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Extracellular Vesicles in Breast Cancer: Tumor Microenvironment Crosstalk, Organotropic Metastasis, Immune Evasion, and Therapeutic Resistance

Naman Chauhan, Irina Nakashidze

Batumi Shota Rustaveli State University, Batumi, Georgia

Abstract

Breast cancer is a biologically heterogeneous malignancy in which disease progression, metastatic dissemination, immune escape, and therapeutic response are shaped by reciprocal interactions between tumor cells and the surrounding microenvironment. Extracellular vesicles (EVs) have emerged as important mediators of these interactions by transferring proteins, lipids, metabolites, and regulatory nucleic acids among malignant, stromal, endothelial, and immune-cell populations. Within the primary tumor microenvironment, EV-mediated signaling contributes to cancer-associated fibroblast activation, metabolic reprogramming, extracellular-matrix remodeling, angiogenic responses, and immune modulation. Hypoxic stress can further alter EV biogenesis and cargo composition, thereby reinforcing tumor adaptation and vascular remodeling. Beyond the primary tumor, breast-cancer-derived EVs participate in the establishment of organ-specific pre-metastatic niches in the bone, lung, liver, and brain by modifying vascular integrity, stromal-cell behavior, immune-cell function, and tissue-specific signaling networks. EV-associated microRNAs, long non-coding RNAs, proteins, and other bioactive cargos have been implicated in osteoclast activation, endothelial barrier disruption, macrophage reprogramming, suppression of antitumor immunity, and the

intercellular transmission of therapy-resistant phenotypes. These multifaceted functions position EVs as potential circulating biomarkers, therapeutic targets, and delivery platforms in breast cancer. However, their clinical translation remains constrained by EV heterogeneity, methodological variability in isolation and characterization, incomplete definition of cargo specificity and biodistribution, and limited prospective validation. This review critically synthesizes current evidence on EV-mediated microenvironmental crosstalk, organotropic metastasis, immune evasion, and therapeutic resistance in breast cancer, and highlights the methodological and translational priorities required to advance EV-based strategies toward clinical application.

KEYWORDS: Extraccellular vesicles; Breast cancer; tumor microenvironment, organotropic metastasis; immune evasion; therapeutic resistance

Introduction

Breast cancer is a disease characterized by molecular and clinical differences among its subtypes, which include Luminal A, Luminal B, HER2-enriched, and triple-negative breast cancer (TNBC) [1] . According to American Cancer Society, TNBC accounts for approximately 10% to 15% of all cases and is defined by its lack of estrogen receptors, progesterone receptors, and HER2 amplification [2]. Because of this, standard hormone-based or HER2-targeted therapies are not effective, leaving more conventional approach of systemic chemotherapy and surgery as the primary treatment option. The responses to such conventional therapies are commonly short-lived often preceding a rapid relapse often with visceral and brain metastasis. Novel therapies such as combination of AKT inhibitors + EZH2 inhibitors, CDK inhibition primed anti-PDL1, combination epigenetic therapy of a DNA methyltransferase (DNMT) inhibitor and a histone deacetylase (HDAC) inhibitor before ER modulator therapy and several other therapies are being explored but remain under investigation [3-5]. Extracellular vesicles (EVs) are lipid bilayer-enclosed particles released by almost all cell types into biological fluids like plasma and urine. Once considered a mechanism for cellular waste disposal, EVs are now recognized as mediators of communication between cells both locally and systemically [6]. These vesicles are categorized by their size and how they are formed. Exosomes originate from the endosomal pathway, while microves-

icles form through the outward budding of the cell membrane. Other types include apoptotic bodies and large oncosomes. In the tumor microenvironment, breast cancer cells release EVs that deliver microRNAs, such as miR-185-5p, miR-652-5p, and miR-1246, to neighboring cells like fibroblasts. This process can change the state of these fibroblasts, leading to alterations in cellular metabolism that support tumor growth [7]. This communication is bidirectional, as fibroblasts also release vesicles that influence the movement and growth of cancer cells. Additionally, low oxygen levels, or hypoxia, within a tumor increase the release of these vesicles. EVs also enter the bloodstream to reach distant organs like the bone, lungs, liver, and brain. At these sites, they prepare a pre-metastatic niche by increasing vascular permeability. Furthermore, EVs can transfer drug resistance by carrying molecules like P-glycoprotein to sensitive cells. Research into these processes aims to identify new biomarkers and clinical targets for treating metastatic breast cancer.

