Evidence-graded extracellular vesicle microRNA transfer in chemotherapy-resistant triple-negative breast cancer: Mechanisms, biomarker readiness and translational barriers (Review)

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Abstract. Chemotherapy resistance limits disease control in triple-negative breast cancer (TNBC). The present narrative review examined how extracellular vesicle (EV)-associated microRNAs (miRNAs/miR) affect drug responses and how far the evidence supports clinical development of EV-miRNA biomarkers and EV-based therapeutic strategies. Across the selected studies, miRNAs promote resistance or increase sensitivity depending on the drug, delivery route and cellular model. The review-specific framework utilized in the present study distinguishes between a linked EV-miRNA causal sequence in TNBC donor and recipient models (Tier 1), incomplete mechanistic attribution or evidence extrapolated from other models, cargoes or treatments (Tier 2) and associative findings (Tier 3). Tier 1, the highest tier in this review-specific framework, requires EV-associated miRNA enrichment, uptake, target engagement, a resistance phenotype and miRNA-specific reversal or rescue. These categories are not validated measures of bias or clinical certainty. The accessible miR-423-5p evidence supports functional modulation but not a complete EV-specific causal chain, and therefore was categorized as Tier 2. Circulating EV-miRNA signatures remain exploratory biomarkers, and engineered miRNA or inhibitor delivery remains preclinical. RNA detection in an EV preparation alone does not establish intravesicular localization. Further development requires controls that attribute effects to transferred cargo, reproducible EV measurements and independent clinical validation.

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Abbreviations: TNBC, triple-negative breast cancer; EV, extracellular vesicle; miRNA, microRNA; EMT, epithelial-mesenchymal transition; pCR, pathological complete response; ctDNA, circulating tumor DNA; TAM, tumor-associated macrophage; P-gp, P-glycoprotein; MISEV, Minimal Information for Studies of EVs

Key words: TNBC, EVs, exosome, miRNA, chemotherapy resistance, liquid biopsy, RNA therapeutics, evidence grading, causal-chain appraisal

Contents

1. Introduction
2. Literature selection and evidence boundaries
3. Biology of exosomes and miRNA sorting
4. EV-associated miRNAs in TNBC chemotherapy resistance
5. Signaling pathways associated with EV-miRNA drug responses
6. Clinical and translational implications
7. Discussion
8. Evidence gaps and future directions
9. Conclusion

1. Introduction

Triple-negative breast cancer (TNBC) lacks the expression of estrogen and progesterone receptors, and human epidermal growth factor receptor 2 overexpression or amplification. This clinical definition guides treatment but encompasses biologically diverse tumors with aggressive behavior and a high risk of recurrence (1-3). Chemotherapy remains a key component of systemic treatment (1,2,4). In the KEYNOTE-522 trial, neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab improved event-free and overall survival rates in early-stage TNBC, although recurrence remained a concern (4,5). In patients with TNBC with residual disease following neoadjuvant systemic therapy, detectable end-of-treatment circulating tumor DNA (ctDNA) and higher

residual cancer burden both independently predicted event-free survival time (6). Understanding how resistant cells survive and proliferate during chemotherapy may explain these outcomes.

Drug efflux, enhanced DNA damage repair, apoptotic evasion, epithelial-mesenchymal transition (EMT), stem-like states and pro-survival signaling contribute to chemotherapy resistance (7-9). Resistance also depends on interactions with cancer-associated fibroblasts, tumor-associated macrophages (TAMs), endothelial and other stromal or immune cells (10,11). Within the tumor microenvironment, soluble regulators such as zymogen granule protein 16B have context-dependent roles in tumor progression and immune modulation. For example, zymogen granule protein 16B has been linked to pancreatic and ovarian cancer cell proliferation and invasion and to modulation of immunosuppressive myeloid-cell functions (12). This provides microenvironmental context, rather than direct evidence of TNBC extracellular vesicles (EVs)-microRNA (miRNA/miR)-mediated resistance. EVs, including exosomes, mediate intercellular exchange of proteins, lipids, mRNAs, miRNAs and other non-coding RNAs (13-16). BC reports address EV-mediated drug resistance, EMT, stemness, immune remodeling and biomarker development (14,17-23). These reports link resistance-associated EV protein and non-coding RNA cargo to recipient-cell pro-survival signaling, EMT and stem-like phenotypes, and identify circulating EV protein and miRNA profiles as exploratory markers of treatment response and prognosis (14,17,19,21).

miRNAs suppress target mRNAs and affect multiple signaling components, including receptors, kinases and transcriptional regulators, because an individual miRNA can regulate multiple targets (24,25). Functional studies have associated EV-associated miRNAs with changes in recipient cell drug responses (26-29). Expression profiling of resistant cells and their EV preparations identifies further candidates but does not establish which miRNAs cause the observed phenotype (30). Reported examples include miR-423-5p, -222 and -221-3p (26,27,31). In TNBC and mixed BC cohorts, circulating EV-miRNA profiles have also been associated with neoadjuvant treatment response or recurrence (32-34). These experimental and clinical findings address associated, but different, questions about resistance to therapy.

The present review investigates whether changes in chemotherapy response can be attributed to a specific EV-associated miRNA and how directly the supporting model applies to TNBC. The present review examines the sequence from donor-cell cargo loading to recipient-cell effects, and subsequently considers the evidence required for biomarker or therapeutic use. TNBC experiments were assessed alongside broader BC studies, clinical associations and engineered delivery approaches, with distinctions between their models and evidence types.

Recent reviews discuss EV-mediated BC chemoresistance (35), EV and miRNA therapies in TNBC (36), miRNAs in BC treatment resistance (37), TNBC-derived EVs (17) and EV-mediated resistance in the BC microenvironment (38). The present review compares selected studies by the completeness of the proposed TNBC EV-miRNA mechanism, the reporting of EV methods and the stage of clinical development. The classification is specific to the present review and has not been externally validated.

2. Literature selection and evidence boundaries

The present narrative review examines mechanistic and translational evidence on EV-associated miRNAs in TNBC chemotherapy resistance; it does not estimate pooled effects or attempt to include every eligible study. The PubMed database (pubmed.ncbi.nlm.nih.gov/) was searched from 1 January 1900 to 30 June 2026. The query combined BC, EV/exosome, miRNA and drug-response or therapeutic-delivery terms, without language or publication-type filters.

Literature selection focused on EV-miRNA-associated changes in chemotherapy response, the signaling pathways involved, circulating EV-miRNAs as clinical markers and barriers to biomarker and therapeutic development. TNBC functional studies, clinical associations and engineered EV delivery were considered as distinct evidence types. Broader BC EV studies and non-vesicular miRNA experiments provided mechanistic context and were distinguished from these evidence types. Studies were selected based on the relevance and contribution to the present review questions. Any differences in opinion were resolved by another author. No prespecified scoring threshold was used, and reasons for not selecting individual studies were not recorded. Selection for discussion and assignment of an evidence tier were distinct decisions.

