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Review

Exosomal microRNAs released from tumor cells can play a role as reliable non-invasive biomarkers in the diagnosis and prognosis of breast cancer

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Abstract

Breast cancer is one of the leading causes of death in women. Breast cancer develops from the milk-producing cells of the breast tissue. Exosomes from breast cancer cells have been linked to proliferation, metastasis, chemoresistance, and carcinogenesis, according to research. Exosomes are membrane-bound extracellular vesicles that can be secreted from cancer cells and contain a variety of contents such as nucleic acid, protein, lipid, etc. MicroRNAs, a component of exosomes, are small non-coding RNAs that dysregulate in various cancers and can function as oncogenic or suppressive RNA. MiRNAs influence cancer progression by binding to the 3' or 5' UTR (untranslated region) of their target. Because of their important role in cancer tumorigenesis, progression, and metastasis, some novel diagnostic and prognosis tools have been developed. In this study, we list some prominent exosomal microRNA, the key function of some specific exosomal miRNA, and their ability to act as a biomarker or a new therapy that they have been researching since 2020.

Keywords: Biomarkers, Breast cancer, miRNA, Exosomal miRNA

1. Introduction

Breast cancer (BC) is one of the most common malignant tumors [1]. Although some treatments, such as surgery, radiotherapy, chemotherapy, and endocrine, can help to increase the long-term survival rate, the overall rate remains low. As a result, scientists are looking for genetic and molecular determinants, such as non-coding RNAs, to aid in early diagnosis. MicroRNAs are single-stranded RNAs that are twenty-two nucleotides long and are one of the non-coding genes [2, 3]. MiRNAs act as transcription regulators because they can form hydrogen bonds with mRNA (UTR3), altering gene expression. As a result, dysregulated miRNA expression can result in uncontrolled cell proliferation and growth, which can lead to cancer [3], making microRNAs a good target for diagnosis, prognosis, and treatment. Biopsies, which are collected non-invasively from largely blood and other liquids, are needed to detect microRNAs (urine, tear, etc.) [3]. Exosomes are vesicles released by cells that are absorbed by a bilayer membrane made up of supermolecules containing cell-specific proteins, lipids, and nucleic acids (including miRNA and lncRNA) [4]. Current exosomal miRNAs show promise in cancer detection and treatment [5], but plasma miRNA measurement cannot replace exosomal miRNA measurement [6]. As a result, each

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plasma sample contains a unique stable microRNA expression pattern [7].

2. Exosomal miRNA

Exosomes can serve as a vehicle for miRNA exchange between living things ("a message in a bottle") and a form of living thing communication. However, it is unknown which miRNAs are modified as payloads via cancer-derived exosomes in order to advance neoplasm proliferation and metastasis. They investigated the features and useful non-uniformity of exosomes produced from cancer cells with diverse pathologic process abilities in the show contemplate. They anticipated that miRNAs modified by exosomes may be important in implementing epigenetic changes in recipient cells, and they identified the crucial cancer-derived exosomal miRNAs. Furthermore, in this manner, these forms of thoughts it was confirmed that cancer-derived exosomal miRNAs in plasma might serve as a biomarker for assessing carcinoma spread. As a result, scientists believe it will assist to rationalize the processes of carcinoma metastasis interfered by exosomes, as well as provide more avenues for prospective therapeutic treatment [8].

This study, to which we also refer, looked at the huge quantity of exosomes generated by various metastatic cancer patients discovered that the invasion and migratory capabilities of exosomes is dependent on the cell from which they were produced. To investigate the role of active cancer-associated fibroblasts (CAFs) in cancer progression, Western blot and immunofluorescence were employed to detect active CAF markers such as transforming growth factor-β (TGF-β), IL-6, CXCL12, and platelet-derived growth factor (PDGF). MiR-146a was discovered as the promoter of nuclear factor-to-cancer-associated fibroblasts (NF-to-CAF) transition by exploring the miRNAs profile. miR-146a can negatively target thioredoxin interacting protein (TXNIP) in order to stimulate the Wnt/-catenin signaling pathway and activate Wnt genes such as Axin2 and Dkk1 [9].

