

# The Emerging Roles of Exosomal miRNAs in Breast Cancer Progression and Potential Clinical Applications

Jie Li<sup>1,\*</sup>, Dejiao He<sup>2,\*</sup>, Yajun Bi<sup>3,\*</sup>, Shengxuan Liu<sup>4</sup>

<sup>1</sup>Department of Thyroid and Breast Surgery, Shenzhen Qianhai Shekou Free Trade Zone Hospital, Shenzhen, 518067, People's Republic of China; <sup>2</sup>Department of Nephrology, Renmin Hospital of Wuhan University, Wuhan, 430060, People's Republic of China; <sup>3</sup>Department of Pediatrics, Dalian Municipal Women and Children's Medical Center (Group), Dalian Medical University, Dalian, Liaoning Province, 116011, People's Republic of China; <sup>4</sup>Department of Pediatrics, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei Province, 430030, People's Republic of China

\*These authors contributed equally to this work

Correspondence: Shengxuan Liu, Department of Pediatrics, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei Province, 430030, People's Republic of China, Tel +86 133 8756 1016, Email tongjishengxuanl@163.com

**Abstract:** Breast cancer remains the leading malignancy in terms of morbidity and mortality today. The tumor microenvironment of breast cancer includes multiple cell types, secreted proteins, and signaling components such as exosomes. Among these, exosomes have a lipid bilayer structure. Exosomes can reflect the biological traits of the parent cell and carry a variety of biologically active components, including proteins, lipids, small molecules, and non-coding RNAs, which include miRNA, lncRNA, and circRNA. MiRNAs are a group of non-coding RNAs of approximately 20–23 nucleotides in length encoded by the genome, triggering silencing and functional repression of target genes. MiRNAs have been shown to play a significant role in the development of cancer owing to their role in the prognosis, pathogenesis, diagnosis, and treatment of cancer. MiRNAs in exosomes can serve as effective mediators of information transfer from parental cells to recipient cells and trigger changes in biological traits such as proliferation, invasion, migration, and drug resistance. These changes can profoundly alter the progression of breast cancer. Therefore, here, we systematically summarize the association of exosomal miRNAs on breast cancer progression, diagnosis, and treatment in the hope of providing novel strategies and directions for subsequent breast cancer treatment.

**Keywords:** breast cancer, tumor microenvironment, exosome, miRNAs, detection, therapy

## Introduction

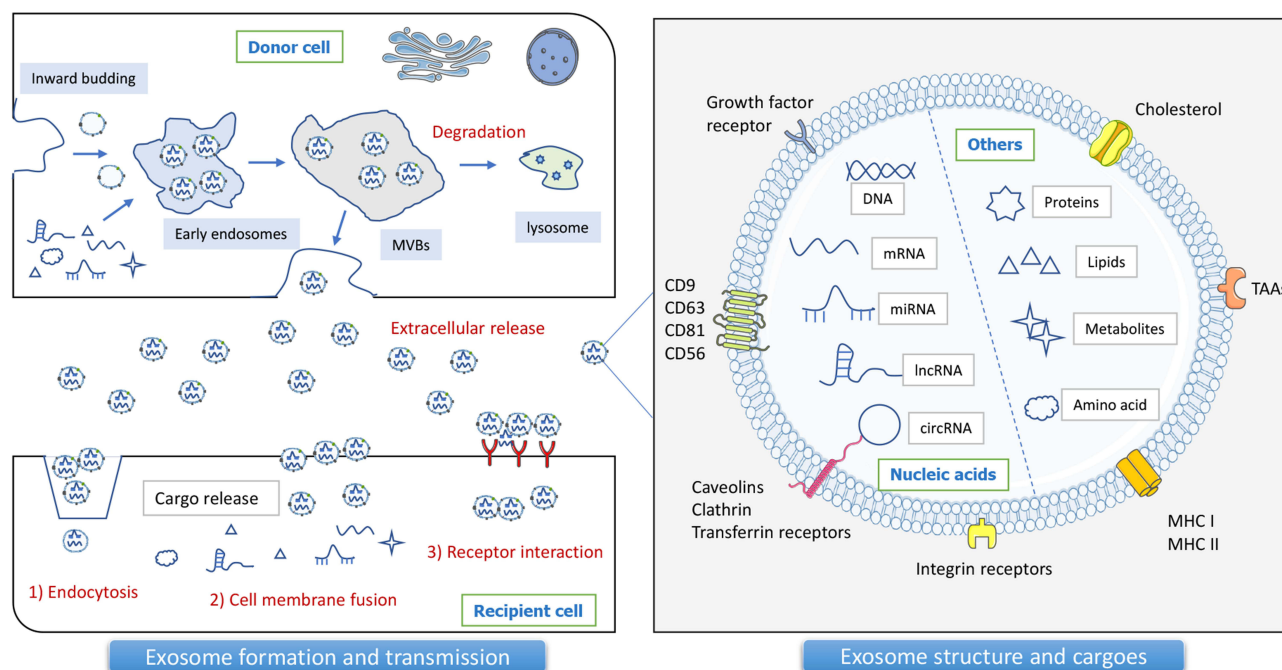
Breast cancer (BC) is a highly prevalent female cancer type with high heterogeneity.<sup>1</sup> Over the course of 19 years, 30,000 fresh instances of cancer have been identified globally, resulting in almost 100,000 fatalities.<sup>2</sup> In addition, BC cancer in women has surpassed lung cancer as the most common cancer worldwide. Approximately 36,850 women lost their lives due to this disease, which made up 3.11% of all cancer occurrences. In addition, BC deaths are expected to rise by more than 50% from 685,000 in 2020 to over 1 million in 2040.<sup>3</sup> The diagnosis of BC primarily relies on radiological, hematological, and clinical evaluation, supplemented by classical biopsy confirmation. The advent of new treatments also holds great promise, such as platinum, poly(ADP-ribose) polymerase (PARP) inhibitors, and antibody-drug conjugates, even cell-based therapy.<sup>4</sup> Despite huge advancements in diagnosis and treatment, BC patients still face core problems such as high incidence, younger age at diagnosis, high metastasis, and high recurrence. The continued exploration of molecular mechanisms will lay the foundation for precise diagnosis and therapy of BC.

