Biomedical Sciences and Clinical Medicine 2024;63(4):266-282.
doi: 10.12982/BSCM.2024.32
https://he01.tci-thaijo.org/index.php/CMMJ-MedCMJ/index

Review Article

Open Access

Perspectives on OncomiR and TSmiRs in Breast Cancer and Assessment of their Regulatory Network

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Received: February 29, 2024;
Revised: May 25, 2024;
Accepted: June 12, 2024

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ABSTRACT

Breast cancer stands as a primary cause of mortality among women, urging the exploration of novel avenues for early detection. MicroRNAs (miRNAs) emerge as promising biomarkers, acting as both oncogenes and tumor suppressors, thus offering the potential for breakthroughs in early detection. Elevated levels of oncogenic miRNAs (OncomiRs) in cancer foster cell proliferation, migration, and metastasis by suppressing tumor suppressor genes. Inhibiting OncomiRs function presents a promising treatment strategy, where synthetic anti-miRs hinder OncomiRs binding to target RNAs, effectively suppressing cancer cell growth and metastasis. Conversely, decreased expression of Tumor Suppressor miRNAs (TSmiRs) in cancer facilitates malignancy progression by failing to suppress cancer-promoting genes. Circulating microRNAs (miRNAs) have gained considerable interest as promising biomarkers for breast cancer, owing to their distinct properties and involvement in cancer progression. An essential benefit of circulating miRNAs is their presence in bodily fluids like blood, serum, plasma, and breast milk. They exhibit remarkable stability within these fluids, safeguarded against degradation through encapsulation within extracellular vesicles or binding with proteins. This stability renders them appealing candidates for non-invasive biomarker identification. This article provides an overview of miRNA's pivotal role in breast cancer and its clinical significance.

KEYWORDS breast cancer, non-invasive, biomarker, miRNA, serum, prognosis

INTRODUCTION

Breast cancer remains the leading cause of mortality among women, contributing significantly to morbidity and mortality worldwide, despite considerable progress in its treatment (1). GLOBOCAN data from 2020 revealed a distressing figure of 19.3 million reported cancer cases and 10.0 million fatalities linked to the disease. Recent statistics indicate a shift in the most commonly diagnosed cancer, with female breast cancer surpassing lung cancer. Female breast cancer now constitutes approximately 2.3 million cases, representing 11.7% of all cancer cases, and contributes to around 684,996 deaths, accounting for 6.9% of total cancer-related fatalities (2) as shown in Table 1. Recent studies have revealed that emerging nations, notably those in Asia, are experiencing an increase in the prevalence of cancer as shown in Table 2 (3). Early detection of breast cancer increases patients' chances of

Table 1. Worldwide breast cancer incidence in 2020

Population	Units	Crude rate	Age-standardized rate	Cumulative risk %	Mortality	5-year prevalence
Asia	1,026,171	45.3	36.8	5.61	346,009	3,218,496
Europe	531,086	137.2	74.3	11.86	141,765	2,138,117
Northern America	281,591	151.2	89.4	14.78	85,787	1,189,111
Latin America and the Caribbean	210,100	63.2	51.9	8.69	57,984	710,039
Africa	186,598	27.8	40.7	6.53	48,407	429,220
Oceania	25,873	121.4	87.8	14.20	5,044	105,734
TOTAL	22,61,419				684,996	7,790,717

survival (4). Mammography is widely recognized as the most reliable method for breast cancer screening. However, other diagnostic examinations and biopsies are needed because of the high probability of false positives (5). Of a huge study of 702,154 cases of breast cancer in the US, around 2% (2,599/171,829) were found to be true positives, while the remaining 171,829 had defective screening mammography results. Due to the abnormal screening mammography results, most of these women underwent expensive and invasive diagnostic procedures that could have been avoided (6). Therefore, a more accurate breast cancer screening technique needs to be developed. Biomarkers can support the early detection of breast cancer. They can help find specific molecules or genetic abnormalities related to cancer cells (7). Biomarker screening in breast cancer involves reporting tumors and the analysis of DNA, RNA, proteins, and other biomolecules in body fluids and has been shown to be a valuable approach for cancer prognosis, diagnosis, personalized treatment, and predicting drug response. Circulating microRNAs (miRNAs) are now widely recognized as potent biomarkers for a variety of diseases, including cancer (8). Non-coding RNAs (ncRNAs) encompass a diverse array of RNA molecules that do not possess the ability to encode proteins. miRNAs are a notable class of non-coding RNA molecules, typically ranging from 19 to 25 nucleotides in length. These ncRNAs play a crucial role in regulating gene expression by inhibiting mRNA translation or facilitating mRNA degradation. This essential function highlights their significance in cellular processes as shown in Figure 1 (9). Furthermore, miRNAs influence cell proliferation, migration, invasion, and differentiation, and are associated with tumorigenesis. Through their regulatory mechanisms, ncRNAs control oncogenes and tumor suppressor gene expression (10). The dysregulation of oncomiRs and tumor suppressor miRs (TS miRs) in breast cancer holds promise for advancing breast cancer detection, diagnosis, prognosis, and treatment. OncomiRs, which promote oncogenesis by inhibiting tumor suppressor genes, and TS miRs, which counteract oncogenic activity, are emerging as valuable biomarkers for breast cancer screening. Typically, oncomiRs are upregulated, while TS miRs are downregulated in cancer cells. Manipulating the levels of these miRNAs can significantly impact cancer cell behavior. Dysregulated oncomiRs contribute to the uncontrolled growth and survival of cancer cells, playing critical roles in breast cancer metastasis and therapy resistance. Identifying and quantifying these oncomiRs in biological samples like blood or tissue biopsies can offer insights into breast cancer's presence and progression (11). Recent reports suggest that circulating miRNAs have been extensively studied and have shown significant potential as biomarkers for both diagnostic and prognostic purposes. These miRNAs can be detected in bodily fluids such as blood and serum during the early stages of breast cancer, allowing for timely intervention (12). The detection of miRNAs typically involves minimally invasive procedures, which enhance patient comfort and facilitate repeated sampling for longitudinal monitoring of disease progression. Additionally, miRNAs offer the potential for personalized medicine by providing insights into tumor biology and identifying therapeutic targets. Their ability to be multiplexed allows for comprehensive molecular characterization of breast cancer, and advancements in detection technologies have made miRNA analysis more accessible and cost-effective (13).

Table 2. Breast cancer cases in 2020 in Asia

Asia continents	Units				Mortality				Prevalence	
Countries	Number	Rank	(%)	Cumulative risk %	Number	Rank	(%)	Cumulative risk %	Number	Cumulative risk %
Afghanistan	3,173	1	13.9	3.11	1,783	2	11.1	2.07	5,930	31.29
Armenia	1,190	2	12.8	5.54	504	2	8.3	2.20	4,084	260.21
Azerbaijan	2,219	1	13.6	3.72	876	3	8.4	1.47	7,286	143.58
Bahrain	244	1	20.1	4.81	66	2	11.1	1.47	868	144.40
Bangladesh	13,028	3	8.3	1.83	6,783	4	6.2	1.03	31,232	38.35
Bhutan	16	11	2.8	0.60	8	14	1.8	0.36	39	10.79
Brunei Darussalam	137	1	13.9	5.88	29	5	6.7	1.30	499	237.06
Cambodia	1,877	3	10.2	2.44	793	3	6.3	1.07	4,242	49.58
China	4,16,371	3	9.1	4.18	1,17,174	8	3.9	1.16	13,90,095	197.04
Gaza Strip and West Bank	892	1	18.7	5.71	355	2	12.3	2.49	2,390	95.05
Georgia	1,942	1	14.7	6.30	910	2	11.1	2.69	6,917	331.28
India	1,78,361	1	13.5	2.81	90,408	1	10.6	1.49	4,59,271	69.28
Indonesia	65,858	1	16.6	4.83	22,430	2	9.6	1.78	2,01,143	148.11
Iran, the Islamic Republic	16,967	1	12.9	3.67	4,810	5	6.1	1.15	55,915	134.46
Iraq	7,515	1	22.2	5.72	3,019	1	15.3	2.42	20 354	102.46
Israel	4,348	1	15.1	8.46	1,194	2	9.1	1.70	17,745	408.17
Japan	92,024	5	8.9	7.98	17,081	7	4.1	1.11	3,28,716	507.88
Jordan	2,403	1	20.8	6.36	758	2	12.2	2.16	7,363	146.17
Kazakhstan	4,390	2	12.4	4.18	1,654	3	7.9	1.58	16,084	166.44
The Democratic Republic of Korea	5,962	2	10.3	3.49	1,791	6	4.5	1.06	12,040	91.42
Republic of Korea	25,814	3	11.2	6.41	3,009	7	3.4	0.68	86,672	338.52
Kuwait	791	1	20.6	5.74	224	1	13.0	1.83	2,805	169.37
Kyrgyzstan	770	3	10.9	2.61	251	6	5.4	0.92	2,056	62.36
Lao People's Democratic Republic	1,080	2	11.8	3.90	437	4	7.0	1.67	2,583	71.28
Lebanon	1,954	1	16.9	6.23	723	2	11.2	2.33	6,385	188.36
Malaysia	8,418	1	17.3	5.29	3,503	2	11.9	2.24	29,453	187.18
Maldives	83	1	16.7	4.77	26	3	9.8	1.86	248	125.50
Mongolia	188	6	3.3	1.17	62	8	1.4	0.42	589	35.41
Myanmar	6,912	4	9.3	2.29	2,972	6	5.6	1.03	15,875	56.32
Nepal	1,973	3	9.6	1.47	1,049	4	7.7	0.79	4,555	28.85
Oman	558	1	15.0	4.00	195	1	9.6	1.55	1,849	106.49
Pakistan	25,928	1	14.5	4.22	13,725	1	11.7	2.38	60,458	56.39
Philippines	27,163	1	17.7	5.66	9,926	3	10.7	2.02	85,206	156.19
Qatar	218	1	14.7	4.91	57	3	8.1	1.59	776	108.39
Saudi Arabia	3,954	1	14.2	3.01	1,095	2	8.4	0.93	13,653	92.99
Singapore	3,662	1	15.5	8.27	921	4	7.6	2.01	15,306	548.98
Sri Lanka	3,975	1	13.4	2.93	1,682	3	10.1	1.25	13,647	122.44
The Syrian Arab Republic	4,388	1	20.9	6.16	1,946	1	15.0	2.91	9,486	108.53
Tajikistan	738	2	12.9	2.06	279	4	7.3	0.91	1,844	38.97
Thailand	22,158	3	11.6	4.12	8,266	3	6.6	1.39	76,440	213.32
Timor-Leste	119	1	14.6	2.72	48	2	8.9	1.13	294	45.08
Turkey	24,175	2	10.3	4.89	7,161	4	5.7	1.39	83,973	196.64
Turkmenistan	1,025	1	14.9	3.24	450	2	10.4	1.59	2,917	95.27
United Arab Emirates	1,030	1	21.4	6.58	222	1	11.7	1.70	3,746	122.66
Uzbekistan	4,454	1	13.9	2.77	2,067	3	9.9	1.41	13,297	79.28
Viet Nam	21,555	3	11.8	3.69	9,345	4	7.6	1.47	60,753	124.65
Yemen	2,894	1	17.6	3.12	1,638	1	13.5	1.95	4,984	33.67

