-proliferative Anti-metastatic	Unknown	[119]
miR-145	EGF receptor, c-Myc, VEGF, N-cadherin, HIF-2α, Mucin 1, HER3	Cell cycle MAP kinase PI3K/AKT	Anti-angiogenic Anti-proliferative Anti-metastatic	Unknown	[67,72,74,119]
miR-146a/b	ICAM1, VHRF1, NF-κB	Cell junctions	Anti-metastatic	Unknown	[74,120]
miR-185	E2F6, DNMT1	Cell cycle	Anti-proliferative	Unknown	[121]
miR-194	Talin 2	Focal adhesion	Anti-metastatic	Unknown	[29,71]
miR-199b-5p	HER2	MAP kinase PI3K/AKT	Anti-proliferative	Unknown	[79]
miR-200a	SLUG, BMI1, ZEB1, ZEB2	wnt/β-catenin MAP kinase Cell cycle	Anti-metastatic Anti-self-renewing	Unknown	[36,39,85]
miR-200c	BMI1, ZEB1, ZEB2	Cell cycle	Anti-self-renewing Anti-Metastatic	MiR mimics Resveratrol	[36,38,85,96,97,122]
miR-205	HER3, E2F, P53	MAP kinase	Anti-metastatic Anti-proliferative Pro-apoptotic	MiR mimics	[19,27,66,98,118,123]
miR-206	ERα, CyclinD2	MAP kinase PI3K/AKT	Anti-metastatic Anti-proliferative	Unknown	[29,71,72,98]
miR-216b	P2X7	Apoptosis	Pro-apoptotic	Unknown	[124]
miR-335	SOX4, TN-C, Sp1, Bcl-w	wnt/β-catenin	Anti-metastatic Pro-apoptotic	MiR mimics	[19,29,71,74]
miR-339-5p	Bcl-6	Cell survival Cell cycle	Pro-apoptotic	Unknown	[125]
miR-342-5p	EGFR, HER2, AKT, PKC	MAP kinase PI3K/AKT	Anti-proliferative	Unknown	[126]
miR-429	ZEB1, CRKL, TUBB2A	wnt/β-catenin MAP kinase Cell cycle	Anti-proliferative Anti-metastatic	Unknown	[102,127]
miR-491-5p	EGFR, HER2	MAP kinase	Anti-proliferative	Unknown	[126]
miR-708	NNAT	Calcium-induced cell migration	Anti-metastatic	Unknown	[98,128]

[a] Intronic miRNAs.

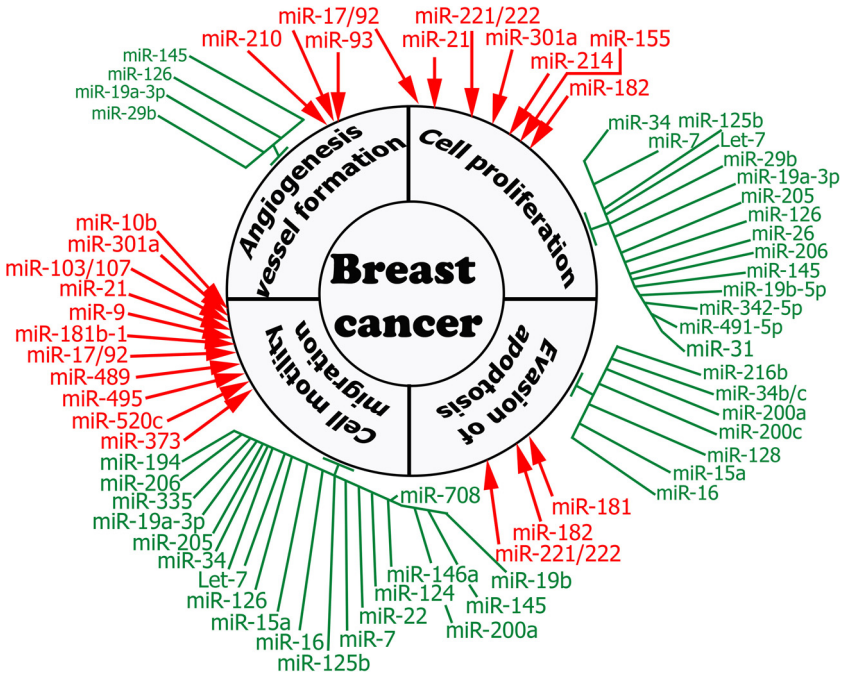

Fig. 1. Different miRNAs affecting the hallmarks of breast cancer. Oncogenic miRNAs and tumor suppressor miRNAs in breast cancer cells are shown in red and green, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

that dissociates from the membranous E-cadherin-linked complex when activated and translocates to the nucleus where it regulates transcription. Abnormal activation of the Wnt/β-catenin signaling pathway can lead to metastatic breast cancer cell invasion [31]. Metastasis has been correlated with a reduced capacity of neighboring cells to attach to each other. Vascular endothelial growth factor (VEGF), β-catenin, and E-cadherin are proteins that control cell migration (Fig. 2). As an oncomiR, miR-489 was found to decrease E-cadherin expression as well as increase Vimentin and N-cadherin expression to activate EMT [32]. MiR-489 also inhibits Smad3 and indirectly affects miR-200c (a tsmiR) levels. In the next sub-section, the role of Smad3 on miR-200c (a tumor suppressor miRNA) and related proto-oncoproteins, such as zinc finger E-box binding homeobox (ZEB)-1 and ZEB2, will be discussed (refer to Fig. 3). As a result of Smad3 inhibition, miR-489 helps breast tumor metastasis through ZEB1 and ZEB2 activation [33]. In fact, miR-489 and miR-200c have opposing functions and inversely modulate cellular pathways of migration. In breast cancer, several studies have shown that when miR-489 levels go up, miR-200c levels go down [34–38]. Thus, the miR-489/miR200c junction may be an effective target for controlling and suppressing EMT [39,40].

c-Myc is an oncoprotein that activates miR-9 (an oncomiR) expression, which consequently leads to cancer metastasis. In breast cancer, metastasis promoted by miR-9 occurs through β-catenin signaling. MiR-9 targets E-cadherin mRNA, which leads to the activation of the β-catenin pathway and finally cell motility [41]. MiR-489 and miR-9 inhibit E-cadherin gene expression and E-cadherin protein translation, respectively. Cells lacking E-cadherin are no longer able to bind neighboring cells. Attachment-disabled cells are primed to move across tissue, which occurs through β-catenin pathway-mediated activation of Rho and Rac proteins and subsequent re-formation of the cytoskeleton (Fig. 2).

2.1.1.3. CD44-TGFβ-SMAD modulators. The MiR-200 family, miR-9, and miR-155 are known to be associated with EMT and the breast cancer stem cell CD44+/CD24- phenotype [42]. MiR-373 and miR-520c promote cell migration by targeting CD44 [43]. In addition to E-cadherin, CD44 is another cell-surface glycoprotein involved in cell–cell interactions and cell migration that plays a crucial role in the metastatic characteristics of a tumor [44]. Based on previous studies, CD44 plays a dual role in controlling cellular shape and promoting cellular invasiveness through an association with other cancer-related receptors, such as VEGF receptors and receptor tyrosine kinases (RTKs) [44–47]. It has been reported that CD44 binding to hyaluronan inhibits apoptosis, which in turn leads to metastatic progression of cancer cells [46]. In addition, it has been shown that interaction of CD44 and matrix metallopeptidase-9 (MMP-9) in the TA3 breast cancer cell line causes collagen IV degradation via TGFβ activation, which promotes the invasiveness of tumor cells [46]. CD44 has been shown to be a direct target of miR-373 and miR-520c in both in vitro and in vivo breast cancer studies [47]. It has also been shown that these miRNAs suppress CD44 mRNA translation [45]; however, the tumorigenic role of CD44 is not a common feature and should not be considered to be applicable to all tumor types. In addition, the role of CD44-associated miRNAs in breast cancer cells remains poorly understood. Therefore, the effects of oncomiRs on CD44 and the prospective results will require additional studies [46].

MiR-181, which is regulated by Activin and tumor growth factor (TGF)-β, may also be overexpressed in breast cancer. The Smad pathway can be targeted by miR-181 as well as miR-489 [23]. Syndecan-1, a heparin sulfate proteoglycan involved in cell matrix adhesion, is transcriptionally down-regulated by another oncomiR, miR-10b. Syndecan-1 down-regulation promotes EMT into metastasis [48,49] and inhibits invasion by down-regulating metalloproteinase activity and interleukin-6 (IL-6) levels; however, miR-10b increases invasiveness by suppressing syndecan-1 [50]. MiR-10b also targets homeobox D10 (Hox-D10), which is a protein involved in cellular differentiation and development. Therefore, miR-10b may promote metastasis when Hox-D10 is inhibited [30,51].

