Review Article

The Emerging Role of MicroRNAs in Breast Cancer

Zhiguang Yang and Zhaoyu Liu

Department of Radiology, Shengjing Hospital of China Medical University, Shenyang, Liaoning 110004, China

Correspondence should be addressed to Zhaoyu Liu; liuzy1226@126.com

Received 4 April 2020; Accepted 10 June 2020; Published 3 July 2020

Academic Editor: Da Li

Copyright © 2020 Zhiguang Yang and Zhaoyu Liu. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Breast cancer (BC) is the most common malignancy in women. Due to BC heterogeneity, complexity, and metastasis, many BC patients do not successfully respond to therapies. Therefore, identifying new biomarkers for the diagnosis, prognosis, and development of new drugs is urgently required. Dysregulation of microRNAs (miRNAs) participates in the tumorigenesis and progression of cancers, especially breast cancer (BC). Several studies demonstrated that miRNAs could perform their function as oncogenes or tumor suppressors. This review describes recent progress on the role of microRNAs in the diagnosis, prognosis, hallmark, and treatment of BC. According to a recent literature survey, miRNAs play a pivotal role in the regulation of hallmarks of cancer, such as proliferation, apoptosis, invasion, metastasis, and tumor stemness. Many miRNAs are potential biomarkers for BC for diagnosis, and some are indicators of prognosis. Moreover, circulating miRNA profiles, as minimally invasive, diagnostic, and prognostic markers, are broadly used in BC therapy, and some miRNAs are good predictors of therapeutic outcomes. Other miRNAs are involved in overcoming chemoresistance and in increasing BC drug sensitivity.

1. Introduction

Breast cancer (BC) is one of the most common malignant tumors and the second leading cause of cancer in women [1]. Approximately, 1.5 million new cases are annually diagnosed with breast cancer [2] and almost 460,000 patients died each year due to BC chemoresistance and metastasis. BC biological characteristics are routinely used for early detection, prognosis, and selection of the therapeutic strategy, including histologic subtype, grade [3], lymph node status, hormone receptor, and human epidermal growth factor receptor 2 (HER2) statuses [4]. Some of the mentioned characteristics are related to patients’ survival and posttreatment clinical outcomes [5]. However, several BC patients, who had similar characteristics, showed different clinical outcomes. Therefore, biological features have limitations with regard to diagnosis, prognosis, and clinical outcomes’ prediction [6]. Thus, novel diagnostic and prognostic approaches are urgently required for the identification of new personalized therapeutic methods that improve BC patients’ quality of life.

MicroRNAs (miRNAs) are a group of small noncoding RNAs that can interrupt the expression of protein-coding genes by binding to their mRNAs and inhibiting therefore their protein translation [7]. So far, an estimated total of 28,000 mature miRNAs was reported to participate in posttranscriptional regulation during cellular processes, including cancer cell proliferation, differentiation, migration, apoptosis, and angiogenesis. miRNA abnormal expressions are also considered to be potential biomarkers of BC as they are stably detected in tumor tissues [8] and in patients’ body fluids, including blood, serum, plasma, and saliva [9, 10]. miRNAs in body fluids, also called circulating miRNAs, are remarkably stable, packaged into extracellular microparticles or bound with lipoproteins, which protect them from RNase digestions [10, 11]. miRNA profiles have been effectively used to classify BC patients as treatment responding or nonresponding groups [12]. Therefore, miRNAs have been clearly demonstrated to potentially regulate BC progression and used as new diagnostic, prognostic, and predictive biomarkers of BC [6].

In this review, we summarize recent publications on miRNA functions in the regulation of BC progression and discuss the clinical potential of miRNAs as biomarkers of early and differential diagnosis and prognosis, and as determinants of chemoresistance and therapy selection. Some
BC therapeutic strategies that involved miRNAs are reviewed, which provides new insights into breast cancer therapy.

2. miRNAs and Breast Cancer

miRNAs are a class of 18 to 24 nucleotides noncoding regulatory RNAs [13], which specifically target mRNA 3′-untranslated regions (3′ UTRs) leading to their translational repression and/or miRNA decay, degradation, or deadenylation [14]. An important characteristic of miRNAs is their capacity to bind to more than a hundred mRNAs’ 3′ UTRs [15]. Interestingly, one transcript can be regulated by various miRNAs [16]. In the human genome, an estimated 60% of genes can be recognized by different miRNAs [17]. miRNAs participate in the regulation of essential biological processes and several diseases. There is a long history about regulatory relationships between miRNAs and hallmark of cancer, especially breast cancer. As early as 2005, Lu et al. reported the differential expression of miRNAs in breast cancer [18]. Subsequently, an increasing number of studies have suggested that miRNAs are closely associated with BC occurrence and development. miRNAs were reported to play two important roles as oncogenes (onco-miRNAs) and tumor suppressors.