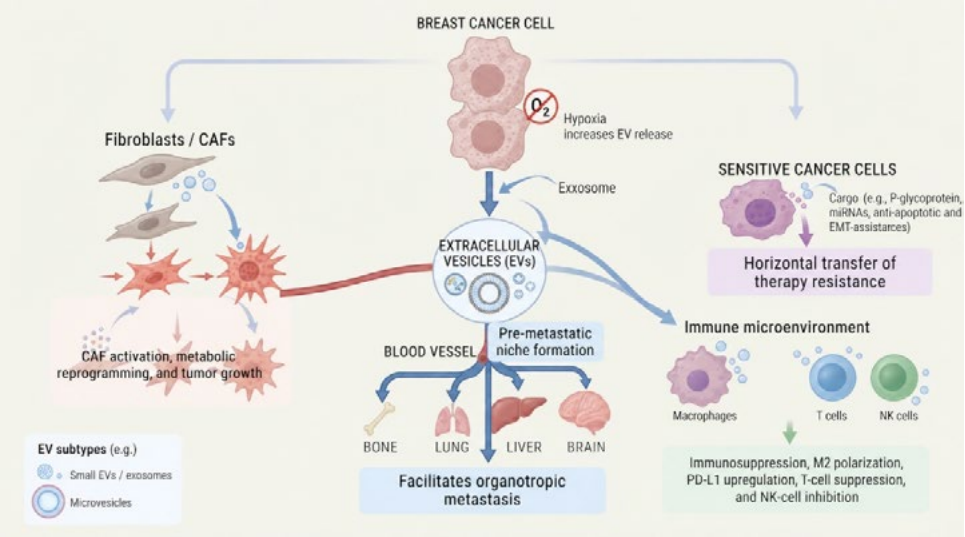


Fig. 1. Extracellular vesicle-mediated communication in breast cancer progression

Breast Cancer Heterogeneity and Extracellular Vesicle Diversity

Breast cancer is characterized by profound molecular and clinical heterogeneity. Standard oncology classifies breast cancer into distinct subtypes based on the expression profiles of estrogen receptors, progesterone receptors, and human epidermal growth factor receptor 2, comprising Luminal A, Luminal B, HER2-enriched, normal-like, and triple-negative (or basal-like) breast cancer; triple-negative breast cancer represents approximately 11%-20% of all cases, exhibiting a highly aggressive clinical

course, early metastatic dissemination, high rates of recurrence, and a complete lack of targetable hormone receptors or HER2 amplification [8]. This absence of receptor targets renders standard endocrine or HER2-targeted therapies ineffective, leaving systemic chemotherapies as the primary standard of care. Standard clinical oncology has also explored combinations such as Trodelvy (sacituzumab govitecan) alongside Keytruda (pembrolizumab) as first-line options for PD-L1-positive metastatic triple-negative breast cancer, or DNA-based therapies like Elenagen, highlighting the need for biomarkers and targeting methods such as PROTAC (Proteolysis Targeting Chimera) alongside delivery systems to counteract the poor cell penetration and instability in vivo [9]. Historically, until the late 1990s, extracellular vesicles were considered simple cellular waste disposal mechanisms. In contemporary cancer biology, however, they are recognized as multifunctional lipid bilayer-enclosed particles released by almost all cell types into biological fluids, such as plasma, urine, saliva, and milk, mediating complex local and systemic intercellular communication. Extracellular vesicles consist of heterogeneous subpopulations that reflect the state of their parental cells at the time of release [10].

