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Clinical Application of MicroRNAs in Breast Cancer Treatment

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ABSTRACT

Background: Recurrence of breast cancer remains a critical problem. Therefore, it is imperative to identify biomarkers that accurately reflect disease state and develop novel drug therapies that are effective even after recurrence. MicroRNAs (miRNAs) are involved in the malignant transformation of various tumors. Circulating miRNAs are promising biomarkers for the diagnosis and treatment of cancers. Additionally, miRNAs are regarded as next-generation drug targets. Currently, various clinical trials are being conducted for anti-cancer drugs using miRNAs. In this review, we summarized recent studies on miRNA functions and circulating miRNAs in breast cancer, and discussed the status of miRNAs as drug discovery candidates. We also discussed the role of extracellular vesicles (EVs) in the clinical application of miRNAs.

Methods: Relevant articles published from 2002 to 2021 were acquired from PubMed database using the following key words: "miRNA" and "breast neoplasia". Clinical trial data were retrieved from the database, ClinicalTrials.gov.

Results: Regulating these miRNAs may provide a new therapeutic strategy. Furthermore, miRNAs may be useful diagnostic and prognostic biomarkers for breast cancer. In addition, miRNAs have potential as anti-cancer agents, and may also be used in combination with other therapies to enhance the efficacies of other drugs.

Conclusion: In summary, miRNAs have shown promise as biomarkers and therapeutic targets. In addition, EVs will be the key to expanding the applications of miRNAs.

INTRODUCTION

According to GLOBOCAN statistics, 2.3 million people worldwide have breast cancer.[1] While good survival rates for breast cancer patients have been obtained with existing drugs, recurrence is often observed 10 years after curative resection, and in most patients, it cannot be cured.[2] In women, breast cancer is the leading cause of cancer-related deaths. Therefore, it is imperative to discover biomarkers that accurately reflect the disease state of patients. There is also an urgent need to discover novel drug therapies that offer therapeutic effects even after recurrence.

MicroRNAs (miRNAs) regulate the expression of several genes and proteins by negatively controlling gene expression.[3] In general, miRNAs bind to complementary sequence sites present in the 3'-untranslated region (UTR) of a target mRNA and induce translational inhibition or degradation; however, miRNAs may act as positive regulators if a

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complementary sequence site is present in the 5'-UTR.[4] Since miRNAs do not require perfect sequence complementarity to bind to the target, one miRNA can suppress the expression of multiple mRNAs. Thus, miRNAs are involved in virtually all the biological processes, including development, differentiation, and metabolism, contributing to the maintenance of homeostasis. Abnormal expression of miRNAs has been observed in many diseases, such as allergies, asthma, diabetes, infectious diseases, and cancers.[3] The abnormal expression of miRNAs in cancer was first reported by Croce *et al*. in 2002.[5] It has been observed that miRNAs are involved in the malignant transformation of various cancer types, including breast cancer. Currently, information about all previously discovered miRNAs can be found in public databases, and data on more than 2,600 human mature miRNA sequences are present in the miRbase database (http://-www.mirbase.org).[6]

It is now known that miRNAs are transported to surrounding cells via extracellular vesicles (EVs).[7-10] All types of cells can secrete EVs that contain various substances such as nucleic acids, lipids, and proteins.[11] An increase in EV secretion is observed in cancer patients and is termed cancer EVs. Cancer EVs have been suggested as potential biomarkers and therapeutic targets.[12-14] The functional roles of miRNAs mediated via cancer EVs has been elucidated in several studies, suggesting that regulating miRNAs involved in cell-cell communication will provide a new therapeutic strategy in treating cancers. Since novel targets for low molecular weight compounds, the mainstay of drug discovery, have been decreasing, miRNAs are regarded as next-generation drug targets.[15]

Circulating miRNAs are considered as promising biomarkers for diagnosis and treatment and are easy to incorporate into daily medical care.[16] Most circulating miRNAs are co-fractionated with proteins such as Argonaute 2, which are bound to high-density lipoproteins or encapsulated in 50–150 nm EVs called exosomes, granting stability to the miRNAs in the extracellular environment.[7,11] As a result, extracellular miRNAs can be detected in other body fluids such as blood, tears, breast milk, and saliva. Currently, several clinical trials for liquid biopsies using circulating miRNAs have been conducted for multiple cancers, including breast cancer.[17-19]

In this review, we outline recent findings on miRNA functions and circulating miRNAs, and summarize the status of miRNAs as drug discovery candidates for breast cancer. In addition, we discuss the role of EVs in the clinical application of miRNAs.