2.1. Onco-miRNAs in Breast Cancer. Many miRNAs targeting tumor-suppressor genes are overexpressed in BC. These miRNAs regulate the tumorigenesis, proliferation, invasion, and migration of cancer cells [19]. miR-10b is highly expressed in early metastatic and recurrent BC patients [20] and is associated with increased proliferation, migration, and invasion of BC cells via E-cadherin targeting [21]. miR-21 was demonstrated to promote the transformation and development of BC via suppressing the programmed cell death protein 4 (PDCD4) expression [22]. miR-155 acts as an onco-miRNA in BC, which inhibition by an antisense oligonucleotide remarkably prevented proliferation and induced cell apoptosis [23, 24]. Moreover, miR-200a has been shown to suppress apoptosis of BC cells by targeting the transcriptional regulator yes-associated protein 1 (YAP1) [25]. Finally, miR-27b targeted the ST14 (suppression of tumorigenicity 14) gene and enhanced the invasion and migration of breast cancer cells. All the discussed miRNAs are summarized in Table 1.

2.2. Tumor-Suppressor miRNAs in BC. Tumor-suppressor miRNAs are usually downregulated in cancer cells. They can inhibit cancer progression via silencing oncogenes and tumor-promoting genes. Many miRNAs, such as lethal-7 family (let-7), miR-26b, miR-124, miR-125a/125b, miR-205, and miR-206, were reported to act as tumor-suppressor miRNAs. miR-26b prevents the tumorigenesis of triple-negative breast cancer (TNBC) cells by targeting DEP domain containing 1 (DEPDC1) and downregulating FOXM1 expression [27]. miR-26b was identified to facilitate G0/G1 cell cycle arrest and to inhibit cellular proliferation via CDK8 targeting [28]. Ma et al. found that miR-26a/26b could inhibit BC progression through inhibiting the expression of ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase 4 (ST8SIA4) [29]. miR-124-3p was reported to be downregulated in BC cells, where it regulates their proliferation and invasion by targeting MGAT5 [30]. miR-205 downregulation enhanced BC bone metastasis and invasion by targeting TG (transglutaminase) 2 [31]. miRNA-205 could also partially decrease the survival of TNBC cells and epithelial-mesenchymal transition (EMT) by targeting the HMGB1-RAGE signaling pathway [32]. Sheng-Nan et al. reported that miR-21-3p expression could be stimulated by berberine, which inhibited MCF-7 proliferation via targeting cytochrome P450 1A1 (CYP1A1) [33]. miR-628 inhibited the migration and invasion of BC cells by targeting SOs1 [34], which suggested that therapeutic strategies that increase its expression may be an effective treatment approach against BC metastasis [35]. All the discussed miRNAs are summarized in Table 2.

3. miRNAs as BC Diagnostic Biomarkers

Breast Cancer is a type of heterogeneous diseases presenting multiple morphological appearances, molecular features, phenotypes, and therapeutic responses [37, 38]. BC therapeutic strategies are dependent on the availability of reliable diagnostic, prognostic, and predictive factors that direct the determination and selection of the appropriate treatments [39]. Circulating miRNAs were reported to be good biomarkers of BC diagnosis. For instance, the circulating miRNAs, such as let-7a, miR-10b, and miR-155, were identified to be highly expressed in melanoma, breast, prostate, colon, and renal cancers. The expression of circulating miR-195 expression is specifically elevated in breast cancer [40]. Circulating miR-21 could be used as a BC biomarker [41]. miR-373 presence in the serum of BC patients was also reported to be a good biomarker [42]. The expression level of circulating miR-16, miR-21, miR-23a, miR-146a, miR-155, and miR-181a may reflect different outcomes in BC [43]. miR-195-5p and miR-495 represent potential circulating molecular markers for BC early diagnosis in minimally invasive surrogate sample sources [44].

miRNAs are used as prognostic biomarker in Breast cancer and accumulating evidence indicated that circulating levels of miRNAs may be associated with the outcomes. PremiR-488 expression may be a new prognostic marker that predicts disease recurrence in BC patients [45]. The circulating miR-21 and miR-125B are regarded as new noninvasive prognostic markers for neoadjuvant chemotherapy response and prognosis of BC patients [46].

4. miRNAs and Breast Cancer Stem Cells (BCSCs)

Cancer stem cells (CSCs) are defined as “a small subset of the cancerous populations, responsible for tumor initiation and growth, and that possesses the characteristic properties of quiescence, indefinite self-renewal, intrinsic resistance to chemotherapy and radiotherapy, and the capability to give rise to differentiated progenies” [47]. They have also been
shown to be responsible for cancer recurrence following chemotherapy. miRNAs were reported to regulate the function of BCSCs by promoting or inhibiting cancer progression. Multiple miRNAs are associated with phenotype of BCSCs. miR-708 was reported to suppress BCSCs’ self-renewal; In addition, the miR-708/CD47 axis was proved to be a good target for TNBC treatment [48]. miR-1 can regulate BCSCs’ proliferation, apoptosis, and EMT by inhibiting ecotropic virus integrations site-1 (Evi-1) [49]. The upregulation of miR-210, induced by hypoxic exposure, promotes BCSCs’ proliferation and tumorgenesis by suppressing the expression of patatin-like protein 2 (PLP2) [50]. miR-21/222 promotes BCSCs’ proliferation, migration, and invasion via regulating phosphatase and tensin homolog (PTEN) [52].