The functions of differentially expressed miRNAs has been shown in Table 1. To make advancement in breast cancer therapy, openness and accurate determination are critical. Agent imaging methods used for breast evaluation include mammography, breast ultrasound, and breast attractive radiation introduction. Furthermore, mammography has a reduced affectivity among younger women and women with large breasts. Mammography approaches have been enhanced by breast ultrasound and attractive reverberation imaging. In any case, these options are not without drawbacks. As a result, various recent initiatives have been made to identify high-risk people for breast cancer. Fluid biopsies have been utilized to help in the identification of breast cancer in the early stages. Fluid biopsies have the advantage of being noninvasive for early cancer diagnosis. It also allows for different redundancy and simple illness tests [10].

The activation of the PI3K/Akt pathway can result in tumor improvement and movement, as well as a problem with DNA repair, which may also contribute to GI. Later studies have shown that supportive mitogen-activated protein kinase signaling unwinds cell cycle checkpoints and allows cells to avoid prolonged G2 arrest by activating the gathering of the promitotic kinase, finally improving GI. DNA damage response (DDR) assures the assistance of GI, and a recent study found that score can be a coordinate poor regulator of DDR. The remember became accomplished in multicenter cohorts, including TCGA-BC, GSE22220, GSE73002, GSE41922, and in-house medical exosome cohorts. In the disclosure cohort, the genome instability-derived miRNAs signature (miGISig) became noteworthy. To validate its worth with the forecast and backbone of BC, the miGISig became linked to an inner approval cohort and distinct outside validation cohorts [11, 12].

2.1. Exosomal miRNAs in TNBC

This study looked at exosomal miRNAs in triple negative breast cancer (TNBC), and we think they employed bioinformatics to identify certain miRNAs and compare their expression to healthy controls. The results revealed that some miRNAs were elevated while others were downregulated, indicating that there are changes in miRNA expression between healthy controls and TNBC. Furthermore, they employed qRT-PCR to demonstrate the potential of certain miRNA as a predictive biomarker [13].

2.2. Urine-derived exosomes as a non-invasive biomarker

Recent research analyzed urine-derived exosomes to identify miR424, miR660, miR423, miR125b, miR194, miR17, let7a, let7d, let7f, and let7I as a non-invasive biomarker to diagnose BC. MiR-424 has been

Table 1. The functions of differentially expressed miRNAs

Name	Function	Reference
miR-223	miR-223 is a coordinator of breast cancer progression	21
miR-1246	miR-382-3p, -598-3p, -1246, and -184 are all implicated in breast cancer development and are possible biomarkers for breast cancer diagnosis	
miR-206	miR-206 promotes cancer development in breast cancer by targeting the full-length Neurokinin-1 receptor	
miR-24	Elevated mir-24-3p has a prognostic effect in breast cancer and is associated with the metastatic process	
miR-373	miR-373 has been linked to cancer formation	
miR-21	In breast cancer, circulating miR-21 has diagnostic and prognostic value	
miR-6875	The discovered combination of miR-1246, miR-1307-3p, miR-4634, miR-6861-5p, and miR-6875-5p may be useful for early diagnosis of breast cancer	
miR-202	miR-202 was shown to be highly increased in whole blood samples from patients with early-stage breast cancer	
miR-219B	Gga-miR-219b inhibits the proliferation, migration, and invasion of the Marek's disease tumor cell MSB1	

identified as a potential biomarker, with dysregulation reported in serum and plasma levels. It has a suppressive role, as does the miR424/503 complex, and its function is opposite to its increased expression. MiR-424 influences cancer development and malignancy. miR-660, Let7-i, Let7-f, Let7-d, and miR-423 have been downregulated and are oncogenic regulators. The increased expression of miR-125b influences malignant development as well as the responsiveness and prognosis to BC treatment [3]. miR-222, miR-194, let7-a, let7-e, and miR-17 have all been shown to be overexpressed. They proposed that a panel of four miRNA types, miR-424, miR-423, miR-660, and let7-i, might be used as a highly specific combinatory biomarker tool in the discrimination of BC based on urine samples [14].