For the PubMed database records, the titles and publication-type metadata were examined and abstracts were assessed when a record appeared relevant or its scope required clarification. The authors made the screening decisions and interpreted the evidence, without independent duplicate screening. Candidate status denotes topical relevance, not completed full-text appraisal or inclusion in the evidence-graded synthesis. Data S1 provides the search scope, query, screening criteria and counts and distinguishes the retrieved records and candidate set from the manuscript bibliography. Table SI provides the record-level screening decisions and reference cross-matches. Table SII summarizes the supplementary search and screening counts.

Evidence-grading framework. The three tiers support an EV-miRNA mechanism of TNBC chemotherapy resistance. Tier 1 included TNBC donor and recipient models, EV-associated miRNA enrichment, recipient-cell uptake, target or pathway engagement, a resistance phenotype and miRNA-specific reversal or rescue supporting the causal sequence. Gain-of-function assesses sufficiency, loss-of-function assesses necessity and reversal or rescue assesses dependence on the proposed intervention or pathway. A single gain- or loss-of-function experiment does not establish the full sequence from donor-cell miRNA loading and EV transfer to target engagement and altered drug response in recipient cells. Tier 2 includes mechanistic evidence with incomplete EV-specific attribution or TNBC relevance, including broader BC models, non-vesicular experiments and other treatment or cargo contexts. Tier 3 comprises abundance, response, survival rate or database associations without functional validation of the proposed association between the measured miRNA and drug response or survival. Resistance-promoting and -sensitizing effects were graded by the same criteria. Experimental details that could not be verified were recorded as uncertain.

Methodological reporting was assessed qualitatively against Minimal Information for Studies of EV (MISEV)2023 (13) and EV-Transparent Reporting And Centralizing Knowledge (TRACK) (39) guidelines, including sample source, EV nomenclature and separation, particle and protein characterization, RNA localization and functional-transfer controls. The tiers are interpretive categories, not validated quality scores. The Grading of Recommendations Assessment, Development and Evaluation approach evaluates certainty across a body of evidence for an outcome (40). The Newcastle-Ottawa Scale assesses specified aspects of observational study quality (41) and the Risk of Bias in Non-randomized Studies-of Interventions tool assesses bias in non-randomized intervention studies (42). These instruments address questions that differ from attribution of a drug-response phenotype to transferred EV cargo. The classification in the present review does not replace the aforementioned guidelines; no formal risk-of-bias assessment was performed.

When EV separation or RNA-localization evidence is incomplete, functional findings can still inform the present review, but they do not establish intravesicular miRNA transfer. Table I provides the RNase and proteinase K treatments and membrane-disruption comparisons, with the examined sources listed in Data S2. Unresolved EV-specific attribution precluded an unqualified Tier 1 assignment.

3. Biology of exosomes and miRNA sorting

Exosomes form within the endosomal system and are released when multivesicular bodies fuse with the plasma membrane. EV preparations from biofluids or conditioned media are heterogeneous, and particle size alone does not establish endosomal origin (13). The MISEV2023 guideline promotes transparent reporting of sample handling, separation, characterization and functional assays (13). The present review retains 'exosome' when describing the terminology used by a source study; findings from mixed small-EV preparations are attributed to the isolated fraction. This distinction matters particularly for blood-based assays, which can recover vesicles from several cell types together with non-vesicular RNA-containing material.

EV identity and cargo localization require different controls. Morphology, particle size and marker expression characterize an EV-enriched preparation but do not indicate that a detected miRNA lies inside vesicles. RNase resistance can arise from protection outside vesicles and should be interpreted alongside controls for membrane disruption and non-vesicular RNA. Accessibility, digestion and permeabilization experiments can help determine the location of a putative active component, as described in the MISEV2023 guideline (13). Early experiments demonstrated RNA transfer between cells through EVs (15). EVs interact with recipient cells through surface binding, fusion and endocytic pathways; however, uptake does not necessarily deliver functional RNA to the cytosol (13,16,43). A proposed miRNA mechanism therefore needs evidence associating donor-cell loading and extracellular transport with recipient-cell entry, access to the regulatory machinery and altered gene expression. Sequence motifs and RNA-binding proteins can influence miRNA enrichment in EVs. For example, small ubiquitin-like modifier-modulated heterogeneous nuclear ribonuclear protein A2/B1 recognizes motifs involved in exosomal miRNA sorting (44). Such mechanisms associate donor-cell state with cargo composition. To establish a role in TNBC drug response, enrichment should be associated with transfer, target or pathway engagement and a functional effect in an appropriate recipient model.

4. EV-associated miRNAs in TNBC chemotherapy resistance

Chemotherapy as a driver of vesicle cargo remodeling. Chemotherapy can alter EV output and cargo. Treatment-induced EV miRNAs have been associated with BC stemness through one cut homeobox 2 (Tier 2) (45). In a miR-378a-3p/miR-378d study (Tier 2), chemotherapy activated donor cell enhancer of zeste homolog 2 (EZH2)/STAT3 and increases miRNA expression. Transferred miRNAs targeted Dickkopf-related protein 3 (DKK3) and NUMB endocytic adaptor protein (NUMB) in recipient cells and activated Wnt/Notch-associated stemness programs (46). Donor-cell regulation of miRNA production and recipient-cell signaling are therefore distinct steps. These findings support investigation of intercellular adaptation during treatment, due to the prognostic relevance of residual disease after neoadjuvant therapy (6). TNBC specificity and EV-specific attribution still warrant separate assessment in the future.

Drug efflux, survival signaling and apoptotic escape. EV preparations from cisplatin-resistant MDA-MB-231 cells increased cisplatin resistance and altered P-glycoprotein (P-gp) expression and apoptosis in recipient cells (Tier 2) (26). Recipient cells exposed to resistant-cell EVs were treated with an miR-423-5p mimic or inhibitor (26). This design supports miRNA-dependent modulation of the response to the preparation, but cannot distinguish the contribution of donor-packaged miR-423-5p from endogenous recipient-cell activity. Intravesicular localization and the complete EV-specific causal sequence remain to be investigated; Table I and Data S2 highlight the source-access limits. Furthermore, increased P-gp expression does not establish direct cisplatin efflux. In a separate, non-TNBC MCF-7 model, exosomes from adriamycin-resistant cells were taken up by sensitive cells and increased recipient miR-222 levels and drug resistance. miR-222 mimics increase resistance, whereas inhibitors decrease it (Tier 2) (27). The accessible report did not resolve the direct downstream target.

EV-associated miR-221-3p has been associated with adriamycin resistance through PI3K regulatory subunit 1 (PIK3R1)-related signaling and metabolism in BC models, although verification of the EV-specific causal sequence remains incomplete (Tier 2) (31). A miR-205/E2F transcription factor 1 (E2F1) study used tamoxifen-resistant MCF-7/TAMR-1 cells. Their exosomes increased recipient-cell miR-205, reduced E2F1 expression and promoted tamoxifen resistance; miR-205 inhibition or E2F1 restoration counteracted these effects (Tier 2) (47). This endocrine-resistance model provides context for EV-associated treatment responses, rather than direct evidence of TNBC chemotherapy resistance. Table I compares the models, treatments, reported

Table I. Representative EV-associated miRNAs and therapeutic cargoes associated with altered drug responses in breast cancer or TNBC, including resistance-promoting and sensitizing effects.

