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Extracellular Vesicles-Derived MicroRNAs: Emerging Game Changers in Cancer Pathogenesis and Therapeutic Response

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ABSTRACT

Effective communication between cells is a fundamental feature of multicellular organisms, occurring through direct contact or the transfer of secreted molecules. Among these mediators, extracellular vesicles (EVs) function as biological messengers that transport bioactive molecules among cells. EVs are secreted by nearly all cell types. The interaction between tumor cells and EV components has been shown to influence various cancer-related processes, including proliferation, metastasis, stemness, chemoresistance, and immune modulation. Among the bioactive cargos of EVs, non-coding RNAs (ncRNAs), particularly microRNAs (miRNAs), play a significant role in shaping the tumor microenvironment. These EV-derived ncRNAs have emerged as promising tools for non-invasive diagnosis, prognosis, and therapeutic intervention across multiple cancer types. This review summarizes the current understanding of the functional roles of EV-derived miRNAs in cancer and highlights their potential clinical applications as novel biomarkers and therapeutic targets in cancer management.
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1. INTRODUCTION

Extracellular vesicles (EVs) are nano-sized, membrane-bound structures initially considered cellular waste, but are now recognized as key mediators of intercellular communication in health and disease[1]. According to the updated guidelines of the International Society for EVs (MISEV2023), these vesicles, as intercellular communicators, carry diverse biomolecules that reflect the physiological or pathological state of their cells of origin[2,3]. These guidelines provide standardized recommendations for EV production, isolation, characterization, and functional studies to enhance reproducibility and rigor in EV research[3].

EVs possess unique characteristics, including stability, low immunogenicity, efficient biodistribution, and targeted accumulation, making them ideal vehicles for molecular transport[4]. EVs are secreted by both normal and cancerous cells and can influence the transcriptional and functional behavior of recipient cells by transferring components from the parent cells[5]. Within the tumor microenvironment (TME), a complex network comprising tumor cells, lymphocytes, dendritic cells (DCs), fibroblasts, macrophages, cancer-associated fibroblasts (CAFs), adipocytes, and tumor vasculature, each cellular component plays a key role in tumor progression and survival[6]. Intercellular trafficking of EVs among tumor cells can alter multiple tumor characteristics, such as proliferation, metastasis, stemness, chemoresistance, and immune evasion[7]. Importantly, tumor-derived extracellular vesicles (tEVs) can also originate from stromal cells in the TME and contribute to tumor progression by modulating stress responses and promoting an immunosuppressive environment[8]. Additionally, EVs can prepare pre-

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metastatic niches at distant sites, facilitating early stages of metastasis[9]. However, their function is not exclusively tumor-promoting. Research has shown that EVs derived from cytotoxic lymphocytes and antigen-presenting cells can enhance anti-tumor immunity[10].

Genetically engineered cells capable of releasing EVs loaded with therapeutic molecules have demonstrated potential in suppressing tumor growth and increasing chemosensitivity[11]. In addition, the presence of EVs in body fluids and their elevated concentration in tumor tissues compared to normal tissues support their potential as non-invasive biomarkers for cancer diagnosis and prognosis[12]. Non-coding RNAs (ncRNAs), including microRNAs (miRNAs), small interfering RNAs, circular RNAs, and long ncRNAs are enriched in EVs and play major roles in cancer progression through direct or indirect regulation of gene expression[13,14]. These molecules regulate transcription, post-transcriptional modifications, and signaling, influencing angiogenesis, immunity, and extracellular matrix remodeling. EV-derived miRNAs have emerged as biomarkers and therapeutic targets in oncology. This review highlights recent insights into their roles in cancer and clinical potential[15,16].