TABLE 1. HETEROGENEITY OF EXTRACELLULAR VESICLES

Extracellular Vesicle Class	Diameter Range	Primary Biogenesis Pathway	Key Protein and Regulatory Markers	Lipid Membrane Enrichment
Exosomes (Small EVs)	3-150 nm	Endosomal pathway; inward budding of early endosomes to form intraluminal vesicles within multivesicular bodies.	CD63, CD81,CD9, Alix Hrs, STAM, RAB31, FLOT2	Cholesterol, sphingomyelin, ceramide [8]
Microvesicles (Ectosomes)	100–1000 nm	Direct outward budding and subsequent fission of the cell's plasma membrane.	Cytoskeletal components, small GTPases, calcium-dependent scramblases	Phosphatidylserine (translocated), cholesterol [8]
Apoptotic Bodies	>	Outward blebbing and cellular disassembly during programmed cell death.	Annexin V, histones, fragmented genomic DNA	Phosphatidylserine (outer leaflet) [8]
Large Oncosomes	1–10 μm	Non-apoptotic plasma membrane shedding from highly active, transformed cancer cells.	Tumor-specific oncoproteins, caveolin-1, lipid raft enzymes	Cholesterol, sphingomyelin

Note: Various classes of vesicles involved in Breast Cancer; they show great heterogeneity

Extracellular Vesicle-Mediated Crosstalk in the Breast Tumor Microenvironment

TME is a regulated network comprising cancer-associated fibroblasts, perivascular-like cells, endothelial cells, immune cells, mesenchymal stem cells, and extracellular matrix components [10]with variations on their methodology and results. The objective of this study is to assess the prevalence of Parkinsonism and its causes in a cohort of individuals age 64 years or older in Bambuí, a Brazilian town. In phase I, 1,186 people older than 64 years responded to a 9-question screening questionnaire for Parkinsonism. In phase II, all subjects who scored > or = 2 points on the test were examined independently by at least 2 movement disorder-trained physicians. A movement disorder senior specialist excluded or confirmed the diagnosis in all suspected cases. The response rate was high for both phases (96% for phase I and 94% for phase II. Single-cell RNA sequencing of triple-negative breast cancer tumors has revealed two distinct functional Cancer-associated fibroblasts (CAF) states (a myofibroblastic phenotype and a state characterized by high growth factor and immunomodulatory gene expression) along with two distinct perivascular-like cell states (differentiated and immature states) [11]. These stromal states exhibit distinct morphologies, spatial relationships, and functional properties in regulating the extracellular matrix. Conventional fibroblast activation is typically tracked using markers such as α-smooth muscle actin α-SMA) and fibroblast activation protein (FAP). Importantly, extracellular vesicles have emerged as primary regulatory players in the activation cascade that activates fibroblasts by the inflammatory mediators and soluble TNF α,β, IL-1,6; as well as direct cell-cell contacts mediated by Jagged1/Notch2 [11,12]. Breast cancer cells actively secrete small extracellular vesicles that deliver regulatory microRNAs-including miR-185-5p, miR-652-5p, and miR-1246-to normal fibroblasts, and therefore support the claim that extracellular vesicles have emerged as a regulatory component in such an activation cascade in breast cancer pathology [12]. Furthermore, small extracellular vesicles support the survival and growth of the primary tumor as the ones containing miR-105 can be transferred from breast cancer cells to cancer associated fibroblasts leading to downregulation of target genes to drive metabolic reprogramming via MYC signaling. Recent studies have revealed that CAFs release their own extracellular vesicles that are internalized by neighboring breast cancer cells, promoting EMT, cell migration, invasion, proliferation, and metabolic alterations thereby facilitating a bidirectional stromal-tumor communication [13]. Moreover, when the extracellular vesicles are mesenchymal stem cell derived, they may contain specific microRNAs, such as miR-205 and miR-31 which support the progression of the primary breast tumor.

Hypoxia, Angiogenesis, and Vascular Remodeling in Breast Cancer

Rapid tumor proliferation lowers the median partial pressure of oxygen to approximately 10mm Hg (1.4%vol/vol$O_{2)}$, relative to 65mm Hg (9.3% vol/vol O_2) in healthy breast tissue. This hypoxia stabilizes hypoxia-inducible factor 1 (HIF-1); its α-subunit is overexpressed in approximately 90% of BRCA1-related breast cancers, correlating with neoadjuvant therapy resistance and reduced survival [14,15].