EV-associated miRNA/cargo[a]	Vesicle sources	Recipient/model	Therapies	Key target/ pathway	Relevance to resistance	Evidence type and source-access limits	Evidence tier (based on the present review)	RNA-localization controls (RNase/ proteinase K/ membrane-disruption comparison)	(Refs.)
miR-423-5p	Cisplatin-resistant MDA-MB-231 cells	Parental/ sensitive MDA-MB-231 cells	Cisplatin	P-gp expression and apoptosis-associated changes; direct cisplatin-efflux mediation not established	Increased cisplatin IC_{50}, enhanced P-gp expression, reduced apoptosis and promoted migration and invasion	Recipient-cell mimic/inhibitor experiments during EV exposure support functional modulation; the contribution of donor-packaged miR-423-5p was not isolated	Tier 2; functional effects with incomplete EV-specific attribution	RNase: NR-PR; proteinase K: NR-PR; paired membrane-disruption protection: NR-PR; public reproduction examined; publisher PDF and any additional supplementary material not obtained	(26)
miR-222	ADR MCF-7 cells	Adriamycin-sensitive MCF-7 cells	Adriamycin	Resistance transfer; exact direct target not fully resolved	Exosomal miR-222 contributed to horizontal transfer of adriamycin resistance; inhibition of miR-222 weakened the resistant phenotype	Functional findings in a non-TNBC model; the direct target remained incompletely defined	Tier 2; non-TNBC model, with unresolved target attribution	RNase: NV; proteinase K: NV; membrane-disruption protection: NV; abstract verified; full methods unavailable	(27)
miR-221-3p	ADR MCF-7 and MDA-MB-231 models	Sensitive breast cancer cells	Adriamycin	PIK3R1, AKT/FOXO3 and glucose metabolism	Reduced adriamycin-induced apoptosis and increased cell survival through PIK3R1-associated metabolic and survival signaling	Functional findings involving PIK3R1-related signaling; full methods were unavailable for appraisal	Tier 2; reported functional perturbation, with incomplete verification of TNBC EV-specific attribution	RNase: NV; Proteinase K: NV; membrane-disruption protection: NV; abstract verified; full methods were unavailable	(31)
miR-155	Cancer stem-like and drug-resistant breast cancer cells	Chemosensitive breast cancer cells, including MDA-MB-231-associated models	Adriamycin and paclitaxel	EMT/stemness phenotypes and recipient-cell C/EBPβ, FOXO3a and TGF-β	EV-associated miR-155 was associated with EMT-like changes, migration, altered drug response and	EV functional findings and recipient-cell transcript changes; separate	Tier 2; EV-associated EMT/stemness findings, with incomplete TNBC	RNase: NR-MS; proteinase K: NR-MS; paired protection: NR-MS; main report and Fig. S1 examined;	(28,48)

Table I. Continued.

EV-associated miRNA/cargo[a]	Vesicle sources	Recipient/model	Therapies	Key target/ pathway	Relevance to resistance	Evidence type and source-access limits	Evidence tier (based on the present review)	RNA-localization controls (RNase/ proteinase K/ membrane-disruption comparison)	(Refs.)
				transcript changes; separate non-vesicular C/EBPβ-dependent mechanism	lower recipient-cell C/EBPβ, FOXO3a and TGF-β transcript levels; separate non-vesicular experiments addressed C/EBPβ-dependent TGF-β responses	non-vesicular mechanistic evidence; These findings did not establish a complete EV-specific causal mechanism	resistance attribution	Triton used for cell staining was not an EV protection assay	
miR-134	EV-enriched preparations from miR-134-transfected Hs578Ts(i)8 cells	Recipient Hs578Ts(i)8 cells	Hsp90 inhibitors 17-AAG and PU-H71; cisplatin comparator	Reduced STAT5B and Hsp90 expression	EV treatment increased sensitivity to Hsp90 inhibitors but did not notably alter cisplatin-induced apoptosis; direct miR-134 transfection increased the cisplatin-apoptosis endpoint	Functional sensitization in TNBC; effects differed by drug and delivery route	Tier 2; incomplete EV-specific chemotherapy-resistance mechanism	RNase A pretreatment of conditioned medium before precipitation reported; proteinase K: NR-MS; paired membrane-disruption protection: NR-MS; main report and complete published supplementary material were examined	(29)
miR-34a-5p	MCF-7 and MCF-7/ADR cells	MCF-7 models	Doxorubicin	Notch1	Regulated doxorubicin resistance through an exosomal miR-34a-5p/ Notch1 axis	Reported Notch1-associated drug-response effects in MCF-7 models	Tier 2; functional findings in a non-TNBC model	RNase: NV; proteinase K: NV; membrane-disruption protection: NV; abstract was verified; full methods were unavailable	(60)
miR-99b-3p	Exosomes from drug-resistant cells	Sensitive cancer cells and macrophage-associated models	Paclitaxel	PPP2CA and macrophage polarization	Promoted chemoresistance and microenvironmental adaptation by inducing macrophage polarization	Reported macrophage and drug-response effects; full methods were unavailable for appraisal	Tier 2; incomplete verification of the TNBC-specific EV mechanism	RNase: NV; proteinase K: NV; membrane-disruption protection: NV; Abstract verified; full methods unavailable	(55)

Table I. Continued.

EV-associated miRNA/cargo[a]	Vesicle sources	Recipient/model	Therapies	Key target/ pathway	Relevance to resistance	Evidence type and source-access limits	Evidence tier (based on the present review)	RNA-localization controls (RNase/ proteinase K/ membrane-disruption comparison)	(Refs.)
miR-222 inhibitor in engineered EVs	Engineered HBL-100-derived EVs	MCF-7/ADR cells and xenografts; non-TNBC context	Anthracycline resistance	PTEN/FN1 axis	Inhibitor-loaded EVs altered adriamycin response *in vitro* and reduced MCF-7/ADR xenograft growth during adriamycin treatment; inhibitor delivery was distinct from miR-222 replacement	Preclinical delivery of a therapeutic miRNA inhibitor	Tier 2 (engineered); non-TNBC preclinical response; no full factorial test of EV-drug interaction was performed	RNase: NR-MS; proteinase K: NR-MS; paired protection: NR-MS; main text, Data S1 and supplementary figures were examined; loading/uptake imaging did not establish topology	(66)

[a]These labels do not establish whether an assay was performed; Data S2 specifies the access source and examined material for each study; RNase pretreatment of conditioned medium is not equivalent to a paired protection assay with and without membrane disruption; protein-bound RNA may also resist nuclease digestion; uptake imaging does not establish intravesicular localization; no row is assigned an unqualified Tier 1 designation; resistance-promoting and -sensitizing effects are graded using the same criteria. EV, extracellular vesicle; miRNA/miR, microRNA; TNBC, triple-negative breast cancer; P-gp, P-glycoprotein; IC_{50}, half-maximal inhibitory concentration; Hsp90, heat shock protein 90; STAT5B, signal transducer and activator of transcription 5B; PIK3R1, phosphoinositide-3-kinase regulatory subunit 1; FOXO3, forkhead box O3; Notch1, Notch receptor 1; PPP2CA, protein phosphatase 2 catalytic subunit α; PTEN, phosphatase and tensin homolog; FN1, fibronectin 1; HER2, human epidermal growth factor receptor 2; AKT, protein kinase B; C/EBPβ, CCAAT/enhancer-binding protein β; EMT, epithelial-mesenchymal transition; TGF-β, transforming growth factor β; ADR, adriamycin (doxorubicin)-resistant; NR-MS, not reported in the main text and supplementary material examined; NR-PR, not reported in a public full-text reproduction, with publisher-version and supplementary verification still pending; NV, not verified because the necessary full methods were not obtained.