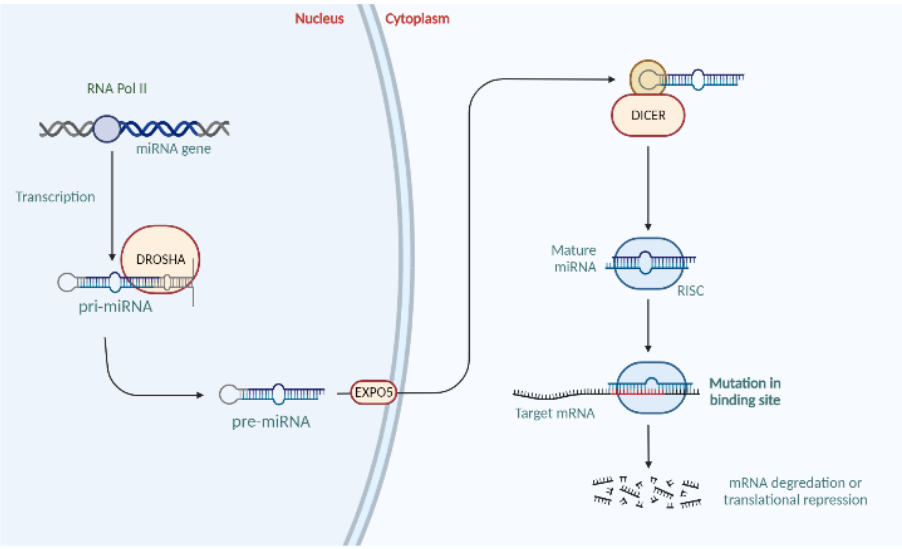


Figure 1. Biogenesis of miRNA

ONCOMIRNAS AS BIOMARKER

OncomiRNAs, also known as oncogenic miRNAs, represent a specific group of microRNAs that have been implicated in the development and advancement of cancer. These specific miRNAs play a role in promoting oncogenesis by exerting influence over various cellular processes, including cell metastasis, proliferation, and apoptosis. As a result, these miRNAs have broad-ranging effects on cancer development and progression. Among cancer cells, OncomiRNAs frequently demonstrate abnormal expression levels when compared to normal cells, and their dysregulation can disrupt gene expression networks relevant to tumorigenesis. OncomiRNAs have gained recognition as promising targets for cancer research in both diagnostic and therapeutic applications. They have achieved this by specifically targeting and modulating the expression of tumor suppressor genes or oncogenes, opening up new possibilities for advancements in the field. Circulating miRNAs, which can be detected in various sources such as tumor tissues, serum, plasma, urine, and patient saliva, hold promise as biomarkers for the early detection and prognostication of breast cancer. Bloodstream miRNAs are released by necrotic and apoptotic cells (9). Like Argonaut 2 (Ago2), miRNAs can circulate cell-free in the bloodstream or encased in membrane vesicles, macrovesicles, or exosomes (14). The comprehensive profiling of miRNAs can identify dysregulated miRNAs throughout breast cancer metastasis and enable the stratification of breast cancer patients for tailored therapeutic interventions. It's important to note that miRNA expression patterns can vary among breast cancer subtypes and individual patients. The dysregulation of TSmiRs and the upregulation of OncomiRNAs play a crucial role in the intricate molecular processes underlying the growth and progression of breast cancer.

TSMIRS IN BREAST CANCER

TSmiRs, although they do not encode proteins, play a crucial role in regulating gene expression and maintaining normal cellular functions. In the context of breast cancer, numerous TSmiRs have been identified, often exhibiting downregulation or functional impairment. This dysregulation results in the aberrant expression of key genes involved in tumor development and progression. The microRNA miR-34a is under direct regulation by the tumor suppressor p53. However, in breast cancer cases, its expression is frequently silenced. By specifically targeting and regulating critical genes involved in cell cycle progression, such as cyclin D1, cyclin E2, and CDK4, miR-34a exerts a powerful influence on cell proliferation. It induces cell cycle arrest and promotes apoptosis, thus playing a significant role in breast cancer pathogenesis. The absence of miR-34a, on the other hand, facilitates tumor growth and confers resistance to apoptosis. miR-34a plays a significant role in regulating both cell cycle progression and apoptosis by directly targeting multiple genes involved in these processes. It directly targets CDK4 and CDK6, which are key regulators of the

cell cycle. Through its inhibitory effects on these genes, miR-34a prompts cell cycle arrest, thereby preventing excessive cell proliferation. Additionally, miR-34a acts by targeting anti-apoptotic genes, including Bcl-2, survivin, and XIAP, thereby facilitating apoptosis and impeding the survival of tumor cells. Several studies have demonstrated that miR-34a exerts inhibitory effects on breast cancer metastasis by selectively targeting genes involved in the epithelial-mesenchymal transition (EMT), a critical process underlying tumor invasion and metastasis. By directly binding to and regulating the expression of transcription factors such as Snail, Slug, and ZEB1, miR-34a effectively counteracts their ability to promote EMT and enhance the metastatic potential of cancer cells. The repression of EMT-related genes by miR-34a hampers the migratory and invasive properties of breast cancer cells. Additionally, miR-34a plays a pivotal role in regulating cancer stem cells (CSCs) in breast cancer, which are characterized by their capacity for self-renewal and initiation of tumor growth.

By specifically targeting important genes, including Notch1, Sox2, and Nanog, miR-34a plays a crucial role in suppressing the stemness properties of CSCs. This targeted regulation effectively reduces the tumorigenic capabilities of CSCs. The decreased expression of miR-34a in breast cancer patients is associated with an unfavourable prognosis, advanced tumor stage, and the presence of lymph node metastasis. As a result, the expression levels of miR-34a hold promising potential as a prognostic biomarker in breast cancer (15). The miR-200 family, which includes miR-200a, miR-200b, miR-200c, miR-141, and miR-429, has gained considerable attention in breast cancer research due to their involvement in multiple aspects of tumor progression and metastasis. These microRNAs play crucial roles in regulating key processes. Furthermore, the miR-200 family has been implicated in the regulation of CSCs in breast cancer. The miR-200 family exerts its regulatory effects by specifically targeting genes, such as BMI1 and Suz12, that are involved in controlling the stemness properties of cancer CSCs. Through this targeting mechanism, the miR-200 family inhibits the characteristics associated with CSCs and diminishes their ability to initiate tumor formation. These findings underscore the importance of the miR-200 family in modulating the behavior of CSCs and highlight its potential as a therapeutic target for suppressing CSC-mediated tumor growth in breast cancer. The miR-200 family has also been implicated in the control of CSCs in breast cancer. In breast cancer, the miR-200 family plays a role in regulating CSCs by targeting specific genes involved in the maintenance of stemness, such as BMI1 and Suz12. Through this mechanism, the miR-200 family inhibits the properties of CSCs and reduces their tumor-initiating potential. These findings highlight the significance of the miR-200 family in the regulation of CSCs and its potential implications for breast cancer treatment strategies. In addition, the aberrant expression of the miR-200 family has been associated with the development of chemoresistance in breast cancer. Particularly, a reduction in the expression of miR-200c has been observed in breast cancer cells that display resistance to chemotherapy. The miR-200 family members exert their influence by targeting genes involved in drug resistance, including ABCG2 and ABCC1. These genes encode ATP-binding cassette transporters that play a crucial role in facilitating the efflux of drugs from cancer cells. Therefore, the dysregulation of the miR-200 family contributes to chemoresistance in breast cancer by modulating the expression of drug efflux transporters. The downregulation of miR-200 family members has been associated with increased expression of drug transporters, leading to the development of drug resistance. Extensive research efforts have been dedicated to investigating the levels of miR-200 family members as potential biomarkers for prognosis and prediction in breast cancer. Decreased expression of miR-200 family members has been correlated with an unfavourable prognosis, heightened aggressiveness of tumors, and an increased risk of metastasis. These findings emphasize the potential of miR-200 family members as valuable prognostic and predictive biomarkers in breast cancer. Moreover, the miR-200 family has demonstrated relevance in predicting treatment response, including resistance to hormonal therapies and chemotherapy. However, it is crucial to acknowledge that the impacts of the miR-200 family in breast cancer can exhibit variability depending on the particular tumor subtype and molecular characteristics. Furthermore,

