

Advances in the study of the breast carcinoma exosomal microRNAs: From basic mechanisms to clinical applications (Review)

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Abstract. Breast carcinoma remains a major global health burden requiring innovative diagnostic and therapeutic strategies. Exosomal miRNAs have emerged as key factors in breast carcinoma that influence tumor progression, metastasis and treatment resistance. Recent studies have elucidated their mechanisms of action, including their roles in regulating oncogenic and tumor-suppressive pathways, modulating the tumor microenvironment and promoting chemo-resistance. Advances in miRNA-based therapies such as miRNA mimics and inhibitors have shown promise in combination treatments, enhancing their therapeutic efficacy. Furthermore, exosomal miRNAs play a role in breast carcinoma calcification, offering novel insights into tumor progression. Unlike previous reviews that focus on a single function or therapeutic potential of miRNAs, the present review systematically integrated the multilevel role of exosomal miRNAs in breast cancer from the two dimensions of oncogenicity and tumor inhibition and

the regulatory mechanism of breast carcinoma calcification and proposes that the exosomal miRNA calcification axis may be a key link connecting tumor metabolism and pathological calcification. Despite the potential of miRNAs, challenges remain in optimizing exosome isolation techniques and standardizing miRNA detection methods for clinical applications. Future research should focus on refining miRNA-based liquid biopsies, developing delivery systems that target exosomes to enhance therapeutic efficacy and early detection strategies and ultimately improving patient survival and quality of life. The present review comprehensively explored the roles of exosomal miRNAs and highlighted their importance in breast carcinoma research. The present review illustrated the potential of exosomal miRNAs as non-invasive biomarkers and therapeutic targets in precision medicine.

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1. Introduction

Breast carcinoma is a global health problem that affects women's quality of life. The World Health Organization estimates that there are >2.26 million new cases and >684,000 deaths worldwide each year (1). The incidence of breast carcinoma varies widely across populations and regions and is influenced by factors such as age, ethnicity and socioeconomic status (2). Despite advances in diagnostic imaging and biomarker research, limitations, such as the low sensitivity of dense breast tissue and variations in screening accessibility, hinder its early detection (3). Furthermore, treatment resistance and metastatic recurrence pose major challenges,

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Abbreviations: miRNAs, microRNAs; TME, tumor microenvironment; ESCRT, endosomal sorting complexes required for transport; MVBs, multivesicular bodies; ILVs, intraluminal vesicles; pre-miRNAs, precursor miRNAs; pri-miRNAs, primary miRNAs; SYNCRIP, synaptotagmin-binding cytoplasmic RNA-interacting protein; TNBC, triple-negative breast carcinoma; ER, estrogen receptor; DOX, doxorubicin

Key words: breast carcinoma, exosomal miRNAs, biomarker, calcification, combination therapy

emphasizing the need for new diagnostic and therapeutic strategies. In this context, exosomal microRNAs (miRNAs) have emerged as critical regulators of breast carcinoma progression, with potential applications in early diagnosis, prognosis and targeted therapy (4,5).

Previous studies have shown that exosomes are small extracellular vesicles secreted by cells that play a key role in intercellular communication by transporting biologically active molecules including proteins, lipids and nucleic acids (6,7). Among them, miRNAs, short non-coding RNA involved in post-transcriptional gene regulation, have been identified as key mediators of tumor growth, metastasis and therapy resistance (8). There is growing evidence that exosomal miRNAs secreted by breast cancer cells act as oncogenes that promote malignant tumor behavior by inhibiting tumor suppressor genes or activating pro-tumor signaling pathways. For example, miR-221/222 can mediate endocrine therapy resistance (9) and high expression of miR-10b is closely associated with distant metastasis in breast cancer (10). The secretion and uptake of these exosomal miRNAs are highly specific and can reshape the tumor microenvironment and drive disease progression. Furthermore, their presence in biological fluids and disease-specific expression patterns make exosomal miRNAs promising non-invasive biomarkers for breast carcinoma (11).

Building on previous findings, recent studies have explored the mechanistic roles of exosomal miRNAs in modulating the tumor microenvironment (TME), facilitating drug resistance and promoting calcification in breast carcinoma. Moreover, the integration of nanotechnology and exosome-based drug delivery systems, such as synthetic miRNA mimics and inhibitors, has opened new avenues for miRNA-targeted therapies. These emerging insights bridge the gap between basic research and clinical applications, bringing exosomal miRNAs closer to becoming practical oncology tools. The aim of the present review was to provide a comprehensive overview of the role of exosomal miRNAs in breast carcinoma, summarize past studies, highlight recent advances and assess their potential in precision medicine. By exploring their diagnostic, prognostic and therapeutic applications, this study contributes to the development of novel strategies to improve breast carcinoma management and patient prognosis.

2. Breast carcinoma

Causes of breast carcinoma. A variety of risk factors associated with breast carcinoma development have been identified. Germline pathogenic variants in the *BRCA1* and *BRCA2* genes confer a markedly elevated risk of breast carcinoma development (12). Endogenous hormonal factors, particularly elevated estrogen and progesterone levels or prolonged exposure to these hormones through early menarche (<12 years), late menopause (>55 years), nulliparity, or advanced maternal age at first childbirth (>30 years), have been mechanistically linked to oncogenesis (13). In addition, lifestyle factors, including physical inactivity, obesity (body mass index ≥ 30 kg/m²), smoking and excessive alcohol consumption (>three drinks/day), have been linked to an increased risk of breast carcinoma development (14). Furthermore, environmental factors, including ionizing radiation and exposure to certain chemicals, are associated with the development of breast carcinoma (15).