effects and RNA-localization controls for representative EV-associated miRNAs and therapeutic cargoes. In another miR-134 study, sensitization depended on the drug and delivery route (Tier 2) (29). EV-enriched preparations from miR-134-transfected Hs578Ts(i)8 cells increased sensitivity to the heat shock protein 90 inhibitors 17-AAG and PU-H71, but did not markedly alter cisplatin-induced apoptosis. Direct miR-134 transfection increased cisplatin-induced apoptosis. These drug- and delivery-dependent sensitizing effects constitute functional evidence but do not establish a complete EV-specific chemotherapy-resistance mechanism.

EMT, stemness and phenotypic plasticity. EV-associated miR-155 transfer has been associated with EMT-like changes and altered chemotherapy response in BC models (Tier 2) (28). The EV study also reported lower CCAAT/enhancer-binding protein β (C/EBPβ), FOXO3a and TGF-β transcript levels in recipient cells following exosome co-culture, including exposure to exosomes from miR-155-overexpressing cells (28). Non-vesicular experiments identified C/EBPβ-dependent changes in TGF-β responses (Tier 2) (48). The EV and non-vesicular study findings do not establish a single sequence of transfer and target engagement. EV-associated miR-378a-3p/miR-378d has also been associated with stemness-associated resistance (46). miR-770 exhibits sensitization involving stathmin 1-related intracellular effects and exosome-related tumor-macrophage communication in TNBC, with an incomplete EV-specific causal sequence (Tier 2) (49). An miR-449 family study used cell mimic- and inhibitor-based gain- and loss-of-function experiments. Increasing miR-449-family expression improves doxorubicin sensitivity, including in resistant MDA-MB-231 cells, and altered cell-cycle regulation (50). These experiments provide non-vesicular mechanistic context and do not establish EV-mediated transfer (Tier 2).

Microenvironmental spread of resistant phenotypes. EVs alter macrophage activation and fibroblast signaling by delivering molecular cargo or activating cell surface signaling, thereby changing inflammatory and stromal support for drug responses (10,11,51-53). TNBC-derived microvesicles carrying miR-221 have been associated with recipient-cell PTEN/AKT/NF-κB signaling and EMT, without establishing a complete TNBC chemotherapy-resistance mechanism (Tier 2) (54). EV-associated miR-99b-3p from drug-resistant cells has been associated with protein phosphatase 2 catalytic subunit, macrophage polarization and paclitaxel resistance (Tier 2) (55). EV/C-X-C motif chemokine ligand (CXCL)1-associated TAMs/programmed death-ligand 1 (PD-L1) signaling provides non-miRNA evidence regarding TNBC chemoresistance and metastasis (Tier 2, contextual) (56). The cargoes, recipients and treatment settings differ across these studies. EV preparations from drug-resistant BC cells alter transporter- and apoptosis-related gene expression, increased recipient-cell viability under selected drug-exposure conditions and induced a pro-inflammatory cytokine response in human macrophages (Tier 2; mixed-cargo context) (52). These experiments do not attribute the effects to a particular transferred miRNA. HCC1806-derived EVs increased proliferation and drug resistance in non-tumorigenic MCF10A cells, whereas MDA-MB-231-derived EVs produced no notable effects under the tested conditions (Tier 2 for the EV phenotype; Tier 3 for attribution to individual miRNAs) (57). The difference between donor models argues against assuming a uniform resistance-transfer effect. These EV-associated miRNA examples and recipient-cell contexts are summarized in Fig. 1.

5. Signaling pathways associated with EV-miRNA drug responses

PIK3R1- and PTEN-related studies implicate PI3K/AKT-associated survival signaling in EV-miRNA responses (Tier 2) (31,54). Among other cargo classes, exosomal annexin A6 has been associated with gemcitabine resistance through EGFR regulation (Tier 2; protein cargo) (58). In the circular RNA (circRNA/circ) SEPT9 study, lactate dehydrogenase A Y10 phosphorylation promoted the release of EV-associated circSEPT9, while recipient-cell effects involved the miR-515-5p/KIAA1429 axis and RNA methylation (Tier 2; circular-RNA cargo) (59). The transferred cargo in this mechanism is circRNA, distinguishing it from the PI3K/AKT miRNA examples.

Expression profiles of resistant cells and their EV preparations generate pathway hypotheses, including MAPK/ERK involvement (Tier 3) (30). By comparison, in a non-TNBC MCF-7 model, exosomes from MCF-7/ADR cells are taken up by sensitive MCF-7 cells and increase doxorubicin resistance. The study examined miR-34a-5p manipulation and Notch1-associated expression changes (60). These findings support model-specific involvement of this axis, but the unavailable full methods limit EV-specific mechanistic appraisal (Tier 2). For miR-378a-3p/miR-378d, the signaling events also need to be located in donor vs. recipient cells: EZH2/STAT3 increased miRNA production in donor cells, whereas miR-378-associated targeting of DKK3/NUMB and activation of Wnt/Notch in recipient cells promote stemness and chemoresistance (46).

TGF-β and NF-κB findings associate EV-associated responses with EMT and inflammation. An miR-155 EV study reported recipient-cell transcript changes (28), whereas non-vesicular miR-155 experiments identified C/EBPβ-dependent changes in TGF-β responses (Tier 2; contextual) (48). A microvesicle miR-221 study reported PTEN reduction and Akt/NF-κB activation in recipient MCF-7 cells, promoting EMT-related changes (Tier 2) (54). miR-99b-3p and non-miRNA EV/CXCL1 studies addressed macrophage polarization and TAM/PD-L1-associated phenotypes, respectively (55,56). These findings involved distinct models and microenvironmental responses (Fig. 2). Table II presents these pathways and distinguishes functional experiments, expression profiling, pathway hypotheses or evidence from other models and cargoes. A shared pathway heading does not establish every listed cargo-pathway relationship.