All the discussed miRNA are summarized in Table 3.

5. miRNAs in Clinical Treatment of Breast Cancer

The use of miRNAs as anticancer treatment strategies has been developed by two methods. The first consists in using miRNAs as pharmaceutical molecules that can increase or decrease miRNA levels in BC based on the synthesis and transmission of specific oligonucleotides. The other is based on regulating miRNAs to improve the efficacy of conventional treatments within combined therapeutic strategies.

Oligonucleotide analogs and antagonists represent two major miRNA therapies. Single-stranded oligonucleotides with miRNA-complementary sequences are used to silence the miRNA function of target proteins. Functional miRNA liposomes have been developed to inhibit SLUG expression and the TGF-β1/SMAD pathway in TNBC cells, and to enhance the efficacy of chemotherapy in mice [53]. Epigenetic strategies using histone deacetylase inhibitors or functionally cooperative miRNAs are effective approaches for eliminating HER3 signal transduction for BC treatment [54]. In addition, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) treatment induces the expression of circulating miRNA via miR-3942-3p/BARD1 and prevents the occurrence of BC through blocking the cell cycle and promoting apoptosis [55].

miRNA antagonists can inhibit the function of miRNAs in human disease, and miRNA analogs are used to repair miRNAs with loss of function, similar to traditional gene therapy. This approach is also known as miRNA replacement therapy. This new therapy attracts more interests as it may provide a new opportunity to develop tumor inhibitors. Moreover, anti-miRNA oligonucleotides (AMOs) [56], locked nucleic acid (LNA)-modified oligonucleotides [57], cholesterol-binding anti-miRNA molecules [58], and 2′-O-methoxymethyl-4′-sulfur RNA (MOE-SRNA) [59] were successfully used to improve transmission efficiency of miRNA or anti-miRNA molecules in vivo. In addition, modified high-efficiency miRNA molecules with long half-lives have also been developed. miRNA mimics or antagomirs were used in nanomaterials’ packages, especially gold nanoparticles, to promote drug efficacy [60–62].

The DTX (docetaxel)/miR-34a nano cocarrier is a new nanoplatform that integrates insoluble drugs and gene/protein drugs, which provides a promising strategy for the treatment of metastatic BC [63].

5.1. miRNAs and BC Chemotargeting. Some methods have been studied for miRNA application as a medical targeting in cancer therapy, including the use of miRNA mimics, which are imitations of increased miRNAs, or antagomirs, which inhibit onco-miRNAs in cancer cells [64]. Gilam et al. identified that mir-96/mir-182 delivery could prevent metastatic breast cancer via targeting palladin in a preclinical model [65]. miR-145 expression is downregulated in BC cells, which is proved to

| miRNA annotation | Function | Target | Ref. |
|------------------|----------|--------|------|
| miR-10b | Increases the proliferation and promotes the migration and invasion of BC cells | E-cadherin | [21] |
| miR-21 | Promotes the transformation and development of BC | PDCD4 | [22] |
| miR-155 | Increases the proliferation and inhibits cell apoptosis of BC cells | FOXO3a | [23, 24] |
| miR-200a | Suppresses apoptosis | YAP1 | [25] |
| miR-27b | Enhances invasion and migration | STAT1 | [26] |

This table provides examples of miRNAs described in the text, with a particular attention on their targeting and function.

| miRNA annotation | Function | Target | Ref. |
|------------------|----------|--------|------|
| miR-206 | Prevents TNBC tumorigenesis | DEPDC1 | [27] |
| miR-26b | Facilitates G0/G1 cell cycle arrest and inhibits cellular proliferation | CDK8 | [28] |
| miR-26a/26b | Inhibits BC progression | ST8IA4 | [29] |
| miR-124 | Inhibits BC cell proliferation and invasion | STAT3/MGAT5 | [30, 36] |
| miR-205 | Reduces BC bone metastasis and invasion | TG2 | [31] |
| miR-21-3p | Inhibits BC cell proliferation | CYP1A1 | [33] |
| miR-628 | Inhibits the migration and invasion of BC cells | SOS1 | [35] |

This table provides examples of miRNAs described in the text, with a particular attention on their targeting and function.
increasing number of studies are reported on the diagnosis, prognosis, and therapy of BC patients. An important role in regulating BC progression and their clinical value is the potential of miRNAs to improve the efficacy of conventional and miRNA therapies. For example, anti-miR-21 oligonucleotides can downregulate RAN-1 and BCL-2 expression resulting in apoptosis induction [68]. Anti-miRNA oligonucleotides may also be used to suppress specific miRNA expression in BC patients by enhancing the efficacy of conventional treatment. For example, anti-miR-21 oligonucleotides can kill BC cells by their binding to HER2, which promotes trastuzumab sensitivity [69]. Furthermore, miR-145 mimics promote BC doxorubicin sensitivity by targeting the multidrug resistance-associated protein-1 [70]. miR-125b-5p overexpression increases tamoxifen sensitivity in BC cells [71]. Furthermore, miR-221/222 expression has been related to tumor tolerance to tamoxifen therapy [72]. miR-451 mimic transfection improves the sensitivity of MCF-7/DOX (doxorubicin)-resistant cells to DOX, which indicates that restoring miRNA expression has the potential of overcoming drug resistance in cancer cells [73]. Pan et al. demonstrated that miR-328 regulates ABCG2 expression, which altered drug resistance of BC cells [74]. miR-346, miR-181a, miR-638, miR-211, miR-212, miR-216, miR-199b, miR-204, miR-328, miR-373, miR-424, and miR-768-3p regulate fulvestrant resistance in BC via the TGF-β signaling pathway [75]. Zhang et al. [76] demonstrated that miR-100 is associated with paclitaxel sensitivity in BC. In addition, miR-140-5p can enhance the doxorubicin sensitivity of BCSCs via the WNT1/ABCB1 pathway [77]. Therefore, miRNAs play an important role in regulating the chemoresistance of breast cancer cells.