Current issues in early diagnosis of breast carcinoma. The primary diagnostic modalities for the early detection of breast carcinoma include histopathological analysis, radiographic imaging and molecular biomarker assays. Conventional mammography demonstrates limited sensitivity (58-72%) in dense breast tissue (Breast Imaging Reporting and Data System density category C/D) (16), leading to false-negative result interpretations and diagnostic delays. Radiographically dense parenchyma, characterized by >50% fibroglandular tissue composition, not only obscures tumor visualization but also demonstrates an independent correlation with 2-6-fold increased breast carcinoma risk through stromal-epithelial interactions (17). While population-based screening programs have reduced mortality rates by 15-40%, they incur substantial healthcare expenditures and induce screening-related anxiety (18). Moreover, equitable implementation remains challenging in low-resource settings due to infrastructure limitations and trained personnel shortages, compounded by heterogeneous international guidelines. Therefore, current early diagnostic technologies for breast cancer are limited by imaging sensitivity and the stability of molecular markers. Future diagnostic strategies should be a combination of imaging and liquid biopsy models, in which exosomal miRNAs are expected to be a key bridge between the two.

3. Exosomes

The concept of exosomes. Exosomes are a class of small membranous vesicles secreted by cells, usually 30-150 nm in diameter and belong to a subgroup of extracellular vesicles. They are found in various body fluids, including blood, saliva and urine and are secreted by a wide range of cell types (19). Proteomic profiling has revealed the complexity of the exosomal cargo, including thousands of proteins, various miRNAs and lipids. The protein composition of exosomes varies depending on their cellular origin and includes cytoplasmic enzymes, fusion proteins, membrane transporter proteins, molecular chaperones and structural proteins (20). The main function of exosomes is to mediate intercellular communication and influence the function of recipient cells. In breast carcinoma, exosomes have been shown to be involved in tumor progression, metastasis and immune evasion.

Exosome formation. Studies have revealed several key mechanisms underlying exosome formation, including endosomal sorting complexes required for transport (ESCRT)-dependent and ESCRT-independent pathways, the role of quadruple transmembrane proteins and the formation of atypical exosomes (21,22). Fig. 1 illustrates the process of exosome formation.

ESCRT-dependent pathway. Exosome formation primarily relies on the ESCRT mechanism. This process begins with early endosomes, which are formed through the endocytosis of the plasma membrane. As the endosomes mature into multivesicular bodies (MVBs), their membrane folds inwards to form intraluminal vesicles (ILVs). These ILVs become exosomes when MVBs fuse with the plasma membrane and are released into the extracellular space (23).

ESCRT-independent pathway. Exosomes are rich in cholesterol, phosphatidylcholine, phosphatidylserine and other lipids that are not only involved in exosome biosynthesis, but

