Orchestrating organotropism: miRNA-driven mechanisms of site-specific metastasis in triple-negative breast cancer (Review)

RIGUDE BU and LIU BO

Department of Thyroid Breast Surgery, The Affiliated Hospital of Inner Mongolia Medical University, Hohhot, Inner Mongolia Autonomous Region 010050, P.R. China

Received October 7, 2025; Accepted February 9, 2026

DOI: 10.3892/ol.2026.15504

Abstract. Triple-negative breast cancer (TNBC), characterized by its aggressive nature and poor prognosis, exhibits a pronounced propensity for organ-specific metastasis, which remains the primary cause of treatment failure and mortality. The present review synthesizes current knowledge on the pivotal role of microRNAs (miRNAs/miRs), particularly those shuttled via tumor-derived exosomes, in orchestrating the complex molecular mechanisms underlying TNBC metastasis to the brain, bone, liver and lungs. In addition, the review highlights how specific miRNAs function as master regulators of organotropic metastasis by facilitating pre-metastatic niche (PMN) formation through miRNA-target gene-microenvironment remodeling cascades. Key mechanisms discussed include: Brain metastasis, in which miR-105 disrupts the blood-brain barrier by targeting zonula occludens protein 1 and miR-19a activates astrocytic STAT3 signaling to promote tumor extravasation and survival; bone metastasis, in which miR-218-5p disrupts the osteoprotegerin/receptor activator of nuclear factor κB ligand balance and miR-21 drives a self-perpetuating osteolysis-growth factor-tumor proliferation loop via programmed cell death 4/nuclear factor of activated T cells 1 and TGF-β feedback; liver metastasis, in which miR-122 reprograms the host metabolism by suppressing pyruvate kinase M2 and O-GlcNAc transferase, and contributes to immune evasion; and lung metastasis, in which miR-200 family members regulate endothelial permeability and epithelial-mesenchymal transition. Common metastasis drivers, including miR-10b, miR-21, the miR-200 family and the miR-221/222 cluster, exhibit both shared and organ-specific functions. Although targeting these miRNA networks holds therapeutic promise, notable challenges persist, including organ-specific delivery efficiency, particularly across the blood-brain barrier, potential toxicity, including miR-10b hepatotoxicity, and scalable exosome engineering for drug delivery. Emerging strategies offering potential solutions include engineered exosomes and localized implantable systems. Understanding the spatiotemporal dynamics of miRNA-mediated organotropism, facilitated by advanced technologies, will be crucial for the future development of precision therapies to combat TNBC metastasis.

Correspondence to: Dr Liu Bo, Department of Thyroid Breast Surgery, The Affiliated Hospital of Inner Mongolia Medical University, 5 Xinhua Street, Hohhot, Inner Mongolia Autonomous Region 010050, P.R. China
E-mail: 491309429@qq.com

Key words: triple-negative breast cancer, organ-specific metastasis, microRNA, molecular mechanisms

Contents

1. Introduction

Breast cancer is the most common malignant tumor in women worldwide, and triple-negative breast cancer (TNBC) is the most aggressive subtype with the poorest prognosis among all types of breast cancer (1,2). Due to the lack of effective targeted therapy options for TNBC, reliance on traditional cytotoxic therapies leads to high recurrence rates and low survival rates for this subtype (3), and metastasis remains the main cause of treatment failure. The 5-year survival rate for patients with locally advanced TNBC without distant metastasis is ~91%; however, once metastasis occurs, this rate drops markedly to 12-15% (4).

Organ-specific metastatic tropism in TNBC is strongly associated with treatment failure. The most common distant metastasis sites for TNBC are reported to be the lung (50.0%), followed by bone (31.8%), the liver (18.2%) and the brain (13.6%) (5). The 5-year survival rate for patients with liver metastasis is <10% and for brain metastasis ~12%, whereas the median survival of patients with bone metastasis is longer than those of patients with visceral (liver and brain) metastases (6).

However, with advances in research into molecular biology and the tumor microenvironment, the traditional 'seed and soil' hypothesis-while conceptually foundational-is no longer sufficient to fully explain the molecular mechanisms underlying organ-specific metastasis (7). Contemporary evidence demonstrates that metastatic tumor cells not only depend on a permissive microenvironment but also actively remodel distant organs to form pre-metastatic niches, while host organs undergo dynamic transcriptional reprogramming in response to invading cancer cells (8,9).

Emerging evidence indicates that microRNA (miRNA/miR)-containing exosomes secreted by tumor cells reach specific organs via the circulatory system, acting as long-range messengers mediating inter-organ communication (10), thereby regulating the spatiotemporal formation of the pre-metastatic niche (PMN) (11,12). In both inter-organ signaling and the spatiotemporal regulation of PMN formation, miRNAs play unique roles in the organ-specific metastasis of TNBC (13,14). The present review describes the incidence patterns and prognostic relevance of organ-specific TNBC metastasis, and focuses on describing the network mechanisms by which miRNAs contribute to this metastasis n particular, the contribution of the miRNA-target gene-microenvironment remodeling axis to metastasis is highlighted, and its potential implications for the development of targeted therapies is explored (Fig. 1).

2. miRNA regulatory networks underlying organ-specific metastasis

Brain metastasis. A study reported that the expression levels of circular RNA (circ)-kinesin family member 4A (KIF4A) in TNBC brain metastases and cell lines are markedly upregulated compared with those in primary TNBC tissue and normal human mammary epithelial cells, respectively. Although no significant difference in miR-637 expression was observed between primary breast cancer and brain metastasis (15), miR-637 expression was found to be notably reduced in brain metastasis. This may be attributed to circKIF4A directly binding to miR-637, thereby acting as a competing endogenous RNA by sponging miR-637, regulating the miR-637-mediated regulation of STAT3 expression and promoting the metastasis of breast cancer to the brain (15). Whilst the mechanism by which circKIF4A reaches the brain remains unclear, this finding highlights a potential regulatory axis involved in breast cancer metastasis and warrants further investigation.

One key mechanism underlying breast cancer brain metastasis is penetration of the blood-brain barrier (BBB). Extracellular vesicles (EVs), particularly exosomes, have been reported to facilitate this process. Exosomal miR-105 preferentially accumulates in brain microvessels and downregulates the expression of tight junction protein zonula occludens-1 (ZO-1); this is supported by clinical evidence demonstrating that elevated exosomal miR-105 levels are negatively associated with ZO-1 (10). The accumulation of exosomal miR-105 increases vascular permeability, which creates conditions favorable for tumor cell extravasation (10). In addition, miR-105 inhibits suppressor of cytokine signaling 1 (SOCS1), relieving its suppression of the JAK-STAT pathway and promoting STAT3 phosphorylation (16). miR-105 also activates the NF-κB signaling pathway, upregulates vascular cell adhesion molecule 1 (VCAM1) expression and increases the exposure of endothelial cell adhesion molecules, further promoting tumor cell adhesion and extravasation (17-20).

Breast cancer cells secrete exosomes and EVs into the circulatory system, which are then taken up by brain endothelial cells via transcytosis, crossing the BBB to enter the brain microenvironment (21). Elevated VCAM1 expression recruits M2-type macrophages, which secrete factors such as IL-6 and TNF-α, thereby remodeling the immune microenvironment (18,19,22), and enabling tumor cells to traverse the BBB and enter brain tissue. Research has reported that breast cancer cells secrete exosomes carrying miR-19a, which recognize receptors on brain microvascular endothelial cells via surface integrin αvβ3, crossing the BBB via transcytosis and preferentially enriching around astrocytes (23). In astrocytes, miR-19a directly inhibits the expression of the tumor suppressor genes PTEN and SOCS1 (23). PTEN loss activates the PI3K-AKT-mTOR pathway, thereby promoting tumor cell survival, whilst SOCS1 inhibition leads to sustained STAT3 phosphorylation. Phosphorylated STAT3 induces the expression of IL-6 and TGF-β, which maintain tumor stem cell properties and induce the construction of a fibrotic matrix that facilitates tumor adhesion and colonization (24-27).

After colonization, breast cancer cells, particularly those from TNBC, secrete exosomes containing miR-122 in brain tissue (28). miR-122 directly binds to the 3' untranslated region (3'-UTR) of pyruvate kinase M2 (PKM2) mRNA, inhibiting its translation and leading to a ~70% reduction in PKM2 activity, which disrupts the final step of glycolysis (29). This causes glycolytic intermediates such as phosphoenolpyruvate (PEP) and 3-phosphoglycerate (3-PG) to accumulate and divert into the pentose phosphate pathway (PPP) and serine synthesis pathway, promoting the production of NADPH and nucleotide precursors that support tumor proliferation (30,31). Consequently, this metabolic reprogramming establishes an energy-rich, antioxidant-enriched and immunosuppressive microenvironment, supporting sustained tumor cell colonization (29,32,33).