6. Clinical and translational implications

Liquid biopsy and treatment-response monitoring. Circulating EV-associated miRNAs have been investigated as biomarkers, although blood-derived preparations can contain both vesicular and non-vesicular RNA (13,14,18,21). In the

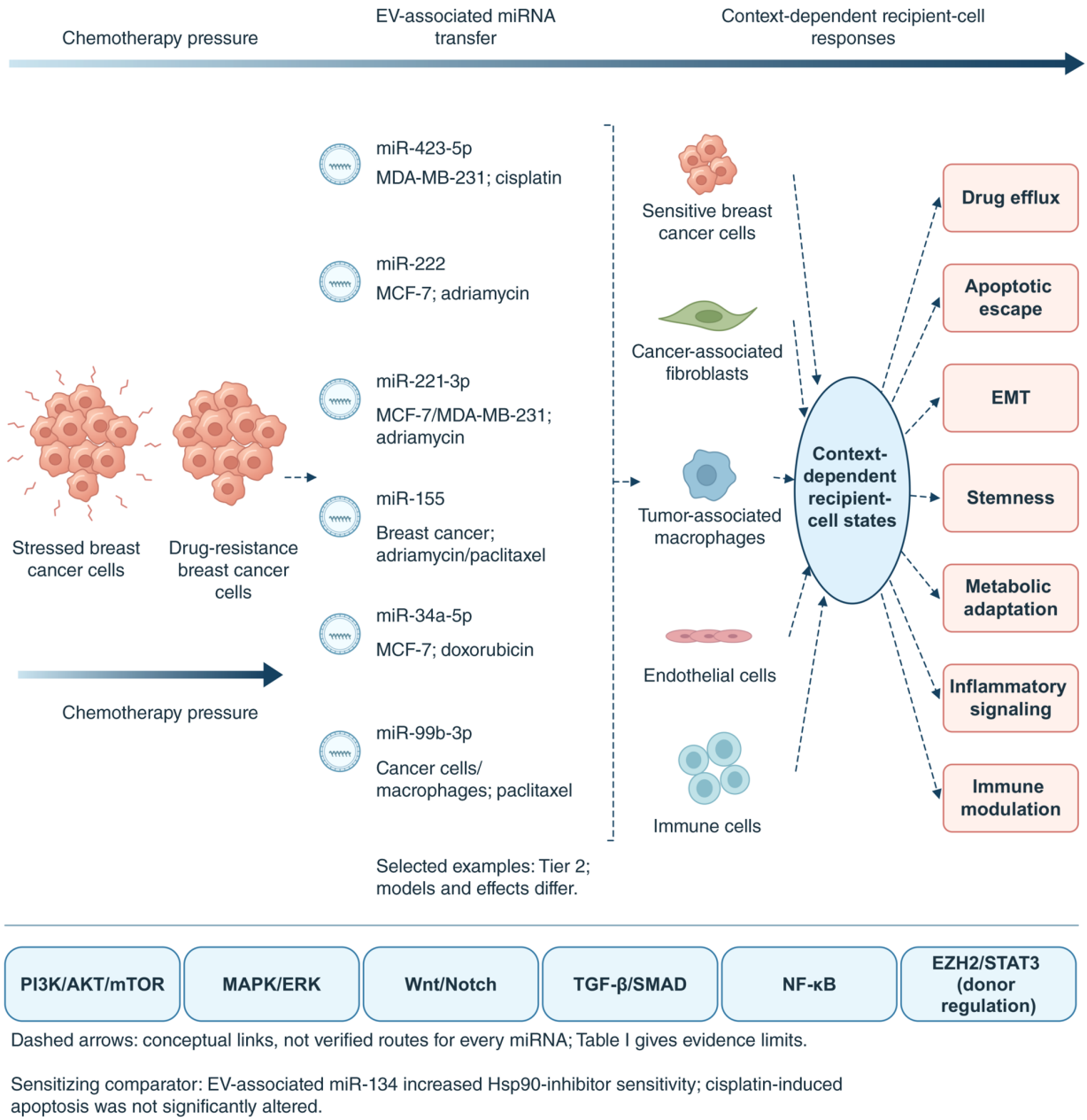


Figure 1. EV-associated miRNAs and recipient-cell responses. In total, six miRNA examples are presented with the breast cancer models and treatment settings and all are classified as Tier 2. The recipient compartments, response boxes and dashed arrows summarize the biological contexts discussed in the present review; these compartments do not establish that every miRNA acts in each recipient cell compartment or causes each depicted drug-response phenotype. Detection in an EV preparation does not demonstrate intravesicular localization. Increased P-gp expression in the miR-423-5p study does not establish direct cisplatin efflux. The bottom boxes represent separate signaling contexts, with EZH2/STAT3 denoting donor-cell regulation. The miR-134 comparator provides EV-associated sensitization to Hsp90 inhibitors; cisplatin-induced apoptosis was not notably altered by the EV preparation. Table I and Data S2 provide the study-level evidence and source-access limits. EV, extracellular vesicle; miRNA/miR, microRNA; EMT, epithelial-mesenchymal transition; P-gp, P-glycoprotein; Hsp90, heat shock protein 90; TNBC, triple-negative breast cancer; CAF, cancer-associated fibroblast; TAM, tumor-associated macrophage; EZH2, enhancer of zeste homolog 2. PI3K, phosphoinositide 3-kinase; TGF-β, transforming growth factor-β; SMAD, SMAD family signal transducer.

GeparSixto trial, plasma exosomal miRNA patterns were associated with molecular subtype and pathological complete response (pCR; Tier 3) (34). In a previous TNBC study, pretreatment serum profiles were compared by pCR status and post-treatment profiles were compared by recurrence status in partly overlapping cohorts (Tier 3) (32). Certain patients in the 24-patient pretreatment response cohort were also included in the 16-patient post-treatment non-pCR recurrence cohort; the two cohorts were therefore not independent. This design did not establish a longitudinal monitoring assay. Another TNBC study identified *Homo sapiens*-miR-6831-5p as a response-associated candidate biomarker using serum sequencing and reverse transcription-quantitative PCR in an additional sample set (Tier 3) (33). A broader circulating miRNA study provides non-EV clinical context (Tier 3) (61). These associations do not demonstrate that a marker causes resistance.

EV protein assays address different clinical questions. For example, a previous study associated residual disease with multidrug resistance protein 1, multidrug resistance-associated protein 1 and BC resistance protein profiles in plasma collected