METHODS

Relevant articles published from 2002 to 2021 were acquired (dated 31/03/2021) from PubMed database using the following key words: “miRNA” and “breast neoplasia”. Clinical trial data were retrieved from the database, ClinicalTrials.gov. This research was supported by AMED under Grant Number JP21 ck010-6555, and The Research Funding for Longevity Sciences (21-22) from the National Center for Geriatrics and Gerontology, Japan.

RESULTS

Functional roles of miRNAs in breast cancer

Increasing evidence has associated miRNA dysregulation with tumor progression and drug resistance in breast cancers (Figure 1). miRNAs in cancer are categorized as either oncogenic or tumor-suppressive depending on their action (Table 1). Certain miRNAs can exhibit dual functions, depending on the type of tissue.[20] For example, miR-122, miR-22 and miR-93 have been reported to have dual functions in patients with breast cancer.[21-25]

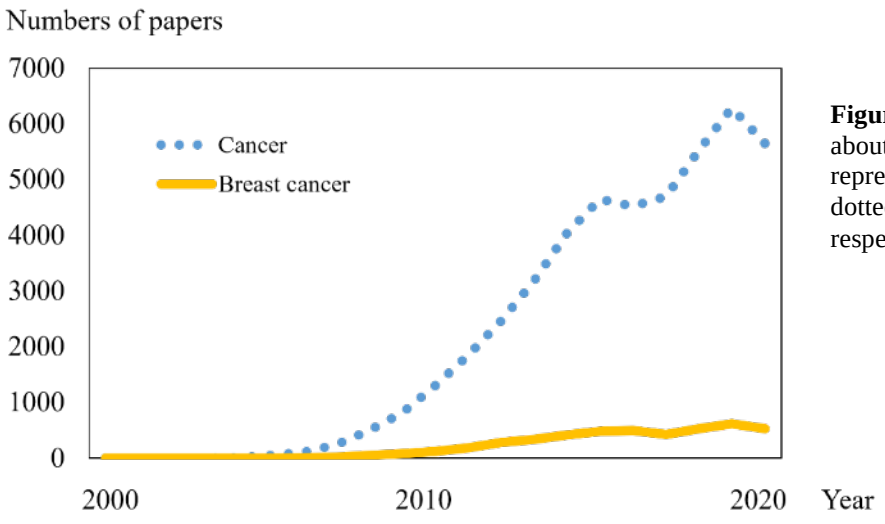

Figure 1. Increase in the number of papers about miRNAs in cancer. Each line represents the numbers of papers as follows: dotted for cancer and solid for breast cancer, respectively.

Table 1. List of functional miRNAs in breast cancer.

A. The role of oncogenic miRNAs.

Oncogenic miRNAs	Target process/signaling pathway	Ref
miR-10b	Pro-metastatic genes	26
miR-105	Metabolic reprogramming of stromal cells	27
miR-122	Reprograming of glucose metabolism	28
miR-106b	PI3K/Akt pathway	25
miR-182-5p	TGF-β/SMAD pathway	29
miR-196a	Estrogen/SPRED1 cascade	30
miR-199a	Network that represses the expression of FOXP2	31
miR-21	Tumor cell apoptosis, IGF signaling	14, 32
miR-25-3p	Akt and MAPK/Erk pathways	33
miR-26a	Mitosis and cytokinesis	34
miR-27b	Cell metabolism through targeting PDHX	35
miR-29a	EMT (H4K20/SUV420H2 axis)	36
miR-31	Signaling pathways including Prlr/Stat5, TGF-β and Wnt/β-catenin	37
miR-93	PI3K/Akt pathway	25