Exosomes are naturally occurring extracellular vesicles of phospholipid bilayers that are secreted by almost all cells and are approximately 40–160 nm in diameter.<sup>5</sup> Exosomes are mainly formed through early endosomes, late endosomes, multiple vesicular bodies (MVBs), fusion with lysosomes, and release. Exosomes have a large number of characteristic

membrane proteins, such as CD63, CD9, CD81, and major histocompatibility complex (MHC) molecules, and exosomes contain profusely biologically active components, including proteins, lipids, small molecule metabolites, mRNA, non-coding RNAs (ncRNAs) and other nucleic acid molecules.<sup>6</sup> Exosomes themselves are highly heterogeneous, therefore the active components, species, and abundance, with spatiotemporal specificity, will have a profound impact on the functional impact of recipient cells. In addition, in the tumor microenvironment (TME), exosomes are important mediators of various cellular interactions<sup>7,8</sup> (Figure 1). Exosomes can act as messengers between tumor cells and non-tumor cells, such as stromal cells and immune cells, thus influencing tumor evolution.

NcRNAs, represented by miRNAs, lncRNAs, and circRNAs, are important players in molecular mechanisms of physiology and pathology by regulating gene expressions at transcriptional and post-transcriptional levels.<sup>9</sup> Multi-omics-based sequencing tools and bioinformatics analysis are currently effective tools for mining potential tumor markers.<sup>10</sup> Multi-omics can adequately screen for exosome-loaded ncRNA species and abundance, which are required for cellular interactions in the tumor microenvironment and during tumor evolution. Notably, miRNAs, consisting of 20–25 nucleotides, are ubiquitous ncRNAs in eukaryotes and are located in the genome. MiRNAs are very popular epigenetic factors that drive gene expression.<sup>11</sup> Studies have shown that miRNAs are involved in almost the entire process of BC, including tumor initiation, invasion and metastasis, and immune system regulation.

Exosomal miRNA is a mapping of parental cells, and can profoundly reflect the biological status of parental cells. Mechanistically, exosome-encapsulated miRNAs have been verified to be delivered from donor cells to recipient cells through receptor-mediated endocytosis, and exert the potentially silencing function of miRNAs on downstream genes, thereby exerting anti-tumor effects.<sup>12</sup> In addition, exosomal miRNAs can also affect the extracellular matrix (ECM), angiogenesis, and immune cell recruitment and polarization through delivery to other cell types in the TME. At present, there are also many breakthroughs in exosome-related BC biology. Exosomes from BC patient cells and serum drive non-tumorigenic epithelial cells to encourage tumor formation in a Dicer-dependent manner.<sup>13</sup> Dysregulation of miRNA expression profile levels is a characteristic of BC cells and is reflected in the miRNA cargo of tumor-derived exosomes.



**Figure 1** Exosome biogenesis, structure, and cargoes. Exosomes are naturally occurring membrane molecules through a complex sequence of biosynthetic processes, including early endosomes, late endosomes, multivesicular bodies (MVBs), and extracellular space release. Specific exosome markers are closely related to the parent cell and the sorting process. Tumor exosome biomarkers mainly include tetraspanins (CD9, CD63, CD81), MVB biogenesis proteins (Alix), antigen-presenting molecules (MHC-I, HSP70), tumor-associated antigens (TAAs), and others. Exosomes encapsulate multiple bioactive substances, including proteins, lipids, metabolites, DNA, and mRNA, as well as ncRNAs, especially miRNAs, lncRNAs, and circRNAs. Exosomes can transfer cargoes from donor cells to recipient cells by means of endocytosis, cell membrane fusion, and receptor interaction.

For example, Scognamiglio et al reported that TNBC-derived exosomes, harboring miR-185-5p, miR-652-5p, and miR-1246, synergistically promoted fibroblasts to change to cancer-associated fibroblasts (CAFs) subtypes and enhanced their migratory function for promoting BC.<sup>14</sup> Exosome-carried miR-181b-5p endowed senescence-mediated doxorubicin resistance by inhibiting BCLAF1 in BC progression.<sup>15</sup> BC-exosome miR-155 could inhibit adipogenesis in preadipocytes and promote browning of white adipose tissue by targeting UBQLN1 in adipocytes, featuring cancer cachexia-related fat loss.<sup>16</sup> In addition, Kim et al showed that RAS activation in BC cells triggered osteolytic bone metastasis by exciting exosome-mediated osteoclast production of miRNAs, including miR-494-3p, to osteoblasts.<sup>17</sup> This feature makes exosomal miRNAs derived from tumor tissue or other body fluids high-value indicators for tumor differential diagnosis, treatment monitoring, and prognosis evaluation.<sup>18</sup>

Given the increasingly prominent roles of exosomal miRNAs in BC, here we highlight the novel roles and mechanisms of exosomal miRNAs, including BC progression regulation, as well as their roles in clinical BC diagnosis and treatment. This field will provide novel exosomal miRNA-based strategies for combating BC.

## Exosome-Derived miRNAs in Remodeling BC Progression

### Exosome-Derived miRNAs from BC Cells

#### Interaction Between BC Cells

BC-derived exosomes can function as paracrine and autocrine components to trigger the functional changes in BC cells. MiR-155, a common oncogenic signal in tumor exosomes, can lead to BC-associated cachexia by reprogramming systemic energy metabolism, regulating transcription of key proteins, and mediating chemoresistance.<sup>19,20</sup> MiR-9 and miR-155 are overexpressed in highly metastatic triple-negative breast cancer (TNBC) cells as well as their exosomes.<sup>21</sup> Bioinformatics studies and luciferase assays showed that miR-9 and miR-155 could specifically inhibit PTEN and DUSP14 respectively, and that their exosome-encapsulated forms could be transferred into MCF-7 cells, thus enhancing the invasive properties of the recipient cells.<sup>21</sup>

Exosomal miR-760, released from CCL18-stimulated metastatic BC cells, enhanced the malignant behaviors of BC cells, including proliferation, invasion, and chemoresistance, through activating the ARF6-mediated Src/PI3K/Akt signaling pathway.<sup>22</sup> BC exosomal miR-134-5p could suppress BC growth by inhibiting ARHGAP1/PI3K/AKT pathway, indicating a therapeutic role for miR-134-5p.<sup>23</sup> MiR-10b from BC exosome also promoted cell invasion ability in vitro by targeting HOXD10 and KLF4.<sup>24</sup> In addition, Ding et al showed that exosomal miR-222 was not only highly expressed in the serum of BC patients with lymphatic metastases, but was also tightly linked to the high invasiveness of BC cell lines.<sup>25</sup> Exosomal miR-222 facilitated migration and invasion of BC cells in vitro, and fostered tumorigenic properties by directly targeting the tumor-suppressive PDLIM2 and consequently activating the NF- $\kappa$ B signal pathway.<sup>25</sup> BC exosomes shuttled miR-1910-3p to breast epithelial cells and BC cells, and activated NF- $\kappa$ B and WNT/ $\beta$ -catenin pathways by suppressing MTMR3 expression, ultimately promoting BC cell propagation, metastasis, and autophagy.<sup>26</sup> Exosomal miR-363-5p was validated to regulate platelet-derived growth factor (PDGF) activity by directly targeting PDGFB to constrain BC cell migration properties.<sup>27</sup> MiR-7641 was an important component of BC cell exosomes and significantly promoted BC tumor growth.<sup>28</sup> Exosomal miR-7-5p downregulation facilitated BC migration and invasion by targeting RYK and engaging the atypical WNT pathway.<sup>29</sup>

It is worth noting that the treatments represented by radiotherapy and chemotherapy can also affect the BC process by triggering changes in exosomal miRNAs. Radiation-induced bystander effect (RIBE), mediated by 2 Gy X-ray, could promote greater invasiveness of MCF-7 cells by enhancing their exosomal secretion.<sup>30</sup> Among them, changes to critical miRNAs in these tumor exosomes, such as up-regulated miR-30a, miR-9a, and down-regulated miR-200b, were responsible for this phenomenon.