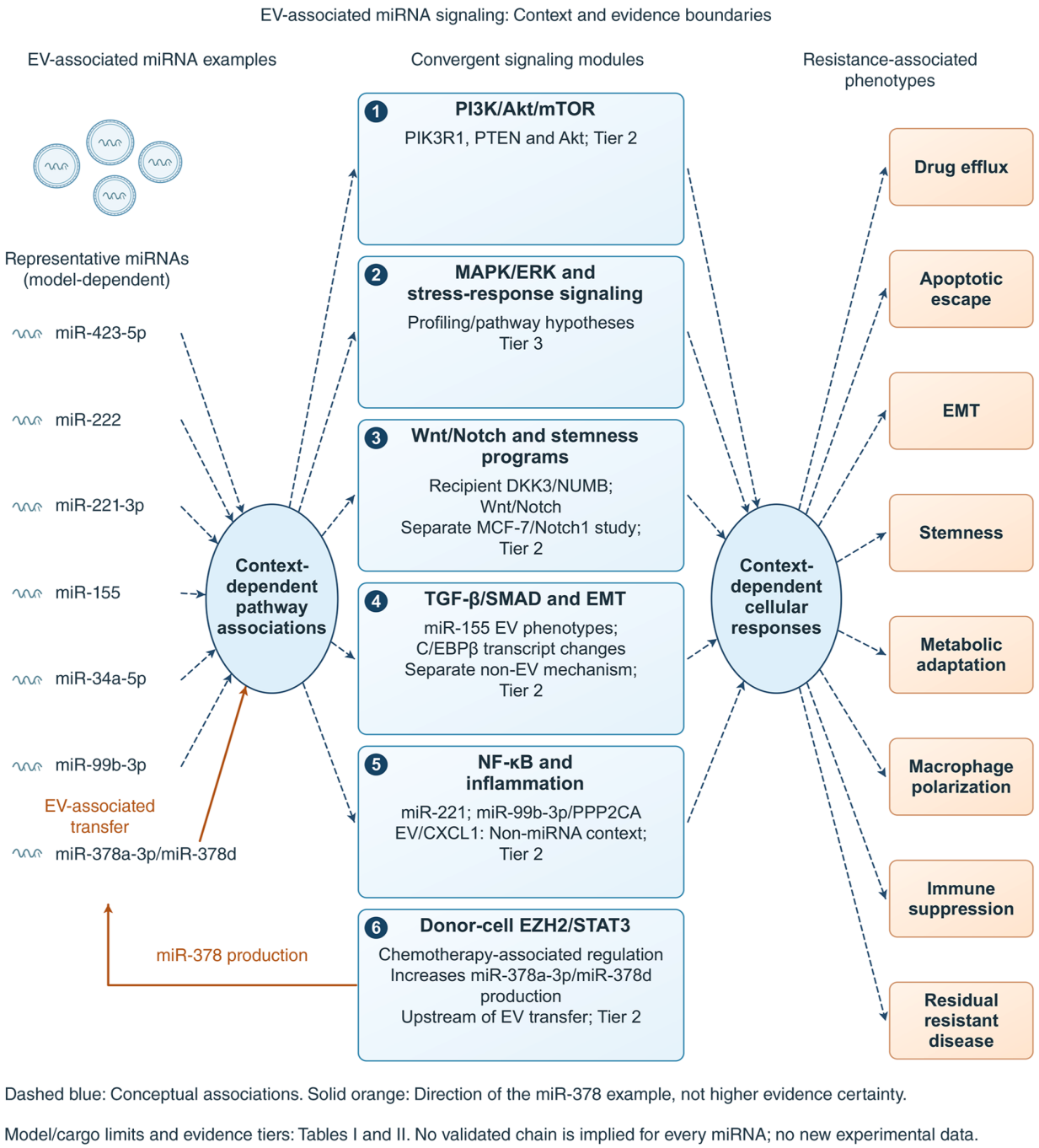


Figure 2. Signaling contexts for EV-associated miRNA responses. Dashed blue arrows indicate conceptual associations. PI3K/AKT-related findings are classified as Tier 2, whereas MAPK/ERK hypotheses from expression profiling are classified as Tier 3. The Wnt/Notch module separates recipient-cell DKK3/NUMB and Wnt/Notch effects in the miR-378a-3p/miR-378d study from MCF-7 miR-34a-5p/Notch1 findings. The miR-155 module distinguishes EV-associated phenotypes and recipient-cell C/EBPβ transcript changes from a separate non-vesicular study of C/EBPβ-dependent TGF-β responses. Neither their juxtaposition nor the transcript changes establish a complete EV-specific causal mechanism. The inflammatory module includes miR-221 and -99b-3p findings and non-miRNA EV/CXCL1 context. Orange arrows associate donor-cell EZH2/STAT3 regulation in box 6 with miR-378 production and subsequent EV-associated transfer. The orange arrows indicate the direction of this example, which remains classified as Tier 2; the arrows do not denote greater evidence certainty. Tables I and II provide the model, cargo and evidence distinctions. EV, extracellular vesicle; miRNA/miR, microRNA; TNBC, triple-negative breast cancer; EMT, epithelial-mesenchymal transition; EZH2, enhancer of zeste homolog 2; DKK3, Dickkopf Wnt signaling pathway inhibitor 3; NUMB, NUMB endocytic adaptor protein; C/EBPβ, CCAAT/enhancer-binding protein β; CXCL1, C-X-C motif chemokine ligand 1; PPP2CA, protein phosphatase 2 catalytic subunit α; PIK3R1, PI3K regulatory subunit 1. PI3K, phosphoinositide 3-kinase; Notch, Notch-family receptor signaling; TGF-β, transforming growth factor-β; SMAD, SMAD family signal transducer.

after neoadjuvant chemotherapy (NAC) and before surgery (Tier 3) (62). These measurements involve post-treatment assessment, not pretreatment miRNA prediction. A separate study associated a proliferation-inducing ligand, CXCL13 and VEGF-A in post-NAC, preoperative serum EV preparations with the overall survival rate (Tier 3) (63). Marker combinations and cut-off values selected within the study cohort require testing in independent samples. Table III summarizes these applications and their validation stages. The biomarker candidates remain at discovery or early validation; clinical use

Table II. Signaling pathways relevant to EV-associated drug responses, with evidence context.

Signaling module[a]	Representative miRNAs/cargo	Key nodes	Biological effects	Interpretation for TNBC chemotherapy resistance	Evidence tier (according to the present review)	(Refs.)
PI3K/AKT/mTOR	miR-221-3p and miR-221; miR-205 as endocrine-therapy context	PIK3R1, PTEN, AKT, FOXO3, caspases and mTOR	Cell survival, metabolic adaptation, apoptosis suppression and EMT tendency	PIK3R1- and PTEN-associated survival signaling; the miR-205 report concerned tamoxifen resistance in MCF-7 cells, not TNBC chemotherapy	Tier 2; incomplete TNBC-specific EV-miRNA attribution	(31,54,47)
MAPK/ERK and stress-response signaling	Differential EV-miRNA profiles; resistance-associated EV cargo	MAPK/ERK-associated expression and pathway hypotheses	Proliferation, stress adaptation and damage tolerance	Profiling identifies pathway hypotheses; EV-level phenotypic findings in MCF10A cells did not establish a specific transferred miRNA mechanism	Tier 3 for individual-miRNA/pathway attribution; EV-level functional effects were assessed separately	(30,57)
Wnt, Notch and stemness programs	miR-378a-3p, -378d and -34a-5p-related axes	Recipient-cell DKK3/NUMB and Wnt/Notch; donor-cell EZH2/STAT3	Stemness, phenotypic plasticity and altered drug response	Donor EZH2/STAT3 increased miR-378 production; recipient miR-378 effects involved DKK3/NUMB and Wnt/Notch	Tier 2; findings differed by model, cargo and cellular compartment	(46,60)
TGF-β/SMAD and EMT	miR-155 and EMT-associated miRNA networks	C/EBPβ, TGF-β response nodes and EMT transcriptional programs	EMT, invasion and cell state transition	EV-related phenotypes and recipient-cell C/EBPβ transcript changes were distinguished from a separate non-vesicular C/EBPβ/TGF-β mechanism; however, neither established the complete EV-specific causal chain	Tier 2; EV phenotypes and transcript changes distinguished from non-vesicular mechanistic evidence	(28,48)
NF-κB and inflammatory microenvironment	miR-221, -99b-3p and EV/CXCL1-associated signaling	PTEN/Akt/NF-κB (p65), PPP2CA and TAM/PD-L1 signaling	Inflammation-like transcription, macrophage polarization and immune suppression	Separate studies associated miR-221 with EMT, miR-99b-3p with macrophage polarization and paclitaxel response, and EV-associated CXCL1 with TAM/PD-L1 signaling	Tier 2; incomplete attribution across distinct miRNA and non-miRNA mechanisms	(54-56)
Engineered EV delivery axes	miR-159, -588 and -222 inhibitor and therapeutic anti-miRNAs	TCF7, PTEN/FN1 and immune microenvironment-associated pathways	Targeted delivery, chemotherapy sensitization and immune modulation	Preclinical delivery approaches, including inhibitor cargo; distinct from endogenous EV-mediated resistance	Tier 2 (engineered); preclinical delivery studies	(64-68)