2.1.2. Cellular proliferation

2.1.2.1. Key targets. Breast Cancer Susceptibility Gene 1 (*BRCA1*), *P16*$^{INK4\alpha}$, tumor protein *53 (TP53)*, and phosphatase and tensin homolog (*PTEN*) genes involved in cell cycle control and DNA repair

play a growth suppressive role in breast cell proliferation and were found to be frequently inactivated in human breast cancer. In contrast, genes such as phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) catalytic subunit A, human EGFR-2 (*HER2*), and epidermal growth factor receptor (*EGFR*) are frequently mutated in breast cancer but play an oncogenic and proliferative role [26,52]. The tyrosine kinase receptors and proteins related to DNA repair are mostly mutated in breast cancer (e.g., ERBB2/Neu and BRCA1, respectively), but restoring their normal function renders cancer cells resistant to therapy [53,54]. BRCA1 expression and ERBB2/Neu (HER2) inactivation were found to be involved in resistance to radiotherapy and chemotherapy, respectively [53,55]. Importantly, several miRNAs directly or indirectly affect these molecules. Figs. 1 and 2 and Table 1 provide a list of oncomiRs and describe the proliferative effects of these miRNAs in detail.

2.1.2.2. PI3K/Akt pathway. Mutations within *PTEN* are involved in the development of various cancers. PTEN is a phosphatase involved in the inhibition of the PI3K/Akt/mammalian target of rapamycin (mTOR) pathway. MiR-21 deactivates the cell division cycle 25A (Cdc25A) protein as well as PTEN [56,57]. As a result of miR-21 overexpression, miR-21 promotes cellular proliferation and metastasis by suppressing PTEN and degrading Cdc25A, which is a regulator of the cell cycle [58]. As previously shown, retinoids have been used to treat estrogen receptor-positive (ER+) breast carcinoma. Accordingly, all-trans retinoic acid (ATRA) suppresses ER+ breast

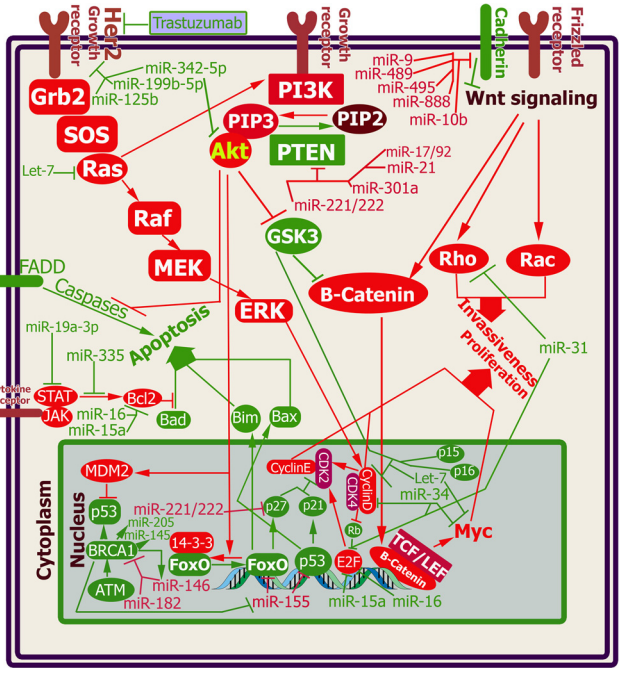

Fig. 2. The most important miRNAs affecting signaling pathways in normal breast tissue. In this figure, green and red colors show the tumor suppressor and oncogenic parts of molecular commanders of a typical breast cell, respectively. In breast cancer, depending on the subtype, oncogenic factors and tumor suppressors are overexpressed (or upregulated) and/or down-regulated, respectively. PI3K: phosphatidylinositide 3-kinase; GSK3: glycogen synthase kinase 3; Grb2: growth factor receptor-bound protein 2; SOS: son of sevenless; Ras: rat sarcoma; Raf: rapidly accelerated fibrosarcoma; MEK: Mitogen/Extracellular signal-regulated Kinase; ERK: extracellular-*signal* regulated kinases; Rho and Rac: Ras-like proteins; Akt: protein kinase B; PIP2: phosphatidylinositol (3,4)-bisphosphate; PIP3: phosphatidylinositol (3,4,5)-trisphosphate, PtdIns(3,4,5)P3; JAK/STAT: Janus kinase/signal transducer and activator of transcription; Bad: BCL2 antagonist of cell death; Bim: BCL2-like 11; Bax: BCL (B cell lymphoma)-associated X; ATM: ataxia telangiectasia mutated; FoxO: forkhead box O; FADD: fas-associated death domain. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

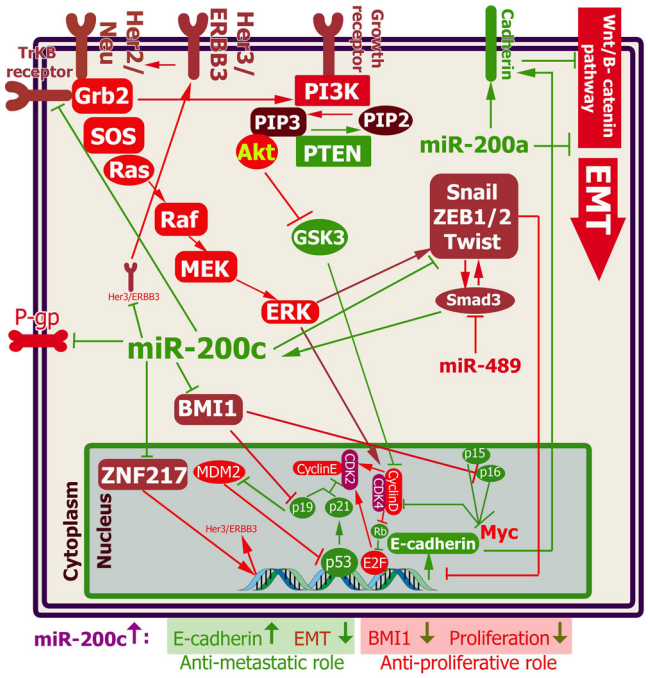

Fig. 3. The miR-200 family members act as key regulators of epithelial mesenchymal transition (EMT). MiR-200c inhibits the zinc finger E-box binding homeobox (ZEB; repressor) complex to activate E-cadherin expression; hence, the epithelial cell junction is strengthened. In contrast, inhibiting proteins such as B cell-specific Moloney murine leukemia virus integration site 1 (BMI1; activates cellular proliferation and immortality) and zinc finger protein 217 (ZNF217; a HER3/HER3 activator) leads to cell cycle arrest. MiR-200c inhibits metastasis and EMT as well as cell proliferation. On the other hand, miR-200c down-regulation may cause drug resistance by increasing permeability glycoprotein (P-gp; an ATP binding cassette [ABC] transporter) levels. TrKB: tyrosine receptor kinase B.

cancer cells by inducing miR-21 expression. ATRA increases the transcription of miR-21 through activation of retinoic acid receptor α as part of a transcriptional complex at the miR-21 promoter [59]. MiR-21 also plays a major role in blocking mismatch repair by targeting MutS homolog 2. Some factors that increase miR-21 (e.g., TGF-β and ATRA) also increase the risk of cancer development through PI3K over-activation. Since the PI3K pathway has substantial cross-talk with other oncogenic pathways, such as the mitogen-associated protein (MAP) kinase pathway, miR-21 is a critical oncogenic miRNA whereby inhibition may be one promising approach to control breast cancer [60].

The human genome contains several pseudogenes recently shown to play a role in tumor suppression [61–63]. Pseudo PTEN transcript 1 (PTENP1), also called PTENP1 long non-coding RNA (PTEN lncRNA), is targeted by miRNAs and recruits miRNAs that can also be bound to PTEN mRNA [62,63]. As mentioned above, the overexpression of miRNA, such as miR-21, can promote uncontrolled cellular proliferation and metastasis. According to Poliseno et al. [63] (2010), PTENP1 transcripts were targeted by PTEN bound miRNAs in 118 breast cancer and 44 normal samples studied. PTENP1 regulates the activity of PTEN by tempting the binding of miRNAs normally bound to PTEN mRNA. The study found that the 3′-UTR of PTENP1 serves as a miRNA target in addition to PTEN mRNA; however, PTENP1 contains 18 missense mutations compared to PTEN mRNA, one of which is located at the first methionine. Consequently, PTENP1 can be transcribed but not translated due to the lack of a methionine initiation codon [63]. The miR-17, miR-21, miR-214, miR-19, and miR-26 families target PTENP1-conserved seed regions [64]. Therefore, PTENP1 might act as an indirect tumor suppressor by decreasing the available pool of miRNAs in cases of breast cancer. Although it appears that PTENP1 may play a role in

miRNA regulation in breast cancer, additional research is required to fully elucidate the mechanistic role.