#### Interaction Between BC Cell-Stroma Cell

BC cell-derived exosomes can stimulate the conversion of normal fibroblasts (NFs) to CAFs. BC-originated exosomes boosted the activation of CAFs via the miR-146a/TXNIP axis, which initiated the Wnt pathway, thereby enhancing the aggressiveness and metastasis capability of BC cells.<sup>31</sup> Additionally, miR-9 of BC exosomes enhanced CAF malignant behaviors to cause tumor growth.<sup>32</sup> CAF-domesticated monocytes secrete exosomal miR-181a to activate AKT signaling

in breast cancer cells and exert pro-tumor effects.<sup>33</sup> Exosomes derived from tumor-adipocyte interactions, containing miR-144 and miR-126, could activate beige/brown differentiation and reshape the metabolism profile in resident stromal adipocytes to elicit BC progression.<sup>34</sup> Hashimoto et al proposed a novel pathway by which tumor-derived hsa-miR-940 was transferred to mesenchymal stem cells (MSCs) via exosomes and promoted the phenotype of bone metastasis.<sup>35</sup>

### Roles in Angiogenesis and Vascular Remodeling

Tumor vascular system disorder is not only an important tumor characteristic, but also a key factor impacting tumor hypoxia, metastasis invasion, and treatment resistance.<sup>36</sup> Feng et al showed that BC cell-released exosomal miR-22-3p, was able to inhibit TAGLN-sustained tumor vascular abnormalities, and enhanced EMT transformation and BC stemness, thereby leading to tumor budding and distant metastasis. Aggressive BC cell lines secreted a specific type of miR-105, a regulator that targeted the tight junction protein ZO-1 to mediate cell migration movement.<sup>37</sup> And in endothelial monolayers, BC-released miR-105 via exosome transfer essentially disrupted the completeness of these naturally formed barricades for blocking metastasis. Further in vivo assay confirmed the inhibition of miR-105 acted to restrain the BC metastasis capability with enhanced vascular integrity.

Endothelial barrier penetration is a key mechanism for proximal and distal tumor metastasis, contributing to nutrient exchange and migration of tumor cells and lymphocytes. Di Modica's study showed that miR-939 expression in the TNBC cohort significantly correlated with lymph node (LN) status and predicted worse disease-free survival.<sup>38</sup> Moreover, overexpressed miR-939 in exosomes released from MDA-MB-231 cells, could be internalized in HUVEC cells, thereby decreasing VE-cadherin and promoting transendothelial migration of MDA-MB-231 cells by disrupting the endothelial barrier.<sup>38</sup>

### Roles in Organotropic Metastasis

Let-7a is a tumor suppressor-like miRNA and is significantly downregulated in various cancer type, including BC. Let-7a, transferred by exosomes, suppressed the proliferation, migration, and invasion of MDA-MB-231 cells by binding to the 3'-UTR region of c-Myc gene with decreased c-Myc expression.<sup>39</sup> Furthermore, the pluripotency factor Lin28B facilitated BC lung metastasis by establishing immunosuppressive pre-metastatic ecological niches with neutrophil recruitment and N2 neutrophil conversion.<sup>40</sup> The release of exosomes with low let-7 characteristics by BC cells was a prerequisite for this process. Both high Lin28B and low let-7s in tumors were indicators of poor prognosis and lung metastasis in BC patients.<sup>40</sup>

Abnormalities in glycolysis and glucose metabolism are one of the main features of cancer. BC tumors reprogram the TME by reprogramming changes in metabolic levels, leading to reprogramming of energy metabolism. High abundance of miR-122 uploaded in BC exosomes enhanced the nutrient supply in the pre-metastatic niche to promote tumor metastasis, through the downregulation of glycolytic enzyme pyruvate kinase.<sup>41</sup> Meanwhile, in vivo inhibition of miR-122 restored the glucose uptake capacity in distant organs, thereby significantly reducing the extent of breast cancer brain metastasis (BCBM) and lung metastases. Moreover, BC-originated exosomal miR-105 enhanced BC growth via MYC-dependent metabolic reprogramming in tumorous stromal CAFs, accompanied by elevated glucose and glutamine metabolism to fuel adjacent BC cells.<sup>42</sup> Wang et al reported an important molecular biological mechanism of tumor exosome-mediated liver metastasis. Specifically, the cancer-secreted exosomal miR-4443 up-regulated matrix metalloproteinase (MMP) in the TME at the primary and distal metastatic sites via downregulation of TIMP2, allowing BC cells to segregate from the primary tumor and metastasize into the neoplastic milieu.<sup>43</sup>

Patients with estrogen receptor (ER)+ have a higher bone metastatic property than negative patients, and this bone-oriented nature of ER tumors is still intriguing. Wu et al found that bone-tropic BC cells secreted miR-19a and integrin-binding sialoprotein (IBSP), leading to an increase in circulating levels.<sup>44</sup> Furthermore, IBSP could recruit osteoclasts to establish an osteoblastic microenvironment in bone, which helped to transport exosomal miR-19a to osteoclasts and induce osteoclast formation. Within this mechanism, ER+ BC cells constructed a distinct TME conducive to bone colonization. Guo et al demonstrated that miR-20a-5p was highly expressed in tumor tissues and MDA-MB-231 cell exosomes.<sup>45</sup> Their further in vitro studies highlighted that miR-20a-5p from BC exosomes could promote tumor cell migration and invasion, and enhanced osteoblast proliferation and differentiation by targeting SRCIN1. In another bone

metastasis study, SCP28, a BC cell line with bone metastasis capacity, was able to cause osteoclast differentiation and activation and reduced bone density through secreted exosomes.<sup>46</sup> Exosomal miR-21 derived from SCP28 cells displayed the ability to regulate PDCD4 protein levels to promote osteoclastogenesis, being an important regulator of bone-metastatic niche formation.