[a]Pathway grouping does not establish every cargo-pathway relationship; evidence is assessed by study. AKT, protein kinase B; anti-miRNA/-miR, microRNA inhibitor; C/EBPβ, CCAAT/enhancer-binding protein β; CXCL1, C-X-C motif chemokine ligand 1; DKK3, Dickkopf Wnt signaling pathway inhibitor 3; EMT, epithelial-mesenchymal transition; EV, extracellular vesicle; EZH2, enhancer of zeste homolog 2; FN1, fibronectin 1; FOXO3, forkhead box O3; MAPK, mitogen-activated protein kinase; miRNA/miR, microRNA; NUMB, NUMB endocytic adaptor protein; p65, RELA proto-oncogene NF-κB subunit; PD-L1, programmed death-ligand 1; PI3K, phosphoinositide 3-kinase; PPP2CA, protein phosphatase 2 catalytic subunit α; TAM, tumor-associated macrophage; TCF7, transcription factor 7; TGF-β, transforming growth factor-β; TNBC, triple-negative breast cancer; PIK3R1, PI3K regulatory subunit 1; Wnt, Wnt-family signaling ligands.

Table III. Clinical and translational studies of EV-associated markers and engineered delivery relevant to TNBC.

First author, year	Application/ evidence context[a]	Samples (n)/ models	Molecular targets	Main finding	Potential value	Key limitation	Validation stage	Evidence tier (according to the present review)	(Refs.)
Stevic *et al*, 2018	Neoadjuvant response prediction	Pretreatment plasma from 435 patients (224 TNBC and 211 $HER2^+$ cases)	Plasma exosomal miRNA signatures	Molecular-subtype-specific exosomal miRNA patterns were associated with pCR	Candidate pretreatment indicators of response	Subtype-dependent associations; independent assay validation and clinical-utility assessment required	Exploratory association in mixed breast cancer subtypes	Tier 3; clinical association	(34)
Sueta *et al*, 2021	TNBC response and recurrence-risk assessment	Serum: 24 pre-treatment cases (12 pCR/12 non-pCR); 16 post-NAC non-pCR cases (8 recurrent/ 8 non-recurrent), with partial overlap	Exosomal miRNA panels including miR-4448, -2392, -2467-3p and -4800-3p	Distinct signatures were observed between pCR and non-pCR groups and between recurrent and non-recurrent non-pCR patients	Candidate associations with response and subsequent recurrence	Small, partly overlapping cohorts; most array candidates were not confirmed by PCR; no validated longitudinal monitoring assay	Exploratory association in small TNBC cohorts	Tier 3; clinical association	(32)
Yang *et al*, 2024	Chemotherapy sensitivity prediction	TNBC serum (6 samples for sequencing and 30 additional samples for RT-qPCR); AC followed by taxane therapy	Exosomal miRNA sequencing; hsa-miR-6831-5p and related candidates	Chemosensitive and resistant groups exhibited different exosomal miRNA profiles	Candidate markers for regimen-specific sensitivity	Small discovery set; additional PCR confirmation does not establish external clinical validation	Exploratory profiling with additional PCR assessment	Tier 3; observational evidence	(33)
Kim *et al*, 2024	Post-treatment EV protein association	Plasma collected after NAC and before surgery; breast cancer cohort with TNBC analysis	EV-associated MDR1, MRP1 and BCRP protein markers	Drug-resistance-marker profiles were associated with residual disease after NAC	Candidate post-treatment assessment of residual disease	Post-NAC sampling; marker-combination selection in the same cohort; not pretreatment miRNA prediction	Exploratory post-treatment protein-marker association	Tier 3; clinical association	(62)

Table III. Continued.

First author, year	Application/ evidence context[a]	Samples (n)/ models	Molecular targets	Main finding	Potential value	Key limitation	Validation stage	Evidence tier (according to the present review)	(Refs.)
Jung *et al*, 2023	Serum EV protein/ biomarker exploration	Post-NAC, preoperative serum from 190 patients with TNBC	APRIL, CXCL13, VEGF-A and associated serum EV markers	Higher EV-associated APRIL, CXCL13 and VEGF-A levels were associated with shorter overall survival rates	Candidate post-treatment prognostic stratification	Retrospective cohort; outcome-derived cut-offs; independent validation needed	Retrospective exploratory biomarker study	Tier 3; prognostic association	(63)
Gong *et al*, 2019	Engineered EV co-delivery	TNBC cell and animal models	A15-targeted exosomes carrying doxorubicin and cholesterol-modified miR-159	Co-delivery enhanced antitumor activity and affected TCF7-related expression	Proof-of-concept for chemotherapy plus miRNA delivery	Preclinical evidence; manufacturing and safety remain to be investigated	Preclinical therapeutic study	Tier 2 (engineered)	(64)
Zhang *et al*, 2024	Engineered EV immune modulation	TNBC models and engineered exosome systems	cRGD-engineered exosomes carrying miR-588	miR-588 EV delivery remodeled an immunosuppressive microenvironment	Therapeutic EV-miRNA modulation of the TME	Not yet clinically validated	Preclinical therapeutic study	Tier 2 (engineered)	(68)
Wang *et al*, 2026	Bioinspired exosomal nanoplatforms	TNBC preclinical models	Plant-derived exosome-like platform carrying sorafenib and endogenous miRNAs	Sensitized ferroptosis and induced immunoactivation	Emerging multimodal therapy platform	Early preclinical stage	Preclinical nanoplatform study	Tier 2 (engineered)	(67)

[a]Clinical association, protein-marker measurement and engineered delivery are separate evidence contexts. AC, doxorubicin and cyclophosphamide; APRIL, a proliferation-inducing ligand; BCRP, breast cancer resistance protein; cRGD, cyclic arginine-glycine-aspartate peptide; CXCL13, C-X-C motif chemokine ligand 13; EV, extracellular vesicle; HER2, human epidermal growth factor receptor 2; MDR1, multidrug resistance protein 1 (P-glycoprotein); miRNA/miR, microRNA; MRP1, multidrug resistance-associated protein 1; NAC, neoadjuvant chemotherapy; pCR, pathological complete response; RT-qPCR, reverse transcription-quantitative PCR; TCF7, transcription factor 7; TME, tumor microenvironment; TNBC, triple-negative breast cancer; TNFSF13, tumor necrosis factor superfamily member 13; VEGF-A, vascular endothelial growth factor A; hsa, *Homo sapiens*.

requires reproducible assays, prespecified cut-off values and independent evidence that the assay improves prediction of treatment response, recurrence or survival beyond established clinical factors.