the interactions between miR-200 family associates and their target genes are intricate, involving multiple signaling pathways (16). Both miR-125a and miR-125b have been recognized as tumor suppressors, displaying the capacity to inhibit cell proliferation and suppress tumor growth. Through their targeted regulation of important genes involved in cell cycle progression, such as CDK6 and E2F3, miR-125a and miR-125b induce cell cycle arrest, effectively restraining tumor cell proliferation. These microRNAs play crucial roles in tumors (17). Notably, miR-214 has been identified as a contributor to tumor growth and metastasis. Its mechanism involves targeting tumor suppressor genes, including PTEN and PDCD4, which results in enhanced cell proliferation, invasion, and migration. Furthermore, miR-214 can enhance the PI3K/AKT signaling pathway, which is closely associated with tumor progression. The regulation of EMT is critical for metastasis, and miR-214 has been identified as a participant in this process in breast cancer. It achieves this by targeting the E-cadherin gene (CDH1), which is responsible for maintaining cell-cell adhesion and suppressing EMT. By inhibiting CDH1, miR-214 disrupts cell adhesion and facilitates the transition to a mesenchymal phenotype. This, in turn, promotes the potential for metastasis (18). Their presence is crucial for tumor development, advancement, and acquiring resistance against therapeutic interventions. Notably, miR-214 has been identified as a regulator of CSCs in breast cancer. It exerts its regulatory effects by targeting important genes involved in maintaining stemness and self-renewal, such as PTEN and p53. Through the modulation of the expression of these genes, miR-214 influences the behavior and functional properties of CSCs in breast cancer. These findings highlight the significance of miR-214 in the regulation of CSCs and its potential as a therapeutic target for breast cancer treatment. Inhibiting these genes, miR-214 can promote CSC characteristics and contribute to tumor aggressiveness. miR-214 has also been connected with the process of drug resistance in breast cancer. It can target genes involved in drug sensitivity, such as PTEN and BIM. Downregulating these genes, miR-214 can confer resistance to chemotherapy and targeted therapies. SOS1 was the target of miR-628, which prevented BC cells from migrating and invading, indicating increasing SOS1 (19). Expression through therapeutic means might be a successful strategy for treating BC metastasis (20). miR-16 functions as a suppressor of various oncogenes implicated in the development of breast cancer. It directly targets genes such as CCND1 (encoding cyclin D1), which promotes cell cycle progression, and BCL2 (encoding anti-apoptotic protein Bcl-2), which inhibits cell death. By downregulating these oncogenes, miR-16 exerts tumor-suppressive effects. miR-16 has demonstrated its ability to target multiple genes involved in angiogenesis, a vital process responsible for tumor progress and metastasis. It targets VEGFA directly and its receptor VEGFR2, thereby suppressing angiogenesis and limiting blood supply to the tumor and playing a key role in the suppression of angiogenesis. Sensitization to chemotherapy is another essential means by which miR-16 enhances breast cancer cells' sensitivity to chemotherapy drugs. Targeting genes related to drug resistance, such as ABCC1 and ABCC5, miR-16 effectively inhibits the function of ATP-binding cassette transporters associated with drug efflux. As a result, the breast cancer cells' sensitivity to chemotherapy drugs is enhanced by reducing the expression of these transporters, i.e., miR-16 alerts breast cancer cells to chemotherapy agents (28). MiRNA-203 has been shown to play a pivotal role in inhibiting EMT in breast cancer cells by targeting critical transcription factors like ZEB1 and Slug (31). ZEB1 and Slug serve as master regulators of EMT, promoting the shift from an epithelial to a mesenchymal phenotype, thus fostering tumor invasion and metastasis. Conversely, miRNA-203 acts as a tumor suppressor by directly targeting and reducing the expression of these transcription factors, consequently impeding the EMT process in breast cancer (43). By inhibiting these genes, miRNA-203 suppresses stemness properties and reduces the tumorigenic potential of CSCs. miRNA-203 is linked to the sensitivity of BC cells to various therapeutic agents. Its dysregulation is involved with resistance to chemotherapy drugs (paclitaxel and doxorubicin). Restoring miRNA-203 expression or modulating its target genes involved in drug resistance may sensitize BC cells to chemotherapy and enhance treatment efficacy (44). miRNA-99a is a regulator of RB1 expression. It directly targets the RB1 mRNA and can downregulate RB1 protein

The references should be listed in numerical order. However, after reference 20, the numbers 21-27, 30, 31, and 31-42 do not appear in the text.

levels by attaching to specific sequences in the 3' (UTR) of the RB1 gene. This targeting results in reduced RB1 activity. By targeting and suppressing RB1 expression, miRNA-99a can potentially pay for the deregulation of the cell cycle and promote breast cancer development (45). miR-31, a tumor suppressor targets multiple oncogenes including RhoA and WAVE3 which are connected in cell migration and invasion. Reduced miR-31 expression enhances tumor cell motility and facilitates the process of metastasis (46). The family of let-7 miRNAs, including let-7a, let-7b, let-7c, let-7d, let-7e, and let-7g, is often downregulated in breast cancer. These miRNAs target various oncogenes, such as HMGA2, KRAS, and c-Myc, which are associated with cell proliferation, differentiation, and metastasis. Reduced let-7 expression contributes to tumor growth and aggressiveness (47). Triple-negative breast cancer (TNBC) is an intrinsic subtype of breast cancer characterized by the absence of ER, PR, and HER2 expression. Within TNBC, certain miRNAs are identified as oncogenic and associated with this subtype. For instance, miR-21 is commonly observed to be upregulated in TNBC and contributes to tumor development, metastasis, and invasion by directing tumor suppressor genes (PTEN and PDCD4). Similarly, miR-155, miR-221/ 222, and miR-10b act as oncogenic in TNBC. Conversely, specific miRNAs function as tumor suppressors in TNBC. Among them, miR-34a, tumor suppressor miRNA is frequently noted to be downregulated in TNBC. It targets genes involved in crucial functions such as cell cycle regulation, apoptosis, and EMT. In TNBC, the miR-200 family members miR-200c, miR-141 and miR-205 have been identified as tumor suppressor microRNAs. They play a crucial role in regulating the process of EMT and have an impact on the metastatic potential of cancer cells. These microRNAs act as key modulators in TNBC, influencing the transition of cancer cells from an epithelial to a mesenchymal phenotype, thereby affecting tumor progression and metastasis (33). A list of expression patterns of TsmiR and their target genes is listed in Table 3.

DIFFERENTIAL EXPRESSION OF CIRCULATING ONCOMIRNAS IN BREAST CANCER

The non-invasive nature of circulating OncomiRNAs makes them particularly appealing as biomarkers for breast cancer. Blood samples or other bodily fluids can be readily obtained, offering a convenient and accessible method for monitoring the status of diseases and evaluating the response to treatment. Changes in the levels of circulating OncomiRNAs during treatment can serve as indicators of treatment response. Alterations in the expression levels of specific OncomiRNAs have been observed in response to various therapies, including chemotherapy, hormone therapy, and targeted therapies. Monitoring these changes can provide valuable information on treatment efficacy and help guide personalized treatment decisions (Table 4).

Emerging research has shed light on the release of miRNAs from apoptotic or necrotic cells into various body fluids such as blood, plasma, serum, breast milk, saliva, and urine. These studies have unveiled the presence of miRNAs in these bodily fluids, highlighting their potential as biomarkers for various diseases and conditions. As a result, there may be a good chance to employ these circulating biomarkers to monitor BC as well as the various stages of this fatal disease. Recent research has demonstrated that serum is a more favourable option among bodily fluids for regulating the expression of miRNAs. This preference arises from the higher concentrations of miRNAs found in serum, which could be attributed to the impact of the clotting process (48). In a study conducted by Huiping Li et al. a signature consisting of miR-16-5p, miR-17-3p, miR-451a, and miR-940 levels was identified. This signature showed significant associations with neutral response rates, time to disease progression, and overall survival in three separate cohorts of HER2+ metastatic breast cancer patients undergoing initial treatment with trastuzumab (49). These findings suggest that a serum miRNA signature has the potential to serve as an indicator of therapeutic efficacy in HER2+ metastatic breast cancer patients receiving trastuzumab treatment. In another study by Natsuko Satomi-Tsushita et al. a combination of miRNAs was identified to assess the response to eribulin in metastatic breast cancer. This combination included miR-296-3p, miR-575, miR-3160-5p, miR-4710, miR-4755-3p, miR-4483, miR-5698, and miR-8089 (50). Further, hsa-miR-3184-5p and hsa-miR-6784-5p have been recognized as key regulators of BC and sensitive serum biomarkers (51).