2.1.2.3. BRCA1 and DNA stability. BRCA1, a well-known tumor suppressor protein, plays a crucial role in breast cancer. BRCA1 is involved in DNA double-strand break repair via homologous recombination. Human BRCA1 mRNA has a 1.5 kb 3′-UTR that serves as a target of seven miRNAs (miR-15a, miR-16, miR-17, miR-182, miR-146a, miR-146b-5p, and miR-638). While loss of function mutations may inactivate BRCA1, overexpressed miRNAs can also target BRCA1 mRNA and inhibit BRCA1 translation. MiR-182 overexpression, for example, decreases the level of BRCA1 in ER+ and ER- (estrogen receptor negative) sporadic breast tumors [65,66]. Reduced levels of BRCA1 make cells highly sensitive to γ-irradiation. To date, seven miRNAs have been shown to decrease BRCA1 levels [66]. Furthermore, BRCA1 targets miR-155, miR-29a, and miR-29b anti-apoptotic oncomiRs and upregulates miR-99b and miR-205 anti-invasion tsmiRs. Therefore, BRCA1 plays a critical role in preventing cancer by regulating both oncomiRs and tsmiRs [66,67]. MiR-146a is involved in nuclear factor-κB (NFκB) and MAP kinase pathways and targets the BRCA1 mRNA 3′-UTR; however, miR-146a can be activated by BRCA1 itself. This loop balances the level of BRCA1/miR-146a. Mir-146a can also repress EGFR and inhibit tumor growth and metastasis (Fig. 2) [66]. Accordingly, BRCA1 not only plays a role in DNA repair, but also suppresses oncogenic signals by activating tsmiRs (e.g., miR-146a). However, BRCA1 up-regulation has also been shown to impart resistance to ionizing and UV radiation therapy. In fact, BRCA1 promotes DNA stability during radiation exposure, and therefore cancer cells would be resistant to radiation [53].

2.1.2.4. JAK/STAT pathway. Activated cell immunity may lead to some types of cancer, and miR-155 has been shown to be overexpressed in breast cancer, especially triple-negative breast cancer. MiR-155 expression is correlated to cytokine production (e.g., interferon-γ and IL-6) through activation of the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway [34,68]. BRCA1 is a protein that suppresses the JAK/STAT pathway by suppressing miR-155 expression [22,34]. MiR-155 also targets telomeric repeat-binding factor 1 and promotes immortalization by activating telomere synthesis of cancer cells [69]. Therefore, miR-155 seems to be important for the initiation and self-renewal of cancer cells.

2.2. Tumor suppressor miRNAs (tsmiRs)

Different tsmiRs have different mechanisms for suppressing breast cancer. Most of them, such as miR-34, miR-126, and Let-7, can affect cellular proliferation, migration, and apoptosis, while miR-335 has only been shown to impart anti-metastatic effects (Figs. 1 and 2; Table 2) [29,71].

2.2.1. Anti-metastatic tsmiRs

2.2.1.1. Anti-metastatic key miRNAs. Previous studies have reported that metastatic transformation occurs at early stages of cancer development and is suppressed by miR-31; however, miR-31 inversely promotes primary growth at later stages [29]. MiR-31 has a dual action: (1) suppression of metastasis, and (2) enhancement of primary tumor growth. MiR-31 expression levels have been shown to be reduced four-fold in a non-metastatic breast cancer cell line (MCF-7), but its expression in a metastatic breast cell line (MDA-MB231) was decreased as much as 100-fold. Nonetheless, miR-31 has been found to be involved in metastasis [29]. MiR-31 targets two specific sequences within RhoA mRNA, which is a protein related to cytoskeleton formation and cell movement. Therefore, post-transcriptional expression of RhoA is affected by miR-31, and RhoA levels are attenuated in non-metastatic breast cancer cell lines [29]. In addition to miR-31, miR-34 is part of another family of tsmiRs that plays a role in the p53 network. MiR-34 also suppresses metastasis by direct targeting of Fos-related antigen 1 (FRA1) [92]. Similar to miR-34, miR-19a-3p suppresses breast cancer progression and metastasis via down-regulation of the FRA1/STAT3 pathway. In this case, miR-19a-3p overexpression down-regulates FRA1, VEGF, and STAT3 [93]. FRA1, one member of the activator protein-1 (AP-1) family, is a transcription factor that is induced by several extracellular and growth factors. FRA1 is involved in metastatic cell movement and is closely related to the extracellular signal regulated kinase 2 (ERK2)-mediated EMT pathway. ERK2/FRA1 modulate ZEB1/2 expression [92]. As described above, ZEB1/2 expression leads to E-cadherin down-regulation. Interestingly, miR-34 and miR-19a-3p may increase E-cadherin levels via FRA1 suppression. MiR-200c is a critical player in this pathway, but other miRNAs, such as miR-489 (an oncomiR) and miR-31, miR-34, and miR-19a-3p (tsmiRs), enhance or suppress the β-catenin-related pathway, which enhances or inhibits metastatic movement, respectively (Fig. 3).

2.2.1.2. SMAD/E-cadherin modulators. The miR-200a-c family members act as tsmiRs. Down-regulation of miR-200a has been observed in breast cancer [94]. When miR-200a is overexpressed, cellular proliferation and Wnt/β-catenin signaling is reduced; however, E-cadherin is upregulated and promotes the formation of cell junctions in epithelial tissue [95]. TGF-β signaling leads to uncontrolled proliferation, inhibition of apoptosis, and increased invasiveness. As the major suppressor of EMT, miR-200c directly targets ZEB1 and ZNF217, which mediate and transcriptionally activate TGF-β signaling, respectively [36,96]. Smad3 is inhibited by miR-489 and has poor binding affinity for DNA, while Snail/ZEB/Twist promote strong binding of Smad3 to DNA (Fig. 3) [39]. In addition, Smad3 increases miR-200c levels, which consequently inhibits ZEB1, ZEB2, B cell-specific Moloney murine leukemia virus integration site 1 (BMI1), zinc finger protein 217 (ZNF217), tyrosine receptor kinase B (TrKB), and permeability glycoprotein (P-gp). ZEB1 and ZEB2 are zinc-finger-containing DNA binding proteins that are major repressors of E-cadherin and IL-2 expression. Consequently, ZEB1/2 activity leads to metastatic movement, whereas BMI1 inactivates tumor suppressor proteins (e.g., p16 and p19) and induces cellular proliferation [97]. Finally, P-glycoprotein [or multidrug resistance protein-1 (MDR-1) or ABCB1] is an ATP binding cassette (ABC) transporter protein that mediates the efflux of drugs entering a cell (Fig. 3). Therefore, miR-200c plays two prominent roles in suppressing oncogenic pathways in breast cancer cells. First, miR-200c suppresses EMT by suppressing the most important proteins involved in EMT, and second, it sensitizes breast cancer cells to chemotherapy through targeting MDR-1 mRNA [36].

2.2.2. Anti-proliferative tsmiRs

2.2.2.1. DNA repair and cell cycle modulators. MiR-335 is an anti-metastatic miRNA that has been shown to be down-regulated in most breast cancer cases [71]. MiR-335 also activates ERα, insulin-like growth factor-1 receptor (IGF1R), and specificity protein-1, which leads to BRCA1 upregulation [66]. MiR-145 is another tsmiR that is down-regulated in breast cancer. p53 and BRCA1 regulate miR-145 expression by recognizing the root of the stem-loop structure in pri-miR-145, and then promoting miR-145 processing by interacting with the DDX5 subunit of Drosha. As a result, miR-145 suppresses EGFR, c-Myc, and VEGF. MiR-145 overexpression may lead to a reduction in resistance to tamoxifen and can inhibit cellular proliferation, metastasis, and angiogenesis [67].

2.2.2.2. Tyrosine kinase receptors (RTKs). A specific tyrosine kinase receptor previously described, HER2, is a potent biomarker in HER2 positive (HER2+) breast cancer sublines. By targeting this type of receptor, miRNAs can suppress cellular proliferation as well as the majority of cell signaling pathways. MiR-491-5p, for example, is a tsmiR that targets EGFR mRNA [126]. ERBB2/Neu receptor overexpression has been reported in approximately one-third of breast cancer cases. MiR-199b-5p inhibits HER2 by targeting HER2 3′-UTRs. MiR-199b-5p can also inhibit Erk1/2 and Akt, as members of MAP kinase and PI3K pathways, respectively [79]. In addition, miR-342-5p is down-regulated in HER2-positive breast cancer cells. MiR-342-5p targets EGFR, Akt2, Ca^{2+}/calmodulin-dependent protein kinase, and protein kinase C. Besides miRNAs that are involved in direct regulation of HER2, such as miR-134, miR-193a-5p, miR-331-3p, miR-453, miR498, miR-541, and miR-552, the down-regulation of other miRNAs, such as miR-342-5p and miR-491-5p, has been clearly shown in HER2+ breast cancer [126]. Moreover, the overexpression of MiR-125b, a well-known tsmiR, has been shown to down-regulate HER2, which leads to a reduction in cell motility and invasiveness [79,114]. MiR-125b down-regulation has been demonstrated in MCF-7 breast cancer cells, whereas its regulation in normal and hormone receptor-negative MDA-MB231 breast cancer cells was nearly identical [15,77,129]. Therefore, before making any treatment decision for breast cancer, the subtype should be first determined, since miRNA silencing may be useful in certain cases such as HER2+ tumors. For HER2+ breast cancer cells lacking miR-125b activity, miR-125b replacement therapy could be a potent therapeutic strategy as discussed below.