B. The role of tumor-suppressive miRNAs.

Tumor-suppressive miRNAs	Target process/signaling pathway	Ref
miR-124	Survival and differentiation of osteoclast progenitor cells	38
miR-125b	Bone microenvironment promoting cancer spread	39
miR-190	TGF-β-induced EMT	40
miR-200 family	CAF activation and ECM remodeling EMT	41, 42
miR-205	EMT	43
miR-206	MKL1/IL11 pathway	44
miR-27b-3p	PI3K/Akt and MAPK/Erk pathways	45
miR-30a	EMT (p53/ZEB2 axis)	46
miR-3178	EMT (Notch1)	47
miR-34a	EMT, and M2 macrophage polarization (MCT-1/IL-6/IL-6R signaling)	
miR-375	EMT	48, 49
miR-451	β-catenin/cyclin D1/c-Myc signaling	50
miR-770	Apoptosis	51
miR-17-92 cluster (miR-18a, miR-20a, miR-93)	EMT (SREBP1) MAPK/Erk pathway pRB/E2F1 pathway and Akt phosphorylation	23, 52, 53

EMT: epithelial to mesenchymal transition, CAF: cancer-associated fibroblasts, ECM: extracellular matrix

miRNAs are involved in metastatic processes. Cancer cells metastasize via their interactions with the tumor microenvironment. The tumor microenvironment is mostly composed of cancer-associated fibroblasts (CAFs), which are activated forms of fibroblasts. CAFs can remodel the composition and structure of the extracellular matrix to support tumor growth. Chatterjee *et al*. reported that miR-222 is involved in the reprogramming of CAFs.[54] Wang *et al*. reported that EV-associated miR-181d-5p is

secreted from CAFs and promotes tumor growth via the involvement of caudal-related homeobox 2 (CDX2) and homeobox A5 (HOXA5) proteins.[8]

miRNAs are also involved in breast cancer treatment. Some miRNAs are related to radio-sensitivity, while others are associated with drug resistance.[55] Shen *et al*. reported that miR-195-5p, miR-203a-3p, and miR-9-5p are packed in EVs released by cells exposed to cytotoxic agents.[9] The same study demonstrated that due to these miRNAs, the surrounding cancer cells acquired stem cell characteristics, resulting in drug resistance.

Breast cancer is treated with either anti-hormone therapy if the tumor is estrogen receptor (ER)-/progesterone carbohy or with anti-human epidermal receptor 2 (*HER2*) therapy if the tumor is *HER2*-positive.[2] ER/PgR-negative and *HER2*-negative breast cancer is defined as triple-negative breast cancer (TNBC); TNBC lacks potential drug targets. Recently, cyclin dependent kinase (CDK)4/CDK6 inhibitors have become the standard cytotoxic agents prescribed in ER/PgR-positive metastatic breast cancers (MBC).[2] For example, miR-135a, miR-222, and miR-575 are involved in conferring resistance to tamoxifen, a drug frequently used in anti-hormone therapy; miR-126, miR-182, and miR-567 are involved in resistance to trastuzumab, which is the standard of anti-HER2 therapy.[56-61] miRNA involvement has also been reported in drug resistance to palbociclib, a CDK4/6 inhibitor. Cornell *et al*. showed that EV-mediated miR-432-5p suppresses the TGF-β pathway and promotes the upregulation of CDK6, which consequently leads to palbociclib resistance; this oncogenic mechanism is different from that involving genetic abnormalities.[10]

Circulating miRNAs as biomarkers of breast cancer

In breast cancer, carbohydrate antigen 15-3 (CA15-3) is the commonly used blood-based biomarker in clinical practice; however, it is considered a poor marker of breast cancer owing to its low sensitivity and specificity.[2] Therefore, biomarkers that can sensitively reflect new diseases have been actively investigated. Numerous studies have suggested that miRNAs can be used in routine clinical practice as biomarkers for early breast cancer diagnosis, prediction of prognosis, and drug response. However, only a few results from these studies are reproducible due to population diversity and variation in research methods.[62] Thus, we selected studies with sample sizes of more than 100 breast cancer patients with validated results since the miRNAs identified in these studies can be reproducible and potentially be used as biomarkers in clinical practice (Table 2).