2.3. miR-1246 and miR-155

Many of the research conducted in 2020 evaluated two chosen miRNAs from microarray profiling in trastuzumab resistance in HER-positive early-stage and metastatic BC patients. They deliberately studied miR-1246 and miR-155. It has been observed that high expression of these miRNAs is related to trastuzumab effect in metastatic patients, poor EFS in early-stage patients, and poor DFS in metastatic patients. Furthermore, they show that miRNAs can predict poor trastuzumab response in both early-stage and metastatic patients. There was n2.4. miR-204-5po discernible relationship between miRNAs and OS [15].

2.4. miR-204-5p

They employed 293T cell lines to manufacture exosomes in investigations on 293T cell lines to show exosome-mediated miR-204-5p administration inhibiting tumor development in BC. Instead of anti-cancer medications, miR-504-5p was enhanced to develop a novel therapeutic. This exosomal miRNA has been found to enhance 5-FU-induced apoptosis and thereby boost 5-FU cytotoxicity [16].

2.5. miR-7641

qRT-PCR and xenograft assays were used by several researchers to investigate exosomal miR-7641. Among other miRNAs, miR-7641 was found to be the most differentially expressed in the metastatic patient. Through exosomes, miR-7641 can transmit its tumor-promoting capability to recipient cancer cells. Patients with distant metastases had higher levels of miR-7641 than those without. Furthermore, bioinformatics analysis revealed a link between this miRNA and BC survival, as well as several biological processes such as apoptotic mitochondrial alterations, cytosolic trafficking, and cytokine production [17].

Furthermore, they have shown that the tumor-promoting power of miR-7641 appears to be transmitted to recipient cancer cells via exosomes, and miR-7641 also increased neoplasm growth in vivo. The study found that individuals with distant metastasis of cancer had significantly higher levels of miR-7641 in their plasma than those without metastasis. Furthermore, bioinformatics research has revealed

that miR-7641 is related to cancer survival, and miR-7641 is tightly related to a number of other essential cellular and natural forms [18].

2.6. miR-500a-5p

In our investigations, we discovered that the majority of researchers that employed next-generation sequencing to screen miRNAs in CAF-derived exosomes discovered that miR-500a-5p was up-regulated. Exosomes with overexpressed miR-500a-5p were identified and delivered to BC cells. This miRNA has been shown to stimulate the development and proliferation of BC cells. It was proposed that miR-500a-5p be inhibited to limit BC development and metastasis [19].

2.7. hsa-miR-423- 5p

A research on the expression level of hsa-miR-423- 5p in plasma, as well as pooled ribonucleic acid sequencing in duplicate, was carried out in five groups of patients. It was discovered that has-miR-423- was overexpressed in patient liquid biopsies. As a consequence, has-miR-423p was established as a BC biomarker [20].

Furthermore, because hsa-miR-423-5p expression is highly associated to the disease, abnormal hsa-miR-423-5p overexpression might be one of the early-warning signals given out by breast cancer cells [21]. In silica, the hsa-miR-423-5p-regulated coding characteristics are widely distributed in tumor-related signaling pathways [22].

2.8. miR-128-1, miR-128-2, and miR-421

Overexpression of miGISig increases genomic instability by activating association S part capture and enhances the occurrence of cancer cells. Because multi-nuclei and micro-nuclei are indicators of genotoxicity and bodily insecurity, they found the recurrence of multi-nuclei and micro-nuclei when the three miRNAs were overexpressed. They first identified the expression levels of miR-128-1, miR-128-2, and miR-421 in BC cells and solid human exocrine gland animal tissue cells, 184A1 and MCF-10A, and then designated the genomically unstable MDA-MB-231 cell line with low-level expression of the three miRNAs to perform the taking once tests.