2.2.3. Pro-apoptotic tsmiRs

MiR-203 is a tsmiR that promotes apoptosis and suppresses cell motility. MiR-203 is upregulated in non-metastatic breast cancer, but miR-203 down-regulation has been reported in metastatic breast cancer. Increased levels of miR-203 can lead to cell cycle arrest, apoptosis, and suppressed cell motility and invasion [130]. It has been shown that miR-15a, miR-16, miR-34b/c, miR-200, and miR-128 may be down-regulated in breast cancer and are involved in apoptosis [131]. Pro-apoptotic miRNAs observed in breast cancer are highlighted in Table 2.

3. miRNA-based therapeutic strategies for breast cancer

3.1. Nucleic acid-based strategies

Nucleic acid-based therapeutic strategies are those in which a chemically modified nucleic acid is used to restore the normal activity of miRNAs. Here, nucleic acid-based strategies are classified into two main categories: (1) miRNA replacement therapy, and (2) anti-miRNA therapy. The latter category is sub-divided into two groups based on the seed sequences and mechanism of action, including antagomiRs and miRNA sponges. Different nucleic acid-based therapeutic strategies are summarized in Fig. 4.

3.1.1. miRNA replacement therapy

3.1.1.1. miRNA mimics. miRNA replacement studies have been conducted in some animal models of cancer; however, this strategy has not yet been performed in breast cancer cells. A replacement strategy seems to be a promising methodology for developing tools to replace malfunctioning tsmiRs and overcome breast cancer [67,132,133]. miRNA mimic delivery is best tolerated by non-tumorigenic cells because the pathways they activate or suppress have already been activated or suppressed by endogenous miRNAs, and normal cells can regulate the pathway while cancer cells cannot [133].

Let-7 was the first miRNA in humans to be discovered and is ordinarily expressed in normal breast cells, and its down-regulation plays a critical role in renewal and metastasis of breast cancer cells [126]. A reduction in Let-7 levels has been reported in self-renewing breast cancer cells, and this reduction can be replaced by lentiviral Let-7 miRNA to decrease cellular proliferation [19]. Although cancer cells are often not detected after chemotherapy or radiotherapy, renewal of the cancer cell population can still occur from a tiny, undetectable accumulation of cancer cells. Therefore, combinatorial treatment as a targeted therapy is crucial for the effective removal of cancer cells.

Regarding breast cancer, BRCA1 up-regulates miR-145 and miR-205 tsmiRs; therefore, loss of BRCA1 causes a reduction in these miRNAs. In this case, using miR-145 and miR-205 mimics might restore the functional roles of BRCA1 even if the protein remains inactive [66]. Furthermore, down-regulated tsmiRs Let-7, miR-205, miR-126, miR-335, and miR-451 can be restored through miRNA replacement therapy [19,27,118].

3.1.2. Anti-miRNA therapy

There are three ways to remove overexpressed oncomiRs: (1) genetic knockout (not discussed in this review), (2) anti-sense oligonucleotides (antagomiRs), and (3) miRNA sponges. LNA oligonucleotides are chemically modified anti-sense molecules that can be used to synthesize anti-miRNA nucleic acids. LNA oligonucleotides possess an internal bridge between the 2′-O and 4′-C at each nucleotide (Fig. 4c) [9,18,134]. As the sequences and mechanism of antagomiRs and miRNA sponges are different (Fig. 4), antagomiRs and miRNA sponges are discussed here as different anti-miRNA strategies; however, both result in miRNA silencing.

3.1.2.1. miRNA antagonists (antagomiRs). AntagomiRs are miRNA antagonists that affect miRNA-related pathways by binding and blocking oncomiRs (Fig. 4) [6,86,135]. These nucleic acid antagonists are one of the known ways to inhibit oncomiRs, and therefore they may be an effective way to treat cancer [89,91,98,136,137]. AntagomiRs are chemically engineered anti-sense oligonucleotides containing 2′-*O*-methylation of ribose residues, 3′-conjugated cholesterol residues, and partial replacement of phosphodiester bonds through phosphorothioate linkages, wherein one of the non-bridging oxygens is replaced by sulfur (Fig. 4b) [30].

In the case of antagomiR therapy, miR-9 and miR-21 are well-known oncomiRs overexpressed in breast cancer that can be knocked-down using anti-sense oligonucleotides [25,41,70,71]. MiR-21 is an oncomiR that regulates several pathways to enhance cancer cell signaling, such as PI3K pathway activation by blocking PTEN and inhibiting apoptosis via B cell lymphoma-2 protein (Bcl2) regulation. It has been demonstrated that antagomiR-21 can affect breast cancer cells through the activation of apoptosis and reduction of cellular proliferation [25,70]. A previous study showed that miR-21 antisense oligonucleotides could restore trastuzumab sensitivity in resistant breast cancer by inducing PTEN expression, while injection of miR-21 mimics showed trastuzumab resistance in a trastuzumab-sensitive breast tumor via PTEN silencing [76].

It has been reported that the overexpression of different miRNAs may be a signature for several kinds of cancer, including breast cancer. Accordingly, 15 upregulated and 12 down-regulated miRNAs are reportedly involved in solid breast tumors, including miR-21, miR-17-5, miR-29b-2, miR-146, miR-155, and miR-181b-1, which have been well-studied. Since miR-182 targets BRCA1, antagomiR-182 may restore activation of BRCA1 [66]. MiR-155 is an overexpressed oncomiR in breast cancer; however, miR-155 has been shown to be strongly upregulated in other normal tissues, such as the pancreas, without causing cancer [77]. On the other hand, miR-10b, another oncomiR that promotes metastasis and has the same function as antagomiR-10b, did not reduce primary breast cancer tumors, but rather suppressed lung tumor metastasis [30]. In these cases, the clinical utility of antagomiR therapy may depend on

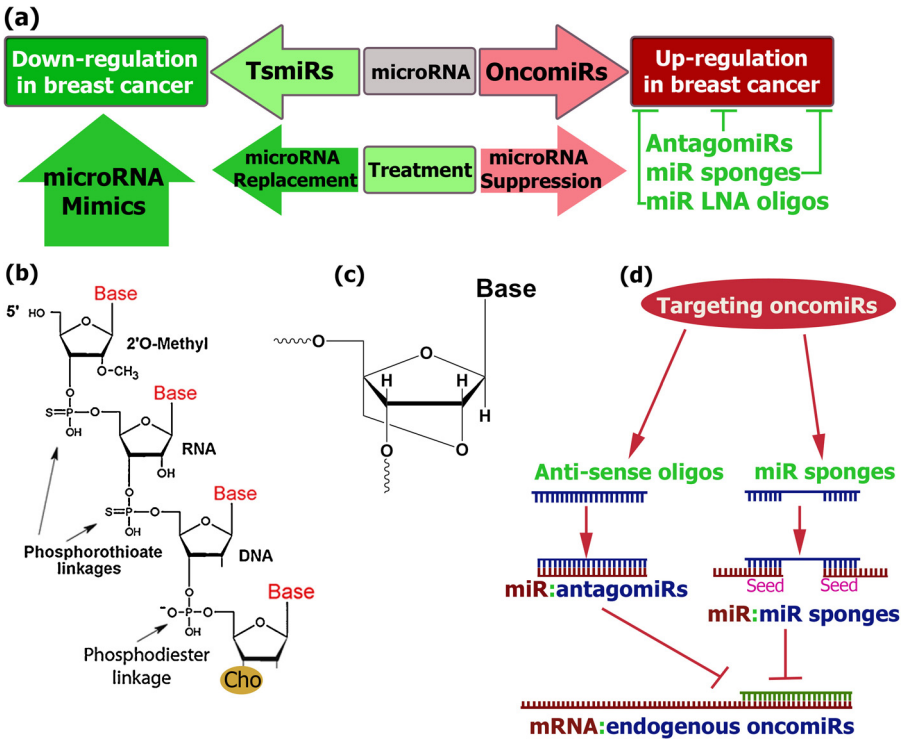

Fig. 4. miRNA-based therapeutic strategies to overcome breast cancer. (a) These strategies can be used to affect oncogenic miRNAs (oncomiRs) and tumor suppressor miRNA (tsmiRs). (b) Structure of antagonistic miRNAs (antagomiRs). AntagomiRs have three modifications, including 3′-conjugated cholesterol, phosphorothioate linkages, and 2′-*O*-methylation, which stabilize their structure. (c) A locked nucleotide (one unit of locked nucleic acid [LNA] anti-sense oligos). (d) The mechanisms by which anti-sense structures (i.e., antagomiRs, LNA, and miR sponges) target and inhibit oncomiRs. MiR sponges have several complementary sequences for binding several miRNA seed sequences. MiR sponges are more effective than antagomiRs and LNA; however, preparation of miR sponges is more difficult and may not be cost effective.

the tissue receiving the antagonists, making it difficult to generalize the effectiveness of antagomiR therapy. In addition, the method by which certain types of anti-sense oligonucleotides are delivered to certain tissues (e.g., breast, pancreas, etc.) is another crucial matter that might not be efficiently captured by such techniques [77].