Table 3. The expression pattern of TsmiR and their target in breast cancer

TsmiR annotation	Targets	Pathways	Function	References
miR-34a-3p	HIF1-α	p53	Migration, invasion, proliferation	15
miR-125b-5p	ST14	VDR	Proliferation invasion and migration	17
miR-628-3p	SOS1	Src MEK1/2	Prevents invasion and migration	20
miR-206	CDK4	NF-κB	Stops TNBC tumorigenesis	21
miR-26b-5p	CDK6	glycolytic	Aids in G0/G1 cell cycle arrest and prevents cellular growth	22
miR-26a-5p	ST8SIA4	NF-κB/PI3K/Akt	Prevents BC progression	23
miR-124-3p	STAT3 MGAT5	Wnt/β-catenin PI3K/ AKT/	Prevents BC cell proliferation and invasion	24
miR-205-5p	TG2	TGFβ1, Wnt, β-catenin NF-κB	Decreases invasion and BC bone metastasis	25
miR-21-3p	CYP1A1	MAT2B	Prevents proliferation	26
miR-29b-3p	TET1 TDG	AKT signalling Wn-t/β-catenin	Facilitate cell growth, proliferation, and apoptosis	27
miR-100-3P	mTOR	Stat5a IL-1ra	Proliferation migration and invasion	27
miR-512-5p	JAG1	Notch2	Proliferation, invasion, migration	28
miR-34a-5p	TGFBR2	TGF-β	Invasion and metastasis	28
miR-16-5p	TGF-β	Wnt/β- catenin ERK	Apoptosis ,invasion and migration.	29
miR-148a-5p	DNMT1 Wnt10b	Wnt/β-catenin	Proliferation and migration	30
miR-204-5p	JAK2	STAT3 BCl-2	Proliferation and apoptosis	34
miR-296-5p	PLK1	MS2bp	Growth, Invasion, Metastasis	35
miR-15a-5p	CCNE1	sONE eNOS	Growth inhibition, suppression of migration	36
miR-22-3p	Twist1	EMT	Migration, invasion, proliferation	37
miR-30b-5p	ITGB3 , IL-8, L-11, CDH11 CTGF	PI3K,	Metastasis , differentiation Proliferation, apoptosis, invasion	38
miR-143-3p	MAPK3, KRAS	RECK signalling	Tumorigenesis, development, metabolism, invasion, proliferation, apoptosis, and metastasis	39
miR-195-5p	MFN2	mTORC2 Akt	Proliferation , migration, and invasion	40
miR-497-5p	PTEN	YAP1	Proliferation	41
miR-26a-5p	HMGA1	Wnt/β- catenin	Invasion and migration	42
miR-126-3p	VEGF-A	PI3K signal	Apoptosis, proliferation, and angiogenesis	43

According to the Xiaoqin Li et al. study, breast cancer patients had a higher blood range of the microRNAs miR-9-5p and miR-148a-3p than normal controls (52). Interestingly, miR-17-5p did not show important differences between the two groups. The study revealed that HER2-positive breast cancer patients had notably higher levels of miR-9-5p in their blood compared to HER2-negative breast cancer patients. Guo et al. conducted a study where they observed significantly decreased levels of miR-455-3p and increased levels of miR-1915-3p in the serum of breast cancer patients. Moreover, patients with infiltrating carcinoma metastases demonstrated elevated levels of miR-1915-3p and lower levels of miR-455-3p compared to those with carcinoma in situ or without lymph node metastasis (53). Another study by Cardinali et al comparing breast cancer patients to healthy controls found that breast cancer patients had significantly elevated levels of four miRNAs in plasma (miR-20b-5p, miR-92a-5p, miR-106a-3p, and miR-106a-5p) and four miRNAs in serum (miR-19b-3p, miR-20b-5p, miR-92a-3p, and miR-106a-5p). These findings contrasted with individuals with benign breast tumors as well as age- and sex-matched healthy

Table 4. The expression pattern of differential expression of Circulating OncomiRNAs in breast

miRNA	Regulation in breast cancer	Functions	Signaling pathways
miR-16-5p	Down-regulated	Tumor suppressor	Apoptosis, cell cycle regulation, PI3K/AKT
miR-17-3p	Up-regulated	Oncogenic, promotes proliferation	PI3K/AKT, TGF-β signaling
miR-451a	Down-regulated	Tumor suppressor	AMPK/mTOR pathway, cell migration
miR-940	Up-regulated	Oncogenic, enhances invasion and migration	Wnt/β-catenin, PI3K/AKT
miR-296-3p	Down-regulated	Tumor suppressor, involved in angiogenesis	PI3K/AKT, VEGF signaling
miR-575,	Up-regulated	Promotes cell proliferation and survival	PI3K/AKT, MAPK, JAK/STAT
miR-3160-5	Up-regulated	Involved in tumor progression	TGF-β, Wnt/β-catenin, Notch
miR-4710	Up-regulated	Influences cell migration and invasion	FAK/SRC, Rho GTPases, Integrin
miR-4755-3p	Up-regulated	Involved in cell growth	mTOR, Ras/Raf/MEK/ERK, Hippo
miR-4483	Up-regulated	Involved in tumorigenesis	NF-κB, Hedgehog, TGF-β
miR-5698	Up-regulated	Implicated in cell proliferation	EGFR, STAT3, NF-κB
miR-8089	Up-regulated	Invasion and migration	MMPs, EMT signaling, AKT/mTOR
hsa-miR-3184-5p	Up-regulated	Tumor suppressor, regulates cell cycle	p53 signaling
hsa-miR-6784-5p	Up-regulated	Tumor suppressor, involved in apoptosis	p53 signaling, PI3K/AKT, MAPK pathways
miR-9-5p	Up-regulated	Promotes metastasis, epithelial-mesenchymal transition (EMT)	Notch signaling, E-cadherin repression
miR-148a-3p	Up-regulated	Tumor suppressor, inhibits metastasis	TGF-β signaling, Wnt/β-catenin
miR-17-5p	Up-regulated	Oncogenic, promotes proliferation	PI3K/AKT, TGF-β signaling
miR-455-3p	Down-regulated	Tumor suppressor, inhibits proliferation and invasion	Wnt/β-catenin, EMT regulation
miR-1915-3p	Up-regulated	Promotes metastasis, regulates apoptosis	PI3K/AKT, apoptosis pathways
miR-20b-5p	Up-regulated	Promotes cell proliferation and survival	PI3K/AKT, MAPK pathways
miR-92a-5p	Up-regulated	Promotes angiogenesis and cell proliferation	Notch signaling, cell cycle regulation
miR-106a-3p	Up-regulated	Promotes cell cycle progression and invasion	TGF-β signaling, E2F signaling
miR-106a-5p	Up-regulated	Promotes cell proliferation and metastasis	PI3K/AKT, E2F signaling
miR-19b-3p	Up-regulated	Promotes cell proliferation and inhibits apoptosis	PI3K/AKT, Wnt/β-catenin
miR-92a-3p	Up-regulated	Promotes cell proliferation and inhibits apoptosis	Notch signaling, cell cycle regulation
miR-21	Down-regulated	Promotes proliferation, invasion, and metastasis	PI3K/AKT, NF-κB, and MAPK pathways
miR-497-5p	Up-regulated	Tumor suppressor, inhibits cell proliferation	PI3K/AKT, cell cycle regulation
miR-1246	Up-regulated	Promotes cell proliferation, invasion, and metastasis	p53 signaling, Wnt/β-catenin
miR-1307-3p	Up-regulated	Involved in tumor progression and metastasis	Cell cycle regulation
miR-4634	Up-regulated	Involved in cancer cell proliferation	PI3K/AKT, NF-κB, and MAPK pathways, Notch signaling,
miR-6861-5p	Up-regulated	Involved in tumor progression	PI3K/AKT, NF-κB, and MAPK pathways, Notch signaling,
miR-6876-5p	Up-regulated	Involved in cancer progression	PI3K/AKT, NF-κB, and MAPK pathways
miR-1246	Up-regulated	Promotes cell proliferation, invasion, and metastasis	p53 signaling, Wnt/β-catenin, Notch signaling,
miR-1307-3p	Down-regulated	Involved in tumor progression and metastasis	cell cycle regulation
let-7a	Up-regulated	Tumor suppressor, inhibits cell proliferation	RAS signaling, HMGA2
miR-574-5p	Up-regulated	Promotes inflammation and tumor progression	JAK/STAT, PI3K/AKT, and NF-κB pathways
miR-155		Promotes inflammation, cell proliferation, and survival	JAK/STAT, PI3K/AKT, and NF-κB pathways

individuals (54). Additionally, Bingjie Cai et al. found higher expression of serum miRNA-21 in breast cancer patients. Increased levels of circulating miR-21 were associated with advanced tumor stage, poor prognosis, and lymph node metastasis in breast cancer (53). The researchers concluded that serum miRNA-21 shows promise as a non-invasive biomarker for breast cancer, based on the aforementioned findings. Zhong et al. conducted a study revealing elevated expression of miR-497-5p in the serum of breast cancer patients. However, in cell lines and tissue samples from the same patients, miR-497-5p was found to be downregulated (55). Another comprehensive analysis performed by Loke et al. involved the study of 4630 serum samples. The results identified a five-miRNA signature comprising miR-1246, miR-1307-3p, miR-4634, miR-6861-5p, and

miR-6876-5p (56). This signature demonstrated high accuracy in detecting breast cancer, including its early stages, thereby highlighting its potential as a robust diagnostic tool. Furthermore, a study conducted by Sheng-kai demonstrated that breast cancer patients exhibit decreased expression of let-7a and an increased range of miR-574-5p, miR-155, and MALAT1 in their serum (57).