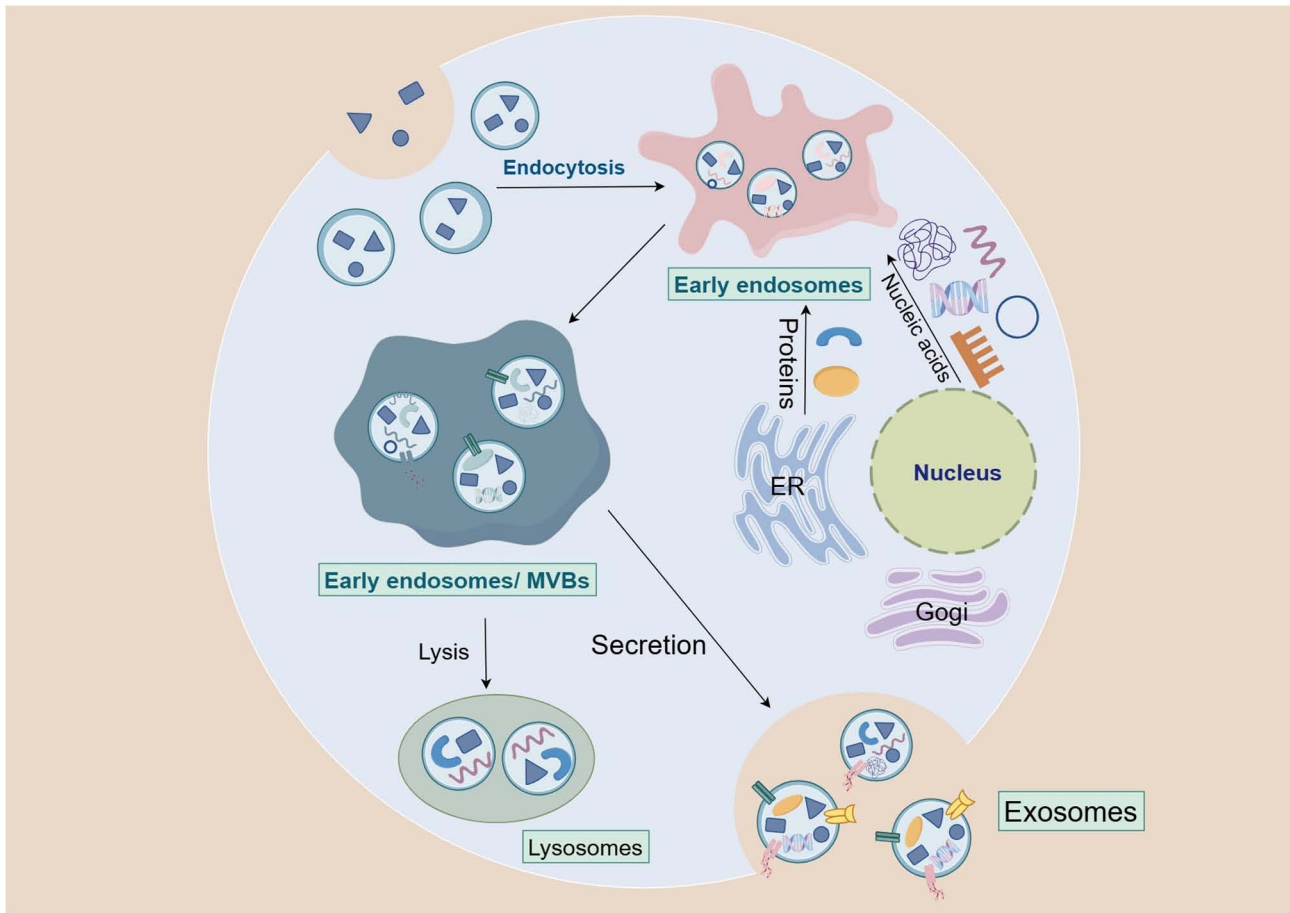


Figure 1. The formation process of exosomes. Cells uptake extracellular substances such as nucleic acids and proteins through endocytosis to form early endosomes and the endoplasmic reticulum provides material support for them. The early endosomes further evolve into multivesicular bodies. Subsequently, some of them fuse with lysosomes and undergo lysis and their contents are degraded; the other part releases exosomes into the extracellular environment through secretion. Exosomes play a crucial role in intercellular communication and are responsible for transmitting biomolecules. This figure was created using Figdraw (www.figdraw.com; Figure ID: TOO1W8c233).

also affect their uptake and function (24). Intracellular cholesterol levels regulate exosome release through the PI3K/AKT signaling pathway: elevated intracellular cholesterol inhibits this pathway, resulting in decreased exosome release, whereas decreased intracellular cholesterol activates this pathway and increases exosome release (25). Additionally, neutral sphingomyelinase 2 promotes ILV and exosome formation by converting sphingomyelin into sphingosine. Moreover, the autophagy-related protein LC3 promotes sphingosine-mediated ILV formation by recruiting the nSMase activator onto endosomal membranes (26).

Role of tetraspanins in exosome formation. Tetraspanins, such as CD9, CD63 and CD81 not only play crucial roles in endosomal membrane invagination and ILV formation but also influence exosome stabilization and facilitate cell-cell communication (27). In terms of cargo sorting, tetraspanins can recognize and bind to specific proteins and nucleic acids and regulate the cargo loading of exosomes (28).

Formation of atypical exosomes. Studies have revealed some mechanisms underlying atypical exosome formation. For instance, certain cell types can generate exosomes via the Golgi pathway or calcium-dependent secretory autophagy (29). In addition, some viruses can hijack the exosome formation mechanism of host cells for their propagation (30).

Exosomal miRNAs

Definition of exosomal miRNAs. Exosomal miRNAs are a class of small non-coding RNAs that are usually 18-22 nucleotides in length and are encapsulated in exosomes. These miRNAs are involved in the post-transcriptional regulation of gene expression by binding to complementary sequences on target mRNAs, leading to miRNA degradation or translational repression (31,32). Exosomal miRNAs are selectively packaged into exosomes, which allows them to be protected from degradation by RNases and transported over long distances through body fluids, such as blood, urine and milk (19). This intercellular communication mechanism is critical for various physiological and pathological processes including cancer progression, immune regulation and tissue homeostasis (33). This property makes exosomal miRNAs potential biomarkers for disease diagnosis and prognosis as well as possible targets for the treatment of cancers, including breast carcinoma.

Mechanisms of exosomal miRNA biosynthesis. Exosomal miRNA biosynthesis is a multi-step process that involves the transcription, processing and selective packaging of miRNAs into exosomes. Studies have shown that precursor miRNAs (pre-miRNAs) associated with processing complexes such as Dicer, Argonaute 2 and TAR RNA-binding protein can be detected in exosomes derived from breast carcinoma