Several clinical trials for the evaluation of circulating miRNAs have been conducted. A total of 10,631 clinical trials recorded before the end of March 2021 were returned after searching the database, ClinicalTrials.gov, using the term “breast cancer.” There are 50 studies focusing on the evaluation of miRNAs as biomarkers. From the database, 11 of these 50 clinical trials completed the observation period, but none of the results have been published.

There was a study using samples collected prospectively within the large context of international randomized clinical studies. Cosimo *et al*. examined the miRNA signatures associated with pathological complete response (pCR) using plasma samples from a NEoALTTO trial in which neoadjuvant anti-HER2 therapy (lapatinib and/or trastuzumab) was administered.[18] Since achieving a pCR after systematic treatment correlates well with good prognosis, pCR is often used for the assessment of therapeutic effects instead of examining overall survival (OS). The authors identified miRNA signatures that discriminate patients with pCR after neoadjuvant therapy and demonstrated that miR-140-5p levels 2 weeks after the start of trastuzumab correlated with event-free survival.

A study using large-scale clinical samples was conducted by Shimomura *et al*. through a microarray profiling using miRNAs obtained from 1,280 breast cancer patients, 2,836 controls, 451 patients with other cancer types, and 63 women with benign breast disease.[69] The authors identified a panel of five miRNAs that distinguished between breast cancer, other cancers, and controls.

With respect to prognostic biomarkers for operatable breast cancer, Wang *et al*. identified a panel of five miRNAs (miR-130b-5p, miR-151a-5p, miR-206, miR-222-3p, and miR-943).[79] The authors reported that patients with three or more highly-expressed miRNAs among the identified panel had shorter disease-free survival than those with 0 to 2 highly-expressed miRNAs after breast cancer radical surgery. In MBC, circulating tumor cells (CTCs) are prognostic biomarkers approved by the US Food and Drug Administration (FDA). However, their use is limited by the enrichment and detection methods used, making them difficult biomarkers to access in routine clinical practice. Therefore, there is still a need for a novel biomarker that can be easily measured. Madhavan *et al*. studied a miRNA signature that can be effectively used in a metastatic setting. First, they examined the miRNAs associated with CTCs in MBC and identified a panel of 16 miRNAs that could predict the OS rate in MBC.[74,77]

Table 2. Circulating miRNAs as promising biomarkers.

Sample Source	Sample Number	miRNAs	Assessment	Ref
Plasma	627	miR-127-3p, miR-148b, miR-376a, miR-376c, miR-409-3p, miR-652, and miR-801	Higher in BC	63
Serum	164	miR-1, miR-92a, miR-133a, and miR-133b	Higher in BC	64
Plasma	172	miR-148b, and miR-133a	Higher in BC	65
Serum	108	miR-15a, miR-18a, miR-107, and miR-425	Higher in BC	66
		miR-133a, miR-139-5p, miR-143, miR-145, and miR-365	Lower in BC	
Serum	137	miR-484	Higher in BC	67
Plasma	199	miR-505-5p, miR-125-5p, miR-21-5p, and miR-96-5p	Higher in BC	68
Serum	1280	miR-1246, miR-1307-3p, and miR-6861-5p	Higher in BC	69
		miR-4634, and 6875-5p	Lower in BC	
Plasma	215	miR-16, miR-148a, and miR-19b	Higher in BC	70
		let-7d, let-7i, miR-103, miR-107, and miR-22*	Lower in BC	
Serum	158	miR-155, miR-574-5p, and MALAT	Higher in BC	71
		let-7a	Lower in BC	
Plasma	257	let-7b, miR-122-5p, miR-146-5p, miR-210-3p, miR-215-5p	Higher in BC	72
Plasma/Serum	200/204	miR106a-3p, miR-106a-5p, miR-20b-5p, and miR-92a-2-5p (Plasma)	Higher in BC (Plasma)	73
		miR-106a-5p, miR-19b-3p, miR-20b-5p, and miR-92a-3p (Serum)	Higher in BC (Serum)	
Plasma	193	miR-141, miR-200a, miR-200b, miR-200c, miR-203, miR-210, miR-375, and miR-801	Higher in CTC-positive MBC	74
Plasma	1254	miR-24-3p	Predicting OS for BC	75
Serum	130	miR-18b, miR-103, miR-107, and miR-652	Predicting relapse in TNBC	76
Plasma	612	miR-141, miR-144, miR-193b, miR-200a, miR-200b, miR-200c, miR-203, miR-210, miR-215, miR-365, miR-375, miR-429, miR-486-5p, miR-801, miR-1260, and miR-1274a	Predicting OS in MBC	77
Plasma	429	miR-140-5p	Predicting Response to neoadjuvant trastuzumab for HER2-positive BC	18
Serum	565	miR-940, miR-451a, miR-16-5p, and miR-17-3p	Predicting Response to trastuzumab for HER2-positive MBC	78