Under hypoxia, primary breast cancer cells upregulate vascular endothelial growth factor A (VEGFA), von Willebrand factor, and eukaryotic translation elongation factor 1A2 (eEF1A2). This activates the PI3K/AKT and MAPK/ERK pathways, synergistically increasing VEGFA expression, particularly in HER2-enriched subtypes. Elevated HIF-1 additionally activates VE-cadherin, matrix metalloproteinases (MMP2, MMP9), Rac1, and Cdc42, driving cell adhesion, cytoskeletal remodeling, and vasculogenic mimicry (VM) [14,16].

Extracellular Vesicles in Organotropic Metastasis and Pre-Metastatic Niche Formation

Systemic dissemination of breast cancer cells to distant organs remains the primary driver of patient mortality by accounting for over 90% breast cancer related deaths [17]. Before circulating tumor cells colonize distant tissues, primary breast cancer-derived extracellular vesicles travel through the bloodstream to distant organs, preparing a favorable pre-metastatic niche characterized by increased vascular permeability, extracellular matrix remodeling, bone marrow-derived cell recruitment, angiogenesis, and immunosuppression [18].

TABLE 2. VESICLES THAT ARE RESPONSIBLE FOR METASTASIS IN SPECIFIC ORGANS THROUGHOUT THE BODY, THEIR TARGETED GENE OR MOLECULAR PATHWAYS, AND THE KEY PRE METASTATIC MECHANISM FACILITATED BY THE VESICLES

Target Metastatic Organ	Primary Vesicle Cargo	Targeted Gene or Molecular Pathway	Key Pre-Metastatic Mechanism	Reference
Bone	miR-21	Downregulates PDCD4 protein levels	Promotes osteoclast differentiation and activation, inducing osteolytic bone resorption.	[19]
Lung	LncRNA NEAT1	Sponges miR-141-3p, derepressing KLF12	Induces epithelial-mesenchymal transition and upregulates MMPs and ABC transporters.	[18]
	NDPK-B	Activates purinergic receptor P2Y1 and VEGFR2	Regulates purinergic signaling to promote endothelial migration, vascular hyperpermeability, and leakage.	[20]
	miR-105	Downregulates ZO-1 tight junction expression	Destabilizes endothelial cell-cell junctions, enhancing vascular permeability and extravasation.	[18]
Liver	miR-197	Downregulates text PPARG expression	Reduces E-cadherin and upregulates Vimentin, inducing epithelial-mesenchymal transition.	[18]
	miR-9-5p	Upregulates HMGCR, DHCR7,CH25H	Accumulates 25-HC, activating LXR (stemness) and M2 TAMs via IL-6/STAT3.	[18]
	Tspan8	Co-transports E-cadherin and p120-catenin	Induces mesenchymal-epithelial transition (MET) to facilitate macrometastatic colonization.	[18]

Note: Various primary vesicle cargos have been identified specific to organ metastasis.

Highly metastatic breast cancer cells, including the SCP28 subline, secrete exosomes enriched with miR-21. Following internalization by osteoclast precursor cells, exosomal miR-21 directly targets and downregulates programmed cell death protein 4 (PDCD4), accelerating osteoclast differentiation and bone degradation. Concurrently, primary breast cancer cells secrete parathyroid hormone-related protein (PTHrP).

PTHrP acts on osteoblasts to upregulate RANKL and downregulate OPG expression, establishing a RANKL/OPG imbalance that drives pathological osteoclast activity and bone resorption. This osteolytic degradation releases matrix-bound growth factors-specifically TGF-β, VEGF, insulin-like growth factors (IGFs), and calcium ions-creating a positive feedback loop that promotes tumor colonization and survival within the bone marrow niche [21].

Lungs are another target, as Exosomes deliver extracellular matrix (ECM) components, including fibronectin and laminin, altering tumor cell adhesion. Exosome-derived long non-coding RNA NEAT1 functions as a competing endogenous RNA (ceRNA) that sponges and downregulates miR-141-3p, thereby derepressing Kruppel-like factor 12 (KLF12) expression. This KLF12 upregulation activates epithelial-mesenchymal transition (EMT) pathways, increases matrix metalloproteinase (MMP) expression to degrade the local ECM, and elevates ATP-binding cassette (ABC) transporter expression, driving lung-specific invasion. Furthermore, exosomal miR-105 downregulates the tight junction protein zonula occludens-1 (ZO-1) in lung endothelial cells. This disrupts tight junctions and induces hyperpermeability, facilitating the extravasation of circulating tumor cells into the lung parenchyma [18,22].