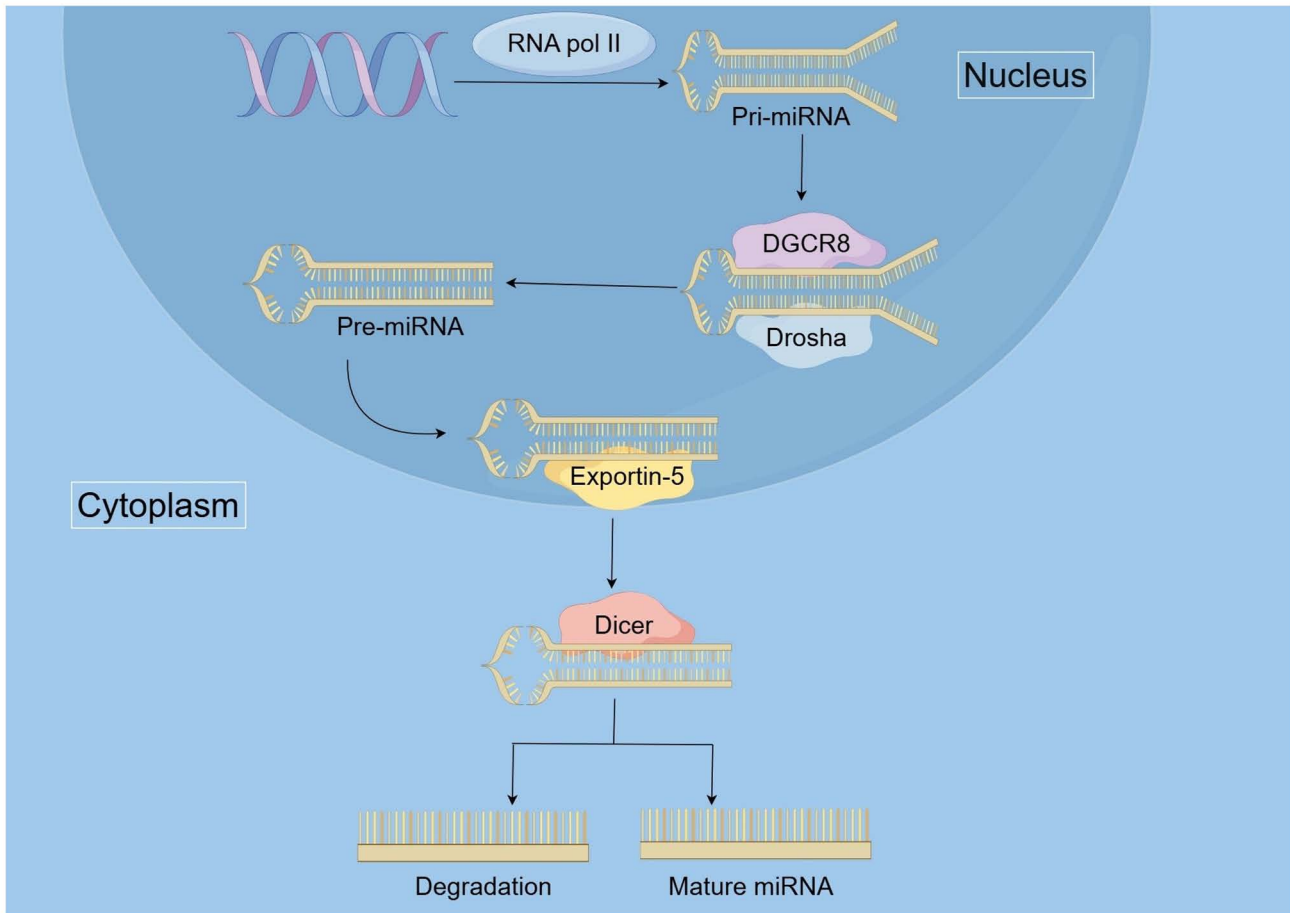


Figure 2. The biosynthesis of miRNA. First, DNA is transcribed by RNA polymerase II to produce a primary miRNA. Subsequently, the primary miRNA in the nucleus is cleaved by a complex composed of Drosha and DGCR8 to form pre-miRNA. Then, the pre-miRNA is transported to the cytoplasm via Exportin-5. Finally, the Pre-miRNA is cleaved again by the Dicer enzyme in the cytoplasm to generate mature miRNA, while the other strand is degraded. Ultimately, the mature miRNA participates in the regulation of gene expression. This figure was created using Figdraw (www.figdraw.com; Figure ID: YSRAU454c4). miRNA, microRNA.

cells. These pre-miRNAs are further processed into mature miRNAs within exosomes, thereby establishing a new mechanism for the integration of miRNAs into exosomes (34). Typically, miRNA biosynthesis begins in the nucleus, where miRNA genes are transcribed by RNA polymerase II to produce primary miRNAs (pri-miRNAs). These pri-miRNAs are then processed by the Drosha-DGCR-8 complex into pre-miRNAs, which is a critical step in the miRNA maturation process (35). The pre-miRNAs are transported from the nucleus to the cytoplasm via Exportin-5, a transport protein that facilitates the movement of pre-miRNAs across the nuclear envelope. In the cytoplasm, Dicer enzymes further process the pre-miRNAs into mature miRNA duplexes (36). This step is essential for the functionalization of miRNAs so that they can be integrated into exosomes. Fig. 2 depicts miRNA biosynthesis.

Several mechanisms have been proposed to explain how specific miRNAs are categorized into exosomes. One of the key mechanisms involves the recognition of exosomal miRNA sequences or motifs by RNA-binding proteins such as hnRNPA2B1, Y-box-binding protein 1 and synaptotagmin-binding cytoplasmic RNA-interacting protein (SYNCRIP). SYNCRIP is involved in the exosomal partitioning of miRNAs by recognizing specific sequences such

as the hEXO motif, which enhances miRNA loading into exosomes. This process is crucial for cell-cell communication and is regulated by the NURR domain of SYNCRIP, which binds to miRNA targets with high affinity (37,38). hnRNPA2B1 binds to specific sequence motifs in miRNAs, thereby controlling their loading into exosomes. Its binding activity is influenced by SUMOylation and alterations in either the motif or hnRNPA2B1 expression levels can modulate the efficiency of miRNA sorting. Notably, hnRNPA2B1 is essential for the selective sorting of miRNAs, such as miR-486a-5p, which has cardioprotective effects (39,40). YBX 1 also facilitates the sorting of miRNAs (such as miR-223) into exosomes by binding to specific sequence motifs. It shuttles between different cellular compartments, suggesting its dynamic role in miRNA sorting and exosome formation (41). In addition, the ESCRT machinery and associated proteins such as ALIX and TSG101 play key roles in exosome biosynthesis and miRNA integration. The ESCRT machinery and related proteins, such as ALIX and TSG101, promote the budding of ILVs into MVBs. miRNAs are selectively sorted into ILVs during this process, which is followed by the formation of MVBs. When MVBs fuse to the cell membrane, ILVs are released as an exosome (42,43).

Table I. Pro-tumorigenic miRNAs in breast carcinoma.

miRNA	Target gene/pathway	Function	Clinical association	(Refs.)
miR-21	PTEN, PDCD4	Anti-apoptosis, chemoresistance	Prognostic marker (Stage III/IV)	(48,49)
miR-155	SOCS1, MMP16	Immune suppression	Predicts immunotherapy resistance	(50,51)
miR-10b	HOXD10	Metastasis	Biomarker for lymph node invasion	(10)
miR-9	CDH1 (E-cadherin)	Induce EMT and promote metastasis	High expression is associated with lung metastases	(52,53)
miR-27a	CTH, xCT	Autophagy pathway	Serum miR-27a levels predict chemotherapy resistance	(54)
miR-221/222	p27, PTEN	Promote cell cycle progression and inhibit apoptosis	Associated with resistance to trastuzumab in HER2+ breast carcinoma	(9)
miR-520b	LATS2 (Hippo pathway inhibitors)	Activates Hippo/YAP signaling	promotes the stemness of breast carcinoma	(55)
miR-182	FOXO1, BRCA1	Promotes proliferation, DNA repair defects	Associated with relapse and chemoresistance	(56,57)
miR-301a	PTEN, SMAD4	Activates Wnt/ β -catenin and TGF- β pathway	associated with reduced overall survival in patients with TNBC	(58,59)
miR-125b	Bak1, ETS1	Suppresses apoptosis, promotes survival	Associated with chemoresistance, recurrence and poor prognosis	(60)

miRNA, microRNA; EMT, epithelial-mesenchymal transition; TNBC, triple-negative breast carcinoma; HER2, Human Epidermal Growth Factor Receptor 2.