BC: breast cancer, MALAT: metastasis-associated lung adenocarcinoma transcript, CTC: circulating tumor cell, MBC: metastatic breast cancer, OS: overall survival, TNBC: triple-negative breast cancer, HER2: human epidermal growth factor receptor 2

They also showed that the patients with recurrence within 2 years could be identified earlier than in clinical diagnosis using a signature composed of six miRNAs from the identified panel (miR-200a, miR-200b, miR-200c, miR-210, miR-215, and miR486-5p).[77]

Emerging role of miRNAs as next-generation drugs

It has been demonstrated that miRNAs may be used as anti-cancer drug agents depending on their expression levels in the tumor tissues.[15] Vectors, miRNA mimics, and small molecule compounds are used to supplement tumor-suppressive miRNAs, while antisense miRNAs (anti-miRs), miRNA sponges, and decoy vectors are used to suppress oncogenic miRNAs. Agents most frequently used in *in vitro* and *in vivo* experiments are miRNA mimics

and locked nucleic acids (LNA)-modified anti-miRs. miRNA mimics are double-stranded synthetic RNAs that mimic endogenous miRNAs, while LNA-modified anti-miRs are anti-miRs that are chemically locked by a bridge that connects the 2'-oxygen and 4'-carbon in a ribonucleotide. Due to this bridge, LNA-modified anti-miRs achieve stable regulation with simple manipulations.

In clinical practice, drugs targeting miRNAs are expected to be used as a combination therapy with other drugs to enhance their therapeutic effects and weaken the resistance to these drugs. In breast cancer, miR-10b plays an important role in metastasis.[26] Antisense miR-10b is ineffective in shrinking primary tumors but is effective for metastatic lesions.[80] Yoo *et al*. showed that the combination of antisense miR-10b with cytotoxic agents after excision of the primary lesion eliminated metastatic lesions without systemic toxicity.[81] The authors used dextran-coated iron oxide nanoparticles (MN-anti-miR-10b) to effectively reach target tissues. Interestingly, MN-anti-miR-10b suppressed brain metastasis, even when used as a monotherapy.[82] Gao *et al*. demonstrated that miR-873 is involved in PDL1-mediated acquisition of stem cell traits, suggesting that drugs targeting the miR-873 axis can be used in combination with immune checkpoint blockers.[83] In TNBC, effective drugs are scarce, and its prognosis is poor. One of the emerging investigational strategies for treating TNBC is to induce *HER2* expression, thus sensitizing it to anti-*HER2* therapy. Ninio-Many *et al*. demonstrated that miR-125a-3p induced *HER2* expression, allowing TNBC cell lines to respond to anti-*HER2* therapy.[84]

Various clinical trials for anti-cancer drugs targeting miRNAs have been conducted (Table 3). The most studied drug that targets miRNAs is the miR-34 mimic represented by MRX34. A multicenter phase I trial in 2013 was conducted to study the effects of MRX34 in patients with advanced solid tumors, primarily liver cancer.[85] Subsequently, patients with liver metastases including those with breast cancer also participated in the trial. However, this trial was terminated due to immune-related adverse events that led to the death of a patient. On the other hand, cobomarsen, an anti-miR-155 agent, has already been approved by the FDA as an orphan drug for mycosis fungoides cutaneous T-cell lymphoma.