### 5.2. miRNAs and BC Chemoresistance

miRNAs disturbance leads to BC chemoresistance, such as the case for miR-125b. miRNA oligonucleotide analogs have the potential to increase the level of specific miRNAs that are lost in BC and to elevate the sensitivity of drugs. The combination with conventional and miRNA therapies could improve the prognostic benefits for BC patients. Yang et al. reported that an miRNA oligonucleotide analog of miR-195 increased drug sensitivity in adriamycin-resistant BC cells, by downregulating RAF-1 and BCL-2 expression resulting in apoptosis induction [68]. Anti-miRNA oligonucleotides may also be used to suppress specific miRNA expression in BC patients by enhancing the efficacy of conventional treatment. For example, anti-miR-21 oligonucleotides can kill BC cells by their binding to HER2, which promote trastuzumab sensitivity [69]. Furthermore, miR-145 mimics promote BC doxorubicin sensitivity by targeting the multidrug resistance-associated protein-1 [70]. miR-125b-5p overexpression increases tamoxifen sensitivity in BC cells [71]. Furthermore, miR-221/222 expression has been related to tumor tolerance to tamoxifen therapy [72]. miR-451 mimic transfection improves the sensitivity of MCF-7/DOX (doxorubicin)-resistant cells to DOX, which indicates that restoring miRNA expression has the potential of overcoming drug resistance in cancer cells [73]. Pan et al. demonstrated that miR-328 regulates ABCG2 expression, which altered drug resistance of BC cells [74]. miR-346, miR-181a, miR-638, miR-211, miR-212, miR-216, miR-199b, miR-204, miR-328, miR-373, miR-424, and miR-768-3p regulate fulvestrant resistance in BC via the TGF-β signaling pathway [75]. Zhang et al. [76] demonstrated that miR-100 is associated with paclitaxel sensitivity in BC. In addition, miR-140-5p can enhance the doxorubicin sensitivity of BCSCs via the WNT1/ABCB1 pathway [77]. Therefore, miRNAs play an important role in regulating the chemoresistance of breast cancer cells.

### 6. Discussion

In this review, we reviewed that miRNAs play important roles in regulating BC progression and their clinical value in the diagnosis, prognosis, and therapy of BC patients. An increasing number of studies are reported on the potential of miRNAs to improve the efficacy of conventional and miRNA therapies. For example, anti-miR-21 oligonucleotides can downregulate RAN-1 and BCL-2 expression resulting in apoptosis induction [68]. Anti-miRNA oligonucleotides may also be used to suppress specific miRNA expression in BC patients by enhancing the efficacy of conventional treatment. For example, anti-miR-21 oligonucleotides can kill BC cells by their binding to HER2, which promotes trastuzumab sensitivity [69]. Furthermore, miR-145 mimics promote BC doxorubicin sensitivity by targeting the multidrug resistance-associated protein-1 [70]. miR-125b-5p overexpression increases tamoxifen sensitivity in BC cells [71]. Furthermore, miR-221/222 expression has been related to tumor tolerance to tamoxifen therapy [72]. miR-451 mimic transfection improves the sensitivity of MCF-7/DOX (doxorubicin)-resistant cells to DOX, which indicates that restoring miRNA expression has the potential of overcoming drug resistance in cancer cells [73]. Pan et al. demonstrated that miR-328 regulates ABCG2 expression, which altered drug resistance of BC cells [74]. miR-346, miR-181a, miR-638, miR-211, miR-212, miR-216, miR-199b, miR-204, miR-328, miR-373, miR-424, and miR-768-3p regulate fulvestrant resistance in BC via the TGF-β signaling pathway [75]. Zhang et al. [76] demonstrated that miR-100 is associated with paclitaxel sensitivity in BC. In addition, miR-140-5p can enhance the doxorubicin sensitivity of BCSCs via the WNT1/ABCB1 pathway [77]. Therefore, miRNAs play an important role in regulating the chemoresistance of breast cancer cells.

### Additional Points

**Highlights.** MicroRNAs can regulate the hallmarks of breast cancer (BC). MicroRNAs are good biomarkers in BC diagnosis and prognosis. MicroRNAs play an important role in BC drug resistance. MicroRNAs may be a good therapeutic targeting approach for BC.

### Conflicts of Interest

The authors declare that they have no conflicts of interest.