## Exosome-Derived miRNAs from Other Cells

CAF-derived exosomes play an integral role in tumorigenesis, epithelial-mesenchymal transition (EMT), metastasis, and immune responsiveness. CAF-exosome miRNAs delivered to BC cells can induce a series of target protein silencing effects and corresponding cascade responses to reshape the malignant behavior of tumors. Focal adhesion kinase (FAK) was an essential kinase for CAFs to promote BC migration and metastasis.<sup>47</sup> Importantly, FAK-null CAFs had correspondingly altered exosomal miRNA expression profiles compared to normal CAFs, such as miR-16 and miR-148a in exosomes contributing to reduced tumor cell activity and metastasis. Liu et al revealed that oncogenic miR-3613-3p was up-regulated in exosomes from TGF- $\beta$ 1 cultured fibroblasts and CAFs from BC tissues.<sup>48</sup> Mechanistically, downregulation of miR-3613-3p in exosomes of CAFs inhibited cell proliferation and metastasis of BC by targeting SOCS2. Exosomal miR-18b of CAFs stimulated nuclear Snail allotropy by targeting TCEAL7 to induce NF- $\kappa$ B pathway activation, leading to enhanced EMT, invasion, and lung metastasis in BC tumors.<sup>49</sup> Chen et al verified that exosomal miR-500a-5p from patient-derived CAFs was internalized and resulted in BC cell proliferation and enhanced pulmonary surface nodules in the xenograft model, by targeting USP28.<sup>50</sup> This suggested that inhibition of CAF-derived miR-500a-5p was a potentially effective intervention for treating BC. CAF exosomal miR-4516 was markedly reduced in TNBC tissue, and its deficiency promoted tumor progression in a FOSL1-dependent pathway.<sup>51</sup>

MSC-derived exosomal miRNAs can act as anti-angiogenic molecules that inhibit blood vessels and affect tumor progression. Pakravan et al deciphered a paracrine mechanism of MSC-derived exosomal miR-100 that restrained angiogenesis by inhibiting mTOR/HIF-1 $\alpha$ /VEGF signaling axis in BC cells.<sup>52</sup> In addition, MSC exosomal miR-16 could target and inhibit VEGF expression, possessing an anti-angiogenic function.<sup>53</sup> In a TNBC study, miR-106a-5p was more abundant in TNBC tissues and BC cells and was positively associated with tumor grade.<sup>54</sup> Functional assays showed that miR-106a-5p derived from bone marrow-mesenchymal stem cells (BMSCs) was a facilitator in enhancing TNBC progression. The incubation with miR-106a-5p-overexpressed exosomes of BMSCs with BC cells endowed more powerful carcinogenic properties in mice. Notably, exosomal miRNAs in patient BMSCs, especially miR-23b, conferred BC cell dormancy in the metastatic niche by inhibiting downstream MARCKS genes.<sup>55</sup> BC cells promoted the release of miR-222/223-rich exosomes from MSCs, which in turn promoted BC cell dormancy and resistance to bone metastases.<sup>56</sup>

Preadipocytes and mature adipocytes are important components in BC TME, and exosomes derived from preadipocytes also possess important functions in modulating the cancer stem cells (CSCs) niches. MiR-140 is lowly expressed in several tumors and is involved in regulating the biological behavior of tumor cells. Gernapudi et al showed that miR-140 expression in preadipocyte-derived exosomes effectively repressed the renewal of CSCs, thus affecting the growth and metastatic properties of BC tumors.<sup>57</sup> Indeed, adipocytes adjacent to BC cells, represented by cancer-related adipocytes (CAAs), are the frontier adipocytes of tumor infiltration, and can interact with BC cells in the manner of carriers such as ncRNA and exosomes, and affect their respective behaviors.

## Exosome-Derived miRNAs in Immune Regulation

### Exosome-Derived miRNAs from BC Cells

Macrophages are the most abundant tumor-infiltrating immune cell type with multiple functions and close interaction with tumors.<sup>58</sup> Macrophages have extremely high tumor heterogeneity, but are usually divided into M1 and M2 types, with M2 being the predominant type of infiltrating tumor-associated macrophages (TAM) that can support tumor metastasis and invasion.<sup>35</sup> Macrophage exosomes are the most studied form of interaction between macrophages and BC tumors.



Blocking the production of M2 macrophage exosomes and the interactions mediated by them may reverse the tumor-suppressive features. 4T1 cell-derived exosomes delivered miR-33 to IL-4-induced M2 macrophages, and thus polarized M2 polarizes to an M1 phenotype, as manifested by increased secretion of TNF- $\alpha$ /IL-1 $\beta$ , and decreased IL-10/TGF- $\beta$  secretion.<sup>59</sup> These macrophages internalized with miR-33 could significantly inhibit the growth and invasion of 4T1 cells. Coincidentally, Moradi-Chaleshtori et al utilized a similar approach to deliver tumor-derived exosomal miR-130 to macrophages, resulting in phenotypic and functional up-regulation of M1 macrophages.<sup>60,61</sup> The effect of repolarization of M2 to M1 made macrophages more potent in killing tumor cells. 4T1 cell exosome-mediated miR-183-5p transfer could enhance NF- $\kappa$ B pathway and secretion of anti-inflammatory IL-1 $\beta$  and IL-6 factors in macrophages by targeting PPP2CA.<sup>62</sup> Exosomal miR-222 released by adriamycin-resistant BC cells conferred M2 macrophage polarization through PTEN/Akt pathway, leading to BC progression.<sup>63</sup> Tumor-derived exogenous miR-148b-3p contributes to BC migration and invasion through TSC2/mTORC1-mediated M2 macrophage polarization.<sup>64</sup> These studies further reinforce the non-negligible roles of specific BC-exosomal miRNAs in TME interactions.

The effect of exosomes secreted by BC cells on macrophages facilitates the establishment of ecological niches associated with BCBM and lung metastasis. The tumor-derived exosomal miR-138-5p was transferred to activate the M2 phenotype and suppressed M1 polarization, which led to an upregulation of the number of niches formed in mouse lung metastases.<sup>65</sup> In addition, the circulating miR-138-5p levels were positively correlated with BC progression. Xing et al demonstrated that lncRNA XIST-mediated elevated expression of BC exosomal miR-503 promoted M1-M2 polarization and M2 functional activation in microglia, consequently leading to T cell proliferation suppression.<sup>66</sup> Thus, exosomal miR-503 is an important substance of the immune microenvironment affecting the interaction between tumor cells and T cells, and the correlated pathway triggered BCBM.