Bone metastasis. Bone metastasis is one of the most challenging complications of breast cancer, and is primarily driven by osteoclast activation (34), osteoblast inhibition (35,36) and the osteolytic cycle (37). These mechanisms are central to the development of bone metastasis and are closely associated with miRNAs (38).

Osteoprotegerin (OPG), receptor activator of nuclear factor κB (RANK) and RANK ligand (RANKL) constitute the key signaling pathway regulating bone homeostasis (39). Activation of this pathway by several factors, including TNF-α, IL-1/11, RANKL, macrophage colony-stimulating factor and endocrine and metabolic-related factors leads to bone loss due to the disruption of bone homeostasis, resulting in an imbalance between bone formation and resorption (40). RANKL is a key regulator of osteoclast differentiation and proliferation. In the RANKL/RANK/OPG axis, RANKL interacts with its receptor RANK on osteoclast precursors, ultimately leading to their maturation. By contrast, OPG acts as a decoy receptor for RANKL, thereby inhibiting the RANKL-RANK interaction and mediating bone remodeling (41-43).

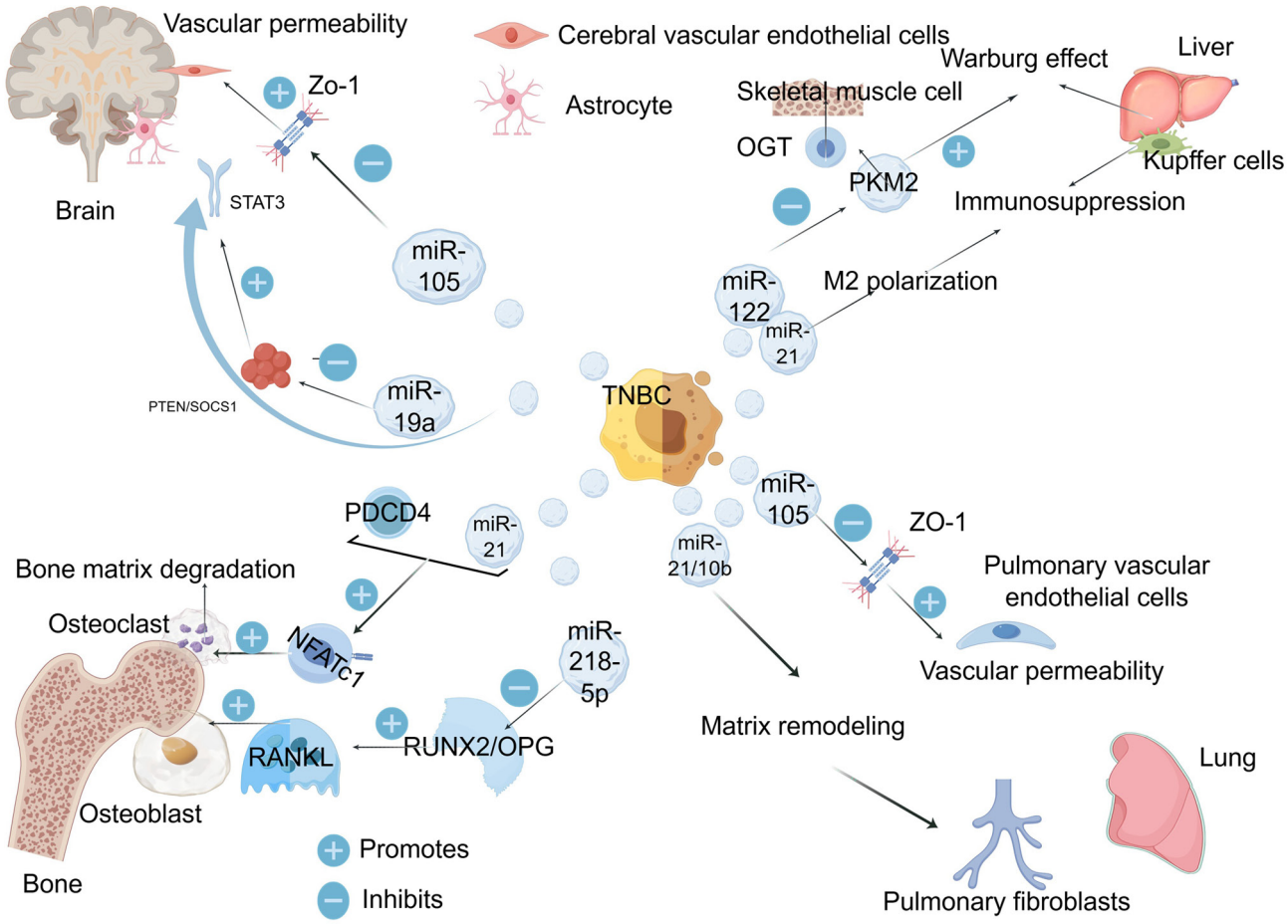

Figure 1. Schematic diagram of exosomal miRNA-mediated organ-specific metastasis in TNBC. The diagram summarizes the key mechanisms by which primary TNBC tumor-derived exosomes deliver specific miRNAs to distinct target organs, namely the brain, bone, liver and lungs, to remodel the microenvironment and facilitate metastasis. In the brain, exosomes deliver miR-105 to endothelial cells, where miR-105 targets ZO-1 to disrupt the blood-brain barrier. miR-19a is delivered to astrocytes, targeting PTEN and SOCS1 to activate STAT3 signaling. In bone, exosomal miR-21 targets osteoclast precursors, inhibiting PDCD4 to activate NFATc1. miR-218-5p targets osteoblasts, inhibiting RUNX2 and OPG. In the liver, exosomal miR-122 targets hepatocytes by inhibiting PKM2, and skeletal muscle cells by inhibiting OGT. Exosomal miR-21 targets liver Kupffer cells, where it inhibits NF-κB signaling. In the lungs, exosomal miR-105 targets endothelial cells by downregulating ZO-1. miR-21 and miR-10b target pulmonary fibroblasts, promoting their activation into cancer-associated fibroblasts. TNBC, triple-negative breast cancer; miRNA/miR, microRNA; ZO-1, zonula occludens protein 1; SOCS1, suppressor of cytokine signaling 1; PDCD4, programmed cell death 4; NFATc1, nuclear factor of activated T cells 1; RUNX2, RUNX family transcription factor 2; OPG, osteoprotegerin; PKM2, pyruvate kinase M2; OGT, O-GlcNAc transferase; RANKL, receptor activator of nuclear factor κB ligand.

RUNX family transcription factor 2 (RUNX2), a key transcription factor in osteoblast differentiation, functions as a transcriptional activator of OPG. Reduced RUNX2 expression leads to decreased OPG levels, thereby accelerating osteolysis (44). The overexpression of miR-218-5p directly suppresses RUNX2; moreover, evidence indicates that miR-218-5p also directly binds to the OPG 3'-UTR, further reducing OPG expression (31). In this context, TNBC cells have been shown to deliver high levels of miR-218 via exosomes (45). Elevated miR-218 inhibits the bone remodeling function of OPG and consequently activates the RANKL/RANK pathway, thereby promoting osteolysis.

Another miRNA, miR-34, serves a key role in osteoblast inhibition during breast cancer bone metastasis. Osterix (Osx) is a core transcription factor for osteoblast differentiation and regulates the synthesis of bone matrix proteins, including type I collagen and osteocalcin. Osx deficiency has been reported to be associated with a ~70% reduction in mineralized nodule formation and a marked impairment in bone repair capacity (46,47). It has been reported that miR-34c directly binds to the 3'-UTR of Osx mRNA, mediating its degradation via the RNA-induced silencing complex, thereby inhibiting Osx protein expression (48-50). In addition to this direct effect, miR-34c also targets large tumor suppressor kinase 1, inhibiting its phosphorylation and inducing the nuclear translocation of Yes-associated protein and transcriptional coactivator with PDZ-binding motif, which further suppresses osteoblast differentiation (51). In addition, Osx deficiency indirectly attenuates Wnt pathway activity by reducing β-catenin nuclear translocation efficiency, ultimately diminishing osteogenesis (52). Therefore, through both direct binding and indirect mechanisms, miR-34c downregulates Osx, impairs bone matrix repair and exacerbates the cancer cell-induced destruction of bone.