---

**Table 3: List of some miRNAs involved in the BCSC phenotype.**

| miRNA annotation | Function | Target | Ref. |
|------------------|----------|--------|------|
| miR-708          | Suppresses BCSCs’ self-renewal | CD47   | [48] |
| miR-1            | Regulates BCSCs’ proliferation, apoptosis, and EMT | Evi-1  | [49] |
| miR-210          | Promotes BCSCs’ migration, proliferation, and self-renewal | E-cadherin | [50] |
| miR-422a         | Attenuates BCSCs’ proliferation and tumorigenesis | PLP2   | [51] |
| miR-221/222      | Promotes BCSCs’ proliferation, migration, and invasion | PTEN   | [52] |

This table provides examples of miRNAs described in the text, with a particular attention on their targeting and function.
References

[1] C. E. DeSantis, J. Ma, A. Goding Sauer, L. A. Newman, and A. Jemal, "Breast cancer statistics, 2017, racial disparity in mortality by state," CA: A Cancer Journal for Clinicians, vol. 67, no. 6, pp. 439–448, 2017.

[2] F. Bray, J. Ferlay, I. Soerjomataram, R. L. Siegel, L. A. Torre, and A. Jemal, "Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries," CA: A Cancer Journal for Clinicians, vol. 68, no. 6, pp. 394–424, 2018.

[3] E. A. Rakha, M. E. El-Sayed, S. Menon, A. R. Green, A. H. S. Lee, and I. O. Ellis, "Histologic grading is an independent prognostic factor in invasive lobular carcinoma of the breast," Breast Cancer Research and Treatment, vol. 111, no. 1, pp. 121–127, 2008.

[4] G. Viale, "The current state of breast cancer classification," Annals of Oncology, vol. 23, no. suppl_10, pp. x207–x210, 2012.

[5] S. E. Singletary, C. Allred, P. Ashley et al., "Revision of the American Joint Committee on Cancer staging system for breast cancer," Journal of Clinical Oncology, vol. 20, no. 17, pp. 3628–3636, 2002.

[6] S. J. Schnitt, "Classification and prognosis of invasive breast cancer: from morphology to molecular taxonomy," Modern Pathology, vol. 23, no. 2, pp. S60–S64, 2010.

[7] M. Ha and V. N. Kim, "Regulation of microRNA biogenesis," Nature Reviews Molecular Cell Biology, vol. 15, no. 8, pp. 509–524, 2014.

[8] J. Shen, S. A. Stass, and F. Jiang, "MicroRNAs as potential biomarkers in human solid tumors," Cancer Letters, vol. 329, no. 2, pp. 125–136, 2013.

[9] H. Qu, W Xu, Y Huang, and S Yang, "Circulating miRNAs: promising biomarkers of human cancer," Asian Pacific Journal of Cancer Prevention: APJCP, vol. 12, no. 5, pp. 1117–1125, 2011.

[10] J. Ashby, K. Flack, L. A. Jimenez et al., "Distribution profiling of circulating microRNAs in serum," Analytical Chemistry, vol. 86, no. 18, pp. 9343–9349, 2014.

[11] J. D. Arroyo, J. R. Chevillet, E. M. Kroh et al., "Argonaute2 complexes carry a population of circulating microRNAs independent of vesicles in human plasma," Proceedings of the National Academy of Sciences, vol. 108, no. 12, pp. 5003–5008, 2011.

[12] C. Cava, "Integration of mRNA expression profile, copy number alterations, and microRNA expression levels in breast cancer to improve grade definition," PloS One, vol. 9, no. 5, 2014.

[13] J. Wang, K.-Y. Zhang, S.-M. Liu, and S. Sen, "Tumor-associated circulating microRNAs as biomarkers of cancer," Molecules, vol. 19, no. 2, pp. 1912–1938, 2014.

[14] H.-O. Iwakawa and Y. Tomari, "The functions of microRNAs: mRNA decay and translational repression," Trends in Cell Biology, vol. 25, no. 11, pp. 651–665, 2015.

[15] B. John, "Human microRNA targets," PLoS Biology, vol. 2, no. 11, 2004.

[16] N. Rajewsky, "microRNA target predictions in animals," Nature Genetics, vol. 38, no. 6, pp. S8–S13, 2006.

[17] R. C. Friedman, "Most mammalian microRNAs are conserved targets of microRNAs," Genome Research, vol. 19, no. 1, pp. 92–105, 2009.

[18] J. Lu, G. Getz, E. A. Miska et al., "MicroRNA expression profiles classify human cancers," Nature, vol. 435, no. 7043, pp. 834–838, 2005.

[19] A. Zaravinos, "The regulatory role of microRNAs in EMT and cancer," Journal of Oncology, vol. 2015, Article ID 865816, 13 pages, 2015.

[20] S. Eissa, M. Mathboli, H. H. Shehata, and N. O. E. Essawy, "MicroRNA-10b and minichromosome maintenance complex component 5 gene as prognostic biomarkers in breast cancer," Tumour Biology, vol. 36, no. 6, pp. 4487–4494, 2015.