## Exosome-Derived miRNAs from Immune Cells

Macrophages also have the nefarious function of delivering exosomal oncogenic miRNAs to BC cells. An earlier study by Yang et al showed that exosomes released by IL-4-activated M2 macrophages conducted miR-223 into BC cells, mediating increased BC cell invasion by inhibiting Mef2c-b-catenin pathway.<sup>67</sup> Yue et al proposed a novel targeting mechanism whereby exosome-derived miR-5100 from PGRN-/- TAMs could attenuate the metastatic ability of BC cells by inhibiting the CXCL12/CXCR4 axis.<sup>68</sup> This regulatory axis might be one of the main reasons for the inhibition of BC lung metastasis in PGRN-/- mice. MiR-503-3p was highly expressed in BC tissues and cell lines. Meanwhile, the macrophage-derived exosome miR-503-3p facilitated glycolysis and reduced mitochondrial oxidative phosphorylation by targeting DACT2 and activating the Wnt/ $\beta$ -catenin pathway in BC cells.<sup>69</sup>

Myeloid-derived suppressor cells (MDSCs), a heterogeneous and plastic group of myeloid precursors with immunosuppressive capacity, are important negative regulators of inflammation and the immune response within TME.<sup>70</sup> Exosomes shuttled by MDSCs are also equipped with the immunosuppressive ability of parental cells. In vivo, miR-9 and miR-181a in BC exosomes activated the JAK/STAT signaling by binding to SOCS3 and PIAS3 accordingly, thereby promoting the expansion of early-stage MDSCs and corresponding immunosuppressive state.<sup>71</sup> DOX-mediated MDSC exosomal miR-126a reduced DOX-caused MDSC death and promoted tumor angiogenesis in a S100A8/A9-dependent manner, and promoted chemoresistance and lung metastasis.<sup>72</sup> Exosomal miRNAs influence immune effects and tumor proliferation, vascular and malignant behavior through their transmission between tumor cells and immune cells (Table 1).

## Exosome-Derived miRNAs in BC Diagnosis

Individualized diagnosis and early screening for BC are essential. Existing conventional diagnostic modalities such as magnetic resonance imaging (MRI), ultrasound (US), mammography, and case-based diagnostic modalities have achieved considerable accomplishments, but there is still room for improvement in terms of non-invasiveness, timeliness, and accuracy. Accurate, efficient, and sensitive exosomal miRNA diagnostic strategies will provide novel and effective tools for BC risk prediction, early screening, and treatment surveillance. Exosomes and exosomal miRNAs isolated from saliva, blood, or body fluid samples of BC patients with in situ tumors or metastases to the brain, lung, bone, or viscera,

**Table I** The Roles of Exosomal miRNA in Immune Regulation in BC

Exosomal miRNA Source	Recipient	Functions	Mechanisms	Ref.
miR-33 (4T1 cells)	Macrophages	Suppressed BC tumor growth and metastasis	Induced M1 polarization in macrophages with elevated TNF- $\alpha$ and IL-1 $\beta$ expression	[49]
miR-130, miR-33 (4T1 cells, MDA-MB-231)	Macrophages	Inhibited BC invasion and metastasis	Resulted in upregulation of M1 and downregulation of M2 specific markers and cytokines	[50,51]
miR-183-5p (4T1 cells)	Macrophages	Promoted tumor growth and metastasis in 4T1 BC model	Promoted the secretion of proinflammatory IL-1 $\beta$ , IL-6, and TNF- $\alpha$ cytokines from macrophages by inhibiting PPP2CA expression	[52]
miR-222 (adriamycin-resistant MCF-7 cells)	Macrophages	Stimulated tumor growth and pre-metastatic niche formation in vivo.	Chemoresistant BC cells released exosomal miR-222 by directly targeting PTEN and caused Akt cascade activation and M2 polarization	[53]
miR-138-5p (MDA-MB-231)	Macrophages	Macrophages treated with exosomal miR-138-5p promoted lung metastasis	Downregulated KDM6B expression, inhibited M1 polarization, and stimulated M2 polarization	[54]
miRNA-503 (XISTlow BCcells)	Macrophages	Promoted Macrophages reprogramming and brain metastasis	Exosomal miRNA-503 triggered M1-M2 polarization of microglia, and thus upregulated immune suppressive cytokines in microglia that suppressed T-cell proliferation.	[55]
miR-223 (Macrophages)	SKBR3, MDA-MB-231	Promoted BC cell invasion.	Exosomes secreted from IL-4-activated macrophages shuttled miR-223 into BC cells and targeted the Mef2c- $\beta$ -catenin pathway	[56]
miR-5100 (PGRN/- TAMs)	MCF-7, T47D	Inhibited the invasion, migration, and EMT of BC cells and lung metastasis	Regulated expression of CXCL12, thereby inhibiting the CXCL12/CXCR4 axis	[57]
miR-503-3p (Macrophages)	CAL-51	Functioned as an oncogene to promote BC cell growth	Promoted glycolysis and inhibited mitochondrial oxidative phosphorylation in BC by targeting DACT2 and activating Wnt/ $\beta$ -catenin signaling pathway	[58]
miR-9, miR-181a (MDA-MB-231, 4T1 cells)	eMDSCs	Inhibited T-cell immunity in situ and promote BC growth	Promoted 4T1 tumor growth in mice via enhancing infiltration and immunosuppressive function of human eMDSCs	[60]
miR-126a (MDSCs)	Th2 cell, endothelial cells	Promoted tumor angiogenesis and lung metastasis	Rescued doxorubicin-induced MDSC death in a S100A8/A9 dependent manner and induction of IL-13+ Th2 cells Th2 cell	[61]

are potentially valuable, non-invasive diagnostic or prognostic biomarkers for accurate BC diagnosis, including differential diagnosis and treatment monitoring.

## Differential Diagnosis

The decreased miR-17-5p, and up-regulated hsa-miR-423-5p and miR-202 in serum exosomes, were fascinating indicators to differentiate BC patients from healthy control.<sup>73–75</sup> Through bioinformatics and experimental validation, Xin et al found that miR-455-5p and miR-1255a were involved in CDKN1B-mediated cell cycle process and SMAD4-mediated TGF- $\beta$  pathway, respectively.<sup>76</sup> Whereas high expression of miR-455-5p (basal-like) and miR-1255a (overall) was correlated with poorer overall survival, and high expression of their target genes was linked to superior overall, non-

recurrence or non-distant metastasis survival. Circulating exosome miR-155 could be used to indicate the prognosis of patients with trastuzumab resistance, showing that higher miR-155 predicted poorer progression free survival (PFS) and event-free survival (EFS).<sup>77</sup> MiR-1246 also has a similar indicator function.<sup>77,78</sup> Exosome-loaded miR-223-3p was associated with BC malignancy and could serve as a predictor for the early detection of invasive BC.<sup>79</sup> In addition, the miR-1910-3p expression alteration in serum exosomes of BC patients might also be regarded as a diagnostic indicator. The detection of serum exosomal miR-1910-3p in combination with tumor marker CA153 in routine blood tests, could significantly improve the sensitivity and specificity of serum diagnosis of BC.<sup>26</sup> Wang et al successfully identified a significantly down-regulated miR-363-5p in the plasma exosomes of BC patients with LN metastasis, which was also confirmed by independent dataset validation.<sup>27</sup> Exosomal miR-363-5p in BC plasma was related to better overall survival (OS) rate, and possessed the potential to differentiate LN+ and LN- BC status. The expression levels of miRNA-21-5p and miR-10b-5p in serum exosomes also could be used for the evaluation of BC diagnosis and prognosis.<sup>80</sup>