AntagomiR therapy can be applied as complementary sequences attached to the seed sequence of endogenous miRNAs or in the form of an LNA oligonucleotide. LNA oligonucleotides were useful for inhibiting breast cancer metastasis through the down-regulation of miR-10b. In earlier stages of orthotopic MDA-MB231-Luc-D3H2LN tumor development, breast cancer metastasis into lymph nodes was reportedly prevented by LNA-containing nanoliposomes [109]. In addition, the use of miR-21 LNA knocked down miR-21 expression and prevented the proliferation of different breast cancer cells [25].

3.1.2.2. miRNA sponges. Sponge RNAs contain complementary binding sites to miRNAs of interest. miRNA sponges are comprised of transgenic cells and block all other miRNAs from the same family [138]. Sponges bind to seed sequences of certain miRNAs that contain two to seven specific sequential nucleotides [30,138]. miRNA sponges have multiple binding sites (usually 4-16). Both RNA polymerase II and III promoters have been used to transcribe miRNA sponges; however, transcripts of RNA polymerase II promoters are more stable due to their capped 5′ and 3′ polyadenylated tails [139]. MiR-9 is an oncomiR that promotes cell migration and metastasis. It has been shown that more than 50% of miR-9 activity is reduced by miR-9 sponges [41]. In addition, miR-21 sponges have been successfully used in MDA-MB231 and MCF-7 breast cancer cell lines, and miR-9 sponges have been used for 4T1 metastatic breast cancer cell lines where metastatic activity was reduced by almost 50% (Fig. 4d) [139]. This result indicates that anti-miRNAs could be effective on different cell lines, but the efficacy and side effects remain crucial, unresolved issues. RNA sponges, for example, contain several seed sequences that may bind to other non-coding RNAs as well as mRNAs. Therefore, the safety of miRNA therapy needs to be fully elucidated to ensure that other important metabolic pathways are not affected.

3.2. Drug-based strategies

In contrast to nucleic acid-based strategies, the expression of miRNAs can be modulated by drugs. Furthermore, some drugs, such as berberine, act as intercalators and are known to be bound miRNA as well as DNA. The effects of berberine on breast cancer cells have been already discussed in a previous review [15]. Some evidence suggests that these drugs can affect miRNA regulation; however, to date few studies has explored these mechanisms and therefore additional assessment is needed.

3.2.1. Stilbenes

Recent studies have explored the effects of natural compounds on miRNA expression known to be involved in several tumor types. Some of these natural products exhibit synergy with chemotherapeutic drugs. Stilbenes, such as resveratrol (PubChem CID: 445154), are a group of polyphenols that have been found to have activity in breast cancer [86]. Resveratrol has been shown to upregulate miR-141 and miR-200c expression in MDA-MB231 breast cancer cells. Increased levels of miR-141 and miR-200c reduce invasiveness and EMT [43]. Indol-3-carbinol (PubChem CID: 161721), which is present in cruciferous vegetables (e.g., broccoli, brussels sprouts, and cabbages), is another stilbene that is converted into active metabolites in the body, such as diindolylmethane (DIM) (PubChem CID: 3071) [58]. In MCF-7 and MDA-MB231 breast cancer cells, diindolylmethane was found to have oncogenic properties. It has also been reported that diindolylmethane upregulates miR-21

expression, which leads to degradation of its target, Cdc25A [43]. In addition, Hagiwara et al. [122] demonstrated that resveratrol can inhibit tumor suppressor miRNAs, such as miR-16, miR-141, miR-143, and miR-200c. Hagiwara et al. also showed that DIM can enhance cancer development, though most studies have found DIM promotes anti-cancer effects, including DNA repair, apoptosis, and cell cycle arrest [140]. Accordingly, clinical and pre-clinical studies of DIM have been initiated [141], though the anti-cancer properties of DIM have not been supported by work conducted in breast cancer to date [122,140]. Therefore, further studies are needed to address the mechanism by which stilbene affects the regulatory miRNA network in order to determine the utility in breast cancer treatment.

3.2.2. Curcumin

Curcumin (PubChem CID: 2889), another polyphenol isolated from plants such as *Curcuma longa*, has been shown to induce miR-181b. This induction inhibits proliferation and metastasis, and promotes apoptosis in breast cancer cells [58,142]. The apoptotic effects of curcumin appear to be mediated by down-regulating Bcl2 via miR-15a and miR-16 upregulation [143]. Curcumin and piperine can inhibit breast cancer stem cell renewal, but do not cause toxicity to differentiated cells. As a potent anti-cancer natural product, curcumin also down-regulates miR-21, thereby suppressing the majority of cell signaling pathways activated by this miRNA (e.g., PI3K/AKT/mTOR pathway) [101].

3.2.3. Flavonoids

Flavonoids are another group of polyphenolic compounds reported to have anti-oxidant and anti-cancer effects. Glyceollins are flavonoids affecting the ER (anti-estrogenic effects) and can be found in soybeans. Glyceollin (PubChem CID: 162807) treatment affects ER-negative breast cancer cells as well. It has been reported that glyceollin treatment in triple-negative breast cancer (MDA-MB231) upregulates tsmiRs (miR-22, miR-29b, miR-29c, miR-30d, miR-34a, miR-195, miR-181c, and miR181d) and down-regulates oncomiRs (miR-21, miR-193a-5p, miR-185, miR-452-5p, miR-486-5p, and miR-224) [144]. Quercetin, another flavonoid, induces apoptosis by down-regulating miR27a in combination with resveratrol [104], whereas Epigallocatechin-3-gallate (PubChem CID: 65064), a strong anti-oxidant flavonoid with anti-cancer activity, has been shown to induce apoptosis via miR-16 upregulation by blocking Bcl2 and miR-21 [108].

3.2.4. HDAC inhibitors

Histone deacetylases are a class of enzymes that remove the acetyl group from specific lysine residues of histones. This kind of modification, which is commonly called as epigenetic modification, leads to an alteration in gene expression. Recently, Hsieh et al. [113] demonstrated that HDAC inhibitors (HDACi) suppress HDAC4 via miR-125a-5p overexpression. An analysis of 300 patients with different subtypes of breast cancer (e.g., Stages I, II, and III, ER+ and ER-, and HER2+ and HER2−) found that miR-125a-5p directly targets HDAC4 and negatively correlates with tumor size ($P < 0.001$) [113]. Another study, using in vitro and in vivo experimental systems, also reported that HDACi mediates miR-125a-5p overexpression through the activation of RUNX3/p300/HDAC5; however, miR-125a-5p modulates HDAC5 by suppressing the protein. Therefore, HDAC5 activity appears to be controlled through a regulatory loop of miR-125a-5p and RUNX3 [145].

3.3. The effects of miRNAs on response to conventional therapy

Breast cancer patients often do no respond to radiation or chemotherapy, and depending on the method used and geographical distribution, some type of resistance to therapy can occur (e.g., tamoxifen). The most common type of resistance is to chemotherapy, but resistance to radiation has also been observed. Drug resistance is a challenging obstacle for overcoming breast cancer. Drug resistance can happen via four mechanisms: (1) increased drug efflux through ATP-binding cassette transporters (ABC transporters), (2) alteration of drug targets, (3) alteration of DNA repair pathways, and (4) evasion of apoptosis [86].

3.3.1. Increased levels of ABC transporters

Different ABC transporter proteins (e.g., ABCB1, ABCG2, ABCC1, and ABCC10) are involved in breast cancer resistance to tyrosine kinase inhibitors [146]. Drugs that inhibit ATP binding (e.g., imatinib, nilotinib, geftinib, erlotinib, and others) can sensitize cells, and combinatorial application with other drugs may reduce resistance to drugs [146]. MiR-328 expression, for example, has been shown to increase mitoxantrone-sensitivity by targeting ABCG2 [20,144]. Mitoxantrone (PubChem CID: 4212), doxorubicin (PubChem CID: 31703), and 7-ethyl-10-hydroxycamptothecin (SN-38; PubChem CID: 104842) are pumped out of cells by ABCG2 [146]. Doxorubicin blocks DNA replicated by acting as a topoisomerase II inhibitor. In addition to ABCG2, doxorubicin is also pumped out of cells by P-glycoprotein (also known as MDR-1 or ABCB1). Increased sensitivity to irinotecan, a topoisomerase 1 inhibitor, has also been observed by miR-451-mediated repression of ABCB1. If miR-451 targets are overexpressed, then miR-451 mimics may be an effective approach for sensitizing cells to certain drugs, such as tamoxifen and irinotecan [147,148]. It has been reported that ectopic expression of miR-451 and miR-298 restores doxorubicin sensitivity in breast cancer [20,144,149]. Doxorubicin sensitivity can also be restored by inhibiting ABCC1 through miR-326 upregulation [150].