In liver metastasis, exosomal miR-9-5p is transferred to hepatocytes and hepatic stellate cells, upregulating cholesterol synthesis enzymes, including HMG-CoA reductase (HMGCR), 7-dehydrocholesterol reductase (DHCR7), and cholesterol 25-hydroxylase (CH25H). This drives the localized accumulation of 25-hydroxycholesterol (25-HC), which activates liver X receptor (LXR) signaling to enhance tumor cell stemness. This 25-HC accumulation additionally drives M2-like macrophage polarization via the IL-6/STAT3 pathway, establishing an immunosuppressive hepatic niche [18].

In triple-negative breast cancer, tumor-derived extracellular vesicles stimulate resident hepatic endothelial cells to release CX3CL1, recruiting CX3CR1-expressing macrophages to the pre-metastatic niche. These recruited macrophages overexpress matrix metalloproteinase 9 (MMP9), causing vascular leakage and facilitating circulating tumor cell extravasation. Finally, tetraspanin 8-positive (Tspan8+) extracellular vesicles transfer E-cadherin and p120-catenin to the hepatic parenchyma, triggering mesenchymal-epithelial transition (MET) to facilitate circulating cancer cell colonization [18].

In Brain metastasis, Small extracellular vesicles (sEVs) serve as critical mediators throughout breast cancer via two primary mechanisms Blood-Brain Barrier (BBB) Disruption in which sEVs cross and physically disrupt the BBB by downregulating tight junction proteins and activating brain endothelial cells, which facilitates the transmigration of circulating tumor cells into the central nervous system, and Niche Induction where Within the brain parenchyma, sEVs target resident astrocytes and microglia to induce a neuro-inflammatory, immunosuppressive pre-metastatic niche that promotes metastatic colonization and subsequent tumor cell proliferation.

Extracellular Vesicle-Mediated Immune Modulation and Therapeutic Resistance

Neoplastic cells utilize EVs to suppress anti-tumor immunity through distinct paracrine pathways. First, EVs induce the polarization of macrophages into a tumor-supportive, M2-like phenotype within the tumor microenvironment (TME). Specifically, triple-negative breast cancer cells undergoing chemotherapy-induced apoptosis secrete apoptotic EVs enriched with the chemokine CXCL1. Phagocytosis of these vesicles by macrophages upregulates the infiltration of programmed death-ligand 1-positive PD-L1+ tumor-associated macrophages, a process inhibitable by Baohuoside I or the XIAOPI formula [10]with variations on their methodology and results. The objective of this study is to assess the prevalence of Parkinsonism and its causes in a cohort of individuals age 64 years or older in Bambuí, a Brazilian town. In phase I, 1,186 people older than 64 years responded to a 9-question screening questionnaire for Parkinsonism. In phase II, all subjects who scored > or = 2 points on the test were examined independently by at least 2 movement disorder-trained physicians. A movement disorder senior specialist excluded or confirmed the diagnosis in all suspected cases. The response rate was high for both phases (96% for phase I and 94% for phase II.

Second, tumor-derived exosomes metabolically reprogram tissue-resident macrophages within the pre-metastatic niche. These exosomes stimulate glycolysis via nuclear factor kappa B (NF-kB) signaling, thereby increasing glucose uptake and accelerating the conversion of pyruvate to lactate. The subsequent intracellular accumulation of lactate upregulates macrophage surface expression of PD-L1, which suppresses adaptive T-cell responses.

Third, tumor vesicles directly impair effector lymphocyte function. HER2-positive breast cancer cells overexpressing Neuromedin U secrete EVs enriched with TGFβ1 and PD-L1, which inhibit cytolytic CD8+ T cells, expand regulatory T-cell populations, and induce T-cell exhaustion. Concurrently, mesenchymal stem cell-derived EVs suppress natural killer (NK) cell cytotoxicity by downregulating key activating receptors, thereby impairing innate elimination of circulating tumor cells.