Beyond osteoclast activation and osteoblast inhibition, miRNAs play a major role in the osteolytic cycle. Exosomes secreted by breast cancer cells carry miR-21, which targets osteoclast precursors and mesenchymal stem cells in the bone microenvironment via surface integrins. Following uptake, the exosomes release large amounts of miR-21, which directly

suppress the expression of programmed cell death 4 (PDCD4), a tumor suppressor gene, in osteoclasts. This suppression activates nuclear factor of activated T cells 1 (NFATc1) signaling, thereby promoting osteoclast differentiation (37). As osteoclast activity intensifies and bone matrix degradation progresses, osteoclasts release TGF-β, forming concentration gradients in the tumor microenvironment that attract breast cancer cells toward the resorption sites (53). This resulting accumulation of tumor cells and TGF-β facilitates the binding of TGF-β to the TGF-β receptor type II on tumor cell surfaces, activating the SMAD2/3 signaling pathway. This activation induces tumor cells to secrete insulin-like growth factor-1 (IGF-1) and platelet-derived growth factor (PDGF), which promote tumor proliferation and survival, as well as tumor angiogenesis and fibroblast activation (54). Increased tumor burden leads to increased miR-21 secretion, which accelerates the osteolytic process by promoting osteoclast-mediated bone resorption and leading to further TGF-β release from the bone matrix. Elevated TGF-β, in turn, upregulates miR-21 transcription via SMAD4 binding to the miR-21 promoter, thereby forming a positive feedback loop. This reciprocal reinforcement leads to persistently high TGF-β concentrations in the bone microenvironment (55). Concurrently, TGF-β induces miR-19a expression, which targets PTEN in osteoblasts, inhibiting bone matrix repair and exacerbating osteolytic destruction (56). In summary, exosomal miR-21 drives the malignant osteolytic cycle of breast cancer bone metastasis through activation of the PDCD4/NFATc1 axis in osteoclasts, leading to bone matrix degradation, the release TGF-β, induction of IGF-1 and PDGF secretion, and subsequent tumor proliferation'.

Liver metastasis. The liver is a common and lethal site of metastasis in TNBC, involving a complex regulatory network in which EVs, particularly exosomes, and miRNAs together modulate metabolism, immune responses and microenvironmental homeostasis (31). miR-122 serves as a central metabolic regulator in this process. Tumor-derived exosomes deliver miR-122 to non-tumor cells in distant organs such as the liver, thereby executing a metabolic reprogramming strategy by directly targeting and inhibiting the translation of PKM2 (29). PKM2 is a key rate-limiting enzyme in glycolysis. Its inhibition reduces hepatic glycolytic capacity, forcing increased glucose availability for tumor cells, while also leading to the accumulation of glycolytic intermediates, including PEP and 3-PG. These intermediates are subsequently diverted into the PPP and the serine synthesis pathway, generating NADPH and nucleotide precursors that support metastatic growth, redox balance and biosynthetic demands (30,31). This metabolic rewiring enhances the Warburg effect, characterized by aerobic glycolysis within tumor cells, supplying energy and biosynthetic precursors required for metastatic growth (29,57).

Circ-phosphoglycerate dehydrogenase (PHGDH) promotes aerobic glycolysis by binding to miR-122-5p, thereby relieving the miR-122-5p-mediated repression of PKM2. Conversely, silencing circPHGDH restores the miR-122-5p-mediated suppression of PKM2, resulting in reduced glycolytic activity and invasive capacity in tumor cells (58).

In addition to its local metabolic functions, miR-122 supports metastasis by inducing systemic cachexia. miR-122 packaged within EVs targets O-GlcNAc transferase (OGT) in skeletal muscle, leading to a reduction in the OGT-mediated O-GlcNAcylation of downstream substrates, (59), particularly that of sarcoplasmic reticulum ryanodine receptor 1, thereby increasing its protein abundance and elevating intracellular calcium ion (Ca^{2+}) levels. The Ca^{2+} overload activates calpain, which degrades myofibrillar structural proteins, including desmin, and ultimately results in muscle wasting (59). This process releases nutrients such as amino acids into the circulatory system, indirectly providing metabolic substrates for liver metastasis growth.

miR-122 also directly disrupts the intrinsic microenvironment of the liver. The absence of miR-22 in hepatocytes upregulates the bile acid synthase hydroxy-δ5-steroid dehydrogenase, 3 β- and steroid δ-isomerase 7, leading to bile acid accumulation, while simultaneously downregulating hepatic nuclear factor 4α. These alterations reshape the hepatic microenvironment in a manner that promotes breast cancer metastasis (60).

The establishment of an immunosuppressive microenvironment represents another key pillar of liver metastasis, primarily driven by exosomal miR-21. Following the uptake of miR-21-carrying breast cancer exosomes by hepatic Kupffer cells, miR-21 suppresses NF-κB activation downstream of the Toll-like receptor 4 signaling pathway. This suppression reduces the release of pro-inflammatory factors, including TNF-α, thereby weakening the antitumor immune response (61). Concurrently, miR-21 induces the polarization of macrophages/Kupffer cells toward an immunosuppressive M2 phenotype, promoting the secretion of immunosuppressive cytokines such as IL-10 (62,63). In a metastatic breast cancer mouse model, these changes were associated with a marked increase in the proportion of myeloid-derived suppressor cells within the liver, a ~60% reduction in T-cell proliferation capacity, and a substantial impairment of the antitumor immunity of the liver microenvironment (61,62). In addition to immunomodulation, tumor-derived EVs and other extracellular particles can induce hepatic metabolic dysfunction, which also facilitates metastasis (62).

Lung metastasis. The development of lung metastasis is driven by a sequential and collaborative miRNA network that orchestrates the following three phases: PMN formation, immune evasion and metastatic colonization.

Phase I: PMN formation by vascular barrier disruption and matrix activation. Circulating exosomal miR-105 targets the tight junction protein ZO-1 in pulmonary vascular endothelial cells, compromising endothelial integrity and increasing vascular permeability, thereby facilitating tumor cell extravasation (10). Concurrently, exosomal miR-21 and miR-10b are internalized by resident pulmonary fibroblasts. miR-10b inhibits the translation of homeobox D10 (HOXD10), a transcriptional repressor of pro-metastatic genes, which leads to the derepression of downstream effectors such as RhoC and matrix metalloproteinases (MMPs) that enhance invasiveness (64,65). miR-21 targets tumor suppressor genes, including PTEN and PDCD4, resulting in the activation of key signaling pathways, including the PI3K/Akt and NF-κB pathways. Through these pathways, miR-21 promotes the activation of fibroblasts and their transformation into cancer-associated fibroblasts (CAFs) (66). Activation of the TGF-β/SMAD

Table I. Core mechanisms by which tumor-derived exosomal microRNAs prime distant organs for triple-negative breast cancer metastasis.

Metastatic site	Key miRNA	Target cells	Molecular target/pathway	Functional outcome	(Refs.)
Brain	miR-105	Endothelial cells	ZO-1, tight junctions	Disrupts blood-brain barrier integrity and promotes extravasation	(10)
	miR-19a	Astrocytes	PTEN and SOCS1 suppression leading to STAT3 activation	Induces a pro-survival niche and metabolic reprogramming	(23)
Bone	miR-21	Osteoclast precursors	PDCD4 suppression leading to NFATc1 activation	Promotes osteoclast differentiation and initiates the osteolytic cycle	(37)
Liver	miR-122	Hepatocytes	PKM2 inhibition affecting glycolysis	Reprograms metabolism by diverting flux to the pentose phosphate and serine pathways for anabolic support	(29)
Lung	miR-200 family	Macrophages and autocrine cells	Sec23a suppression in the secretory pathway	Inhibits secretion of metastasis suppressors IGFBP4 and TINAGL1, and promotes metastatic colonization	(68,69)

miRNA/miR, microRNA; ZO-1, zonula occludens protein 1; SOCS1, suppressor of cytokine signaling 1; PDCD4, programmed cell death 4; NFATc1, nuclear factor of activated T cells 1; PKM2, pyruvate kinase M2; IGFBP4, insulin-like growth factor-binding protein 4; TINAGL1, tubulointerstitial nephritis antigen-like 1.

pathway further sustains this phenotypic switch and drives extracellular matrix remodeling. Activated CAFs secrete substantial amounts of IL-6, TGF-β and extracellular matrix components, remodeling the pulmonary interstitium into a pro-inflammatory and fibrotic PMN (66). Additionally, miR-24 contributes to the establishment of a pro-angiogenic and immunosuppressive microenvironment by downregulating the methyltransferase adenosine phosphomethyladenosine gene in pulmonary stromal cells (67).

Phase II: Establishing an immunosuppressive niche. Tumor-derived exosomes reaching the alveoli deliver miR-122 to alveolar macrophages (29). miR-122 inhibits glycolysis in these macrophages by suppressing PKM2, inducing a metabolic shift that promotes their polarization toward an immunosuppressive M2 phenotype, thereby weakening local immune surveillance (29). Conversely, tumor-associated macrophages (TAMs) secrete exosomes carrying miR-223-3p, which are internalized by breast cancer cells. miR-223-3p suppresses the chromatin regulator chromobox 5, leading to epigenetic derepression of pro-metastatic genes such as MMPs, consequently increasing tumor cell invasiveness (66).