2. Characteristics of EVs

1.2. Origin and biogenesis of exosomes

EVs are often broadly classified into apoptotic bodies, microvesicles, and exosomes, according to their proposed biogenesis and physical characteristics[17]. The biogenesis, transport, and release of exosomes involve a multistep process. During exosome formation, internal proteins from the trans-Golgi network (TGN) and cell surface proteins, such as activated growth factor receptors, are internalized. Some of these proteins undergo ubiquitylation on their cytosolic domains, a process essential for their sorting and incorporation into intraluminal vesicles (ILVs) within multivesicular bodies (MVBs)[18]. Early endosomes are formed via inward budding of the plasma membrane. These endosomes then mature, during which ILVs accumulate inside them through continued inward budding of the endosomal membrane, forming MVBs (Fig. 1). MVBs can follow three fates: degradation via lysosomal fusion, recycling back to the trans-TGN, or fusion with the plasma membrane to release ILVs as exosomes[19]. The uptake of exosomes by recipient cells occurs through direct membrane fusion, receptor-ligand interactions, or receptor-mediated endocytosis[20]. The biogenesis and secretion of ILVs are tightly linked to the sorting of cargo molecules. One primary mechanism responsible for ILV formation is the endosomal sorting complex required for transport (ESCRT), though ceramide can also initiate ILV formation independently of ESCRT[21,22]. The five core ESCRT components, ESCRT-0, -I, -II, -III, and VPS4 (vacuolar protein sorting-related protein 4), work sequentially in this process[23]. ESCRT-0 identifies and retains ubiquitinated proteins at the endosomal membrane. ESCRT-I and -II promote membrane budding into the MVB lumen, while ESCRT-III forms constriction structures, facilitating scission with the help of the ATPase VPS4[24]. Additionally, cargo sorting can occur via alternative mechanisms independent of ubiquitination[25]. Fusion of MVBs with the plasma membrane is mediated by SNARE proteins (v-SNAREs on vesicles and t-SNAREs on target membranes), Rab GTPases, tethering factors, and other accessory proteins. Once secreted, exosomes interact with target cells through various mechanisms, including surface receptor engagement, direct membrane fusion, or uptake via phagocytosis, micropinocytosis, and lipid raft-, clathrin-, or caveolin-mediated endocytosis, subsequently entering the endosomal system[26]. Nevertheless, the specific mechanisms underlying cargo sorting and MVB formation require further elucidation.

2.2. Content of EVs

EV cargos vary depending on the cell of origin and can function in autocrine or paracrine signaling, influencing both proximal and distal target cells. EVs can carry different types of nucleic acids, like DNAs and RNAs, proteins, lipids, and other complex components in the cell (Fig. 1)[27]. EVs' mRNAs can be translated into proteins within recipient cells, altering their transcriptomic and proteomic profiles[28]. For instance, Zomer et al. have demonstrated that EVs derived from aggressive tumor cells can transfer metastatic potential to less aggressive cells through RNA-mediated mechanisms[29]. EVs also contain various ncRNAs[30]. MiRNAs, which are approximately 19–22 nucleotides in length, are abundant endogenous ncRNAs that play key roles in regulating protein biosynthesis[31]. In terms of miRNAs biogenesis, most miRNAs are transcribed as pri-miRNAs, processed by Drosha and Dicer, and incorporated into RISC to regulate gene expression[32]. Interestingly, the packaging of the miRNAs into EVs can occur selectively and then be transferred to target cells, where they influence gene expression and cellular pathways. These miRNAs may be asymmetrically distributed relative to the expression levels in the source cells[33]. miRNAs from EVs can thus dynamically regulate the transcriptome of recipient cells, with either beneficial or detrimental effects depending on the physiological or pathological context[34]. Notably, EVs provide strong protection for their RNA cargo,