The miR-200 family member, miR-200c is a potent tumor suppressor. MiR-200c upregulation has been shown to decrease P-glycoprotein levels, resulting in chemosensitivity to epirubicin in breast cancer (Fig. 3) [86]. MiR-200c is associated with E-cadherin upregulation and cell sensitivity to drugs. Therefore, these dual functions make miR-200c a promising target for concomitantly suppressing metastasis and drug resistance.

3.3.2. Alteration of drug targets

HER2 is targeted by trastuzumab, but down-regulation of HER2 and related proteins (e.g., HER3) affect therapeutic value of trastuzumab [151]. MiR-205, which is normally a tsmiR, inhibits the effects of some tyrosine kinase inhibitors by targeting HER3 [144]. A major cause of mortality of subjects with HER2-positive breast cancer is resistance to trastuzumab. This drug, also known by the brand name Herceptin, is a recombinant monoclonal antibody that specifically binds the extracellular domain of HER2 and potentially blocks HER2/neu receptors on the surface of human breast cancer cells. The main mechanism is unclear, but it has been reported that TGF-β signaling is elevated in trastuzumab-resistant cells. In breast cancer, the cross-talk between HER2 and TGF-β signaling pathways is reported to be related to trastuzumab resistance [36].

It has been previously shown that miR-21 overexpression is associated with resistance to cisplatin and decreased PTEN activity [152]. MiR-21 overexpression may increase topotecan resistance. Inhibition of miR-21 has been found to sensitize MCF-7 cells to topotecan [144], and consequently, loss of PTEN expression causes resistance to trastuzumab [98]. In fact, these results demonstrate the importance of the PI3K pathway and down-regulation of PTEN. Since the PI3K pathway is closely associated with other oncogenic pathways, such as MAP kinase and TGFβ, it plays a potent role in activating cellular machinery related to proliferation and cell growth. When this pathway becomes activated in tumor cells, a greater resistance to therapy is often observed [37]. Therefore, therapeutic strategies that can suppress PI3K activation are very

important. Anti-miR-21 therapy is a promising therapy that may block this pathway, and an antagomiR-21 may lead to a decrease in the cellular growth rate and increased sensitivity to therapy.

More than 70% of breast cancer cases are ER+ and can be treated with tamoxifen (PubChem CID: 2733526), which is a drug that specifically binds and blocks the ER. Over 40% do not respond to such treatment. The down-regulation of MiR-126 and miR-10a is an independent predicator of tumor relapse in early postmenopausal breast cancer patients. MiR-126 is associated with blood vessel formation and may be related to angiogenesis. Therefore, down-regulation of miR-126 may be an effective anti-angiogenic treatment for cancer; however, miR-126 is related to tamoxifen resistance in ER-positive breast cancer cases [153]. OncomiR-10a elicits its apoptotic and proliferative effects by targeting HoxA1, a protein involved in the regulation of anti-apoptotic factor Bcl2. It has been reported that oncomiR-10a not only has a dual action, but may also play a role in resistance to tamoxifen [153].

Another anti-breast cancer drug, fulvustrant (PubChem CID: 104741), is a selective ER down-regulator (SERD) that affects ER+ breast cancer cells (e.g., MCF-7). The use of fulvustrant is important in the resistance to tamoxifen and aromatase inhibitors. It has been reported that fulvustrant causes overexpression of miR-221/222 in SERD-resistant cell lines. In these cell lines, miR-221/222 promote cell cycle progression by activating β-catenin [86]. In addition, the tumor suppressor protein p27 can be targeted by miR-221/222, resulting in cell cycle activation. MiR-221/222 are two oncomiRs that can be targeted and inhibited by antagomiRs, which has been shown to lead to cell cycle arrest in ER-positive breast cancers [87] (Table 3).

The most invasive subtype of breast cancer is known as triple-negative breast cancer (TNBC), whereby ERBB2/Neu (HER2) receptors, ER, and progesterone receptor (PgR) are not expressed. The triple-negative subtype exhibits the greatest resistance to chemotherapy, and therefore identifying novel miRNA-based therapeutic strategies will play a critical role in the future treatment of such patients [170]. In triple-negative breast cancer, miR-106b, miR-17/92, miR-200 (a-c), miR-21, and miR-155 are upregulated, while miR-126, miR-145, and miR-205 are down-regulated [68]. MiR-155 upregulation can lead to paclitaxel and doxorubicin resistance in breast cancer cases, especially in invasive breast cancer subtypes. MiR-155 overexpression also causes resistance to other drugs, such as paclitaxel and doxorubicin, through the inhibition of FOXO3a (Fig. 2) [68,115].

MiR-375 overexpression has been shown to restore the sensitivity of cells to trastuzumab by targeting IGF1R. IGF1R is associated with drug resistance, and its suppression may increase drug sensitivity [167]. Furthermore, miR-145 enhances sensitivity to drugs (e.g., tamoxifen) by targeting P-glycoprotein [67]. Ectopic miR-221/222 expression also causes resistance to tamoxifen through targeting of p27 and ERα [67]. Moreover, 14-3-3ξ has positive effects on HER2 and TGF-β, which promote EGFR and mitogen-associated protein kinase elevation. Tamoxifen can indirectly enhance 14-3-3ξ by down-regulating miR-451. Moreover, it has been demonstrated that activation of 14-3-3ξ through tamoxifen administration may gradually cause resistance to tamoxifen [144].

Taxanes, such as paclitaxel (PubChem CID: 4666), bind to the β-subunit of tubulin heterodimers to reduce microtubule involvement in the cell cycle. Although taxanes can stabilize microtubules and arrest cells in the G2/M-phase of the cell cycle, resistance to taxanes has been observed after repeated cycles of chemotherapy. Genetic alteration of seven identified isotypes of β-tubulin may be associated with drug resistance. Lobert et al. [171] showed that paclitaxel reduced miR-100 levels in MCF-7 breast cancer cells. This reduction caused a two- to three-fold increase of β-tubulin II, whereas miR-200c was found to regulate β-tubulin III mRNA. Microtubule-associated drugs, such as taxols, may have altered targets that lose sensitivity to these drugs; therefore, some degree of drug resistance may appear in these cases [171].

3.3.3. Alterations in DNA repair pathways

Proteins related to DNA repair play a major role in radioresistance. It well-known that mutations involved in the dysregulation of DNA repair proteins, such as BRCA1, increase the risk of developing breast cancer; however, BRCA1 dysfunction makes cancer cells more sensitive to radiotherapy. In fact, radiation (e.g., γ- and UV radiation) leads to the fragmentation of DNA, and BRCA activation stabilizes DNA, which consequently results in radioresistance [37]. As previously mentioned, miR-146 and miR-182 target BRCA1; however, it is currently unknown whether silencing of these miRNAs has any benefit in breast cancer. Therefore further studies are needed to assess the beneficial effects of BRCA1 re-activation.

3.3.4. Evasion of apoptosis

MiR-125b, a tsmiR, was found to be down-regulated in non-metastatic MCF-7 breast cancer cells, while overexpression may be correlated with resistance to paclitaxel [115]. MiR-125b upregulation has been shown to increase taxol resistance in breast cancer by targeting Bcl2 homologous antagonist killer 1 (BAK1), an anti-apoptotic protein [144]. In contrast, miR-27b plays a completely different role in drug resistance. MiR-27b targets cytochrome P450 (CYP) 1B1, an enzyme related to drug metabolism [144]. In addition, CYP1B1 metabolizes estrogen to produce oxidative intermediate compounds that trigger apoptosis in a caspase-independent manner [144]. By suppressing CYP1B1, miR-27b promotes resistance to drug-induced apoptosis (e.g., Taxol-induced apoptosis) [15,172].

3.4. Nanoformulas and miRNA-based therapy

In vivo delivery of antagomiRs, miRNA mimics, and miRNA sponges is challenging and often does not result in the desired therapeutic effects. The application of nanomaterials as nanoplatforms is referred to as optical and electrochemical sensing of miRNAs. In fact, three types of nanoplatforms have been designed: (1) plasmonic/optical-based (e.g., gold, silver, magnetic, quantum dots, and graphene oxide), (2) electrochemical labeled-miRNAs (e.g., hyaluronic acid-based, gold, ruthenium oxide, and osmium oxide), and (3) electrochemical label-free miRNAs (e.g., gold, quantum dots, silicon nanowire, polymer nanowire, nanopores, and carbon nanotubes) [21]. While the application of nanoparticles for drug delivery (cisplatin and tamoxifen) has been studied in breast cancer cells, few studies have reported nanoparticle delivery of RNA molecules to treat breast cancer.

Researchers have recently designed an RNAi nanoplatform that targets tumors. Accumulation of nanoformulas can occur through CD44-mediated endocytosis [109]. This nanoparticle can deliver both RNAs and lipophilic drugs as well as release its cargo (RNAs and/or drugs) in two steps. pH was shown to trigger RNA release in the late endosome, whereas *hyaluronidase* triggers drug release. Hyaloronan-5β-cholanic acid conjugates can act as a platform for hydrophobic anti-cancer drugs. The effects and cytotoxicity of this novel technique have been measured and reported in an ovarian cell line (OVCAR8/ADR) [173]; however, the positive surface charge by which RNA molecules can bind to nanoparticles remains a challenge because it may cause nonspecific cellular reactions [173].