Beyond immunomodulation, EVs operate as functional vectors for the horizontal transfer of drug resistance. Breast cancer cells resistant to Paclitaxel, Adriamycin, Doxorubicin, or Cisplatin encapsulate resistance-associated biomolecules-including P-glycoprotein efflux transporters, anti-apoptotic factors targeting PTEN and BIM, and epithelial-mesenchymal transition regulators acting via the Wntβ-catenin or TGF-β pathways-into secreted vesicles. Internalization of these vesicles by sensitive recipient cells transfers the drug-resistant phenotype [10]with variations on their methodology and results. The objective of this study is to assess the prevalence of Parkinsonism and its causes in a cohort of individuals age 64 years or older in Bambuí, a Brazilian town.

In phase I, 1,186 people older than 64 years responded to a 9-question screening questionnaire for Parkinsonism. In phase II, all subjects who scored > or = 2 points on the test were examined independently by at least 2 movement disorder-trained physicians. A movement disorder senior specialist excluded or confirmed the diagnosis in all suspected cases. The response rate was high for both phases (96% for phase I and 94% for phase II. Furthermore, vesicles selectively incorporate membrane-type matrix metalloproteinases, such as MT1-MMP and ADAM10, which maintain proteolytic activity in the extracellular space and degrade the extracellular matrix to facilitate invasion and metastasis [23].

Discussion

Collectively, the studies reviewed here support extracellular vesicles (EVs) as important mediators of communication between breast cancer cells and the surrounding stromal, vascular, and immune compartments. Their biological effects are unlikely to reflect a single conserved mechanism; rather, they depend on EV source, molecular cargo, recipient-cell phenotype, breast cancer subtype, microenvironmental conditions, and treatment exposure. EVs should therefore be considered components of a broader intercellular signaling network rather than independent determinants of tumor behavior. This distinction is particularly important because much of the mechanistic evidence summarized in this review derives from experimental systems that may not fully reproduce the complexity and heterogeneity of human breast tumors. Within the primary tumor microenvironment, EV-mediated signaling may contribute to reciprocal adaptation between malignant and stromal cells. Breast cancer-derived EVs can alter fibroblast phenotype and metabolism, whereas EVs released by cancer-associated fibroblasts can influence tumor-cell migration, invasion, proliferation, epithelial-mesenchymal plasticity, and metabolic adaptation. These interactions occur alongside cytokine signaling, direct cell-cell communication, and extracellular-matrix remodeling, indicating that EVs represent one component of an integrated tumor-stroma signaling system. Hypoxic conditions further modify this network by increasing EV release and altering EV cargo composition. Together with established hypoxia-responsive pathways, these changes may contribute to endothelial dysfunction, vascular remodeling, angiogenic signaling, and tumor adaptation. However, the relative contribution of EV-mediated signaling to these processes is likely to vary across tumor subtypes and experimental models.

The systemic effects of tumor-derived EVs may be particularly relevant to metastatic progression. Experimental evidence indicates that circulating EVs can modify

distant tissues by influencing vascular permeability, stromal-cell behavior, extracellular-matrix organization, local metabolism, and immune responses. The organ-specific examples discussed in this review illustrate the diversity of these mechanisms. EV-associated miR-21 has been linked to PDCD4 downregulation and osteoclast activation in bone; miR-105-mediated ZO-1 disruption and NEAT1/miR-141-3p/KLF12 signaling have been associated with endothelial and metastatic changes relevant to the lung; EV-associated miR-9-5p and other signaling pathways may contribute to metabolic and immune remodeling in the liver; and breast cancer-derived EVs may influence blood–brain barrier integrity and neuroglial responses during brain metastatic progression. These examples should be regarded as representative rather than exhaustive. Organotropism remains a multifactorial process that also depends on tumor-intrinsic characteristics, survival of circulating tumor cells, vascular accessibility, immune surveillance, and tissue-specific host factors. EV-mediated pre-metastatic niche formation is therefore best interpreted as one component of a broader metastatic cascade.