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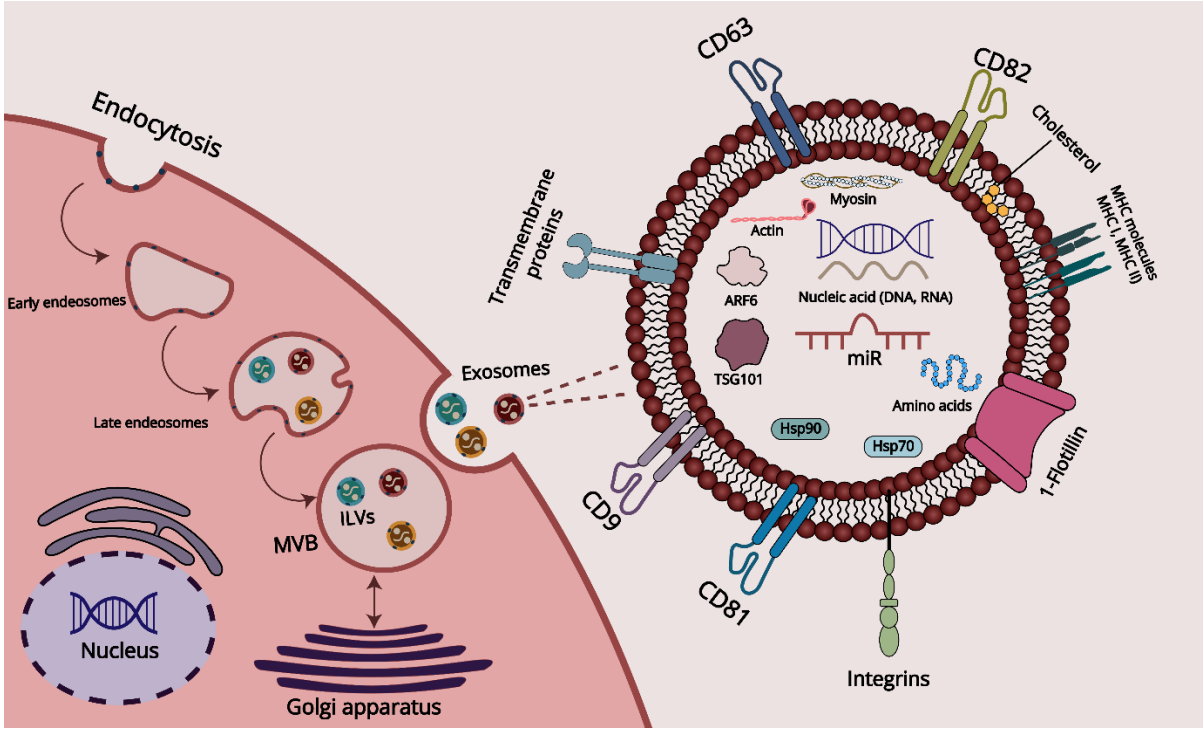

Fig. 1. Biogenesis and content of EVs. Exosome biogenesis is a complex process that involves the formation of ILVs within MVBs. These ILVs are then sorted into exosomes, which are small, secreted vesicles that carry various molecules, including proteins, nucleic acids (mRNA, miRNA, and DNA), and lipids. EVs are a crucial part of the cell intercellular communication and play a role in various biological processes, including cancer progression.

contributing to the remarkable stability of miRNAs during transport and delivery[35]. Furthermore, EVs carry different types of proteins such as integrin, heat shock protein tetraspanins (CD9, CD63, CD81, and CD82), cytokines, MHC molecules, and others[12]. Lipids such as cholesterol, sphingomyelin, and phosphatidylcholine serve as anchoring platforms for membrane proteins in EVs, facilitating membrane fusion, separation, and uptake processes[36].

3. Functional roles of EV-derived miRNAs in cancer

Tumor-associated EVs contain more specific proteins and RNAs than normal EVs, making them promising non-invasive biomarkers for the detection, monitoring, and prognosis of various cancers. In addition to their diagnostic potential, tEVs influence a wide range of cell types within the TME and exert multiple effects, including (i) promoting tumor angiogenesis by modulating endothelial cells and increasing vascular endothelial growth factor (VEGF) expression[37]; (ii) enhancing epithelial-mesenchymal transition (EMT), as well as initiating pro-/pre-metastatic niche formation and metastasis[38]; (iii) augmenting the immunosuppressive functions of myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs)[39]; (iv) protecting tumor cells from apoptosis while inducing apoptosis in DCs, cytotoxic T cells, and impairing natural killer cell function[40-42]; (v) reprogramming the differentiation or polarization of various cell types toward pro-tumorigenic, immunosuppressive, anti-inflammatory, and chemoresistant phenotypes, such as the transformation of fibroblasts into CAFs[43], macrophages into M2-polarized tumor-associated macrophages (TAMs)[44], and neutrophils into N2-polarized neutrophils[45]. Overall, EV-derived miRNAs carried by tEVs play crucial roles in shaping the TME by inducing chemoresistance, immunotherapy resistance, dormancy, stemness, and EMT (Fig. 2). Remarkably, EV-derived miRNAs can convert “hot tumors” (inflamed and immunologically active) into “cold tumors” (non-inflamed and immunologically inactive), which are less responsive or entirely unresponsive to immunotherapy. In the following sections, we review recent research on the functional roles of EV-derived miRNAs across different cancer types and explore their potential clinical applications, while the preceding text highlights the general oncogenic behaviors, such as metastasis, chemoresistance, and immune evasion, that are commonly influenced by tEVs in a wide range of malignancies.