[21] L. Ma, J. Teruya-Feldstein, and R. A. Weinberg, "Tumour invasion and metastasis initiated by microRNA-10b in breast cancer," Nature, vol. 449, no. 7163, pp. 682–688, 2007.

[22] M. M. Abdulhussain, N. A. Hasan, and A. G. Hussain, "Interrelation of the circulating and tissue MicroRNA-21 with tissue PDCD4 expression and the invasiveness of Iraqi female breast tumors," Indian Journal of Clinical Biochemistry: IJCB, vol. 34, no. 1, pp. 26–38, 2019.

[23] S.-R. Zheng, G.-L. Guo, Q. Zhai, Z.-Y. Zou, and W. Zhang, "Effects of miR-155 antisense oligonucleotide on breast carcinoma cell line MDA-MB-157 and implanted tumors," Asian Pacific Journal of Cancer Prevention, vol. 14, no. 4, pp. 2361–2366, 2013.

[24] C.-M. Zhang, J. Zhao, and H.-Y. Deng, "MiR-155 promotes proliferation of human breast cancer MCF-7 cells through targeting tumor protein 53-induced nuclear protein 1," Journal of Biomedical Science, vol. 20, no. 1, p. 79, 2013.

[25] S.-J. Yu, J.-Y. Hu, X.-Y. Kuang et al., "MicroRNA-200a promotes aneuploidy resistance and metastasis by targeting YAP1 in human breast cancer," Clinical Cancer Research, vol. 19, no. 6, pp. 1389–1399, 2013.

[26] Y. Wang, R. Rathinam, A. Walch, and S. K. Alalhari, "ST14(Suppression of tumorigenicity 14) gene is a target for miR-27b, and the inhibitory effect of ST14 on cell growth is independent of miR-27b regulation," Journal of Biological Chemistry, vol. 284, no. 34, pp. 23094–23106, 2009.

[27] L. Zhang, Y. Du, S. Xu et al., "DEPDC1, negatively regulated by miR-26b, facilitates cell proliferation via the up-regulation of FOXM1 expression in TNBC," Cancer Letters, vol. 442, pp. 242–251, 2019.

[28] J. Li, X Li, X Kong, Q Luo, J Zhang, and L Fang, "MiRNA-26b inhibits cellular proliferation by targeting CDK8 in breast cancer," International Journal of Clinical and Experimental Medicine, vol. 7, no. 3, pp. 558–65, 2014.

[29] X. Ma, W. Dong, Z. Su et al., "Functionional roles of sialylation in breast cancer progression through miR-26a/26b targeting ST8SIA4," Cell Death & Disease, vol. 7, no. 12, Article ID e2561, 2016.

[30] G. Yan, Y Li, L. Zhan et al., "Decreased miR-124-3p promoted breast cancer proliferation and metastasis by targeting MGAT5," American Journal of Cancer Research, vol. 9, no. 3, pp. 585–596, 2019.

[31] S. Seo, Y. Moon, J. Choi et al., "The GTP binding activity of translutaminase 2 promotes bone metastasis of breast cancer cells by downregulating microRNA-205," American Journal of Cancer Research, vol. 9, no. 3, pp. 597–607, 2019.

[32] L. Wang, F.-b. Kang, J. Wang, C. Yang, and D.-W. He, "Downregulation of miR-205 contributes to epithelial-mesenchymal transition and invasion in triple-negative breast cancer by targeting HMGBl-RAGE signaling pathway," Anti-Cancer Drugs, vol. 30, no. 3, pp. 225–232, 2019.

[33] T.-F. Lo, W.-C. Tsai, and S.-T. Chen, "MicroRNA-21-3p, a berberine-induced miRNA, directly down-regulates human methionine adenosyltransferases 2A and 2B and inhibits hepatoma cell growth," PloS One, vol. 8, no. 9, 2013.

[34] S.-N. Lo, C.-W. Wang, Y.-S. Chen et al., "Berberine activates aryl hydrocarbon receptor but suppresses CYPIA1 induction"
through miR-21-3p stimulation in MCF-7 breast cancer cells,” *Molecules*, vol. 22, no. 11, p. 1847, 2017.

[35] C. Lin, B. Gao, X. Yan et al., “MicroRNA 628 suppresses migration and invasion of breast cancer stem cells through targeting SOST,” *OncoTargets and Therapy*, vol. 11, pp. 5419–5428, 2018.

[36] J. Zhang, “MiR-124 suppresses growth of human colorectal cancer by inhibiting STAT3,” *PloS One*, vol. 8, no. 8, 2013.

[37] K. Polyak, “Heterogeneity in breast cancer,” *Journal of Clinical Investigation*, vol. 121, no. 10, pp. 3786–3788, 2011.

[38] C. M. Perou, T. Sorlie, M. B. Eisen et al., “Molecular portraits of human breast tumours,” *Nature*, vol. 406, no. 6797, pp. 747–752, 2000.

[39] D. F. Hayes, C. Isaacs, and V. Stearns, “Prognostic factors in breast cancer: current and new predictors of metastasis,” *Journal of Mammary Gland Biology and Neoplasia*, vol. 6, no. 4, pp. 375–392, 2001.