REGULATORY NETWORK OF ONCOMIRNAS IN EARLY BREAST CANCER

Oncogenic miRNAs are essential for the growth of breast cancer. The key oncogenic miRNAs involve angiogenesis, metastasis, invasion, cell migration, and apoptosis inhibition. According to a clinical investigation, the overexpression of miR-17, which is activated by the oncoprotein c-Myc, is connected to increased cell proliferation, lower overall survival, and progressive clinical stage in breast cancer patients (58). According to a study by Luengo-Gil, miR-20a has been found to enhance angiogenesis and stimulate the growth of glomeruloid microvasculature in breast cancer. This effect is likely attributed to the overexpression of VEGFA, a key factor involved in angiogenesis (59). Another study by Mehrgou, A. highlights the crucial role of miR-21 overexpression in promoting cell proliferation and contributing to a more severe phenotype in pregnancy-associated breast cancer (60). Furthermore, Yang et al. discovered that overexpressing miR-181a and miR-181b facilitates the formation of cellular spheres, regulates the cell cycle, enhances cell proliferation, and promotes resistance to chemotherapy (61). A list of expression patterns of OncomiRNAs and their target genes is shown in Table 5 (16, 44, 59, 62-83). To gain a deeper understanding of the biological and molecular roles of specific miRNAs, a comprehensive literature survey was conducted. The mirWalk database, accessible at http://mirwalk.umm.uni-heidelberg.de/, was employed to predict the target genes associated with the top 10 upregulated and downregulated miRNAs. From this analysis, a total of 215 target genes were predicted for the upregulated miRNAs, while 118 target genes were identified for the downregulated miRNAs as shown in Figures. 2 and 3. To further investigate the functional characteristics of these target genes, a Gene Ontology (GO) analysis was performed. This analysis aimed to categorize the upregulated target genes based on their involvement in biological processes and molecular functions. The ClueGO plug-in, integrated within the Cytoscape platform, was utilized for this purpose. A statistical significance threshold ($p < 0.05$) was applied, along with Bonferroni step-down analysis, to ensure reliable results as shown in Table 6. This comprehensive analysis is instrumental in the identification of potential therapeutic targets and biomarkers for breast cancer diagnosis, prognosis, and the development of personalized treatment strategies for patients.

The GO term GO:0090201 is not directly connected to BASP1, BCL2, HES1, JAG1, NOTCH1, or NOTCH2 and reflects the control of cytochrome c release from mitochondria. Although these proteins and genes have various cellular functions, they do not specifically play a role in the release of cytochrome c. It is important to note that certain proteins, including BCL2, are indeed connected in the regulation of cytochrome c release. BCL2 is a protein known for its anti-apoptotic function, as it inhibits the release of cytochrome c from mitochondria. This effect is achieved through interactions with pro-apoptotic proteins like BAX and BAK, which control the release of cytochrome c. Conversely, HES1, JAG1, NOTCH1, and NOTCH2 are components of the Notch signaling pathway, which is involved in cell fate determination and development. These elements contribute to the intricate regulatory processes of cellular functions. Although the Notch pathway is not directly associated with the regulation of cytochrome c release, it is involved in other cellular processes and gene expression regulation. GO:0016241, the regulation of macroautophagy, a cellular process that involves the degradation and recycling of cellular components through the formation of autophagosomes, is represented. It is regulated by a complex interplay of various genes and proteins. AKT1 is known to modulate autophagy through its downstream targets and signaling pathways. BNIP3L is a helpful regulator of autophagy and is implicated in the induction of mitophagy, a selective form of autophagy that targets damaged mitochondria for degradation. MTOR forms complexes with other proteins and functions as a central node in the signaling pathways that control autophagy. It negatively regulates autophagy, inhibiting the formation of autophago-

Table 5. The expression pattern of OncomiRNAs and their target in breast cancer

OncomiRNAs annotation	Targets	Pathways	Function	Reference
hsa-miR-200a-3p	TP53INP1	YAP1 TP53INP1	Suppresses apoptosis	16
hsa-miR-203a-5p	Akt2/ SOCS3	p53	Proliferation, apoptotic	44
hsa-miR-20a-5p	BECN1, ATG16L	Autophagy lysosome pathway Genomic	Genomic damage and tumour growth Metastasis growth, and proliferation	59
hsa-miR-20b-5p	Tumor suppressor PTEN	PI3K AKT mTOR	Invasion, metastasis, proliferation, EMT,	62
hsa-miR-29a-3p	TET1	STAT3 JAK	migration	63
hsa-miR-105-5p	GOLIM4	Exosome delivery to epithelial barrier cells	Proliferation and metastasis	64
hsa-miR-106b-5p	SIX1 SMAD7	TGF-β	Tumor-initiating and EMT	65
hsa-miR-155-5p	SOCS1 MMP16	TGF-β and STAT3	Chemoresistance, proliferation and metastasis, progression, cell cycle	66
hsa-miR-181a-5p	SOCS3 PIAS3	STAT JAK signalling	Differentiation, apoptosis, cell cycle regulation, proliferation	67
hsa-miR-196a-5p	CCA	β-catenin axis HAND1 Wnt	Proliferation and migration	68
hsa-miR-210-3p	GPD1L CYG	HIF-1alpha-dependent pathway	Invasion ,cell proliferation, and migration	69
hsa-miR-374a-5p	WIF1, PTEN, WNT5A	Wnt/β-catenin signaling	Metastasis	70
hsa-miR-375	PI3K	MAPK signalling	Metastasis	71
hsa-miR-504-3p	CDK6	CDK6 to mediate the ERK signalling pathway	Migration	72
hsa-miR-21-5p	PTEN, Cdc25, PDCD4 Maspin, TPM1	-PDCD4	EMT, invasion, metastasis , migration, and proliferation	73
hsa-miR-181b-3p	CBX7 Bim	DNA damage repair pathway	Chemoresistance Sphere formation, and proliferation	74
hsa-miR-301a-3p	PTEN	AKT/mTOR Wnt/ β -catenin PI3K/	Invasion, metastasis , and proliferation.	75
hsa-miR-10b-5p	E-cadherin	Akt EMT TWIST-1P13K	Proliferation, invasion, and metastasis	76
hsa-miR-373-5p	CD44	AKT PI3K	Migration, invasion, and metastasis	77
hsa-miR-495-3p	E-cadherin, JAM-A, and REDD1; repression of JAM-A	AKT mTOR Wnt/ β -catenin PI3K	Migration, EMT, invasion and metastasis, and cell migration	78
hsa-miR-520a-3p	CD44	Wnt/ β -catenin	Migration and invasion	79
hsa-miR-9-5p	Cyclin D1 E-cadherin	Wnt/ β -catenin	Angiogenesis and metastasis Migration, invasion	80
hsa-miR-93-5p	PTEN; LATS2	Akt PI3K pathway,	Metastasis and angiogenesis	81
hsa-miR-200a-3p	YAP1	EMT- EGF	Suppresses apoptosis	82
hsa-miR-301a-3p	ESR1	ER signalling	Invasion	83

somes. The PI3K/AKT/mTOR signaling pathway, which adversely regulates autophagy, is known to be activated by PIK3CA. TBK1 participates in the control of autophagy, particularly in reaction to viral infections and inflammation. TP53 can also modulate autophagy, either promoting or inhibiting it depending on the context. AKT1, BNIP3L, MTOR, PIK3CA, TBK1, and TP53 are all associated with the various signaling pathways and cellular processes that modulate autophagy, highlighting

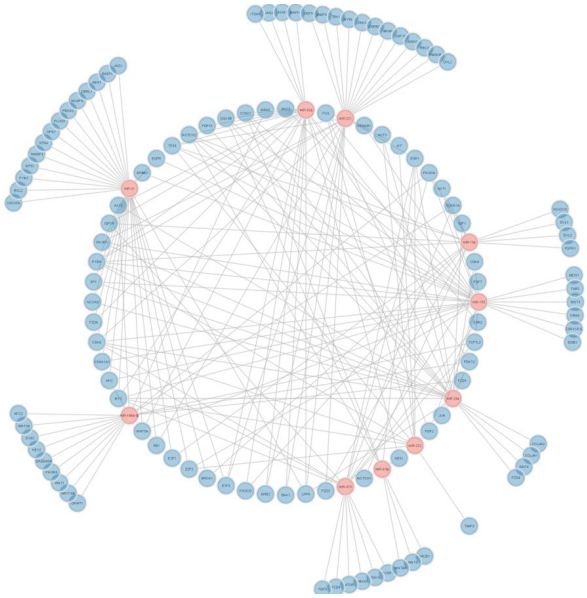


Figure 2. Upregulation miRNA-Targets interaction network analysis

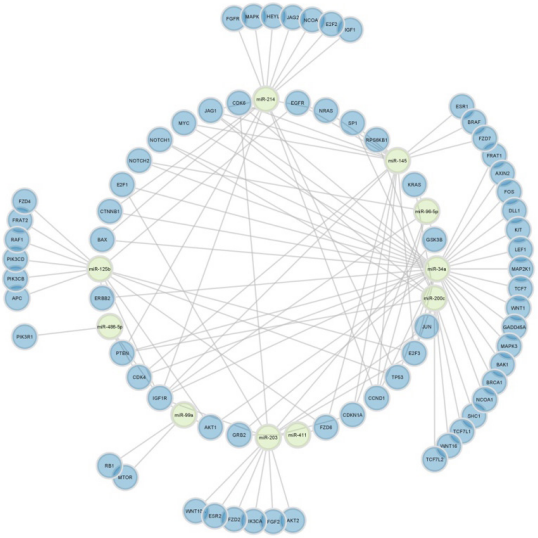


Figure 3. Downregulation miRNA-Target interaction network analysis

Table 6. List of gene ontology terms for predicted upregulated miRNA-target genes