Phase III: Dual role of miR-200 in metastatic colonization and growth. The function of the miR-200 family exhibits spatiotemporal context dependence during metastasis (68). In the early stages of dissemination, high levels of miR-200 within tumor cells help maintain E-cadherin expression and an epithelial phenotype, potentially inhibiting initial detachment from the primary tumor (68). However, during later stages of metastatic colonization, miR-200 actively remodels the pulmonary microenvironment to support clonal expansion. A key mechanism involves the inhibition of the vesicular transport protein Sec23a, which suppresses the secretion of tumor suppressor factors, including insulin-like growth factor-binding protein 4 (IGFBP4) and tubulointerstitial nephritis antigen-like 1 (68,69). This effect complements the contact-induced upregulation of miR-199a-3p by mesenchymal stem cells, which enhances tumor stemness by suppressing the transcription factor forkhead box P2, thereby boosting metastatic potential (70). Concurrently, miR-9 induces pulmonary fibroblasts to release vascular endothelial growth factor, which promotes angiogenesis in metastatic foci (71).

3. Common regulatory mechanisms and organ-specific patterns

Common regulatory miRNAs. Several miRNAs, including miR-10b, miR-21, the miR-200 family and the miR-221/222 cluster, are recurrently involved in multiple metastatic sites. However, their mechanistic contributions exhibit pronounced organ-specific adaptations (Table I).

miR-10b is a quintessential pro-metastatic miRNA. Its core mechanism across contexts involves inhibition of HOXD10, leading to the derepression of pro-invasive genes such as RhoC and MMPs (64,72). However, its downstream effects vary by organ. In liver metastasis, miR-10b primarily promotes intrahepatic colonization via activation of the PTEN/Akt axis (73,74), whereas in lung metastasis it contributes to CAF

activation and PMN formation (66). By contrast, its roles in brain and bone metastasis remain incompletely characterized.

miR-21 functions as a central amplifier of metastatic progression. Its common mechanism is the targeting of tumor suppressors such as PDCD4 and PTEN (37,55). In bone metastasis, it drives the osteolytic cycle via the PDCD4/NFATc124 axis, whereas in liver metastasis it polarizes Kupffer cells to an M2 phenotype via the suppression of NF-κB signaling, which promotes immunosuppression (61,62). Additionally, in the lungs, miR-21 facilitates fibroblast activation and CAF formation (62). Although high levels of miR-21 have been associated with brain metastasis, the precise stromal targets are yet to be elucidated (75).

The miR-200 family epitomizes functional pleiotropy and context-dependency. While generally associated with maintenance of the epithelial phenotype, miR-200 family members display a temporal shift during metastasis. miR-200 supports lung and liver colonization by inhibiting Sec23a-mediated secretion of tumor suppressors, such as IGFBP4, as well as by regulating mesenchymal-epithelial transition (68,76). In the specific organ microenvironment of breast cancer brain metastasis, certain members of the miR-200 family (especially miR-141)- or an miRNA cluster composed of the miR-200 family and miR-29-actually promote brain metastasis by directly inhibiting the expression of the ADAM12 protein (77,78). Conversely, in bone metastasis, the downregulation of miR-429, another miR-200 family member, is associated with metastatic progression (79).

Finally, the miR-221/222 cluster promotes metastasis predominantly by targeting PTEN, activating the Akt pathway and downregulating E-cadherin (73,80). Strong associations have been reported with liver metastasis, where miR-221/222 enrich cancer stem cell (CSC) populations via PTEN/Akt signaling, and with lung metastasis, where they drive EMT by targeting the transcriptional repressor GATA binding 1 and the tumor suppressor PTEN (73,81). In brain metastasis, miR-221/222 compromises the BBB via E-cadherin loss (80). However, evidence supporting a role in bone metastasis is lacking.

Organ-specific miRNAs and metastasis mechanisms. In brain metastasis, miR-105 is characteristically expressed and secreted by metastatic breast cancer cells. Within the endothelial monolayer, tumor-secreted exosomes enriched in miR-105 accumulate, where miR-105 disrupts tight junctions and the integrity of natural metastatic barriers. The primary underlying mechanism is that miR-105 targets the endothelial tight junction protein ZO-1, thereby disrupting BBB permeability and facilitating tumor cell extravasation (10,82).

Another miRNA associated with brain metastasis is miR-19a, which activates the STAT3 signaling pathway in astrocytes, inducing the secretion of IL-6 and TGF-β release and forming a tumor survival-promoting microenvironment. Simultaneously, it suppresses glutamate transporter solute carrier family 1 member 2 in astrocytes, hijacking neural metabolism to promote tumor growth (82).

In bone metastasis, miR-218-5p inhibits OPG, thereby activating the RANKL/RANK/NFATc1 signaling pathway and enhancing osteoclast differentiation, leading to osteolytic destruction (31). Similarly, miR-21 targets the tumor suppressor PDCD4, leading to NFATc1 activation and increased osteoclast activation. In parallel, miR-21 induces the release of TGF-β from the bone matrix, which stimulates tumor cells to secrete IGF-1 and PDGF, thereby establishing a cycle from osteolysis to growth factor release and tumor proliferation (83,84).

In liver metastasis, miR-122-5p has been shown to regulate the mobility of breast cancer cells. Specifically, miR-122-5p is abundantly present in hepatocyte-derived exosomes, and is capable of suppressing syndecan-1 expression and increasing the invasive ability and survival of breast cancer cells. These findings indicate that the liver metastasis of breast cancer is highly likely to be associated with miR-122-5p (85).

miR-598-5p inhibits breast cancer growth and lung metastasis by targeting phosphatidic acid phosphatase type 2 domain-containing protein 1A (86). Similarly, miR-134 inhibits breast cancer lung metastasis by suppressing SLUG and the EMT markers E-cadherin and N-cadherin (87). By contrast, Ras-related protein Rab1A promotes lung metastasis by facilitating the sorting of the tumor-suppressive miR-200c into exosomes, thereby reducing the inhibitory effect of miR-200c within tumor cells. The exosomal miR-200c derived from metastatic cells suppresses the immune response of $F4/80^+$ macrophages, thereby contributing to immune evasion. Notably, the administration of anti-Rab1A antibodies reduced the transport of miR-200c into exosomes and inhibited the metastasis of breast cancer to the lung (88). In addition, TAM-derived EVs have been reported to shuttle miR-660, which promotes the lung metastasis of breast cancer via activation of the Kelch like family member 21-mediated IKKβ/NF-κB p65 axis (89).

4. miRNA-targeted therapeutic strategies and challenges

Inhibiting pro-metastatic miRNAs. miRNAs serve important roles in the promotion of tumor growth and metastasis. Therefore, the identification of inhibitors of pro-metastatic miRNAs has become a major topic in the treatment of breast cancer.

Breast cancer metastasis suppressor 1 (BRMS1) suppresses metastasis in multiple tumor types without blocking tumorigenesis. Mechanistically, BRMS1 forms complexes with the transcriptional corepressor SIN3, histone deacetylases (HDACs) and selected transcription factors that alter metastasis-associated gene expression. Notably, BRMS1 upregulates the expression of several metastasis-suppressing miRNAs, including miR-146a, miR-146b and miR-335. Collectively, these findings indicate that BRMS1 coordinates the regulation of multiple metastasis-related miRNAs, potentially through the recruitment of BRMS1-containing SIN3:HDAC complexes to miRNA promoters, although the precise targets are yet to be identified (90).

Furthermore, miR-155 is upregulated in breast cancer. Research using soft agar colony formation assays and tumor xenograft models has demonstrated that the inhibition of miR-155 notably reduces cancer cell proliferation *in vitro* and *in vivo*, indicating that miR-155 may be a potential therapeutic target for breast cancer (91).

Supplementing tumor-suppressive miRNAs. The tumor-suppressive let-7 family of miRNAs has been identified to induce apoptosis, inhibit proliferation and suppress the

self-renewal capacity of CSCs. In a study assessing the inhibitory effect of let-7 miRNAs on the self-renewal capacity of TNBC CSCs, radiotherapy was found to suppress TNBC stem cell self-renewal by inhibiting cyclin D1 expression and Akt1 phosphorylation. Notably, let-7d enhanced the radiation-induced tumor suppression and synergized with radiotherapy to further inhibit CSC renewal. Western blotting, immunofluorescence and luciferase reporter assays suggested that reduced cyclin D1/Akt1/Wnt1 signaling activity contributed to the observed let-7-induced radiosensitization. Let-7 was shown to directly inhibit cyclin D1 expression, leading to hypophosphorylation of Akt1, and the suppression of mammosphere formation. Furthermore, let-7d-induced Akt1 inhibition exhibited tumor-suppressive effects comparable to those obtained with Akt inhibitors (92).

miR-708-3p has been reported to suppress EMT in breast cancer cells by directly targeting EMT activators, including zinc finger E-box binding homeobox 1, cadherin 2 (N-cadherin) and vimentin, thereby functioning as a cancer-suppressing miRNA in breast cancer (93). miR-381-3p expression is markedly downregulated in breast cancer tissues and cell lines. Functional studies have shown that the overexpression of miR-381-3p inhibits breast cancer proliferation and invasion in MDA-MB-231 and SKBR3 cells, whereas its knockdown promotes these behaviors. Mechanistically, miR-381-3p suppresses EMT by targeting Sox4 and Twist1 to regulate TGF-β signaling and inhibit breast cancer progression (94). Collectively, these findings support the upregulation of tumor-suppressive miRNAs as another potential therapeutic approach for the suppression of breast cancer progression.