[40] S. Khalighfard, “Plasma miR-21, miR-155, miR-10b, and Let-7a as the potential biomarkers for the monitoring of breast cancer patients,” *Scientific Reports*, vol. 8, no. 1, pp. 1–11, 2018.

[41] J. Shi, “Considering exosomal miR-21 as a biomarker for cancer,” *Journal of Clinical Medicine*, vol. 5, no. 4, p. 42, 2016.

[42] C. Eichelser, I. Stückrath, V. Müller et al., “Increased serum levels of circulating exosomal microRNA-373 in receptor-negative breast cancer patients,” *OncoTarget*, vol. 5, no. 20, pp. 9650–9663, 2014.

[43] S. P. Fortis, C. K. Vaxevanis, L. G. Mahaira et al., “Serum miRNA-based distinct clusters define three groups of breast cancer patients with different clinicopathological and immune characteristics,” *Cancer Immunology, Immunotherapy*, vol. 68, no. 1, pp. 57–70, 2019.

[44] S. Mishra, A. K. Srivastava, S. Suman, V. Kumar, and Y. Shukla, “Circulating miRNAs revealed as surrogate molecular signatures for the early detection of breast cancer,” *Cancer Letters*, vol. 369, no. 1, pp. 67–75, 2015.

[45] T. Masuda, Y. Shinden, M. Noda et al., “Circulating pre-microRNA-488 in peripheral blood is a potential biomarker for predicting recurrence in breast cancer,” *Anticancer Research*, vol. 38, no. 8, pp. 4515–4523, 2018.

[46] B. Liu, F. Su, M. Chen et al., “Serum miR-21 and miR-125b as markers predicting neoadjuvant chemotherapy response and prognosis in stage II/III breast cancer,” *Human Pathology*, vol. 64, pp. 44–52, 2017.

[47] J. D. O’Flaherty, “The cancer stem-cell hypothesis: its emerging role in lung cancer biology and its relevance for future therapy,” *Journal of Thoracic Oncology*, vol. 7, no. 12, pp. 1880–1890, 2012.

[48] W. Tan, H. Tang, X. Jiang et al., “Metformin mediates induction of miR-708 to inhibit self-renewal and chemoresistance of breast cancer stem cells through targeting CD47,” *Journal of Cellular and Molecular Medicine*, vol. 23, no. 9, pp. 5994–6004, 2019.

[49] L. Wu, T. Wang, D. He, X. Li, and Y. Jiang, “miR-1 inhibits the proliferation of breast cancer stem cells by targeting EVI-1,” *OncoTargets and Therapy*, vol. 11, pp. 8773–8781, 2018.

[50] T. Tang, Z. Yang, Q. Zhu et al., “Up-regulation of miR-210 induced by a hypoxic microenvironment promotes breast cancer stem cell metastasis, proliferation, and self-renewal by targeting E-cadherin,” *The FASEB Journal*, vol. 32, no. 12, pp. 6965–6981, 2018.

[51] Y. Zou, Y. Chen, S. Yao et al., “MiR-422a weakened breast cancer stem cells properties by targeting PLP2,” *Cancer Biology & Therapy*, vol. 19, no. 5, pp. 436–444, 2018.

[52] B. Li, Y. Lu, L. Yu et al., “miR-221/222 promote cancer stem-like cell properties and tumor growth of breast cancer via targeting PTEN and sustained Akt/NF-κB/BOX-2 activation,” *Chemico-Biological Interactions*, vol. 277, pp. 33–42, 2017.

[53] Y. Yan, X.-Q. Li, J.-L. Duan et al., “Nanosized functional miRNA liposomes and application in the treatment of TNBC by silencing Slug gene,” *International Journal of Nanomedicine*, vol. 14, pp. 3645–3667, 2019.

[54] X. Liu, “Development of effective therapeutics targeting HER3 for cancer treatment,” *Biological Procedures Online*, vol. 21, no. 1, p. 5, 2019.

[55] J. Zhao, H. Zou, C. Han, J. Ma, J. Zhao, and J. Tang, “Circular RNA BARD1 (Hsa_circ_0001098) overexpression in breast cancer cells with TCDD treatment could promote cell apoptosis via miR-3942/BARD1 axis,” *Cell Cycle*, vol. 17, no. 24, pp. 2731–2744, 2018.

[56] J. Weiler, J. Hunziker, and J. Hall, “Anti-miRNA oligonucleotides (AMOs): ammunition to target miRNAs implicated in human disease?” *Gene Therapy*, vol. 13, no. 6, pp. 496–502, 2006.

[57] U. A. Örom, S. Kauppinen, and A. H. Lund, “LNA-modified oligonucleotides mediate specific inhibition of microRNA function,” *Gene*, vol. 372, pp. 137–141, 2006.

[58] J. Kritzfeldt, N. Rajewsky, R. Braich et al., “Silencing of microRNAs in vivo with “antagomirs”,” *Nature*, vol. 438, no. 7068, pp. 685–689, 2005.

[59] N. Minakawa, N. Saito-Tarashima, and A. Matsuda, “RNA biososteres: chemistry and properties of 4’-thioRNA and 4’-selenoRNA,” in *Synthesis of Therapeutic Oligonucleotides*, pp. 233–252, Springer, Berlin, Germany, 2018.