GO ID	GO Terms	No. of Genes	*p*-value
GO:0061515	Myeloid cell development	3	0.05
GO:0048599	Oocyte development	4	0.05
GO:0016241	Regulation of macroautophagy	4	0.05
GO:0090201	Negative regulation of release of cytochrome c from mitochondria	6	0.05
GO:0030316	Osteoclast differentiation	3	0.05
GO:0030510	Regulation of BMP signaling pathway	5	0.05
GO:0090288	Negative regulation of cellular response to growth factor stimulus	5	0.05
GO:1902106	Negative regulation of leukocyte differentiation	5	0.05
GO:0043388	Positive regulation of DNA binding	4	0.05
GO:2001244	Positive regulation of intrinsic apoptotic signaling pathway	4	0.05
GO:0072132	Mesenchyme morphogenesis	4	0.05

the complexity and multifaceted nature of autophagy regulation. GO:0030510 represents the regulation of the BMP (bone morphogenetic protein) signaling pathway, which is associated with several cellular processes, including embryonic development, tissue homeostasis, and cell differentiation. This GO term describes the processes and factors that modulate the activity and output of the BMP signaling pathway. HES1, NOTCH1, and NOTCH2 are all elements of the Notch signaling pathway, which interacts with and modulates BMP signalling. Notch signaling can crosstalk with BMP signaling to regulate cellular responses and developmental processes. HES1 is a downstream transcriptional effector of Notch signaling and can influence the activity of the BMP pathway. WNT1 and WNT5A are members of the Wnt family of secreted glycoproteins. It is well established that Wnt signaling pathways interact with and control BMP signaling in a context-dependent manner. WNT1 and WNT5A can modulate BMP signaling by influencing the expression of BMP receptors, antagonists, or downstream effectors. GO:1902106 represents the negative regulation of leukocyte differentiation. This term describes the processes and factors that inhibit or suppress the differentiation of leukocytes, which are a type of white blood cell involved in immune responses. CDK6, CTNNB1, ERBB2, MYC, and PIK3R1 are associated with the negative regulation of leukocyte differentiation. These genes represent factors that can modulate signaling pathways and gene expression programs involved in the differentiation of leukocytes, potentially inhibiting or suppressing the differentiation process. Breast cancer cells can directly interact with leukocytes and manipulate their differentiation and function. This can occur through the secretion of specific factors or by modulating signaling pathways involved in leukocyte differentiation. Although the specific gene ontology term "negative regulation of leukocyte differentiation" may not be directly associated with breast cancer, it is important to recognize that the immune system and leukocytes play crucial roles in the tumor microenvironment and the body's immune response against cancer. These factors significantly contribute to the complex interplay between the immune system and breast cancer, highlighting the impact of leukocyte differentiation and function on the development and progression of the disease. Tumors can release various factors like cytokines, growth factors, and immune checkpoint molecules such as PD-L1 that suppress the immune response and inhibit leukocyte differentiation. GO:0043388 represents the positive regulation of DNA binding. This term describes processes or factors that enhance or promote the binding of DNA by proteins, transcription factors, or other DNA-binding molecules. CTNNB1, HES1, IGF1, and RB1 are associated with the promotion of DNA binding by transcription factors or other DNA-binding molecules, thereby influencing gene expression and cellular processes.

BBC3 is a gene that is transcriptionally activated by TP53 (tumor protein p53) and plays a significant role in positively regulating the intrinsic apoptotic pathway, as well as responding to DNA damage and various stress signals. TP53, also known as p53, can exert a positive regulatory effect on the intrinsic apoptotic pathway by facilitating the transcription of pro-apoptotic genes, including BBC3, while inhibiting the expression of anti-apoptotic genes. Through its involvement in initiating the intrinsic apoptotic pathway, TP53 serves as a critical component in regulating programmed cell death. GO:0072132 represents mesenchyme morphogenesis. This term describes the processes and factors involved in the formation and association of mesenchymal tissues during growth and tissue remodelling. EY2 is known to interact with various signaling pathways, including the Notch signaling pathway, to influence mesenchymal cell behaviour and tissue morphogenesis. MYC can influence mesenchyme morphogenesis by modulating gene expression programs that control cell behaviour and tissue remodelling during development. NOTCH1 is involved in mesenchyme morphogenesis by regulating the behavior and differentiation of mesenchymal cells through its interaction with other signaling pathways and transcription factors. In summary, the genes HEY2, MYC, NOTCH1, and WNT5A are associated with mesenchyme morphogenesis indicate elements that affect how genes are expressed and how cells behave, and tissue remodeling during the formation and organization of mesenchymal tissues. GO:0048599 represents oocyte development. This term describes the processes and factors involved in the development, maturation, and

differentiation of oocytes, which are the female reproductive cells involved in reproduction and embryonic development. BCL2, CTNNB1, IGF1, and WNT4 are associated with oocyte development.

These genes play crucial roles in regulating the growth, maturation, and differentiation of oocytes. They are involved in a wide range of cellular processes, including apoptosis, gene expression, and signaling pathways, contributing significantly to various aspects of oocyte development. Their involvement contributes significantly to the development and maturation of oocytes during reproductive processes. GO:0061515 represents myeloid cell development, encompassing the intricate processes underlying the differentiation and proliferation of various immune cells, including monocytes, macrophages, granulocytes, and dendritic cells. While breast cancer predominantly arises from epithelial cells, the tumor microenvironment and immune response, notably involving myeloid cells, intricately influence disease progression. Genes like KIT and MEIS1 are pivotal in regulating critical facets of myeloid progenitor cell growth, survival, and differentiation. Specifically, KIT contributes broadly to these processes, while MEIS1 plays a more specialized role in the specification and maturation of myeloid progenitor cells, orchestrating gene expression alongside other transcription factors and co-factors to promote myeloid cell differentiation. NOTCH2 further regulates the transition of myeloid progenitors into mature myeloid cells, such as monocytes and macrophages. Conversely, genes like BCL2, CTNNB1, IGF1, and WNT4 are predominantly associated with oocyte development, delineating pathways crucial for folliculogenesis and ovarian function, rather than myeloid cell differentiation. They stand for elements that are crucial to the development, maturation, and differentiation of oocytes. These genes control cellular processes that aid in the growth and maturation of oocytes throughout reproductive processes, including apoptosis, gene expression, and signaling pathways (84).

CONCLUSIONS

This review aims to offer a comprehensive and updated understanding of breast cancer, with a focus on its current epidemiology, prognostic biomarkers, and potential therapeutic strategies. Given the increasing incidence and mortality rates of breast cancer over recent decades, miRNAs have emerged as clinically relevant in diagnosis, prognosis, and treatment. Targeting genes regulated by OncomiRNAs and TS-miRNAs elucidates key processes like proliferation, apoptosis, and metastasis. TS miRs play essential roles in maintaining normal cellular functions by inhibiting processes such as cell proliferation and invasion. The loss of specific TS miRs in breast cancer is associated with increased tumor aggressiveness and poorer prognosis. Dysregulated in cancer, these genes often belong to pivotal pathways like PI3K/AKT/mTOR and MAPK/ERK. OncomiRNAs promote tumorigenesis by altering gene expression in these pathways, driving aggressive cancer behavior. Gene ontology analysis categorizes miRNA-regulated genes based on biological processes and molecular functions, shedding light on breast cancer pathogenesis. However, this review may lack coverage of the exploration of specific breast cancer subtypes or mechanisms. Generalizing miRNA's significance across all breast cancer subtypes may overlook the disease's heterogeneity. Further research on tissue- or circulating- specific miRNAs as biomarkers in breast cancer holds promise for improved diagnosis and prognosis. Thus, findings from these studies underscore the potential utility of miRNAs in clinical practice.

ACKNOWLEDGMENTS

The authors would like to express their gratitude to the technical team of the Department of Bioinformatics at Sathyabama Institute of Science and Technology, Chennai, India for providing computational resources and support.

FUNDING

The authors did not receive any financial support for conducting the research, authoring this article, or its publication.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

ADDITIONAL INFORMATION

Authors contributions

JCH: Reviewed and compiled the paper, con-

ceived and designed the protocol, reviewed relevant papers, and contributed to the manuscript compilation. GLP: Assisted in comprehending the bioinformatic tools integrated into the paper and contributed to understanding the role of miRNA in breast cancer, which aided in the manuscript& compilation.

Availability of data and materials

The authors affirm that the data and materials are accessible and transparent.