Exosome engineering. The BBB inherently limits the entry of therapeutic drugs into the brain. Exosomes, a type of membrane-bound secreted lipid vesicle, are able to penetrate the BBB and may be used to deliver anticancer drugs to brain tumors at therapeutic levels. The capacity of exosomes to traverse the BBB is attributed primarily to transcytosis, an active transport mechanism involving endocytic uptake by brain endothelial cells, intracellular vesicular trafficking and exocytosis on the abluminal side (95-97). This process occurs predominantly via receptor-mediated transcytosis (RMT), wherein surface ligands on exosomes engage specific receptors on cerebral endothelial cells triggering internalization (97). Inflammation and the presence of metastatic tumor cells have been shown to enhance exosome trafficking across the barrier, although the precise molecular regulators remain under investigation (98). Engineered exosomes have been explored to exploit these pathways for targeted central nervous system (CNS) delivery. Engineering chimeric antigen receptor (CAR)-natural killer cell-derived exosome disguised nano-bombs for enhanced HER2-positive breast cancer brain metastasis therapy (99). These exosomes were dually modified: Surface expression of anti-HER2 single-chain variable fragment from CAR construct for tumor cell recognition, and conjugation with T7 peptide (HAIYPRH), which binds the transferrin receptor on brain endothelial cells. This design enhanced BBB penetration via RMT and achieved selective targeting of HER2-positive breast cancer brain metastases in orthotopic mouse models, significantly extending survival (99). Zhao *et al* (100) engineered exosomes from human adipose-derived mesenchymal stem cells (hAMSCs) modified to express anti-CD19 antibodies on their surface. These anti-CD19-Exos were loaded with methotrexate (MTX) and demonstrated enhanced BBB permeability in an *in vitro* model comprising hCMEC/D3 endothelial cells and astrocytes. In an intracranial CNS lymphoma model, systemically administered anti-CD19-Exo-MTX achieved sustained drug levels in cerebrospinal fluid, reduced disease burden and prolonged survival compared to free MTX or unmodified Exo-MTX. Mechanistic analysis indicated that exosome interaction with cerebrovascular endothelial cells and astrocytes facilitated endocytosis and subsequently facilitated the transportation of MTX across the barrier (100).

5. Clinical bottlenecks

Organ-targeted delivery efficiency. Although exosomes show promise for tumor-targeted therapy, several challenges remain. For example, exosome isolation and purification methods lack standardization, and variability in cargo composition, size and exosome source complicates their use in tumor therapy. In addition, achieving a high drug-loading efficiency in exosomes is challenging, and the scaling up of exosome production is a core bottleneck for this therapeutic approach (101).

miR-10b inhibitor hepatotoxicity. Research indicates that therapeutic miR-10b inhibition in breast cancer treatment requires strict dosage control. A preclinical study revealed that a ~25-mg/kg dose (the drug is miR-10b antagomir, administered systemically, specifically via intravenous injection) is associated with elevated levels of the liver toxicity markers aspartate aminotransferase and alanine aminotransferase, whilst antitumor activity requires relatively high doses. This narrow therapeutic window is a major obstacle to the clinical translation of miR-10b-targeted therapies in breast cancer (102,103). These toxic effects may be attributable to the hepatic accumulation of oligonucleotides and potential immune activation (104).

6. Conclusions

The metastasis of TNBC to distant organs is not a random event but a finely orchestrated process mediated by tumor-derived exosomes acting as systemic messengers. The present review delineates a unifying paradigm in which primary tumors release exosomes packed with specific miRNAs that home to distant organs, where they reprogram stromal cells, including endothelial cells, astrocytes, osteoclasts, hepatocytes, fibroblasts and macrophages, by targeting key genes. This 'exosomal miRNA-stromal target gene-microenvironment reprogramming' axis drives the formation of a PMN, thereby establishing the 'soil' for the subsequent 'seed'.

Organ-specific metastasis is the leading cause of mortality in patients with TNBC, with complex molecular mechanisms dependent on the microenvironment of each target organ. The present review systematically summarizes the core role of exosome-mediated miRNA signaling in inter-organ communication during in the formation of the PMN for TNBC metastasis. In brain metastasis, miR-105 promotes tumor

colonization by targeting ZO-1 and thereby disrupting the BBB, while miR-19a activates STAT3 signaling in astrocytes. In bone metastasis, miR-218-5p disrupts the OPG/RANKL balance, while miR-21 forms an osteolytic feedback loop linking bone resorption with growth factor release and tumor proliferation. In liver metastasis, miR-122 dominates metabolic reprogramming by inhibiting PKM2, and contributes to immune evasion, and in lung metastasis, members of the miR-200 family regulate endothelial permeability and the EMT process. Collectively, these findings demonstrate that a cascade reaction in which miRNA interacts with a target gene and induces microenvironment remodeling is a common framework for organ metastasis.

Despite these advances, innovation in organ-targeted delivery systems remains a major translational challenge. A recent study by Jiang *et al* (105) provides a novel example of an emerging therapeutic strategy. This comprises a degradable puncture implant loaded with $Cu_{0.5}Mn_{2.5}O_4$ nanoparticles, which releases ions slowly to induce cuproptosis and activate the cyclic GMP-AMP synthase-stimulator of interferon genes pathway. This increases intratumoral $CD8^+$ T cell infiltration, and so may have potential for use in the local precision therapy of inoperable TNBC.

TNBC organ specificity is determined by complex miRNA regulatory networks that integrate intrinsic tumor cell properties, such as EMT and stemness, with the reshaping of distant microenvironments via exosome-mediated inter-organ communication. Although miRNA-targeted therapies face challenges such as delivery efficiency, hepatotoxicity and scalable production, advances in engineered exosomes, implantable slow-release systems and artificial intelligence-based prediction models hold promise (106). Combining targeted therapy with immune modulation may be a precise approach with the potential to improve the outcomes of patients with metastatic TNBC. Future research integrating single-cell sequencing, spatial transcriptomics and dynamic imaging are necessary to decipher the spatiotemporal heterogeneity of the metastatic process, ultimately advancing the clinical translation of miRNAs as key regulators of organ-specific metastasis.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

LB was responsible for revising the manuscript and updating content, building frameworks and developing ideas. RB was responsible for writing the manuscript and initial language editing. Data authentication is not applicable. Both authors read and approved the final version of the 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.