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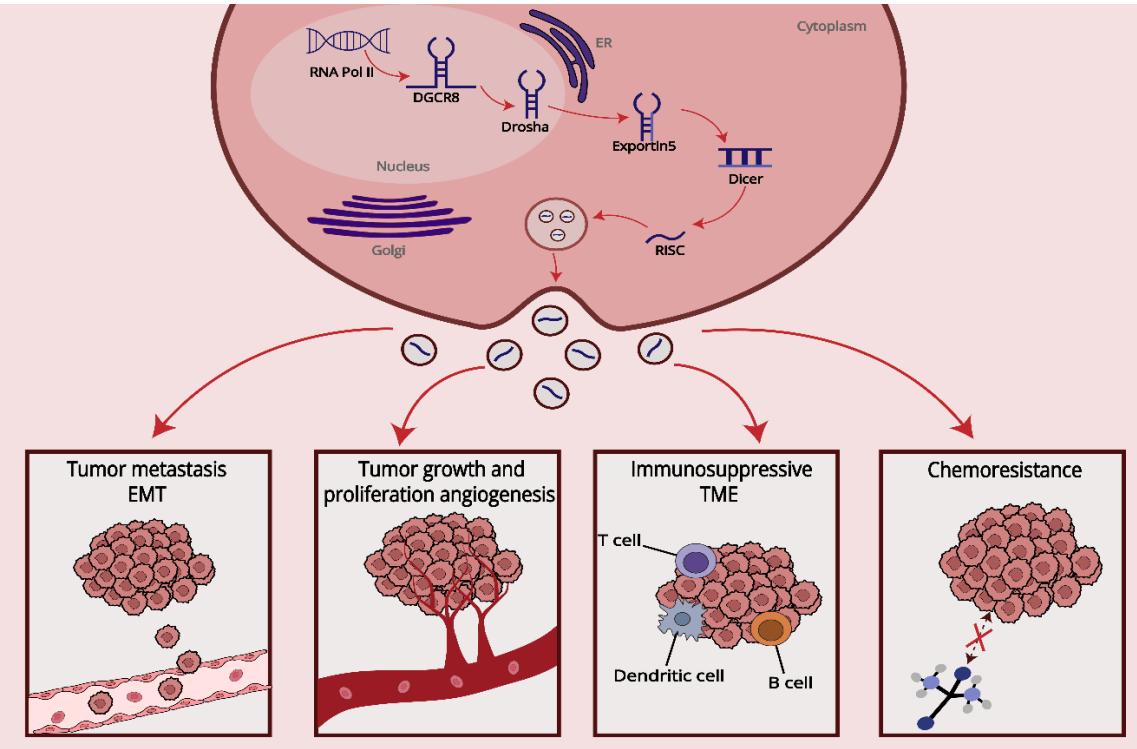

Fig. 2. Key roles of EV-derived miRNAs in cancer. EV-derived miRNAs are involved in various aspects of cancer development, including cell proliferation, invasion, metastasis, and resistance to therapy. From left to right, EV-derived miRNAs play a role in the EMT, a process that allows cancer cells to invade surrounding tissues and metastasize to other parts of the body. In terms of tumor proliferation, EV-derived miRNAs can influence the growth of malignant cells by modulating the expression of genes involved in the cell cycle. Also, they stimulate angiogenesis by increasing related gene expression, like VEGF, to facilitate tumor proliferation. In TME, EV-derived miRNAs can influence the interaction between cancer cells and the surrounding cells, including cancer cells and immune cell and potentially influence the immune response to the tumor. Moreover, they can contribute to drug resistance by altering the sensitivity of cancer cells to chemotherapy and other treatments. ER: endoplasmic reticulum