REFERENCES

1. Hou Z, Zheng J, Zhang C. Direct ultrasensitive electrochemical detection of breast cancer biomarker-miRNA-21 employing an apt sensor based on a microgel nanoparticle composite. Sens Actuators B Chem. 2022;367:132067.
2. Seale K, Ruffin K, Tkaczuk K. Circulating Biomarkers in Breast Cancer. Clin Breast Cancer. 2021;22:319-331.
3. Xia C, Dong X, Li H, Cao M, Sun D, He S, et al. Cancer statistics in China and United States, profiles, trends, and determinants. Chin Med J (Engl). 2022;135:584-90.
4. Momenimovahed Z, Salehiniya H. Epidemiological characteristics of and risk factors for breast cancer in the world. Breast Cancer (Dove Med Press). 2019;11: 151-64.
5. Mustapha M, Ozsahin D, Ozsahin I, Uzun B. Breast cancer screening based on supervised learning and multi-criteria decision-making. Diagnostics (Basel). 2022;12:1326. PubMed PMID: 35741136.
6. Wang Y, Yin W, Lin Y, Yin K, Zhou L, Du Y, et al. Downregulated circulating microRNAs after surgery: potential noninvasive biomarkers for diagnosis and prognosis of early breast cancer. Cell Death Discov. 2018;4:21. PubMed PMID: 30109140.
7. Zou R, Loke S, Tan V, Quek S, Jagmohan P, Tang Y, et al. Development of a microRNA Panel for the Classification of Abnormal Mammograms for Breast Cancer. Cancers (Basel). 2021;13:2130. PubMed PMID: 33925125.
8. Jang Y, Kim Y, Kang K, Kim K, Park Y, Kim C. Multiple microRNAs as biomarkers for early breast cancer diagnosis. Mol Clin Oncol. 2021;14:31. PubMed PMID: 33414912.
9. Gahlawat A, Fahed L, Witte T, Schott S. Total circulating microRNA level as an independent prognostic marker for risk stratification in breast cancer. Br J Cancer. 2022; 127:156-62.
10. Yao Y, Liu R, Gao C, Zhang T, Qi L, Liu G, et al. Identification of prognostic biomarkers for breast cancer based on miRNA and mRNA co-expression network. J Cell Biochem. 2019;120:15378-88. PubMed PMID: 31037764.
11. Wong JS, Cheah YK. Potential miRNAs for miRNA-based therapeutics in breast cancer. Noncoding RNA. 2020;6:29. PubMed PMID: 32668603
12. Davarinejad O, Mohammadi P, Ghavi D. Identifying miRNA signature for predicting and treatment of breast cancer using the transcriptomic data of 7,000 breast tumors. Research Square [Internet]. 2022. Available from: https://assets-eu.researchsquare.com/files/rs-1551331/v1/5f0a7b42-e175-4bc0-971c-e815f054e58b.pdf?c=1651655662
13. Zou R, Loke S, Tang Y, Too H, Zhou L, Lee S, et al. Development and validation of a circulating microRNA panel for the early detection of breast cancer. Br J Cancer. 2022;126:472-81.
14. Wu HJ, Chu PY. Recent discoveries of macromolecule- and cell-based biomarkers and therapeutic implications in breast cancer. Int J Mol Sci. 2021;22:636. PubMed PMID: 33435254.
15. Mansoori B, Silvestris N, Mohammadi A, Khaze V, Baghbani E, Mokhtarzadeh A, et al. miR-34a and miR-200c have an additive tumor-suppressive effect on breast cancer cells and patient prognosis. Genes (Basel). 2021;12:267. PubMed PMID: 33673143
16. Yu S, Yang L, Hong Q, Kuang X, Di G, Shao Z. MicroRNA-200a confers chemoresistance by antagonizing TP53INP1 and YAP1 in human breast cancer. BMC Cancer. 2018;18:74. PubMed PMID: 29329575
17. Samra N, Rashad M, ElMoneim N, Sanaa S, Maher K. The prognostic value of vitamin D receptor and its up-stream miR-27b and miR-125a expression in breast cancer patients. Gene Rep. 2021;23:101121.
18. Rahmani A, Talebian S, Nourbakhsh M, Avan A, Shahidsales S, Ferns G. Role of regulatory miRNAs of the PI3K/AKT signaling pathway in the pathogenesis of breast cancer. Gene. 2020;737:144459. PubMed PMID: 32045660.
19. Lo S, Wang C, Chen Y, Huang C, Wu T, Li L, et al. Berberine Activates Aryl Hydrocarbon Receptor but Suppresses CYP1A1 Induction through miR-21-3p Stimulation in MCF-7 Breast Cancer Cells. Molecules. 2017;22:1847. PubMed PMID: 29143794
20. Lin C, Gao B, Yan X, Lei Z, Chen K, Li Y, et al. MicroRNA 628 suppresses migration and invasion of breast cancer stem cells through targeting SOS1. Onco Targets Ther. 2018;11:5419-28.
21. Zhang L, Du Y, Xu S, Jiang Y, Yuan C, Zhou L, et al. DEPDC1, negatively regulated by miR-26b, facilitates cell proliferation via the up-regulation of FOXM1 expression in TNBC. Cancer Lett. 2019;442:242-51.
22. Li J, Li X, Kong X, Luo Q, Zhang J, Fang L. MiRNA-26b inhibits cellular proliferation by targeting CDK8 in breast cancer. Int J Clin Exp Med. 2014;7:558-65.
23. Ma X, Dong W, Su Z, Zhao L, Miao Y, Li N, et al. Functional roles of sialylation in breast cancer progression through miR-26a/26b targeting ST8SIA4. Cell Death Dis. 2016;7:2561. PubMed PMID: 28032858
24. Yan G, Li Y, Zhan L. Decreased miR-124-3p promoted breast cancer proliferation and metastasis by targeting MGAT5. Am J Cancer Res. 2019;9:585-96.
25. Seo S, Moon Y, Choi J, Yoon S, Jung K, Cheon J, et al. The GTP binding activity of transglutaminase 2 promotes bone metastasis of breast cancer cells by downregulating microRNA-205. Am J Cancer Res. 2019; 9:597-607.
26. Lo T, Tsai W, Chen S. MicroRNA-21-3p, a berberine-induced miRNA, directly down-regulates human

methionine adenosyl transferases 2A and 2B and inhibits hepatoma cell growth. PLoS One. 2013;8:e75628. PubMed PMID: 24098708
27. Kwon J, Factora D, Dey S, Kota J. A systematic review of miR-29 in cancer. Mol Ther Oncolytics. 2019;12:73-194.
28. Wang W, Liu Y, Guo J, He H, Mi X, Chen C, Xie J, et al. miR-100 maintains phenotype of tumor-associated macrophages by targeting mTOR to promote tumor metastasis via Stat5a/IL-1ra pathway in mouse breast cancer. Oncogenesis. 2018;7:97. PubMed PMID: 30563983
29. Haghi M, Taha M, Javeri A. Suppressive effect of exogenous miR-16 and miR-34a on tumorigenesis of breast cancer cells. J Cell Biochem. 2019;120:13342-53.
30. Moes M, Le Béchec A, Crespo I, Laurini C, Halavatyi A, Vetter G, et al. A novel network integrating a miRNA-203/SNAI1 Feedback loop which regulates epithelial to mesenchymal transition. PLoS ONE. 2012;7: e35440. PubMed PMID: 22514743
31. Chi Y, Jin Q, Liu X, Xu L, He X, Shen Y, et al. MiR-203 inhibits cell proliferation, invasion, and migration of non-small-cell lung cancer by downregulating RGS17. Cancer Manag Res. 2017;108: 2366-72.
32. Li D, Wang J, Ma L, Yang H, Jing J, Jia M, et al. Identification of serum exosomal miR-148a as a novel prognostic biomarker for breast cancer. Eur Rev Med Pharmacol Sci. 2020;24:7303-9.
33. Muller V, Oliveira-Ferrer L, Steinbach B, Pantel K, Schwarzenbach H. Interplay of lncRNA H19/miR-675 and lncRNA NEAT1/miR-204 in breast cancer. Mol Oncol. 2019; 13:1137-1149. PMCID: PMC6487715
34. Kong Y, Yang L, Wei W, Lyu N, Zou Y, Gao G, et al. CircPLK1 sponges miR-296-5p to facilitate triple-negative breast cancer progression. Epigenomics. 2019;11:1163-76.
35. Li Y, Guo X, Wei Y. LncRNA SNHG7 inhibits proliferation and invasion of breast cancer cells by regulating miR-15a expression. J BUON. 2020;25:1792-8.
36. Zhu S, Wang X, Wang J, Xi G, Liu Y. Downregulation of miR-22 contributes to epithelial-Mesenchymal transition in osteosarcoma by targeting twist. Front Oncol. 2020;10:406. PubMed PMID: 32391253
37. Zhang Q, Liu S, Zhang J, Ma X, Dong M, Sun B, et al. Roles and regulatory mechanisms of miR-30b in cancer, cardiovascular disease, and metabolic disorders. Exp Ther Med. 2021;21:44. PubMed PMID: 33273973
38. Hui Z, Peng Y, Jian W, Yuqiang Z, Mingchao Z, Zaijun W, et al. Clinical significance of tumor miR-21, miR-221, miR-143, and miR-106a as biomarkers in patients with osteosarcoma. Int J Biol Markers. 2019;34:184-93.
39. Purohit P, Edwards R, Tokatlidis K, Saini N. MiR-195 regulates mitochondrial function by targeting mitofusin-2 in breast cancer cells. RNA Biol. 2019;16:918-29.
40. Li X, Wang Q, Rui Y, Zhang C, Wang W, Gu J, et al. HOXC13-AS promotes breast cancer cell growth through regulating miR-497-5p/PTEN axis. J Cell Physiol. 2019;234:22343-51.
41. Liu J, Mi B, Wang Y, Shi C, Mi X, Lu Y, et al. miR-26a suppresses osteosarcoma migration and invasion by directly targeting HMGA1. Oncol Lett. 2018;15:8303-10.
42. Alhasan L. MiR-126 Modulates Angiogenesis in Breast Cancer by Targeting VEGF-A mRNA. Asian Pac J Cancer Prev. 2019;20:193-7.
43. Shinden Y, Hirashima T, Nohata N, Toda H, Okada R, Asai S, et al. Molecular pathogenesis of breast cancer: impact of miR-99a-5p and miR-99a-3p regulation on oncogenic genes. J Hum Genet. 2021;66:519-34.
44. Bahmanpour Z, Sheervalilou R, Choupani J, Shekari Khaniani M, Montazeri V, Mansoori Derakhshan S. A new insight on serum microRNA expression as novel biomarkers in breast cancer patients. J Cell Physiol. 2019;234:19199-211.
45. Gharib A, Khalifa A, Eed E, Banjer H, Shami A, Askary A, et al. Role of MicroRNA-31 (miR-31) in Breast Carcinoma Diagnosis and Prognosis. In Vivo. 2022;36:1497-502.
46. Song X, Liang Y, Sang Y, Li Y, Zhang H, Chen B, et al. circHMCU promotes proliferation and metastasis of breast cancer by sponging the let-7 family. Mol Ther Nucleic Acids. 2020;20,518-33.
47. Wang H, Peng R, Wang J, Qin Z, Xue L. Circulating microRNAs as potential cancer biomarkers: the advantage and disadvantage. Clin Epigenetics. 2018;10:59. PubMed PMID: 2971339.
48. Li H, Liu J, Chen J, Wang H, Yang L, Chen F, et al. A serum microRNA signature predicts trastuzumab benefit in HER2-positive metastatic breast cancer Patients. Nat Commun. 2019;9:1614. PubMed PMID: 29691399.
49. Satomi-Tsushita N, Shimomura A, Matsuzaki J, Yamamoto Y, Kawauchi J, Takizawa S, et al. Serum microRNA-based prediction of responsiveness to eribulin in metastatic breast cancer. PLoS One. 2019;14:e0222024. PubMed PMID: 31483849.
50. Chen JW, Dhahbi J. Identification of four serum miRNAs as potential markers to screen for thirteen cancer types. PLoS One. 2022;17:e0269554. PubMed PMID: 35687572.
51. Li X, Tang X, Li K, Lu L. Evaluation of serum MicroRNAs (miR-9-5p, miR-17-5p, and miR-148a-3p) as Potential biomarkers of breast cancer. Biomed Res Int. 2022;2022:9961412. PubMed PMID: 35111850.
52. Guo J, Liu C, Wang W, Liu Y, He H, Chen C, et al. Identification of serum miR-1915-3p and miR-455-3p as biomarkers for breast cancer. PLoS One. 2018;13: e0200716. PubMed PMID: 30048472
53. Cai B, Guo S, Li Y. MoS 2-based sensor for the detection of miRNA in serum samples related to breast cancer. Analytical methods. 2018;10:230-6.
54. Cardinali B, Tasso R, Piccioli P, Ciferri MC, Quarto R, Del Mastro L. Circulating miRNAs in Breast Cancer Diagnosis and Prognosis. Cancers (Basel). 2022;14:2317. PubMed PMID: 35681895
55. Zhong H, Yang J, Zhang B, Wang X, Pei L, Zhang L, et al. LncRNA GACAT3 predicts poor prognosis and promotes cell proliferation in breast cancer through regulation of miR-497/CCND2. Cancer Biomark. 2018;22: 787-97.
56. Loke SY, Lee ASG. The future of blood-based biomarkers for the early detection of breast cancer. Eur J Cancer. 2018;92:54-68.
57. Huang S, Luo Q, Peng H, Li J, Zhao M, Wang J, et al. A