High expression of hsa-miR-576-3p and low expression of hsa-miR-130a-3p in serum exosomes of BC patients were significantly correlated with the prognosis of BCBM patients.<sup>81</sup> In addition, hsa-miR-340-5p levels were closely related to Ki67+ tumor cells, while hsa-miR-342-3p levels were negatively relevant to the tumor stage. Li et al used qRT-PCR to confirm that serum exosomal miR-148a was differentially distributed in patients with benign and malignant breast tumors and healthy controls.<sup>82</sup> Specifically, there was a significant association between serum exosomal miR-148a enrichment and LN metastasis, TNM staging, and differentiation, and BC patients with low serum exosomal miR-148a expression levels had poorer overall and disease-free survival. Therefore, serum exosomal miR-148a was a high-value target for differentiating BC patients from healthy volunteers and for determining tumor prognosis. The up-regulated exosomal hsa-miR-21-5p in plasma can be used as an effective biomarker to differentiate healthy individuals from BC patients, with a sensitivity and specificity of 86.7% and 93.3%, respectively.<sup>83</sup> MiR-7641 was significantly associated with survival prognosis of BC patients, with significantly higher plasma expression levels in patients with metastasis.<sup>28</sup>

In addition to serum and plasma indicators, exosomal miRNAs present in other body fluids, such as tears, urine, and saliva, can also serve as potential indicators for BC differential diagnosis. MiR-21 and MMP-1 in urinary exosomes were used as combined diagnostic indicators by Ando et al and were able to achieve a sensitivity and specificity of 95% and 79% for metastatic BC.<sup>84</sup> This indicated that urinary exosomal miRNAs in tumor patients still had a diagnostic value that was not weaker than blood specimens. Inubushi et al proposed a novel perspective that miR-21 and miR-200c were highly expressed in tear exosomes from patients with metastatic BC, which might be biomarkers for metastatic BC diagnosis.<sup>85</sup> However, the number of case analyses included in this study was relatively small and this novel concept deserved further exploration.

Single exosomal miRNA indicator has shown prognostic efficacy, while the model constructed by multiple indicators can provide a more comprehensive and clear understanding of the disease. The combinational predictive model based on miR-421, miR-128-1, and miR-128-2 associated with genomic instability (GI) in plasma exosomes, was regarded as a signature for BC early diagnosis and prognosis.<sup>86</sup> Notably, the combination of plasma exosomal miR-1246 and miR-21 is also an ideal method to indicate BC status compared to their separated levels.<sup>87</sup> There are few relevant studies at present, but it is very valuable.

## Treatment Monitoring

During treatment, the contents of exosomes undergo dynamic and specific changes in tumor tissue and body fluids represented by blood. Corresponding changes in exosomal miRNA expression abundance are effective indicators of disease treatment effects. Li et al found that the expression level of specific miRNA in serum exosomes was significantly correlated with LN metastasis and the clinical stage of BC.<sup>88</sup> Among them, miR-3662, miR-146a, and miR-1290 were up-regulated in serum exosomes, and they were ponderable biomarkers for monitoring BC patient status during surgery and chemotherapy.

In another related study, the exosomal miR-21 and miR-105 expression levels were higher in metastatic patients before neoadjuvant therapy.<sup>89</sup> During neoadjuvant therapy, exosomal miRNA-21 expression levels were directly connected with tumor size and negatively linked to Ki67 expression. Finally, elevated exosomal miR-21, miR-222, and miR-155 levels were remarkably related to the existence of circulating tumor cells (CTCs). Exosomal expression levels of



miR-3662, miR-146a, and miR-1290 in serum have attracted much attention, specifically for monitoring patient status during surgery and chemotherapy.<sup>88</sup> These studies collectively suggest that exosomal miRNA-based liquid biopsy and related diagnostic methods can serve as a useful complementary tool to evaluate the diagnosis, treatment, and prognostic monitoring for BC management.

## Exosome-Derived miRNAs in BC Treatment

### Drug Resistance

Exosomes of multiple cell sources, including BC cells, and stem cells, are involved in BC drug resistance and therapeutic progression. Exosomes from drug-resistant BC cells propagate chemoresistance by a horizontal transfer of miRNAs. Aberrant miRNA and exosomal miRNA expression levels in the serum of BC patients are intensively implicated in resistance to multiple therapeutic agents for BC.<sup>90,91</sup> In immunotherapy, anti-PD-1 treatment promoted the expression of lymphocyte-derived exosomal miRNA-4315 and suppressed BIM-mediated tumor apoptosis, endowing the potential of exosomal miRNA-4315 in blood as patient stratification for anti-PD-1 treatment.<sup>92</sup> Exosome-shuttled miR-567 restrained the trastuzumab resistance, and could be internalized by recipient BC cells to enhance the curative effect of chemotherapy by inhibiting ATG5 in BC.<sup>93</sup>

The expression profiles of miRNAs in TNBC chemotherapy-sensitive and drug-resistant tissues are quite heterogeneous. Among them, miR-770 was closely related to chemotherapy resistance, and its high expression implied a better BC prognosis.<sup>94</sup> It was found that exosomal miR-770 could be transferred to TNBC cells, resulting in enhanced DOX resistance and metastasis both in vitro and in xenograft model. Exosome-mediated transfer of miR-3613-5p and miR-181b-5p also promoted doxorubicin resistance in BC cells, by targeting PTEN and BCLAF1 respectively.<sup>15,95</sup> Andreeva et al identified miR-181a-2 as a key miRNA mediating tamoxifen drug resistance.<sup>96</sup> This action was consistent with a continuous blocking of oestrogen receptors and promotion of the PI3K/Akt pathway. Exosomal miRNA-205 derived from tamoxifen-resistant MCF-7 promoted BC chemoresistance and tumorigenesis, but was triggered by binding to E2F1.<sup>92</sup> Furthermore, exosomal miR-221/222 and miR-9, were critical supporters of tamoxifen-related resistance in ER+ BC.<sup>97,98</sup> Exosomal miR-423-5p also mediated the cisplatin resistance in TNBC cells.<sup>78</sup>

Emerging findings have revealed that horizontally transferred exosomal miRNAs are key mechanisms of chemotherapy resistance through which BC cells acquire CSC-like characteristics and drug resistance transmission. For instance, miR-155 regulated the stemness and chemoresistance of BC cells and CSC cells.<sup>20</sup> Chemotherapy-induced miR-378a-3p and miR-378d in BC exosomes, which enhanced BC stemness characterized by WNT and NOTCH activation, leading to DOX and PTX chemoresistance via activation of EZH2/STAT3 signaling in xenograft models.<sup>93</sup> Consistent with this, chemotherapeutic medicine plus EZH2 inhibitor tazemetostat significantly relieved exosome-mediated resistance in a nude mouse tumor xenograft model.