References

1. Wu SY, Wang H, Shao ZM and Jiang YZ: Triple-negative breast cancer: New treatment strategies in the era of precision medicine. Sci China Life Sci 64: 372-388, 2021.
2. Denkert C, Liedtke C, Tutt A and von Minckwitz G: Molecular alterations in triple-negative breast cancer-the road to new treatment strategies. Lancet 389: 2430-2442, 2017.
3. Bianchini G, Balko JM, Mayer IA, Sanders ME and Gianni L: Triple-negative breast cancer: Challenges and opportunities of a heterogeneous disease. Nat Rev Clin Oncol 13: 674-690, 2016.
4. Llévenes P, Chen A, Lawton M, Rondón-Ortiz AN, Qiu Y, Seen M, Monti S and Denis GV: Plasma exosomes in insulin resistant obesity exacerbate progression of triple negative breast cancer. BMC Cancer 25: 1089, 2025.
5. Reddy SM, Barcenas CH, Sinha AK, Hsu L, Moulder SL, Tripathy D, Hortobagyi GN and Valero V: Long-term survival outcomes of triple-receptor negative breast cancer survivors who are disease free at 5 years and relationship with low hormone receptor positivity. Br J Cancer 118: 17-23, 2018.
6. Ding L, Xu Y, Li C and Chen X: Clinical characteristics, prognosis, and prognostic factors of patients with second primary triple-negative breast cancer: A study based on surveillance, epidemiology, and end results database. Eur J Cancer Prev 34: 316-328, 2025.
7. Alzubi MA, Turner TH, Olex AL, Sohal SS, Tobin NP, Recio SG, Bergh J, Hatschek T, Parker JS, Sartorius CA, *et al*: Separation of breast cancer and organ microenvironment transcriptomes in metastases. Breast Cancer Res 21: 36, 2019.
8. Wang C, Fan P, Zhou Y, Ma M, Zhong H, Liu L, Chen Q and Xu K: Heterogeneous tissue-specific macrophages orchestrate metastatic organotropism of breast cancer: Implications for promising therapeutics. J Transl Med 23: 692, 2025.
9. Qixiang MA, Xiaodan Z, Kaiwen HU and Chao AN: New thoughts upon seed and soil hypothesis of tumor metastasis. Cancer Res Prev Treat 42: 1049-1053, 2015.
10. Zhou W, Fong MY, Min Y, Somlo G, Liu L, Palomares MR, Yu Y, Chow A, O'Connor STF, Chin AR, *et al*: Cancer-secreted miR-105 destroys vascular endothelial barriers to promote metastasis. Cancer Cell 25: 501-515, 2014.
11. Navarro G, Gómez-Autet M, Morales P, Rebassa JB, Llinas Del Torrent C, Jagerovic N, Pardo L and Franco R: Homodimerization of CB_2 cannabinoid receptor triggered by a bivalent ligand enhances cellular signaling. Pharmacol Res 208: 107363, 2024.
12. Bai S, Wei Y, Liu R, Xu R, Xiang L and Du J: Role of tumour-derived exosomes in metastasis. Biomed Pharmacother 147: 112657, 2022.
13. Peinado H, Zhang H, Matei IR, Costa-Silva B, Hoshino A, Rodrigues G, Psaila B, Kaplan RN, Bromberg JF, Kang Y, *et al*: Pre-metastatic niches: Organ-specific homes for metastases. Nat Rev Cancer 17: 302-317, 2017.
14. Ganesh K and Massagué J: Targeting metastatic cancer. Nat Med 27: 34-44, 2021.
15. Wu S, Lu J, Zhu H, Wu F, Mo Y, Xie L, Song C, Liu L, Xie X, Li Y, *et al*: A novel axis of circKIF4A-miR-637-STAT3 promotes brain metastasis in triple-negative breast cancer. Cancer Lett 581: 216508, 2024.
16. Li J, Liu M, Zeng B and Wang Z: Propofol induces hepatocellular carcinoma cell apoptosis via regulating miR-105/JAK2/STAT3 axis. Cytokine 148: 155649, 2021.
17. Morad G, Carman CV, Hagedorn EJ, Perlin JR, Zon LI, Mustafaoglu N, Park TE, Ingber DE, Daisy CC and Moses MA: Tumor-derived extracellular vesicles breach the intact blood-brain barrier via transcytosis. ACS Nano 13: 13853-13865, 2019.

18. Lee JY, Park K, Lee E, Ahn T, Jung HH, Lim SH, Hong M, Do IG, Cho EY, Kim DH, *et al*: Gene expression profiling of breast cancer brain metastasis. Sci Rep 6: 28623, 2016.
19. Sato R, Nakano T, Hosonaga M, Sampetrean O, Harigai R, Sasaki T, Koya I, Okano H, Kudoh J, Saya H and Arima Y: RNA sequencing analysis reveals interactions between breast cancer or melanoma cells and the tissue microenvironment during brain metastasis. Biomed Res Int 2017: 8032910, 2017.
20. Zhang B, Li X, Tang K, Xin Y, Hu G, Zheng Y, Li K, Zhang C and Tan Y: Adhesion to the brain endothelium selects breast cancer cells with brain metastasis potential. Int J Mol Sci 24: 7087, 2023.
21. Chen X, Feng J, Chen W, Shao S, Chen L and Wan H: Small extracellular vesicles: From promoting pre-metastatic niche formation to therapeutic strategies in breast cancer. Cell Commun Signal 20: 141, 2022.
22. Sharma R, Sharma R, Khaket TP, Dutta C, Chakraborty B and Mukherjee TK: Breast cancer metastasis: Putative therapeutic role of vascular cell adhesion molecule-1. Cell Oncol (Dordr) 40: 199-208, 2017.
23. Zhang L, Zhang S, Yao J, Lowery FJ, Zhang Q, Huang WC, Li P, Li M, Wang X, Zhang C, *et al*: Microenvironment-induced PTEN loss by exosomal microRNA primes brain metastasis outgrowth. Nature 527: 100-104, 2015.
24. Priego N, Zhu L, Monteiro C, Mulders M, Wasilewski D, Bindeman W, Doglio L, Martínez L, Martínez-Saez E, Ramón Y Cajal S, *et al*: STAT3 labels a subpopulation of reactive astrocytes required for brain metastasis. Nat Med 24: 1024-1035, 2018.
25. Altea-Manzano P, Doglioni G, Liu Y, Cuadros AM, Nolan E, Fernández-García J, Wu Q, Planque M, Laue KJ, Cidre-Aranaz F, *et al*: A palmitate-rich metastatic niche enables metastasis growth via p65 acetylation resulting in pro-metastatic NF-κB signaling. Nat Cancer 4: 344-364, 2023.
26. Wormald S, Zhang JG, Krebs DL, Mielke LA, Silver J, Alexander WS, Speed TP, Nicola NA and Hilton DJ: The comparative roles of suppressor of cytokine signaling-1 and -3 in the inhibition and desensitization of cytokine signaling. J Biol Chem 281: 11135-11143, 2006.
27. Yamamoto T, Matsuda T, Muraguchi A, Miyazono K and Kawabata M: Cross-talk between IL-6 and TGF-beta signaling in hepatoma cells. FEBS Lett 492: 247-253, 2001.
28. Cao M, Isaac R, Yan W, Ruan X, Jiang L, Wan Y, Wang J, Wang E, Caron C, Neben S, *et al*: Cancer-cell-secreted extracellular vesicles suppress insulin secretion through miR-122 to impair systemic glucose homeostasis and contribute to tumour growth. Nat Cell Biol 24: 954-967, 2022.
29. Fong MY, Zhou W, Liu L, Alontaga AY, Chandra M, Ashby J, Chow A, O'Connor STF, Li S, Chin AR, *et al*: Breast-cancer-secreted miR-122 reprograms glucose metabolism in premetastatic niche to promote metastasis. Nat Cell Biol 17: 183-194, 2015.
30. Al Ageeli E: Dual roles of microRNA-122 in hepatocellular carcinoma and breast cancer progression and metastasis: A comprehensive review. Curr Issues Mol Biol 46: 11975-11992, 2024.
31. Rathore D, Jain S, Patel S, Dharwal N, Shukla N, Desai C, Shah J and Dave HV: MicroRNA-driven organ-specific metastasis in triple-negative breast cancer: Biogenesis, mechanisms, and therapeutic approaches. Med Oncol 42: 296, 2025.
32. Arya SB, Chen S, Jordan-Javed F and Parent CA: Ceramide-rich microdomains facilitate nuclear envelope budding for non-conventional exosome formation. Nat Cell Biol 24: 1019-1028, 2022.
33. Kanchan RK, Siddiqui JA, Mahapatra S, Batra SK and Nasser MW: microRNAs orchestrate pathophysiology of breast cancer brain metastasis: Advances in therapy. Mol Cancer 19: 29, 2020.
34. Udagawa N, Koide M, Nakamura M, Nakamichi Y, Yamashita T, Uehara S, Kobayashi Y, Furuya Y, Yasuda H, Fukuda C and Tsuda E: Osteoclast differentiation by RANKL and OPG signaling pathways. J Bone Miner Metab 39: 19-26, 2021.
35. Xiong S, Hu M, Li C, Zhou X and Chen H: Role of miR-34 in gastric cancer: From bench to bedside (Review). Oncol Rep 42: 1635-1646, 2019.
36. Uehara N, Shibusawa N, Mikami Y, Kyumoto-Nakamura Y, Sonoda S, Kato H, Yamaza T and Kukita T: Bone metastatic mammary tumor cell-derived extracellular vesicles inhibit osteoblast maturation via JNK signaling. Arch Biochem Biophys 750: 109821, 2023.
37. Yuan X, Qian N, Ling S, Li Y, Sun W, Li J, Du R, Zhong G, Liu C, Yu G, *et al*: Breast cancer exosomes contribute to pre-metastatic niche formation and promote bone metastasis of tumor cells. Theranostics 11: 1429-1445, 2021.
38. Ell B and Kang Y: SnapShot: Bone metastasis. Cell 151: 690-690.e1, 2012.
39. Kiechl S, Werner P, Knoflach M, Furtner M, Willeit J and Schett G: The osteoprotegerin/RANK/RANKL system: A bone key to vascular disease. Expert Rev Cardiovasc Ther 4: 801-811, 2006.
40. Baud'huin M, Lamoureux F, Duplomb L, Rédini F and Heymann D: RANKL, RANK, osteoprotegerin: Key partners of osteoimmunology and vascular diseases. Cell Mol Life Sci 64: 2334-2350, 2007.
41. Takayanagi H: RANKL as the master regulator of osteoclast differentiation. J Bone Miner Metab 39: 13-18, 2021.
42. Yu T, Wang Z, You X, Zhou H, He W, Li B, Xia J, Zhu H, Zhao Y, Yu G, *et al*: Resveratrol promotes osteogenesis and alleviates osteoporosis by inhibiting p53. Aging (Albany NY) 12: 10359-10369, 2020.
43. Wu L, Luo Z, Liu Y, Jia L, Jiang Y, Du J, Guo L, Bai Y and Liu Y: Aspirin inhibits RANKL-induced osteoclast differentiation in dendritic cells by suppressing NF-κB and NFATc1 activation. Stem Cell Res Ther 10: 375, 2019.
44. Wang FS, Wang CJ, Chen YJ, Huang YT, Huang HC, Chang PR, Sun YC and Yang KD: Nitric oxide donor increases osteoprotegerin production and osteoclastogenesis inhibitory activity in bone marrow stromal cells from ovariectomized rats. Endocrinology 145: 2148-2156, 2004.
45. Liu B, Tian Y, Li F, Zhao Z, Jiang X, Zhai C, Han X and Zhang L: Tumor-suppressing roles of miR-214 and miR-218 in breast cancer. Oncol Rep 35: 3178-3184, 2016.
46. Gao M, Zhang Z, Sun J, Li B and Li Y: The roles of circRNA-miRNA-mRNA networks in the development and treatment of osteoporosis. Front Endocrinol (Lausanne) 13: 945310, 2022.
47. Nakashima K, Zhou X, Kunkel G, Zhang Z, Deng JM, Behringer RR and de Crombrugghe B: The novel zinc finger-containing transcription factor osterix is required for osteoblast differentiation and bone formation. Cell 108: 17-29, 2002.
48. Tomasetti M, Monaco F, Rubini C, Rossato M, De Quattro C, Beltrami C, Sollini G, Pasquini E, Amati M, Goteri G, *et al*: AGO2-RIP-Seq reveals miR-34/miR-449 cluster targetome in sinonasal cancers. PLoS One 19: e0295997, 2024.
49. Yang X, Yang J, Lei P and Wen T: LncRNA MALAT1 shuttled by bone marrow-derived mesenchymal stem cells-secreted exosomes alleviates osteoporosis through mediating microRNA-34c/SATB2 axis. Aging (Albany NY) 11: 8777-8791, 2019.
50. Xu M, Jin H, Xu CX, Bi WZ and Wang Y: MiR-34c inhibits osteosarcoma metastasis and chemoresistance. Med Oncol 31: 972, 2014.
51. Wu X, Xiang H, Cong W, Yang H, Zhang G, Wang Y, Guo Z, Shen Y and Chen B: PLOD1, a target of miR-34c, contributes to cell growth and metastasis via repressing LATS1 phosphorylation and inactivating Hippo pathway in osteosarcoma. Biochem Biophys Res Commun 527: 29-36, 2020.
52. Wang S, Zhang S, Xu H, Zhang M, Liu X, Liu S, Li H and Hu Y: Ano5 deficiency leads to abnormal bone formation via miR-34c-5p/KLF4/β-catenin in gnathodiaphyseal dysplasia. Int J Mol Sci 26: 5267, 2025.
53. Padua D, Zhang XH, Wang Q, Nadal C, Gerald WL, Gomis RR and Massagué J: TGFbeta primes breast tumors for lung metastasis seeding through angiopoietin-like 4. Cell 133: 66-77, 2008.
54. Mohammad KS and Akhund SA: From tumor to bone: Growth factor receptors as key players in cancer metastasis. Front Biosci (Landmark Ed) 29: 184, 2024.
55. Han M, Wang F, Gu Y, Pei X, Guo G, Yu C, Li L, Zhu M, Xiong Y and Wang Y: MicroRNA-21 induces breast cancer cell invasion and migration by suppressing smad7 via EGF and TGF-β pathways. Oncol Rep 35: 73-80, 2016.
56. Liu Z, Xin B, Zhang N, An P, Shi Y, Yang J, Wan Y, He Y and Hu X: LSD1 modulates the bone metastasis of breast cancer cells through hnRNPA2B1-mediated sorting of exosomal miRNAs. Cell Death Discov 10: 115, 2024.
57. Faubert B, Solmonson A and DeBerardinis RJ: Metabolic reprogramming and cancer progression. Science 368: eaaw5473, 2020.