panel of serum noncoding RNAs for the diagnosis and monitoring of response to therapy in patients with breast cancer. Med Sci Monit. 2018;24:2476-88.
58. Hesari A, Azizian M, Darabi H, Nesaei A, Hosseini SA, Salarinia R, et al. Expression of circulating miR-17, miR-25, and miR-133 in breast cancer patients. J Cell Biochem. 2019;120:7109-114.
59. Luengo-Gil G, Gonzalez-Billalabeitia E, Perez-Henarejos SA, Navarro Manzano E, Chaves-Benito A, Garcia-Martinez E, et al. Angiogenic role of miR-20a in breast cancer. PLoS One. 2018;13:e0194638. PubMed PMID: 29617404
60. Mehrgou A, Akouchekian M. Therapeutic impacts of microRNAs in breast cancer by their roles in regulating processes involved in this disease. J Res Med Sci. 2017;22:130. PubMed PMID: 29387117
61. Yang C, Tabatabaei S, Ruan X, Hardy P. The dual regulatory role of MiR-181a in breast cancer. Cell Physiol Biochem. 2017;44:843-56.
62. Zhou W, Shi G, Zhang Q, Wu Q, Li B, Zhang Z. MicroRNA-20b promotes cell growth of breast cancer cells partly via targeting phosphatase and tensin homologue (PTEN). Cell Biosci. 2014;4:62. PubMed PMID: 25364498.
63. Chen Q, Yin D, Zhang Y, Yu L, Li XD, Zhou ZJ, et al. MicroRNA-29a induces loss of 5-hydroxymethylcytosine and promotes metastasis of hepatocellular carcinoma through a TET-SOCS1-MMP9 signaling axis. Cell Death Dis. 2017;8:e2906. PubMed PMID: 28661477
64. Mahmoudian M, Razmara E, Mahmud Hussen B, Simiyari M, Lotfizadeh N, Motaghed H, et al. Identification of a six-microRNA signature as a potential diagnostic biomarker in breast cancer tissues. J Clin Lab Anal. 2021;35:e24010. PubMed PMID: 34528314.
65. Sagar SK. miR-106b as an emerging therapeutic target in cancer. Genes Dis. 2021;9:889-899.
66. Hosseini Mojahed F, Aalami A, Pouresmaeil V, Amirabadi A, Qasemi Rad M, Sahebkar A. clinical evaluation of the diagnostic role of MicroRNA-155 in breast cancer. Int J Genomics. 2020;2020:9514831. PubMed PMID: 32964011
67. Jiang M, Zhang W, Zhang R, Liu P, Ye Y, Yu W, et al. Cancer exosome-derived miR-9 and miR-181a promote the development of early-stage MDSCs via interfering with SOCS3 and PIAS3 respectively in breast cancer. Oncogene. 2020;39:4681-94.
68. Maryam M, Naemi M, Hasani S. A comprehensive review on oncogenic miRNAs in breast cancer. J Genet. 2021;100:15. PubMed PMID: 33764337
69. Du Y, Wei N, Ma R, Jiang S, Song D. A miR-210-3p regulon that controls the Warburg effect by modulating HIF-1α and p53 activity in triple-negative breast cancer. Cell Death Dis. 2020;11:731. PubMed PMID: 32908121
70. Karami Fath M, Azargoonjahromi A, Kiani A, Jalalifar F, Osati P, Akbari Oryani M, et al. The role of epigenetic modifications in drug resistance and treatment of breast cancer. Cell Mol Biol Lett. 2022;27:52. PubMed PMID: 35764927
71. Li Y, Hu Q, Luoreng Z, Yang J, Wang X, Ma Y, et al. Differential mRNA expression profiling reveals the role of MiR-375 in inflammation of bovine mammary epithelial cells. Animals (Basel). 2022;12:1431. PubMed PMID: 35681895
72. Jia Y, Jia Y, Shi Y, Zhao W, Martin J, Wang X, et al. Integrative analysis of LncRNA-mRNA signature reveals a functional LincRNA in triple-negative breast cancer. Holistic Integrative Oncology. 2022;1:9.
73. Abdulhussain M, Hasan N, Hussain A. Interrelation of the Circulating and Tissue MicroRNA-21 with Tissue PDCD4 Expression and the Invasiveness of Iraqi Female Breast Tumors. Indian J Clin Biochem. 2019; 34:26-38.
74. Taha M, Mitwally N, Soliman A, Yousef E. Potential diagnostic and prognostic utility of miR-141, miR-181b1, and miR-23b in breast cancer. Int J Mol Sci. 2020;21:8589. PubMed PMID: 33202602
75. Zheng J, Huang Y, Yao L, Liu Y, Liu S, Hu X, et al. Elevated miR-301a expression indicates a poor prognosis for breast cancer patients. Sci Rep. 2018;8:2225. PubMed PMID: 29396508.
76. Sheedy P, Medarova Z. The fundamental role of miR-10b in metastatic cancer. Am J Cancer Res. 2018;8: 1674-1688.
77. Wei F, Cao C, Xu X, Wang J. Diverse functions of miR-373 in cancer. J Transl Med. 2015;13:162. PubMed PMID: 25990556
78. Cao M, Nie W, Li J, Zhang Y, Yan X, Guan X, et al. MicroRNA-495 induces breast cancer cell migration by targeting JAM-A. Protein Cell. 2014;5:862-72.
79. Petri B, Klinge C. Regulation of breast cancer metastasis signaling by miRNAs. Cancer Metastasis Rev. 2020;39:837-86.
80. Khafaei M, Rezaie E, Mohammadi A, Shahnazi Gerdehsang P, Ghavidel S, Kadkhoda S, et al. miR-9: From function to therapeutic potential in cancer. J Cell Physiol. 2019;234:14651-65.
81. Li N, Miao Y, Shan Y, Liu B, Li Y, Zhao L, et al. MiR-106b and miR-93 regulate cell progression by suppression of PTEN via PI3K/Akt pathway in breast cancer. Cell Death Dis. 2017;8:e2796. PubMed PMID: 28518139
82. Deng J, Xu Y, Wang G. Identification of potential crucial genes and key pathways in breast cancer using bioinformatic analysis. Front Genet. 2019;10:695. PubMed PMID: 31428132
83. Fontana A, Barbano R, Dama E, Pasculli B, Rendina M, Morritti M, et al. Combined analysis of miR-200 family and its significance for breast cancer. Sci Rep. 2021;11:2980. PubMed PMID: 33536459
84. Lettlova S, Brynychova V, Blecha J, Vrana D, Vondrusova M, Soucek P, et al. MiR-301a-3p suppresses estrogen signaling by directly inhibiting ESR1 in ERα positive breast cancer. Cell Physiol Biochem. 2018; 46: 2601-15.