### Drug Delivery Based on Stem Cell-Derived Exosomes

Stem cell-derived exosomes have exhibited prospective advances in treating various cancer types, due to their encapsulated lethal effector molecule. Exosomes derived from human umbilical cord-derived MSCs (HUCMSCs), BMSCs, and adipose-derived stem cells (ADSCs), are supposed to be the most common stem cell types in BC treatment. MiR-342-3p is lowly expressed in patients with metastatic tumors. MiR-342-3p uploaded in MSC exosomes not only inhibited metastasis and chemoresistance of BC cells by targeting ID4,<sup>99</sup> but also by inhibiting INHBA/IL13R $\alpha$ 2 axis.<sup>100</sup> Exosomal miRNA-551b-3p from BMSCs suppressed BC progression by modulating TRIM31/Akt signaling.<sup>101</sup> MiR-1236 carried by ADSC exosomes promoted the resistance response of BC cells to cisplatin, specifically involving two distinct mechanisms related to SLC9A1 downregulation and Wnt/ $\beta$ -linked protein inactivation.<sup>102</sup> Similarly, Du et al showed that HUCMSC exosome had anticancer effects in ER- MCF-7 cells.<sup>103</sup> Specifically, HUCMSC exosome-derived miR-21-5p inhibited the expression level of ZNF367 by binding to the ZNF367 3'UTR, leading to reduced MCF-7 cell invasiveness. MiR-3182 from HUCMSC-exosomes internalized by TNBC cells, caused diminished invasiveness of recipient cells and induced apoptosis by targeting the mTOR-S6KB1 pathway.<sup>104</sup> MiR-148b-3p derived from

HUCMSC exosomes could target TRIM59 to inhibit BC progression.<sup>105</sup> These results suggest that exosomal miRNAs harboring tumor-killing effects might be credible therapeutic candidates in BC therapy. Sheykhan et al exploited the function of ADSC-derived exosomes on T-47D tumor cells.<sup>106</sup> Their results showed that ADSC exosome-mediated miR-145 delivery effectively inhibited tumor cell apoptosis and metastasis.

## Discussion

Exosomes are involved in multiple cellular interactions in BC TME and consequently have a fundamental impact on BC processes. However, because of the wide range of sources of exosomes, the direction and results of exosome propagation deserve to be explored in depth. Moreover, ncRNA substances in exosomes can influence the expression of receptor cells in an epigenetic manner. In terms of tumor immune effects, since most studies have focused on the interaction between macrophages and tumor cells, the exosomal interaction properties and the influence of other humoral and cellular immune cells are also a direction worth investigating. It is worth mentioning that exosomes secreted by the same cell at different stages or conditions are different. The exosome-rich component of early and advanced tumors differs greatly in their ability to direct and domesticate the metastatic niche.<sup>107</sup> This highlights that maternal exosomes have different effects on recipient cells in different stages of the same cell.

The main separation methods for exosomes include differential centrifugation, density gradient centrifugation, sedimentation, filtration, size exclusion chromatography, kit extraction, immunoaffinity, and microfluidics. However, realizing high-purity, high-efficiency and non-invasive separation of exosomes is still the main challenge for exosome separation at present. This is because various separation methods possess their advantages and disadvantages, such as expensive equipment, insufficient purity, and protein contamination. A combination of multiple separation methods can be used to obtain a higher quality yield of exosomes than a single method.

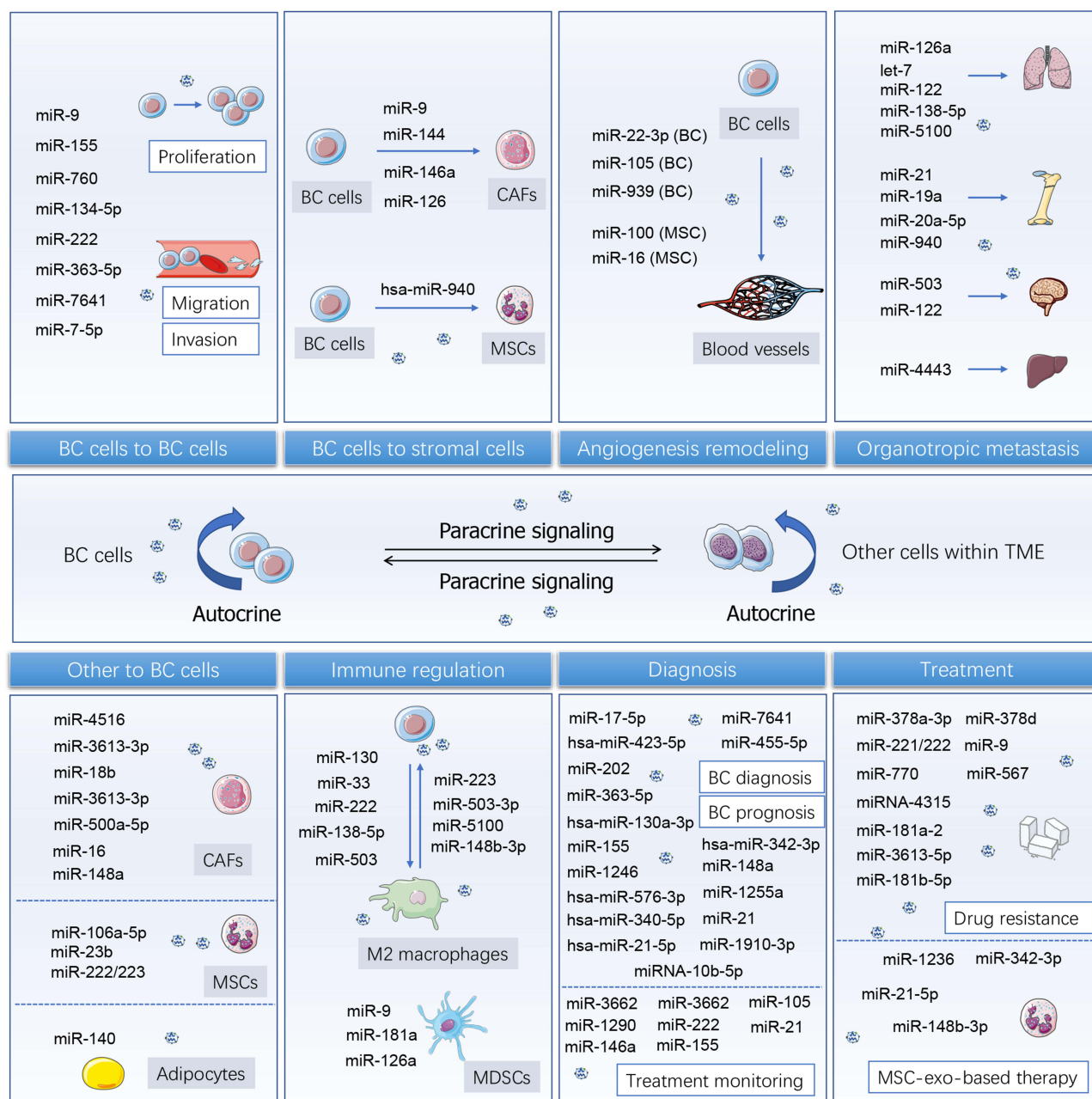
For detection approaches, the identification of exosomes is mainly dependent on morphological features, particle size, and signature proteins, which are detected by electron microscopy, dynamic light scattering, nanoparticle tracer analysis, Western blot method, and flow cytometry. Of these methods, the main advantage of exosome size-based assays is their simplicity, rapidity, and suitability for high-throughput analyses, but their accuracy is relatively low. In contrast, assays that characterize biofunctional molecules in exosomes are usually more accurate, but the sample pre-processing steps are cumbersome and time-consuming. The miRNAs in exosomes are often still analyzed by conventional qPCR. The combination of multiple methods is the current mainstream of exosome detection.