MiRNA mimics were transfected into MDA-MB-231 cells and refined for 48 hours, during which time the expression levels of miR- 128-1, miR-128-2, and miR-421 were significantly increased. Using a high-content framework, we discovered that overexpression of miR-128-1, miR-128-2, and miR-421 dramatically increased the number of multinuclei and micronuclei inside the MDA-MB-231 cell line [23, 24].

3. MiRNAs and the genes that they target

3.1. miR-455-5p/ CDKN1B & miR-1255a/ SMAD4

The TCGA sequencing database was utilized by scientists to discover two exosomal miRNAs, miR-455-5p and miR-1255a, as therapeutic targets for breast cancer. Increased levels of miR-455-5p have been demonstrated to inhibit CDKN1B. CDKN1B, also known as p27Kip1, is a cyclin-dependent kinase that suppresses the cell cycle, and its downregulation in BC cells causes tumor development, mitosis, and poor prognosis. miR-1255a also has an oncogenic function in BC by downregulating SMAD4, altering the TGF-signaling pathway. By reducing their targets, CDKN1B and SMAD4, both miRNAs may have an effect on nearby or distant non-malignant recipient cells. Nonetheless, the connection between miR-455-5p and miR-1255a between CDKN1B and SMAD4 has yet to be established [25].

Researchers employed bioinformatics to identify miR-27a-3p, a novel implicated miRNA in BC that can allow cancer cells to avoid the immune system. The affinity of miR-27a-3p was confirmed using a dual-luciferase reporter assay. Endoplasmic reticulum stress has been shown to boost the expression and release of this miRNA. Furthermore, BC cells transmitted miR-27a-3p to macrophages, causing the MAGI2/PTEN/PI3K axis to be targeted for immune evasion. MAGI2 is a target for miR-27a-3p, an important protein for PTEN that upregulates to inhibit the PI3K/AKT signaling pathway. MiR-27a-3p promotes PD-L1 expression in macrophages by inhibiting MAGI2 [26].

3.3. miR-1910-3p and MTMR3

Exosomal miR-1910-3p has been studied by scientists. By overexpressing this miRNA, they were able to demonstrate proliferation and migration of BC cells. It was discovered that boosting miR-1910-3p decreases apoptosis while increasing autophagy, implying that miR-1910-3p has a role in decreasing apoptosis. This miRNA's gene target is myotubularin-related protein 3 (MTMR3), which is expressed at a reduced level in BC cells. By targeting MTMR3, miR-1910-3p can

activate the NF-B signaling pathway, boosting proliferation and migration, inducing autophagy, regulating the expression of wnt 2, wnt 3, wnt 5, wnt 10b, -catenin, and activating the wnt/-catenin signaling pathway. Furthermore, exosomes enriched in miR-1910-3p were shown to move to the BC microenvironment and stimulate migration and proliferation. Because of its specificity and sensitivity, miR-1910-3p is a promising biomarker [27].

3.4. miR-181d-5p and HOXA5

The researchers employed ChIP and dual-luciferase reporter assays to investigate the interaction between miR-181d-5p and HOXA5. Their findings show that miR-181d-5p is highly expressed in BC cells, but CDX2 and HOXA5 are downregulated. CDX2 can bind to the HOXA5 promoter, increasing its expression; moreover, CDX2 is a target for miR-181d-5p. Overexpression of HOXA5 can raise E-cadherin and vimentin levels while decreasing N-cadherin, Slug, Snail1, Twist1, ZEB1, and ZEB2 levels, indicating inhibition of cell proliferation, invasion, migration, and EMT while promoting cell death in breast cancer miR-181d-5p, through downregulating CDX2, can reduce HOXA5 levels, boosting EMT, proliferation, invasion, and migration while suppressing apoptosis in breast cancer cells [28].

3.5. miR-3613-3p and SOCS2

Scientists investigated CAF exosomes containing miR-3613-3p to demonstrate the role of this miRNA in BC. They employed Real-time PCR and microarray to discover the overexpression of miR-3613-3p, which inhibited SOCS2. SOCS2 can be activated by cytokines and regulated by miRNA. SOCS2 has the ability to modulate several signaling pathways that contain growth hormone signaling relevant to cell growth. Overall, it has been demonstrated that miR-3613-3p functions as an oncogenic miRNA by downregulating SOCS2 expression, resulting in metastasis and cell proliferation. It has been proposed that miR3613-3p can be employed as a nonspecific biomarker for BC and as a possible biomarker for prognosis prediction [29].