[60] N. L. Rosi, “Oligonucleotide-modified gold nanoparticles for intracellular gene regulation,” *Science*, vol. 312, no. 5776, pp. 1027–1030, 2006.

[61] A. Elbakry, A. Zaky, R. Liebl, R. Rachel, A. Goepferich, and M. Breunig, “Layer-by-layer assembled gold nanoparticles for siRNA delivery,” *Nano Letters*, vol. 9, no. 5, pp. 2059–2064, 2009.

[62] J.-S. Lee, J. J. Green, K. T. Love, J. Sunshine, R. Langer, and D. G. Anderson, “Gold, poly (β-amino ester) nanoparticles for small interfering RNA delivery,” *Nano Letters*, vol. 9, no. 6, pp. 2402–2406, 2009.

[63] L. Zhang, “Cytosolic co-delivery of miRNA-34a and docetaxel with core-shell nanocarriers via caveolae-mediated pathway for the treatment of metastatic breast cancer,” *Scientific Reports*, vol. 7, Article ID 46186, 2017.

[64] R. Garzon, G. Marcucci, and C. M. Croce, “Targeting microRNAs in cancer: rationale, strategies and challenges,” *Nature Reviews Drug Discovery*, vol. 9, no. 10, pp. 775–789, 2010.

[65] A. Gilam, “Local microRNA delivery targets Palladin and prevents metastatic breast cancer,” *Nature Communications*, vol. 7, p. 12868, 2016.

[66] Y. Akaoy, Y. Nakagawa, and T. Naoe, “MicroRNAs 143 and 145 are possible common onco-microRNAs in human cancers,” *Oncology Reports*, vol. 16, no. 4, pp. 845–850, 2006.

[67] L. X. Yan, Q. N. Wu, Y. Zhang et al., “Knockdown of miR-373 in human breast cancer cell lines inhibits proliferation, in vitro migration and in vivotumor growth,” *Breast Cancer Research*, vol. 13, no. 1, p. R2, 2011.

[68] G. Yang, D. Wu, J. Zhu et al., “Upregulation of miR-195 increases the sensitivity of breast cancer cells to Adriamycin treatment through inhibition of Raf-1,” *Oncology Reports*, vol. 30, no. 2, pp. 877–889, 2013.
[69] C. Gong, Y. Yao, Y. Wang et al., "Up-regulation of miR-21 mediates resistance to trastuzumab therapy for breast cancer," *Journal of Biological Chemistry*, vol. 286, no. 21, pp. 19127–19137, 2011.

[70] M. Gao, L. Miao, M. Liu et al., "miR-145 sensitizes breast cancer to doxorubicin by targeting multidrug resistance-associated protein-1," *Oncotarget*, vol. 7, no. 37, pp. 59714–59726, 2016.

[71] C. Kim, E. J. Go, and A. Kim, "Recurrence prediction using microRNA expression in hormone receptor positive breast cancer during tamoxifen treatment," *Biomarkers*, vol. 23, no. 8, pp. 804–811, 2018.

[72] T. E. Miller, K. Ghoshal, B. Ramaswamy et al., "MicroRNA-221/222 confers tamoxifen resistance in breast cancer by targeting p27Kip1," *Journal of Biological Chemistry*, vol. 283, no. 44, pp. 29897–29903, 2008.

[73] O. Kovalchuk, J. Filkowski, J. Meservy et al., "Involvement of microRNA-451 in resistance of the MCF-7 breast cancer cells to chemotherapeutic drug doxorubicin," *Molecular Cancer Therapeutics*, vol. 7, no. 7, pp. 2152–2159, 2008.

[74] Y.-Z. Pan, M. E. Morris, and A.-M. Yu, "MicroRNA-328 negatively regulates the expression of breast cancer resistance protein (BCRP/ABCG2) in human cancer cells," *Molecular Pharmacology*, vol. 75, no. 6, pp. 1374–1379, 2009.

[75] F. Xin, M. Li, C. Balch et al., "Computational analysis of microRNA profiles and their target genes suggests significant involvement in breast cancer antiestrogen resistance," *Bioinformatics*, vol. 25, no. 4, pp. 430–434, 2009.

[76] B. Zhang, R. Zhao, Y. He et al., "Micro RNA 100 sensitizes luminal A breast cancer cells to paclitaxel treatment in part by targeting mTOR," *Oncotarget*, vol. 7, no. 5, pp. 5702–5714, 2016.

[77] D. Wu, J. Zhang, Y. Lu et al., "miR-140-5p inhibits the proliferation and enhances the efficacy of doxorubicin to breast cancer stem cells by targeting Wnt1," *Cancer Gene Therapy*, vol. 26, no. 3-4, pp. 74–82, 2019.

[78] S. D. Selcuklu, M. T. A. Donoghue, K. Rehmet et al., "MicroRNA-9 inhibition of cell proliferation and identification of novel miR-9 targets by transcriptome profiling in breast cancer cells," *Journal of Biological Chemistry*, vol. 287, no. 35, pp. 29516–29528, 2012.