3.1. EV-derived miRNAs: orchestrators of tumor cell proliferation and growth

Uncontrolled cellular proliferation is a defining hallmark of cancer and a prerequisite for tumor progression, which is driven by both intrinsic alterations and extrinsic signals from the TME. EV-derived miRNAs are key mediators in this process, regulating cell cycle progression, apoptosis, metabolism, angiogenesis, and immune responses. They act by suppressing tumor suppressors and activating oncogenic pathways such as JAK/STAT, PI3K/AKT/mTOR, along with transforming growth factor-beta (TGF-β). For instance, Song et al. have shown that EVs derived from renal cancer cells are enriched with miR-9-5p, downregulating suppressor of cytokine signaling 4 (SOCS4), activating JAK/STAT signaling, which in turn enhances proliferation and invasion while inhibiting apoptosis. They have also proposed that EV-derived miR-9-5p could serve as a diagnostic and prognostic biomarker in renal carcinoma[46]. EV-derived miRNAs can reprogram stromal cells, including CAFs, mesenchymal stem cells (MSCs), and TAMs, to promote tumor proliferation. Jiang et al. have demonstrated that the upregulation of miR-181b-3p in EVs derived from CAFs promotes proliferation and migration while reducing the apoptosis of colorectal cancer (CRC) cells by targeting SNX2[47]. Moreover, EV-derived mir-10b-5p downregulates KLF11 in fibroblasts and phosphatase and tensin homolog (PTEN) in gastric cancer (GC) cells, leading to the activation of TGFβR1 and PI3K/AKT/mTORC1 signaling pathways, respectively. Thus, miR-10b-5p mediates interactions between GC cells and fibroblasts within the TME to enhance proliferation[48]. Beyond the primary tumor, EV-derived miRNAs exert systemic effects, preparing metastatic niches and contributing to therapy resistance. For example, Zhou et al. have demonstrated that EV-derived miR-21-5p from Schwann cells promotes proliferation, migration, and lymph node metastasis in lung adenocarcinoma by targeting the metalloproteinase inhibitor RECK[49]. Collectively, EV-derived miRNAs induce tumor proliferation by modulating oncogenic signaling and stromal interactions. Their central roles make them both biomarkers and potential therapeutic targets in cancer.

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3.2. EV-derived miRNAs as drivers of tumor metastasis and invasion