Studies have also highlighted the role of post-transcriptional modifications, such as uridylation and adenylation, in the sorting of miRNAs into exosomes. For example, the addition of uridine residues to the 3' terminus of miRNAs enhances their incorporation into the exosomes (44). Furthermore, the lipid composition of the exosomal membrane, particularly in the presence of ceramide, has been implicated in the sorting process (45). Once packaged into exosomes, miRNAs are protected from degradation by RNases and can be transported to recipient cells via circulation or other body fluids. After uptake by recipient cells, exosomal miRNAs regulate gene expression and influence various cellular processes, including proliferation, apoptosis and metastasis, thus playing an important role in breast carcinoma progression and therapy resistance (46).

4. Mechanism of miRNA action in breast carcinoma

miRNAs that promote breast carcinoma development. A variety of miRNAs have been identified as key factors in the development and progression of breast carcinoma. These oncogenic miRNAs exert their oncogenic effects through a variety of mechanisms, including the repression of tumor suppressor genes, activation of pro-tumor signaling pathways and promotion of epithelial-mesenchymal transition (47). High expression of oncogenic miRNAs is associated with poor prognosis and advanced disease stage, highlighting their potential as therapeutic targets and diagnostic biomarkers for breast carcinoma. Table I lists miRNAs that contribute to breast carcinoma development and progression (9,10,48-60).

miRNAs that inhibit breast carcinoma development and progression. Table II (61-92) summarizes the miRNAs that inhibit breast carcinoma development and progression by targeting oncogenes, regulating cell cycle progression and promoting apoptosis. Their low expression in breast carcinoma tissues suggests that restoring their expression may be a promising strategy for cancer therapy. Further investigation of the mechanisms by which they exert their cancer inhibitory effects may provide valuable insights into the development of new therapies (93).

Role of miRNA in calcification. Calcification, particularly microcalcification, is a common radiological feature observed in mammographic imaging of breast carcinoma. Calcifications are generally categorized into two types: Macrocalcifications and microcalcifications. Macrocalcifications are larger, coarser calcium deposits that are typically benign and often related to aging, inflammation, or past injuries. Radiologically, microcalcifications appear as fine, granular specks, while macrocalcifications present as larger, often round or irregular, dense opacities. Microcalcifications are predominantly composed of hydroxyapatite, consisting of small calcium phosphate deposits within the breast tissue and are often associated with malignant lesions (94). Their chemical composition, particularly the carbonate content and protein-matrix ratio, correlates with the grading of pathological breast carcinoma and may serve as a diagnostic and prognostic indicator (95). These calcifications are thought to originate from cellular debris, necrosis, or active mineralization processes mediated by tumor cells and the TME.

Table II. Tumor-suppressive miRNAs in breast carcinoma.

miRNA	Target gene/pathway	Function	Clinical association	(Refs.)
miR-519d	MMP3, STAT3, Ki-67	Inhibits tumorigenesis and metastasis	Associated with poor prognosis for breast carcinoma	(61-63)
miR-328-3p	Ki-67, HMGA2	Inhibits proliferation, migration and invasion	Associated with poor prognosis for breast carcinoma	(63,64)
miR-34a	SIRT1, BCL2	Induces apoptosis and arrests the cell cycle	Associated with drug resistance in breast carcinoma	(65-67)
miR-200c	KRAS, ZEB1,	Anti-EMT	Predicts recurrence risk	(68,69)
miR-7	EGFR, MRP1	Inhibits EGFR signaling and focal adherens kinase activity	Restoration of miR-7 enhances paclitaxel sensitivity	(70,71)
miR-16-5p	ANLN, TP53	Induces apoptosis and arrests the cell cycle	Associated with poor prognosis in patients with TNBC	(72,73)
miR-125b	HER2, MUC1	Inhibition of HER2+ breast carcinoma growth	Low expression is associated with trastuzumab resistance	(74,75)
miR-145	STIM1	Inhibits angiogenesis	Associated with poor prognosis in patients with metastatic breast carcinoma	(76,77)
miR-195	SEMA6D, IRS1	Inhibits tumor growth	Modulates chemotherapy response	(78,79)
miR-206	Cdc42, EVI-1	Enhances chemotherapy sensitivity	Associated with a malignant phenotype of breast carcinoma stem cells	(80-82)
miR-497	PI3K-AKT, Mucin1, Slug	Inhibits proliferation, migration, EMT	Associated with tamoxifen resistance	(83,84)
miR-205	HER3, CLDN11, MED1	Inhibits EMT and drug resistance	Enhances trastuzumab sensitivity	(85-87)
miR-204-5p	TGFBR2, AKT, PI3K	Impairs cell proliferation and inhibits tumor progression	Altering the immune microenvironment of breast carcinoma	(88-90)
miR-489	SUZ-12, MDC-1, ULK1, LAPTM4B	Regulates epigenetics and inhibits autophagy	The most proliferative in TNBC cells	(91,92)

miRNA, microRNA; EMT, epithelial-mesenchymal transition; EGFR, epidermal growth factor receptor; HER2, Human Epidermal Growth Factor Receptor 2; TNBC, triple-negative breast carcinoma.