58. Shen J, Ma Z, Yang J, Qu T, Xia Y, Xu Y, Zhou M and Liu W: CircPHGDH downregulation decreases papillary thyroid cancer progression through miR-122-5p/PKM2 axis. BMC Cancer 24: 511, 2024.
59. Yan W, Cao M, Ruan X, Jiang L, Lee S, Lemanek A, Ghassemian M, Pizzo DP, Wan Y, Qiao Y, *et al*: Cancer-cell-secreted miR-122 suppresses O-GlcNAcylation to promote skeletal muscle proteolysis. Nat Cell Biol 24: 793-804, 2022.
60. Huang JH, Li YH, Hong JZ, Li RN, Wang R, Chen ZQ, Li SY, Chi YL, Huang JY and Zhu Y: Bile acid accumulation induced by miR-122 deficiency in liver parenchyma promotes cancer cell growth in hepatocellular carcinoma. Mol Ther Nucleic Acids 36: 102560, 2025.
61. Yi M, Xu L, Jiao Y, Luo S, Li A and Wu K: The role of cancer-derived microRNAs in cancer immune escape. J Hematol Oncol 13: 25, 2020.
62. Wang G, Li J, Bojmar L, Chen H, Li Z, Tobias GC, Hu M, Homan EA, Lucotti S, Zhao F, *et al*: Tumour extracellular vesicles and particles induce liver metabolic dysfunction. Nature 618: 374-382, 2023.
63. Bautista J and López-Cortés A: Deciphering organotropism reveals therapeutic targets in metastasis. Front Cell Dev Biol 13: 1677481, 2025.
64. Ma L, Teruya-Feldstein J and Weinberg RA: Tumour invasion and metastasis initiated by microRNA-10b in breast cancer. Nature 449: 682-688, 2007.
65. Frankel LB, Christoffersen NR, Jacobsen A, Lindow M, Krogh A and Lund AH: Programmed cell death 4 (PDCD4) is an important functional target of the microRNA miR-21 in breast cancer cells. J Biol Chem 283: 1026-1033, 2008.
66. Galardi A, Fogazzi V, Tottone C, Giussani M, Pupa SM, Cosentino G and Iorio MV: 'Small extracellular vesicles: Messengers at the service of breast cancer agenda in the primary and distant microenvironments'. J Exp Clin Cancer Res 44: 216, 2025.
67. Camps C, Saini HK, Mole DR, Choudhry H, Reczko M, Guerra-Assunção JA, Tian YM, Buffa FM, Harris AL, Hatzigeorgiou AG, *et al*: Integrated analysis of microRNA and mRNA expression and association with HIF binding reveals the complexity of microRNA expression regulation under hypoxia. Mol Cancer 13: 28, 2014.
68. Kundu ST, Byers LA, Peng DH, Roybal JD, Diao L, Wang J, Tong P, Creighton CJ and Gibbons DL: The miR-200 family and the miR-183~96~182 cluster target Foxf2 to inhibit invasion and metastasis in lung cancers. Oncogene 35: 173-186, 2016.
69. Korpal M, Ell BJ, Buffa FM, Ibrahim T, Blanco MA, Celià-Terrassa T, Mercatali L, Khan Z, Goodarzi H, Hua Y, *et al*: Direct targeting of Sec23a by miR-200s influences cancer cell secretome and promotes metastatic colonization. Nat Med 17: 1101-1108, 2011.
70. Cuiffo BG, Campagne A, Bell GW, Lembo A, Orso F, Lien EC, Bhasin MK, Raimo M, Hanson SE, Marusyk A, *et al*: MSC-regulated microRNAs converge on the transcription factor FOXP2 and promote breast cancer metastasis. Cell Stem Cell 15: 762-774, 2014.
71. Lefebvre CC, Giowachini P, Derrien J, Naour M, Corre I, Thirouard L, Douillard E, Chiron D, Guillonneau F, Treps L, *et al*: MCL-1 as a molecular switch between myofibroblastic and pro-angiogenic features of breast cancer-associated fibroblasts. Cell Death Dis 16: 603, 2025.
72. Ma L: Role of miR-10b in breast cancer metastasis. Breast Cancer Res 12: 210, 2010.
73. Li B, Lu Y, Yu L, Han X, Wang H, Mao J, Shen J, Wang B, Tang J, Li C and Song B: miR-221/222 promote cancer stem-like cell properties and tumor growth of breast cancer via targeting PTEN and sustained Akt/NF-κB/COX-2 activation. Chem Biol Interact 277: 33-42, 2017.
74. Zhuang G, Wu X, Jiang Z, Kasman I, Yao J, Guan Y, Oeh J, Modrusan Z, Bais C, Sampath D and Ferrara N: Tumour-secreted miR-9 promotes endothelial cell migration and angiogenesis by activating the JAK-STAT pathway. EMBO J 31: 3513-3523, 2012.
75. Bautista-Sánchez D, Arriaga-Canon C, Pedroza-Torres A, De La Rosa-Velázquez IA, González-Barrios R, Contreras-Espinosa L, Montiel-Manríquez R, Castro-Hernández C, Fragoso-Ontiveros V, Álvarez-Gómez RM and Herrera LA: The promising role of miR-21 as a cancer biomarker and its importance in RNA-based therapeutics. Mol Ther Nucleic Acids 20: 409-420, 2020.
76. Dykxhoorn DM, Wu Y, Xie H, Yu F, Lal A, Petrocca F, Martinvalet D, Song E, Lim B and Lieberman J: miR-200 enhances mouse breast cancer cell colonization to form distant metastases. PLoS One 4: e7181, 2009.
77. Debeb BG, Lacerda L, Anfossi S, Diagaradjane P, Chu K, Bambhroliya A, Huo L, Wei C, Larson RA, Wolfe AR, *et al*: miR-141-mediated regulation of brain metastasis from breast cancer. J Natl Cancer Inst 108: djw026, 2016.
78. Duhachek-Muggy S and Zolkiewska A: ADAM12-L is a direct target of the miR-29 and miR-200 families in breast cancer. BMC Cancer 15: 93, 2015.
79. Mock K, Preca BT, Brummer T, Brabletz S, Stemmler MP and Brabletz T: The EMT-activator ZEB1 induces bone metastasis associated genes including BMP-inhibitors. Oncotarget 6: 14399-14412, 2015.
80. Pan Y, Li J, Zhang Y, Wang N, Liang H, Liu Y, Zhang CY, Zen K and Gu H: Slug-upregulated miR-221 promotes breast cancer progression through suppressing E-cadherin expression. Sci Rep 6: 25798, 2016.
81. Matsas S, Ruiz Simões A, Nazareth Aguiar P Jr, Abdou Y, Krontiras H and Del Giglio A: Prognostic role of miR-190, miR-221, and miR-381 in breast cancer: A systematic review and meta-analysis. Eur Rev Med Pharmacol Sci 29: 301-312, 2025.
82. Bayat M and Sadri Nahand J: Exosomal miRNAs: The tumor's trojan horse in selective metastasis. Mol Cancer 23: 167, 2024.
83. Deng Z, Rong Y, Teng Y, Zhuang X, Samykutty A, Mu J, Zhang L, Cao P, Yan J, Miller D and Zhang HG: Exosomes miR-126a released from MDSC induced by DOX treatment promotes lung metastasis. Oncogene 36: 639-651, 2017.
84. Li J, Huang L, He Z, Chen M, Ding Y, Yao Y, Duan Y, Zixuan L, Qi C, Zheng L, *et al*: Andrographolide suppresses the growth and metastasis of luminal-like breast cancer by inhibiting the NF-κB/miR-21-5p/PDCD4 signaling pathway. Front Cell Dev Biol 9: 643525, 2021.
85. Uen Y, Wang JW, Wang C, Jhang Y, Chung JY, Tseng T, Sheu M and Lee S: Mining of potential microRNAs with clinical correlation-regulation of syndecan-1 expression by miR-122-5p altered mobility of breast cancer cells and possible correlation with liver injury. Oncotarget 9: 28165-28175, 2018.
86. Guo X, Yang F, Yu L, Wen R, Zhang X and Lin H: MiR-598-5p inhibits breast cancer tumor growth and lung metastasis by targeting PPAPDC1A. Chin J Physiol 66: 103-110, 2023.
87. Jiang Z, Pei L, Xie Y, Ye Q, Liang X, Ye Y and Liu S: Ruyiping formula inhibits metastasis via the microRNA-134-SLUG axis in breast cancer. BMC Complement Med Ther 21: 191, 2021.
88. Liu Y, Tang J, Qiu X, Teng LA, Sriwastva MK, Han X, Li Z, Liu M, Liu S, Da D, *et al*: Rab1A-mediated exosomal sorting of miR-200c enhances breast cancer lung metastasis. Breast Cancer (Dove Med Press) 15: 403-419, 2023.
89. Li C, Li R, Hu X, Zhou G and Jiang G: Tumor-promoting mechanisms of macrophage-derived extracellular vesicles-enclosed microRNA-660 in breast cancer progression. Breast Cancer Res Treat 192: 353-368, 2022.
90. Edmonds MD, Hurst DR, Vaidya KS, Stafford LJ, Chen D and Welch DR: Breast cancer metastasis suppressor 1 coordinately regulates metastasis-associated microRNA expression. Int J Cancer 125: 1778-1785, 2009.
91. Zuo J, Yu Y, Zhu M, Jing W, Yu M, Chai H, Liang C and Tu J: Inhibition of miR-155, a therapeutic target for breast cancer, prevented in cancer stem cell formation. Cancer Biomark 21: 383-392, 2018.
92. Sun H, Ding C, Zhang H and Gao J: Let-7 miRNAs sensitize breast cancer stem cells to radiation-induced repression through inhibition of the cyclin D1/Akt1/Wnt1 signaling pathway. Mol Med Rep 14: 3285-3292, 2016.
93. Lee JW, Guan W, Han S, Hong DK, Kim LS and Kim H: MicroRNA-708-3p mediates metastasis and chemoresistance through inhibition of epithelial-to-mesenchymal transition in breast cancer. Cancer Sci 109: 1404-1413, 2018.
94. Yu YZ, Mu Q, Ren Q, Xie LJ, Wang QT and Wang CP: miR-381-3p suppresses breast cancer progression by inhibition of epithelial-mesenchymal transition. World J Surg Oncol 19: 230, 2021.
95. Yang T, Martin P, Fogarty B, Brown A, Schurman K, Phipps R, Yin VP, Lockman P and Bai S: Exosome delivered anticancer drugs across the blood-brain barrier for brain cancer therapy in Danio rerio. Pharm Res 32: 2003-2014, 2015.
96. Kamerkar S, LeBleu VS, Sugimoto H, Yang S, Ruivo CF, Melo SA, Lee JJ and Kalluri R: Exosomes facilitate therapeutic targeting of oncogenic KRAS in pancreatic cancer. Nature 546: 498-503, 2017.
97. Abdelsalam M, Ahmed M, Osaid Z, Hamoudi R and Harati R: Insights into exosome transport through the blood-brain barrier and the potential therapeutical applications in brain diseases. Pharmaceuticals (Basel) 16: 571, 2023.