EV-mediated immune modulation and therapeutic resistance provide additional examples of how intercellular communication may influence disease progression. Tumor-associated EVs have been reported to alter macrophage phenotype and metabolism, contribute to PD-L1-associated immunosuppressive signaling, impair T-cell responses, and reduce natural killer-cell activity in selected experimental settings. In parallel, drug-resistant breast cancer cells can transfer P-glycoprotein, regulatory miRNAs, and other resistance-associated cargo to therapy-sensitive recipient cells. Such transfer may influence drug efflux, survival and apoptosis pathways, epithelial-mesenchymal signaling, and therapeutic responsiveness. These findings support EV-mediated horizontal transfer as one potential mechanism contributing to the spread of resistant phenotypes within heterogeneous tumors. Nevertheless, treatment resistance is inherently multifactorial and also involves clonal selection, genomic and epigenetic adaptation, altered drug transport and metabolism, and microenvironmental protection. EV-dependent mechanisms should therefore be interpreted within this wider biological context.

The ability of EV cargo to reflect aspects of parental-cell biology has generated considerable interest in their use as minimally invasive biomarkers and therapeutic platforms. EV-associated proteins and nucleic acids may provide information about tumor state, metastatic behavior, or therapeutic response, while the intrinsic capacity of EVs to transport biologically active molecules has stimulated investigation of engineered EV-based delivery approaches. However, substantial barriers remain before these applications can be translated reliably into routine clinical practice. EV populations are heterogeneous, and differences in sample collection, separation, purification, characterization, normalization, and functional testing complicate comparisons across studies. Terminology also requires careful standardization; operational descriptors such

as small extracellular vesicles should be preferred when vesicle biogenesis has not been directly demonstrated. In addition, many proposed EV biomarkers and therapeutic strategies remain supported primarily by preclinical evidence. Prospective clinical studies, independent replication, standardized analytical workflows, and quantitative assessment of EV abundance and cargo will therefore be required to establish reproducibility and clinical utility.

A further limitation of the current literature is the predominance of cell-culture and animal-model studies for many specific EV cargos and signaling pathways. These studies provide important mechanistic insight but do not necessarily establish the magnitude or clinical relevance of the same mechanisms in patients. Differences in EV isolation methods, experimental dose, tumor subtype, recipient-cell model, and disease stage may also contribute to variability between studies. Future work should therefore integrate standardized EV characterization with physiologically relevant models and well-annotated patient cohorts. Combining EV profiling with tumor genomics, transcriptomics, proteomics, immune phenotyping, and longitudinal treatment data may help distinguish reproducible disease-associated signals from model-specific observations and identify the EV-associated mechanisms most likely to have diagnostic, prognostic, or therapeutic value.

More broadly, breast cancer is a biologically and molecularly heterogeneous disease in which differences in gene and epigenetic regulation, non-coding RNA activity, and metabolic state may contribute to variability in tumor behavior, invasiveness, biomarker profiles, and therapeutic response [24-27]. This broader heterogeneity provides important context for interpreting EV-mediated signaling as one component of the complex and dynamic breast cancer ecosystem

Fig. 2 integrates the principal themes of this review by linking breast cancer heterogeneity and EV diversity with tumor-stroma communication, hypoxia-associated adaptation, selected mechanisms involved in organ-specific metastatic niche formation, immune modulation, and therapy resistance. The pathways depicted are representative and context dependent rather than exhaustive. Taken together, the available evidence supports EVs as biologically relevant participants in the evolving breast cancer ecosystem, while also emphasizing that their effects occur within a larger network of tumor-intrinsic, stromal, vascular, metabolic, and immune processes. A clearer definition of reproducible EV-associated mechanisms, together with methodological standardization and prospective clinical validation, will be essential for determining which findings can ultimately support clinically useful biomarkers or therapeutic strategies.