In fact, different RNAs might require different nanoplatforms for proper delivery. As mentioned, miR-10b and miR-21 are expected to be upregulated in breast cancer. Some silicon nanowires have been constructed to detect miR-10b and miR-21 [109], which are the two most common oncomiRs identified in breast cancer; the

Table 3
miRNAs involved in current therapies for breast cancer.

miRNAs	Affected target	miRNA action	Experimental systems	References
miR-7	P-glycoprotein	Docetaxel sensitive Cisplatin sensitive	MCF-7; MDA-MB-231; MCF-7/CDDP	[102,154]
miR-10b[a]	HoxA-1	Tamoxifen resistance	Patient (N = 93; ER+)	[153]
miR-16	Bcl2, CDK6, CCND1	Docetaxel sensitive	MCF-7; MDA-MB-231	[102]
miR-21	HMSH2 PTEN	Cisplatin resistance Doxorubicin resistance Topotecan resistance	MCF-7; MDA-MB-231; MCF10A; MCF10A/HER2; MCF10A/vec	[60]
miR-29a	DNMT	Adriamycin resistance Docetaxel resistance	MCF-7; MDA-MB-231; MCF-7/Doc; MCF-7/Adr	[102,155]
miR-30a	CDK6, MTDH	Docetaxel sensitive	MCF-7; MDA-MB-231	[102,106,156]
miR-34a	Bcl2, CCND1	Docetaxel resistance	MCF-7; MDA-MB-231	[102]
miR-95[b]	SGPP1	Radiation sensitive	MCF-7; MCF-7/Doc; MCF-7/Adr	[157]
miR-100	β-tubulin isotypes	Paclitaxel sensitivity	MDA-MB-231; MCF10A Mice xenografts	[86]
miR-118	BRCA1	Cisplatin sensitivity	MCF7/DDP	[158]
miR-125a-5p	HER3	Docetaxel sensitive	MCF-7; MDA-MB-231	[102]
miR-125b	E2F3 BAK	Trastuzumab sensitivity Taxol resistance	Patients (N = 56; primary tumors, invasive ductal carcinoma) MDA-MB-231	[117]
miR-126[a]	IGFBP2	Tamoxifen resistance Docetaxel sensitive	Patient (N = 93; ER+)	[153]
miR-128	ABCC5	Doxorubicin sensitivity	SKBr3; MCF-7; patients (N = 77)	[159]
miR-155	FOXO3a	Paclitaxel resistance Doxorubicin resistance	Patients (N = 77, primary; N = 38, recurrent; Stages I, II, III, and IV)	[160]
miR-182	BRCA1	PARP inhibitors resistance Cisplatin resistance	MDA-MB-231; MCF10A Mice xenografts	[86]
miR-200c[b]	P-glycoprotein	Doxorubicin sensitivity Radiation sensitive	MDA-MB-231; MCF10A Mice xenografts P53 (null) claudin-low tumors	[37,38,86,161]
miR-205	HER3	Trastuzumab sensitivity	SKBr3; MCF7; HEK293	[162]
miR-222	PTEN	Adriamycin resistance Docetaxel resistance	MCF-7; MDA-MB-231	[102,155]
miR-221/222[a]	P27kip1	Tamoxifen resistance Fulvustrant resistance	MCF-7; OHT^R	[163]
miR-298	P-glycoprotein ABCG2	Doxorubicin sensitivity	MCF-7; MCF/Vp; MDA-MB-231; T47D; MDA-MB-468;	[20,144,164]
miR-301[a]	PTEN	Tamoxifen resistance	MCF-7/HER2; MCF-7/pcDNA MCF-7/HER2Δ16	[165]
miR-326	MRP-1	Doxorubicin sensitivity	SKBr3; BALB/c nude mice Patients (N = 40; HER2+; HER2−)	[150]
miR-328	ABCG2	Mitoxantrone sensitivity Doxorubicin sensitivity SN-38 sensitivity	MCF-7; MCF/Vp; MDA-MB-231; T47D; MDA-MB-468; TamR Patients (Primary tumors)	[20,144,146]
miR-342[a]	P27/Kip1	Tamoxifen sensitive	MCF-7; MCF-7/Doc	[166]
miR-345	ABCC1	Cisplatin resistance	MCF-7; MDA-MB-231; MCF-7/CDDP	[154]
miR-375[a]	IGF1R	Trastuzumab sensitivity Tamoxifen sensitive	MDA-MB-231; MCF-7; Hs578T; T47D	[167,168]
miR-429	TUBB2A	Taxol resistance	MCF-7; MDA-MB-231	[102]
miR-451[a]	P-glycoprotein ABCG2 ABCB1	Doxorubicin sensitivity Irinotecan sensitivity Tamoxifen sensitivity	MCF-7; MCF/Vp; MDA-MB-231 T47D; MDA-MB-468; MCF10A Mice xenografts	[20,86,144,161]
miR-452	APC4	Docetaxel sensitive	MCF-7/DOC	[169]
miR-638[b]	BRCA1	UV sensitive	Triple negative breast cancer cell lines	[53]

[a] miRNAs which affect hormone therapy.
[b] miRNAs which affect radiotherapy.

level of miR-21 has been found to be four-fold higher than miR-10b in normal tissues. Molecular devices have been made using poly-L-lysine and DNA probes based on complementary miR-10b-specific sequences [174]. For example, researchers have used poly-L-lysine to deliver antagomiR-10b in ER-negative breast cancer cells (MDA-MB231) [174].

Recently, Devulapally et al. [73] delivered anti-miR-21 (antagomiR-21) and anti-miR-10b (antagomiR-10b) to a triple negative breast cancer (TNBC) cell line, MDA-MB-231, in both culture and xenograft mice using poly(D,L-lactide)-block-poly(ethylene glycol) polymer nanoparticles (PLGA-b-PEG). In that study, the authors first loaded nanoparticles with antagomiR-21 and

antagomiR-10b and then evaluated serum uptake, release profile, and subsequent blocking of endogenous miRNAs (miR-21 and miR-10b) in cell culture and xenografts. Molecular imaging showed that the corresponding miRNAs were successfully blocked. The study also observed a 40% reduction in tumor growth when a low dose of antagomiR-loaded nanoparticles (0.15 mg/kg) was used [73]. Together, these findings indicate that anti-miRNA and nanotechnologies may be efficacious at blocking metastasis.

4. miRNA-based therapy and clinical evidence

Several studies have shown the role of miRNAs in prognosis and diagnosis of breast cancer, but some scientists believe that patterns of miRNAs in serum and plasma may be helpful biomarkers for non-metastatic breast cancer as well [175,176]. Other studies have reported biomarkers for invasive breast tumors as well as non-metastatic breast cancer. Heneghan et al. [176], for example, demonstrated that miR-195 and let-7a levels were decreased in non-invasive breast cancer cases ($n = 148$). Table 4 compares reported miRNAs and their utility for prognosis and diagnosis. Jung et al. [177] compared breast cancer patients who received chemotherapy ($n = 29$; HER2+) with patients who did not receive chemotherapy ($n = 43$; $n = 29$, HER2+; $n = 35$, PgR+) and found that miR-210 circulation levels directly correlated with trastuzumab resistance as well as tumor presence. The clinical effects of miRNAs on resistance to chemotherapy was also analyzed for miR-128, which targets ABC transporter C5 (ABCC5) and Bmi1 [159]. In that study, ectopic expression of miR-128 resulted in breast cancer-initiating cells being sensitive to doxorubicin, which consequently led to enhanced DNA fragmentation and pro-apoptotic effects. Conversely, reduction in miR-128 resulted in increased ABCC5 and Bmi1, ultimately leading to drug resistance and metastasis, respectively. Another study demonstrated that patients with early stage breast cancer had significantly reduced levels of miR-155, miR-181b, and miR-24 after surgical resection and a reduction in miR-19a after therapy compared to levels at the time of diagnosis ($n = 63$). In addition, the levels of these miRNAs are markedly increased in patients with a high risk of breast cancer suggesting that they may be useful biomarkers with prognostic and diagnostic value [82].