98. Li Y, Liu R and Zhao Z: Targeting brain drug delivery with macromolecules through receptor-mediated transcytosis. Pharmaceutics 17: 109, 2025.
99. Tao B, Du R, Zhang X, Jia B, Gao Y, Zhao Y and Liu Y: Engineering CAR-NK cell derived exosome disguised nano-bombs for enhanced HER2 positive breast cancer brain metastasis therapy. J Control Release 363: 692-706, 2023.
100. Zhao M, Li Q, Chai Y, Rong R, He L, Zhang Y, Cui H, Xu H, Zhang X, Wang Z, *et al*: An anti-CD19-exosome delivery system navigates the blood-brain barrier for targeting of central nervous system lymphoma. J Nanobiotechnology 23: 173, 2025.
101. Schapira M, Calabrese MF, Bullock AN and Crews CM: Targeted protein degradation: Expanding the toolbox. Nat Rev Drug Discov 18: 949-963, 2019.
102. Yang C, Kim SH, Bianco NR and Robbins PD: Tumor-derived exosomes confer antigen-specific immunosuppression in a murine delayed-type hypersensitivity model. PLoS One 6: e22517, 2011.
103. Ma L, Reinhardt F, Pan E, Soutschek J, Bhat B, Marcusson EG, Teruya-Feldstein J, Bell GW and Weinberg RA: Therapeutic silencing of miR-10b inhibits metastasis in a mouse mammary tumor model. Nat Biotechnol 28: 341-347, 2010.
104. Dai L, Yu P, Fan H, Xia W, Zhao Y, Zhang P, Zhang JZH, Zhang H and Chen Y: Identification and validation of new DNA-PKcs inhibitors through high-throughput virtual screening and experimental verification. Int J Mol Sci 25: 7982, 2024.
105. Jiang Y, Zhang W, Liu L, Wu Y, Li W, Liang J, Shen H, Fang S, Huang X, Chu Z, *et al*: Gelatin methacryloyl xerogel puncture implants loaded with $Cu_{0.5}Mn_{2.5}O_4$ nanoparticles synergizes cuproptosis and STING activation for enhanced breast cancer immunotherapy. ACS Nano 19: 27902-27918, 2025.
106. Lawson DA, Bhakta NR, Kessenbrock K, Prummel KD, Yu Y, Takai K, Zhou A, Eyob H, Balakrishnan S, Wang CY, *et al*: Single-cell analysis reveals a stem-cell program in human metastatic breast cancer cells. Nature 526: 131-135, 2015.