Exosomal miRNAs have been increasingly recognized as important regulators of tumor progression and the TME. Although there have been few direct studies on the relationship between exosomal miRNAs and breast carcinoma calcification in existing literature, the following potential mechanisms can be hypothesized based on their known biological functions and associated signaling pathways.

Promoting calcium salt deposition by regulating tumor cell death and necrosis. miR-1246 (96,97) is highly expressed in breast carcinoma cells (such as MDA-MB-231) and promotes cell proliferation and chemoresistance by inhibiting cyclin-G2. Under hypoxic conditions, tumor cells may undergo hyperproliferation and release calcium and phosphate ions, thereby contributing to the formation of microcalcifications. Similarly, miR-373 (98) is markedly enriched in the serum exosomes of patients with triple-negative breast carcinoma (TNBC) and its overexpression inhibits estrogen receptor (ER) expression and reduces apoptosis. ER-negative tumors are more susceptible to

calcification, which may be associated with abnormal cellular metabolism and calcium efflux.

Mediating extracellular matrix remodeling and calcified microenvironment formation. The miR-200 family (99,100) is enriched in exosomes derived from metastatic breast carcinoma and promotes the maintenance of an epithelial phenotype by inhibiting ZEB2 and upregulating E-cadherin. Reversal of the epidermal-mesenchymal transition may be accompanied by aberrant deposition of extracellular mesenchymal components such as type IV collagen, which promotes calcification. Additionally, miR-92b (101) enhances tumor cell invasiveness by targeting MTSS1L, an actin-binding protein. Alterations in the mechanical properties of the extracellular matrix induced by such cytoskeletal remodeling may accelerate the nucleation and crystallization of calcium salts.

Immunosuppressive microenvironment and inflammation induced calcification. miR-155-5p and miR-29a-3p (102) are carried by tumor-associated macrophage-secreted

exosomes that inhibit CD8⁺ T cell cytotoxicity and upregulate programmed cell death receptor-1 (PD-L1) expression. During chronic inflammation, the cytokines released by macrophages may activate fibroblasts and promote stromal calcification. miR-9 and miR-155 (99) induce metastatic breast carcinoma cells (such as MDA-MB-231) to be delivered to low metastatic cells (such as MCF-7) via exosomes, activate the nuclear factor- κ B pathway, promote release of inflammatory factors and indirectly drive calcification.

Regulation of metabolic reprogramming and calcium homeostasis. Downregulation of miR-30b has been observed in recurrent breast carcinoma, whereas overexpression of its target gene, *CCNE2*, may influence calcium channel activity through the PI3K/AKT signaling pathway (99). Disruption of calcium homeostasis via this mechanism may contribute to the formation of microcalcifications. Additionally, miR-16 (103) exhibits antiangiogenic properties by inhibiting the expression of vascular endothelial growth factor. Impaired angiogenesis may result in localized hypoxia, which activates hypoxia-inducible factors that subsequently upregulate the expression of calcium-binding proteins.

Promoting osteogenic differentiation and ectopic calcification. miR-21 (97) is highly expressed in plasma-derived exosomes from patients with breast carcinoma and targets PTEN, leading to activation of the PI3K/AKT/mTOR pathway. This pathway induces the expression of osteogenesis-related genes, thereby contributing to ectopic calcification. By contrast, miR-34a (103) reduces the stem cell properties of breast carcinoma cells by inhibiting NOTCH1 expression. Inhibition of the NOTCH signaling pathway may dysregulate osteogenic differentiation and promote calcium salt deposition. Together, these multi-layered regulations reveal that exosomal miRNAs form a systematic miRNA calcification interaction network by affecting cell death, matrix remodeling, immune inflammation and osteogenic signaling. This network is the biological basis of the proposed exosomal miRNA calcification axis to explain the relationship between tumor microenvironment changes and calcification formation and at the same time provide a new theoretical framework for understanding the molecular mechanism of breast cancer calcification.

5. Multiple applications of miRNAs in breast carcinoma (Fig. 3)

Therapeutics

miRNA mimics and inhibitors. Recent dual strategy advances in miRNA-based therapeutics have emphasized the use of synthetic miRNA mimics to restore tumor suppressor miRNAs. For example, the use of miRNAs from the let-7 family (104) and anti-miRNA oligonucleotides to inhibit oncogenic miRNAs such as miR-21 (105) and miR-155 (106). A phase I clinical trial demonstrated that MRX34, a liposomal miRNA-34a mimic, exhibited antitumor activity in metastatic breast carcinoma by targeting the PD-L1 and MET pathways, although challenges in delivery efficiency remain (107,108). Novel nanoparticle-based delivery systems such as exosome-like vesicles can be effective in improving the stability and tumor targeting of miRNA analogs in TNBC models (109). By contrast, anti-miRNA inhibitors such as anti-miR-21 and anti-miR-155 oligonucleotides inhibit

oncogenic miRNAs. Preclinical studies have shown that anti-miR-155 acts synergistically with immune checkpoint inhibitors to reprogram the TME, reduce immunosuppressive myeloid cell infiltration and enhance T cell responses in metastatic models (110).

Combination therapy. The synergistic effects of miRNA therapeutics with conventional therapies have gained increasing attention. Hyaluronic acid-based nanocarriers can target CD44-overexpressing TNBC cells and efficiently co-deliver doxorubicin (DOX) and miR-542-3p. This system provides an effective strategy for reversing TNBC resistance by enhancing intracellular drug accumulation, upregulating the expression of the p53 tumor suppressor protein, directly downregulating the apoptosis inhibitory protein survivin, overcoming chemotherapy resistance through multiple pathways and markedly inducing synergistic apoptosis *in vitro* (111). Functional exosome-mediated co-delivery system of DOX and hm-miR159 provides a promising and innovative combination therapy to address the challenge of TNBC chemoresistance (112). Furthermore, emerging strategies that combine miRNA inhibitors with immune checkpoint inhibitors can reprogram the TME in metastatic breast carcinoma, thus offering a potentially powerful avenue for enhancing immunotherapeutic efficacy (113).