Table 3. Clinical trials using miRNAs as anti-cancer drugs.

Therapeutic agent	Carrier	Disease	Clinical trial phase	Status
miR-34 mimic (MRX34)	Liposomal carrier	Liver and solid cancer	Phase I (NCT01829971)	Terminated
miR-16 mimic (TargomiR)	EnGeneIC Delivery Vehicle	NSCLC and Malignant pleural mesothelioma	Phase I (NCT02369198)	Completed
Anti-miR-155 (Cobomarsen)	Oligonucleotide inhibitor	Lymphoma and leukemia	Phase I (NCT02580552)	Completed
Anti-miR-155 (Cobomarsen)	Oligonucleotide inhibitor	CTL (Mycosis fungoides type)	Phase II (NCT03713320)	Terminated
Anti-miR-10b	Oligonucleotide inhibitor	Glioblastoma	Phase I (NCT01849952)	Recruiting

NSCLC: non-small cell lung cancer, CTL: cutaneous T-cell lymphoma

DISCUSSION

Blood, saliva, and urine can be used to assess the levels of miRNAs. Testing for miRNAs has become easy to incorporate into routine medical care, leading to a high accuracy of diagnosis and efficient monitoring of the treatment. However, several issues need to be resolved before they can be used clinically.[86] In the pre-analysis stage, various patient factors must be considered such as the patient's diet, medication intake, and age, as well as laboratory factors such as sample collection method and handling. Although reliable methods for measuring the levels of miRNAs (polymerase chain reaction (PCR)-based, microarray, and next-generation sequencing) are available, significant inter-platform differences have been pointed out. Currently, quantitative PCR is considered the gold standard technique. In the post-analysis stage, the primary concern is the absence of a standardized data normalization method.

There are currently no approved liquid biopsies for breast cancer. However, cell-free DNAs (cf-DNAs) are the clinically-used biomarkers for the detection of epidermal growth factor receptor (EGFR) mutations in lung cancers. The detection rates of EGFR mutations were improved by using a combination of cf-DNAs and EVs.[87] Although the identified EVs may differ between studies, early diagnosis may be achieved by using miRNAs detected in EVs from breast cancer patients.[88,89] It should be noted that there is no consensus on the markers that label EVs in human samples.[12,13] However, these studies suggested that

miRNAs in cancer EVs can be used as potential biomarkers that reflect the state of the disease.

While drugs targeting one molecule are considered mainstream, drugs targeting miRNAs can regulate several genes with one agent producing unprecedented therapeutic effects. Furthermore, they are easier to screen for highly effective read sequences than chemically synthesized drugs, and the obtained read sequences can be used as new drugs. Therefore, once the development scheme is completed, rapid development can be achieved. The development of a drug delivery system (DDS) is essential for drugs targeting miRNAs.[90] DDS using viral vectors is not ideal for clinical settings owing to the risk of strong inflammation. Attempts have been made to attach aptamers and ligands to drugs that target miRNAs. It has become possible to deliver drugs stably and safely to target tissues by encapsulation in EVs.[14,91-95] For the routine application of drugs targeting miRNAs in cancer, it is necessary to monitor the long-term effects at the pre-clinical stages and to consider immune-related side effects.[96]

CONCLUSION

In summary, miRNAs in breast cancer are in the early stages of clinical application as biomarkers and therapeutic targets, and their application is likely to dramatically change the clinical practice. In addition, EVs will be key to expanding the range of applications of miRNAs. With regard to the versatility of clinical applications, reviewing what we already know regarding miRNAs in breast cancer is vital before conducting further research.

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CONFLICT OF INTEREST

There are no conflicts of interest to declare through all steps of this study.

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