For the diagnostic application, exosome-related diagnostics have shown huge prospects and are accompanied by the potential to revolutionize the strategy of clinical diagnosis and management of BC. This is essential because exosomal miRNA levels and contents are an accurate reflection of parental BC cells. However, there are currently non-homogeneous processes for the isolation and purification of exosomes. This causes non-uniformity in exosome purity, recovery, and particle size, which in turn affects the evaluation of BC diagnosis, metastasis, and treatment monitoring. In addition, the lack of standardized methods among different studies has resulted in significant differences in key metrics such as threshold, sensitivity, specificity, and detection limit for exosomal miRNA diagnosis.

Finally, in the aspect of therapeutic application, the genetic substances in exosomes can be used as targets for tumor therapy, and on the other hand, exosomes can also be used as vectors for targeted therapies. Highly expressed substances in BC exosomes can be intervened with specific inhibitors or antibodies, thus cutting off the malignant propagation pathway of tumors. In addition, blocking exosome secretion from BC or evil cells and their interaction also produces effective tumor eradication. Tumor-derived exosomes possess tumor-targeted homing recognition, high biosafety, and secretion, whereas non-tumor exosomes, represented by MSCs, can be genetically programmed or uploaded with drugs that carry tumor-killing factors to curb BC growth.

## Conclusion

Collectively, exosome-derived miRNAs possess the ability to promote tumor growth, proliferation, metastasis, and invasion, as well as the colonization of specific organs, demonstrating their potential values in clinical BC diagnosis and treatment (Figure 2). This field will provide novel exosomal miRNA-based strategies for combating BC.



**Figure 2** Exosome-derived miRNAs are emerging supporters in breast cancer progression, diagnosis, and treatment. Exosomes are important carriers for close interaction between BC cells and adjacent BC cells, stromal cells, vascular cells, and immune cells. Exosomal miRNAs shuttling between receptors and ligands can cause malignant remodeling of receptor cells, and then promote tumor growth, proliferation, metastasis, and invasion, as well as the colonization of specific organs. Tumor-derived exosomal miRNAs or circulating exosomal miRNAs show characteristic expression in different stages of specific diseases or under treatment, thus being endowed as tumor diagnostic markers.

Exosome-encapsulated miRNAs and other biomolecules have the potential to indicate tumor subtype, metastasis, and prognosis due to their abundance and expression characteristics. At present, exosomal miRNAs have not demonstrated a confirmatory diagnosis of different subtypes. Therefore, the subsequent explorations of prognosis, estrogen receptor status, and potential metastasis by exosomal miRNAs for different breast tumor subtypes, are an urgent need for future advancement. Besides, targeted blockade or activation strategies based on exosomal miRNAs have the potential to provide novel therapeutic strategies for inhibiting breast cancer progression, suppressing chemoresistance, and adjuvant augmentation of conventional therapy. Exosomes can also be used as drug delivery carriers for RNAs, proteins, small molecules, and other drugs for combating BC. Overall, exosome-based therapeutic modalities are emerging and fascinating strategies for BC tumor treatment.

Up to the present, most of the studies on exosomes are still in the preclinical stage, and the subsequent continuous and in-depth research is promising.

## Abbreviations

BMSCs, bone marrow mesenchymal stem cells; BC, breast cancer; BCBM, breast cancer brain metastasis; CSCs, cancer stem cells; CAFs, cancer-associated fibroblasts; CTCs, circulating tumor cells; EMT, epithelial-mesenchymal transition; ER, estrogen receptor; EFS, event-free survival; ECM, extracellular matrix; FAK, focal adhesion kinase; HUCMSCs, human umbilical cord-derived MSCs; IBSP, integrin-binding sialoprotein; LN, lymph node; MRI, magnetic resonance imaging; MHC, major histocompatibility complex; MMP, matrix metalloproteinase; MSCs, mesenchymal stem cells; MVBs, multiple vesicular bodies; MDSC, myeloid-derived suppressor cells; ncRNAs, non-coding RNAs; NFs, normal fibroblasts; PDGF, platelet-derived growth factor; PARP, poly(ADP-ribose) polymerase; PFS, progression-free survival; RIBE, radiation-induced bystander effect; TNBC, triple-negative breast cancer; TME, tumor microenvironment; TAMs, tumor-associated macrophages; US, ultrasound.

## Acknowledgments

Jie Li, Dejiao He and Yajun Bi are co-first authors for this study. We thank the institute for providing the funding and the individuals for offering help during the manuscript process.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

This work was supported by Nature Science Foundation of Hubei Province (2020CFB685).

## Disclosure

All the authors declare that there is no conflict of interest in this work.

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