Recent progress in the targeted delivery of therapeutic miRNAs has greatly advanced their therapeutic potential. In terms of carrier design, lipid nanoparticles and exosome-mimetic vesicles have emerged as prominent platforms for enhancing the stability, bioavailability and tumor-targeting capability of therapeutic miRNAs. For instance, Ohno *et al* (114) engineered exosomes derived from HEK293 cells by displaying the *GE11* peptide via a Lamp2b fusion protein on their surface, constructing engineered exosomes that specifically recognize EGFR. These exosomes efficiently delivered miRNAs to EGFR-positive breast tumors *in vivo* and markedly suppressed tumor growth. Similarly, RGD-modified exosomes, which target $\alpha v \beta 3$ integrin, have been used to co-deliver miR-34a to TNBC. This approach not only directly induces tumor cell apoptosis but also remodels the immunosuppressive microenvironment by downregulating PD-L1, thereby enhancing CD8⁺ T cell infiltration (115,116). Although several miRNA formulations have entered early phase clinical trials, challenges remain regarding delivery efficiency, immune tolerance and large-scale production. Continued optimization of targeted delivery systems is therefore crucial for the successful clinical translation of miRNA-based therapeutics.

Early diagnosis. Exosomes carry various biomarkers associated with breast carcinoma, such as carcinoembryonic antigen and carbohydrate antigen 125, which have potent therapeutic diagnostic properties (117). A systematic review conducted up to March 2023 analyzed 46 articles and found that exosomal miRNAs were markedly associated with the clinicopathological features of breast carcinoma (118). The present review emphasized that exosomal miRNAs such as miR-16, miR-21 and miR-155, have been analyzed in at least three studies and are suitable for selection as potential biomarkers. These miRNAs could provide information regarding early diagnosis, disease progression, recurrence, treatment response and metastasis. Analyzing exosomal miRNAs in blood samples is a simple and noninvasive method that is important for the early detection of