Analysis of tumor suppressor miRNAs thought to be key therapeutic biomarkers can lead to the development of tsmiR mimics. In contrast, oncogenic miRNAs may serve as diagnostic biomarkers. For example, the miR-125 family, including miR-125a-5p and miR-125b, are potential tumor suppressor miRNAs that have the potential to be therapeutic biomarkers. Hsieh et al. [113] demonstrated that the level of miR-125a-5p, which targets HDAC4, is negatively correlated with breast cancer progression. Interestingly, lower levels of miR-125a-5p in serum correlated with shorter survival. Therefore, a decreased level of miR-125a-5p may be a prognostic factor, but application of this as a prognostic factor will require further analysis in healthy individuals and standardization of expression levels. It has been reported that miR-125b is down-regulated in invasive breast cancer cells. Zhang et al. [116] compared miR-125b levels in MCF-7, MDA-MB-231, MDA-MB-435, and MDA-MB-453 cell lines as well as 105 invasive breast cancer tissues and 40 normal paired adjacent tissues. Interestingly, they found that hypermethylation of the miR-125b promoter is partially responsible for the reduction in miR-125b expression. In addition, a study conducted by Wang and colleagues reported that circulating miR-125b may be involved in 5-Fluorouracil (5-FU; PubChem CID: 3385) resistance. Analysis of 56 breast cancer patients have shown that 46% did not respond to 5-FU. Accordingly, an in vitro study showed that ectopic expression of miR-125b increased resistance to chemotherapy. These results suggest that in patients receiving chemotherapy, miR-125b may be a marker for drug resistance and should be followed [117].

In addition to miR-125 members, it has been reported that miR-34a levels are decreased in triple negative breast cancer both in cell lines (MDA-MB-231) and primary samples at time of surgery [110]. Another research group obtained 15 paired breast carcinoma tumors and adjacent normal tissue and detected the up-regulation of circulating miR-21 and down-regulation of circulating miR-34b/c in tumor tissue. This study confirmed the role of miR-21 and miR-34b/c as an oncomiR and tsmiR, respectively. In another study, sera from 113 breast cancer patients with HER2+ and HER2− subtypes were screened for miR-21, miR-10b, and miR-19a expression. Serum miR-21 levels in non-metastatic (HER2+) breast cancer was higher and serum miR-10b levels in metastatic (HER2−) breast cancer were higher compared to normal controls [178]. As two important oncomiRs, miR-21 and miR-10b activate PI3K and Wnt/β-catenin pathways, respectively. Therefore miR-21 and miR-10b may act as biomarkers for HER2+ and HER2− breast cancers, respectively. Nevertheless, several studies strongly suggest that miR-21 is a promising diagnostic factor for breast cancer, especially for non-invasive tumors, whereas miR-34 members are the best option for designing miRNA mimics as a promising therapeutic strategy for invasive breast cancer.

5. Future directions and challenges

Most published works to date have shown that miRNAs have many targets among cellular pathways and can be used for targeted therapy of breast cancer; however, pre-clinical and clinical studies are rare and further confirmation of the impact of in vivo miRNA-targeted cancer therapy are required. As discussed earlier, miRNAs act as regulators of cell signaling and post-transcriptional modifications, and a better understanding of their roles could yield novel approaches for treating cancer. miRNAs appear to be optimal drug targets and could be used in combination with other drugs or therapies to reduce the treatment time period. Fomivirsen is the first RNA-based drug approved by the US Food and Drug Administration (FDA) in 1998. It is a synthetic 21-long antisense oligonucleotide modified with phosphorothioate (which provides resistance to nuclease-mediated degradation) used as antivirals for the treatment of cytomegalovirus retinitis [180]. In addition, only two candidate miRNAs have reached clinical trials: SPC3649 (Santaris Pharma, Horsholm, Denmark), a miR-122 anti-sense LNA, and MRX34 (Mirna therapeutics, Inc.), a liposomal miR-34 mimic [137]. MiR-34 is a tumor suppressor miRNA that is down-regulated in metastatic breast cancer.

miRNA-based therapy may be useful for treating breast cancer. Four crucial hallmarks of breast cancer, proliferation, evasion of apoptosis, motility/migration, and vessel formation, may be affected by miRNA. As discussed earlier, there are two categories of cancer-affecting miRNAs known as tsmiRs and oncomiRs. According to Fig. 1, a large number of miRNAs affect cellular proliferation and migration, while angiogenesis and apoptosis may also be affected by lower expression levels of miRNAs. Moreover, existing challenges, such as differential regulation of signaling pathways by miRNAs at various stages of cancer development, have made miRNA targeting difficult. Considering the promising role of miRNA in breast cancer treatment, such challenges need to be overcome. At the moment, the most promising miRNAs for their therapeutic potential are miR-21 and miR-34. MiR-21 is a key regulator of mitogenic signaling pathways (PI3K and MAPK) and has been shown to be a great target for non-metastatic breast

Table 4
Circulating miRNAs involved in the prognosis and diagnosis of breast cancer.

miRNAs	Role as biomarker	Targeted breast cancer	Experimental systems	References
(tsmiR) let-7a	Diagnostic	Non-invasive breast cancer	Patients (N = 148)	[176]
tsmiR-10b	Prognostic Therapeutic	Invasive breast cancer	Patients (N = 113; HER2+ and HER2− breast cancer cases)	[178]
tsmiR-16	Diagnostic	Non-invasive breast cancer	Patients (N = 96, biomarker discovery; N = 152, biomarker validation)	[175]
oncomiR-19a	Prognostic Diagnostic	Risk of breast cancer Early stage of breast cancer	Patients (N = 63)	[82]
oncomiR-21	Diagnostic	Non-invasive breast cancer	Patients (15 pairs of breast carcinoma tumors) Patients (N = 113; HER2+ and HER2− breast cancer cases)	[178,179]
oncomiR-24	Prognostic Diagnostic	Risk of breast cancer Early stage of breast cancer	Patients (N = 63)	[82]
oncomiR-25	Diagnostic	Non-invasive breast cancer	Patients (N = 96, biomarker discovery; N = 152, biomarker validation)	[175]
tsmiR-34b/c	Therapeutic	Invasive breast cancer	Patients (15 pairs of breast carcinoma tumors)	[179]
tsmiR-34a	Therapeutic	Invasive breast cancer	Fresh tissues MDA-MB-231	[110]
tsmiR-125a-5p	Prognostic Therapeutic	Invasive breast cancer	Patients (N = 300)	[113]
tsmiR-125b	Prognostic Therapeutic	Drug resistant invasive breast cancer	Patients (N = 56; Primary tumors, invasive ductal carcinoma; 105 invasive breast cancer) MDA-MB-231	[116,117]
tsmiR-128	Prognostic	Drug resistant Primary tumors	Patients (77 primary tumors of breast cancer cases)	[159]
oncomiR-155	Prognostic Diagnostic	Risk of breast cancer Early stage of breast cancer	Patients (N = 63)	[82]
oncomiR-181b	Prognostic Diagnostic	Risk of breast cancer Early stage of breast cancer	Patients (N = 63)	[82]
tsmiR-195	Diagnostic	Non-invasive breast cancer	Patients (N = 148)	[176]
tsmiR-210	Prognostic	Drug resistant non-invasive breast cancer	Patients (N = 29, received chemotherapy; N = 43, did not received chemotherapy)	[177]
oncomiR-222	Diagnostic	Non-invasive breast cancer	Patients (N = 96, biomarker discovery; N = 152, biomarker validation)	[175]
oncomiR-324-3p	Diagnostic	Non-invasive breast cancer	Patients (N = 96, biomarker discovery; N = 152, biomarker validation)	[175]

cancer. In addition, miR-34 levels could be restored by miR-34 mimics as an approach for treating metastatic breast cancer.

Anti-sense miRNA therapy (e.g., LNAs, antagomiRs, and miR sponges) may be a promising strategy to inhibit tumors. Based on this review, it can be concluded that: (1) oncomiRs overexpressed in breast cancer (e.g., miR-21, miR-181, and miR-182) activate at least two hallmarks of cancer, demonstrating their potential as targets for breast cancer treatment; (2) oncomiRs, such as miR-155, are targets of tumor suppressor molecules (e.g., BRCA1), and such oncomiRs may be therapeutic targets; (3) the number of miRNAs suppressing breast cancer are strikingly higher than oncomiRs, and therefore suppressing oncomiRs with anti-sense RNA may be an easier approach, especially when at least two different anti-sense miRNAs are used in combination. Taken together, data indicate that anti-miR-21 (antagomiR-21) and anti-miR-10b (antagomiR-10b) in combination have synergistic effects on suppressing cancer cell proliferation.

miRNA-based therapies must overcome some challenges before reaching clinical trials. Similar to other drugs, the efficacy and safety of miRNA need to be studied further since miRNAs target many molecules in both normal and cancer cells [109]. Whenever miRNA-based agents are injected into blood, half-life must be long enough for them to reach target tissues. Furthermore, cellular delivery and entry are also challenges that need to be investigated in the future.

6. Conclusion

miRNA-based therapies represent powerful and targeted tools for addressing the high rate of mortality associated with breast cancer each year. However, the most useful application of miRNAs is their coadministration with other drugs to increase cell sensitivity and overcome drug resistance. In order to be a useful therapy, RNAs (anti-sense or mimics) must be stable for efficient delivery to cancer cells. MiR-21 and miR-34 are the most promising miRNAs that can be silenced or restored to control non-invasive and invasive breast cancer, respectively. However, mi-RNA delivery is still a challenge, and different delivery strategies, such as nano-delivery and liposome-mediated delivery, need to be optimized.

Conflicts of interest

The authors declare no conflicts of interest.

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