3.6. miR-4443 and TIMP2

Exosomal miR-4443, which enhances tumor metastasis in BC by down-regulating TIMP2, was examined by scientists using tagging and transfected exosomes. TIMP2 (a member of the TIMP family) can limit metastasis by blocking MMP (zinc-dependent endopeptidases), which breakdown extracellular matrix, allowing invasion and migration to occur. This miRNA is produced by BC cells in the microenvironment and promotes liver metastasis [30].

4. BC and immunocytes

Researchers employed miRNA microarrays to investigate the relationship between BC and immunocytes. The IL-6 high breast cancer exosome-derived miR-9 and miR-181a regulate SOCS3 and PIAS3 post-transcriptionally, respectively, activating the JAK/STAT signaling pathway and promoting the formation of eMDSCs. As a result, tumor development was sped up and immune escape was demonstrated. They investigated target treatment against myeloid-derived suppressor cells (eMDSCs), namely by blocking the STAT3 signaling pathway via the miR-9/SOCS3 and miR-181a/PIAS3 ceRNA networks, which might be a more successful therapy [31].

5. Conclusion

According to prior research in the field of exosomal microRNA, several exosomal microRNAs have been identified as major biomarkers for the diagnosis and prognosis of cancer and other diseases. It is possible to determine the intensity and stage of sickness by screening exosomal microRNAs; in this case, miR-3613-3p [32], and miR-4443,[33] induce metastasis.
Exosomal miRNAs can be used to detect cancer and track its progression by observing how they are dysregulated. This property has several advantages, the most important of which is that it may be used to identify cancer at an early stage Researchers employed miR-181-5p, miR-30a-3p, miR-30e-3p, and miR-361-5p to accurately diagnose non-small cell lung cancer at an early stage [34].
In addition, miRNA screening can help predict cancer prognosis. Elevated levels of miR-23b-3p, miR-10b-3p, and miR-21-5p in exosomes were linked to poor overall survival in non-small cell lung cancer (NSCLC) patients, according to researchers [32]. Rather of collecting samples from blood and bodily fluids, emerging technologies such as size-based approaches, precipitation, immune-affinity capture-based techniques, and microfluidic-based techniques can make exosome extraction from clinical samples more

efficient and straightforward [33, 35]. They are not affected by age, gender, BMI, or other variable traits, giving them the potential to become appropriate biomarkers for people from all walks of life [36, 37].
MicroRNA has become increasingly frequent throughout time as technology has advanced. Regardless of the advantages and practicality of exosomal microRNAs, there remain still obstacles to overcome [37]. To begin with, biological bodily fluids are a rich supply of exosomes from a variety of sources, making the separation of tumor cell-derived exosomes more difficult [38]. Adverbial adverbial adverbial adverbial adverbial adverbial adverbial adverbial Tears were examined for biomarkers in BC in a research, and certain particular miRNA were found.
Second, despite the fact that numerous isolation procedures have been proposed, the purity and quality of exosomes vary depending on the strategy, and there is currently no standard methodology for exosome separation and identification [37]. Third, current exosome isolation techniques are frequently complicated and time-consuming, with drawbacks such as aggregation and insufficient removal of contaminating biological molecules; whereas a selective, reproducible, robust, simple, fast, and high-throughput isolation technique is critical for the field of exosomes research [39]. To summarize, exosomal miRNAs can play an important role as biomarkers for cancer prediction and diagnosis; nevertheless, several issues must be addressed.

Authors' contributions

MK and GS developed the study concept, design, analyzing data and drafted manuscripts. FK and FR scientific editing and critical revisions of the manuscript. All authors read and approved the final manuscript.

Conflict of interests

There is no conflict of interest.

Ethical declarations

It is declared that this article has been completely written ethically.

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