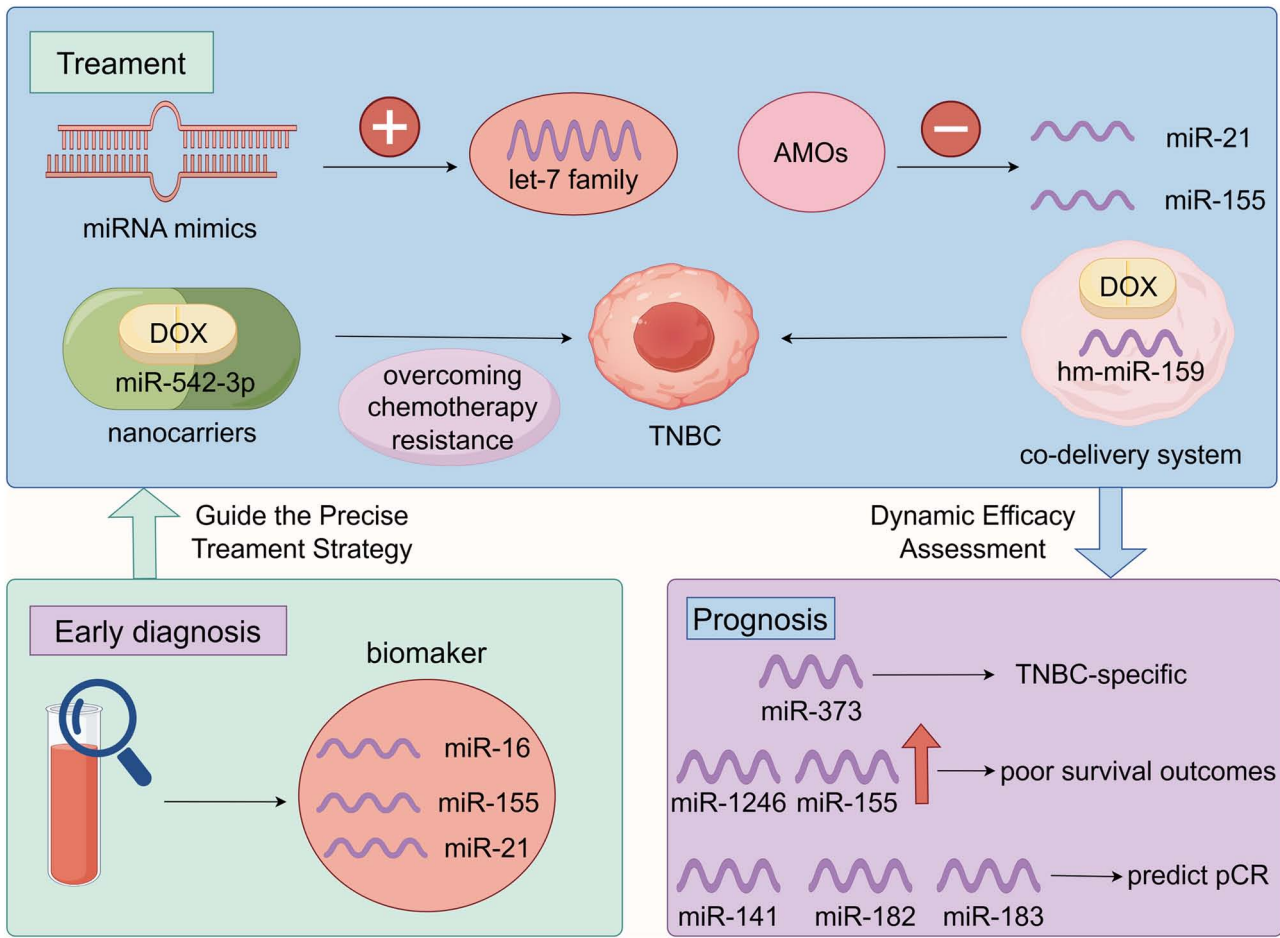


Figure 3. Multiple applications of miRNAs in breast carcinoma. First, in terms of treatment, miRNA mimics can be used to restore tumor-suppressive miRNAs such as the let-7 family and AMOs can also be used to inhibit oncogenes. Hyaluronic acid-based nanocarriers can target CD44-overexpressing TNBC cells and efficiently co-deliver doxorubicin (DOX) and miR-542-3p. This system provided an effective strategy for reversing TNBC resistance. At the same time, the functional exosome-mediated co-delivery system of DOX and hm-miR159 also provides a solution for overcoming chemotherapy resistance in TNBC. Secondly, early diagnosis of breast carcinoma can be made by using detection biomarkers such as miR-16, miR-155 and miR-21. Finally, in terms of prognosis, miR-373 is a specific biomarker for TNBC. High expression of miR-1246 and miR-155 was associated with poor survival outcomes. Dynamic monitoring of miR-141, miR-182 and miR-183 can predict pathologic complete response. This figure was created using Figdraw (www.figdraw.com; Figure ID: YAIUO55ccc). miRNA, microRNA; AMOs, anti-miRNA oligonucleotides; TNBC, triple-negative breast carcinoma; DOX, doxorubicin.

breast carcinoma (118). A study published in 2024 explored the advancement of serum exosomal miR-21 as a molecular diagnostic marker for breast carcinoma and its efficacy was assessed for the early detection and clinical diagnosis of breast carcinoma (119). However, its application in early diagnosis presents several challenges. The primary bottleneck is that the identification technology itself is complex, time-consuming and expensive. In addition, its diagnostic specificity must be improved to accurately differentiate breast cancer from other malignancies. Finally, whether serum or plasma should be preferred for cancer detection using exosomal miRNAs needs to be studied further.

Prognosis. Exosomal miRNAs have been recognized as important biomarkers for the prognostic assessment of breast carcinoma because of their high stability and specificity. For example, miRNA-373 is a specific biomarker for TNBC and its expression level correlates with the degree of malignancy and prognosis of breast carcinoma (120). Similarly, the expression levels of miR-1246 and miR-155 are markedly elevated in drug-resistant breast carcinoma cells compared to

drug-sensitive cells and this differential expression has been associated with poor progression-free survival and overall survival in patients (121). Additionally, dynamic monitoring of exosomal miRNAs (such as miR-141, miR-182 and miR-183) during neoadjuvant therapy can predict pathologic complete response, thereby enabling more informed and personalized treatment decisions (122).

6. Concluding remarks and perspectives

Breast carcinoma remains an enormous global health challenge that requires the continuous exploration of novel diagnostic and therapeutic strategies. Exosomal miRNAs have emerged as pivotal regulators of breast carcinoma pathogenesis, providing valuable insights into tumor progression, metastasis and therapy resistance. The present study reviewed the role of exosomal miRNAs in breast carcinoma, highlighting their dual functions as oncogenic drivers and tumor suppressors, as well as their utility as diagnostic biomarkers and therapeutic potential. In the present review, the dual oncogenic and inhibitory roles of exosomal miRNAs

were described, focusing on their multilevel regulatory mechanisms in TME, drug tolerance and pathological calcification. Based on the analysis of relevant literature, the present review proposed a conceptual model of exosomal miRNA calcification axis, which suggests that exosomal miRNAs may play a bridging role in breast cancer calcification and progression by regulating cell metabolism, immune inflammatory response and osteogenic signaling pathways. However, there are several challenges and opportunities in translating these findings into clinical practice. For example, there is no perfect methodology for the extraction and purification of exosomal RNAs. The differences in miRNA expression levels between studies may be related to the heterogeneity of sample sources, analytical methodologies and patient populations. Further studies are needed to fully elucidate the role of exosomal miRNAs in breast carcinoma calcification. The combination of advanced imaging techniques, such as high-resolution mammography and molecular imaging, as well as exosomal miRNA analysis, may provide new insights into the mechanisms of calcification and its clinical significance. Additionally, the development of exosomal miRNA-based therapeutics may provide new avenues for the prevention and treatment of breast carcinoma calcification. Overall, the present review provided a systematic framework for the study of exosomal miRNAs in breast cancer and demonstrates their potential value in pathological calcification, precise diagnosis and treatment. In the future, with technological progress and multidisciplinary research, exosomal miRNAs are expected to become an important breakthrough in understanding the complex biology of breast cancer and achieving personalized treatment.

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Authors' contributions

ZMC was responsible for research conceptualization, original draft preparation and reviewing the entire manuscript. PH conducted supplementary analysis, responded to reviewers' comments and updated and integrated relevant literature during the revision. DYY performed calibration of the full text, organized the logical flow and improved the language. SL contributed to the conception and design of the study, participated in developing the manuscript framework, critically revised the manuscript for important intellectual content and provided final approval of the version to be published. SQC guided and oversaw the entire research process, supervised the completion of the present review and provided final approval of the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, DeepSeek was used to provide suggestions for the logical organization and language polishing of some paragraphs and ChatGPT was utilized to assist in optimizing sentence expressions and enhancing text fluency. Using these tools, the content was reviewed sentence by sentence. The accuracy of the professional concepts was verified and the expressions generated by the AI were adjusted to conform to the research and the writing style of the authors. The originality and scientific nature of the content were ensured and full responsibility for the content of the publication was assumed by the authors.

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