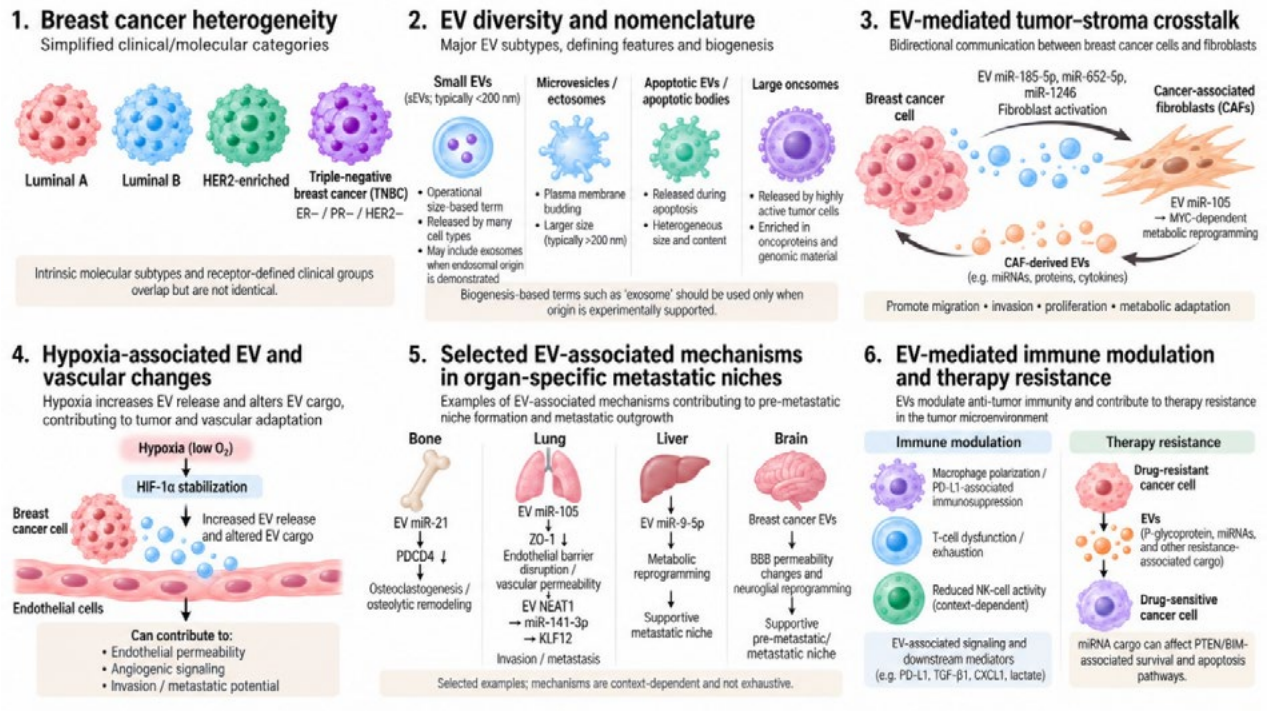


Fig. 2. Extracellular vesicle–mediated mechanisms in breast cancer progression, metastasis, and therapy resistance. The schematic summarizes representative EV-associated processes discussed in this review, including EV diversity, tumor-stroma crosstalk, hypoxia-associated adaptation, selected mechanisms contributing to organ-specific metastatic niches, immune modulation, and horizontal transfer of therapy-resistance-associated phenotypes. The illustrated pathways are context dependent and are not intended to represent an exhaustive model of breast cancer progression.

Conclusion

Extracellular vesicles (EVs) are mediators of communication in breast cancer, particularly in subtypes like triple-negative breast cancer that lack standard therapeutic targets. These vesicles, including exosomes and microvesicles, transfer cargo such as microRNAs and proteins to surrounding cells. Within the tumor microenvironment, this interaction activates fibroblasts and changes cellular metabolism to support tumor growth. Factors such as low oxygen levels, or hypoxia, increase EV secretion, which further supports blood vessel growth and tissue remodeling. Beyond the local environment, EVs travel through the bloodstream to prepare distant organs for metastasis. In the bone, lungs, liver, and brain, these vesicles increase vascular permeability and create conditions that allow cancer cells to survive and grow. This process involves the delivery of molecules that reprogram local cells and suppress immune responses

through signaling pathways like PD-L1 and TGFβ1. Furthermore, EVs carry components that transfer drug resistance between cells, such as efflux transporters and anti-apoptotic factors. Because EVs reflect the state of their origin cells and contribute to cancer progression, they are used to study new biomarkers and treatments for managing metastasis and drug resistance.

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