Therapeutic targeting and engineered vesicle delivery. Candidate resistance-associated miRNAs may be targeted with inhibitors, mimics or antisense oligonucleotides or by disrupting vesicle release and uptake. An effective intervention should account for donor-cell loading, extracellular transport, recipient-cell uptake and compensatory signaling, as well as intracellular miRNA abundance (13,43).

EV-based delivery has exhibited preclinical activity. A15-targeted exosomes co-delivering doxorubicin and cholesterol-modified miR-159 produced antitumor effects in TNBC models (Tier 2; engineered) (64). Vesicle-coated nanocarriers delivered anti-miR-21 and -10b in BC models (Tier 2; engineered) (65). In an miR-222 study, engineered EVs carried an miR-222 inhibitor rather than replacement miR-222, altering PTEN/fibronectin 1-associated signaling and adriamycin response in MCF-7 cells and reducing MCF-7/adriamycin-resistant xenograft growth during adriamycin treatment (Tier 2; engineered; non-TNBC model) (66). Both xenograft EV groups received adriamycin; without a full factorial comparison, this result does not demonstrate an EV-drug interaction or pharmacological synergy. Plant-derived exosome-like platforms have combined sorafenib with endogenous miRNAs in TNBC models (Tier 2; engineered) (67), and miR-588-loaded engineered exosomes have been investigated for C-C motif chemokine ligand 5-associated modulation of the TNBC microenvironment (Tier 2; engineered) (68). These studies evaluated delivery strategies and do not clinically validate endogenous EV-miRNA resistance mechanisms.

Therapeutic development requires control of source cells, cargo loading, targeting, biodistribution, immune safety, storage and batch consistency (13,43). Vesicles may carry pro-tumorigenic signals alongside therapeutic cargo. Cellular context also serves a key role in target selection: miRNAs that increase drug sensitivity in a tumor model may have different effects in immune, stromal or normal epithelial cells. Delivery route, chemotherapy regimen and toxicity assessment should therefore be chosen for the intended TNBC setting.

7. Discussion

The studies reviewed in the present study support EV-associated changes in drug response; however, attribution to a specific transferred miRNA remains to be elucidated. No selected example in the present review received an unqualified Tier 1 assignment; miR-423-5p is classified as Tier 2 because the accessible evidence does not establish the full EV-specific sequence. This judgment is limited to the studies assessed here and does not describe the frequency of causal mechanisms across the field. Distinguishing functional effects from cargo localization and clinical performance clarifies the evidence still warranted for each candidate.

Differences in EV preparation and RNA measurement complicate comparison across studies. Plasma and serum contain vesicles from tumor and immune cells, platelets, endothelial cells and non-malignant tissues, and separation methods can enrich different fractions. Collection conditions, hemolysis, RNA extraction, spike-in controls and normalization can also affect measured miRNA abundance (13,32). Differences in reported EV-miRNA associations may therefore reflect technical variation as well as biology. Meaningful comparisons across cohorts require these variables to be reported alongside particle and protein characterization and quality control thresholds. Associations with pCR, recurrence or chemotherapy sensitivity do not establish a resistance mechanism (32,33). Mechanistic interpretation warrants an experimental association from donor-cell perturbation through EV transfer and recipient-cell target engagement to a reversible drug-response effect. Findings from broader BC models, non-vesicular experiments and engineered delivery systems cannot automatically be generalized to endogenous EV-miRNA transfer in TNBC. TNBC heterogeneity is another key factor because pathway dependencies and treatment responses differ among subtypes (3,8). An EV-miRNA measurement may reflect tumor burden or treatment-induced stress rather than a process that sustains resistance.

Clinical studies should investigate whether EV-miRNA measurements improve a defined treatment decision or prognostic estimate. Relevant neoadjuvant endpoints include pCR, residual cancer burden, early molecular response, recurrence-free survival rate and post-treatment residual disease signals (4-6,32-34,62). Comparisons with clinicopathological factors, imaging and available molecular markers establish whether an EV-miRNA assay provides information on treatment response or prognosis beyond these existing assessments. Multicenter evaluation is warranted to assess whether its performance persists across EV collection and separation protocols. Furthermore, clinical and mechanistic findings inform one another. A response-associated miRNA can be assessed in relevant TNBC models and then developed as a biomarker, therapeutic target or both. An association between miRNA abundance and treatment response can justify biomarker validation; therapeutic targeting requires evidence that changing the miRNA alters the relevant phenotype.

Unavailable original retrieval and screening records prevent retrospective verification of the initial literature selection; the PubMed database search described in Data S1 does not resolve this limitation. In the present review, screening was not independently duplicated. The 103 relevant candidates were not all appraised in full text or included in the evidence tables; the bibliography is not exhaustive. Although the PubMed database search had no language filter, limited full-text access may have influenced selection and interpretation. No formal risk-of-bias assessment, inter-rater reliability analysis or validated clinical-certainty framework was used in the present study. These methodological limitations may introduce selection bias, and the strength of the evidence remains to be validated in future research.

8. Evidence gaps and future directions

The immediate methodological priority is reproducible EV and RNA measurement. Reporting should include sample collection and storage, hemolysis, separation, characterization, RNA quality, normalization and negative controls, guided by the MISEV2023 (13) and EV-TRACK (39) guidelines.

Clinical candidates require independent assay testing against a prespecified endpoint and cut-off value, with added value assessed against existing clinical and molecular information. Mechanistic studies should resolve the uncertain step for each candidate: Cargo loading, functional entry into recipient cells, target engagement or attribution of the drug-response effect. Donor-cell perturbation and reversal or rescue are particularly relevant when candidates originate from profiling or non-vesicular experiments. For engineered EV delivery therapies, assessment should also include loading, targeting, biodistribution, immune effects, manufacturing consistency and effects on non-tumor cells. Combining EV-miRNA measurements with ctDNA, tumor transcriptomics, proteomics or spatial and single-cell data may potentially help identify cellular sources and distinguish treatment-associated signals. Such combinations should address a specific question, such as whether an EV-miRNA signal originates from tumor rather than stromal or immune cells, or whether it adds response-prediction information beyond ctDNA or tumor profiling.

9. Conclusion

In summary, EV-associated miRNAs can modulate drug responses in experimental BC systems, with resistance-promoting or -sensitizing effects that depend on the model, drug and delivery route. The primary unresolved issue for TNBC is the attribution of these effects to specific transferred cargo. The present review-specific tiers distinguish functional activity in EV-enriched preparations from evidence of intravesicular localization and clinical performance, without replacing assessment of bias or clinical certainty. Circulating EV-miRNA profiles remain candidate biomarkers, and engineered miRNA or inhibitor delivery remain preclinical strategies. The evidence reviewed in the present study does not support routine clinical use of these assays or therapies.

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Authors' contributions

FZ and ZL conceived the present review. FZ, YZ and JW performed the literature search and organized the evidence tables. FZ drafted the manuscript. YZ, JW and ZL reviewed and edited the manuscript. FZ prepared the figures. ZL provided supervision. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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