Metastasis is the major cause of cancer mortality, involving sequential steps of cell detachment, invasion, intravasation, circulation, extravasation, and colonization. These processes depend on interactions between tumor and stromal cells that regulate plasticity, motility, and organotropism[50]. EV-derived miRNAs are key mediators of this cascade, as they transfer regulatory signals that drive EMT, matrix remodeling, angiogenesis, immune evasion, and pre-metastatic niche formation[51]. Mechanistically, EV-derived miRNAs induce EMT, a phenotypic switch characterized by loss of epithelial markers (e.g., E-cadherin) and gain of mesenchymal traits (e.g., vimentin and N-cadherin), via the direct suppression of EMT repressors such as PTEN, SOCS3, or through the activation of canonical pathways, including Wnt/β-catenin, TGF-β/Smad, IL6/STAT3, and PI3K/AKT/mTOR[52]. By promoting EMT, these miRNAs endow tumor cells with enhanced motility and invasiveness (Table 1). For example, CRC-derived EVs from CAPS1-overexpressing cells stimulate the migration of normal colonic epithelial cells[53], while CAF-derived EV-associated mir-92a-3p activates Wnt/β-catenin to enhance stemness, EMT, and chemoresistance[54]. In breast cancer (BC), EV-derived mir-92b-5p regulates the migration, adhesion, and spreading of mammary epithelial cells via the downregulation of MTSS1L and has been proposed as a non-invasive biomarker for metastatic detection[55]. In addition, EV-derived miRNAs modulate stromal cell behavior, as they can polarize macrophages to an M2-like immunosuppressive phenotype[56], activate hepatic stellate cells (HSCs) and fibroblasts into tumor-promoting CAFs[57], and compromise endothelial cell junction integrity, thus facilitating intravasation, vascular permeability, and pre-metastatic niche formation[58]. Notably, hypoxia within the primary TMV enhances the selective packaging of certain miRNAs into EVs (e.g., miR-301a-3p and miR-4299), which further stabilizes transcriptional regulators like hypoxia inducible factor 1 subunit alpha (HIF-1α), which creates a feedback loop that sustains metastatic competency[59]. Functionally, EV-derived miRNAs regulate multiple steps of metastasis, making them both effectors and biomarkers of disease progression[60]. Zhao et al. have demonstrated that miR-181a-5p-enriched EVs from highly metastatic CRC cells activate HSCs by targeting SOCS3 and activating the IL6/STAT3 pathway, thus contributing to colorectal liver metastasis (CRLM). In turn, activated HSCs release CCL20 causes establishing a CCL20/CCR6/ERK1/ 2/Elk-1/miR-181a-5p axis that remodels the liver microenvironment and facilitates pre-metastatic niche formation[61]. Similarly, EV-derived mir-934 from CRC cells induces M2 macrophage polarization through PTEN downregulation and PI3K/AKT activation, thereby promoting CRLM[44]. Lung cancer EV-derived mir-193a-3p, miR-210-3p, and miR-5100 activate STAT3, promoting EMT and invasion[62]; however, CAF-derived miR-345-5p carried by EVs, targets CDKN1A to accelerate CRC metastasis[63]. In GC, hypoxia-induced EV-derived miR-301a-3p, stabilizes HIF-1α by inhibiting PHD3, driving proliferation, EMT, and dissemination[64]. EV-derived mir-16-5p from BMSCs inhibits EMT and tumor growth via the erythropoietin-producing hepatocellular A1/nuclear factor-κB (EPHA1/NF-κB) axis, highlighting its tumor-suppressive role[65]. Additionally, adipose-derived EV-associated mir-421 downregulates Chromobox protein homolog 7 (CBX7) and induces epigenetic changes to enhance metastasis[66]. At distant sites, miRNAs carried by EVs establish a favorable microenvironment for colonization by suppressing tumor-suppressive signals and reprogramming local immunity. For instance, EV-derived miR-21 has been linked to brain metastasis in lung cancer through ERK/STAT3 signaling[67]. Given EV-derived miRNAs significant contribution to metastatic progression and their detectability in body fluids, they hold promise as prognostic and diagnostic biomarkers, as well as potential therapeutic targets in metastatic cancers.

3.3. EVs-derived miRNAs as inducers of tumor angiogenesis

Angiogenesis, the sprouting of new vessels from pre-existing vasculature, is essential for tumor growth and metastasis. As tumors grow beyond the capacity of their existing blood supply, they induce angiogenesis. This process not only is primarily driven by VEGF but also involved additional signaling pathways, including fibroblast growth factor (FGF), platelet-derived growth factor, epidermal growth factor, and transforming growth factor-beta (TGF-β) signaling[68]. In TME, EVs-mediated delivery of oncogenic miRNAs plays a pivotal role in reprogramming endothelial and stromal cells toward pro-angiogenic phenotypes (Table 2). Mechanistically, EV-derived miRNAs modulate multiple signaling cascades that govern angiogenesis. They frequently enhance the VEGF/VEGFR axis, stimulate the PI3K/AKT/mTOR and ERK/MAPK pathways, and inhibit tumor-suppressive regulators of angiogenesis such as PTEN and PHDs. These actions collectively result in the increased endothelial cell proliferation, migration, and capillary-like tube formation[37]. Moreover, EV-derived miRNAs can compromise endothelial junction integrity, thereby

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Table 1. Role of EV-derived miRNAs in tumor metastasis

EVs-derived miRNA and source	Cancer type	Target	Effect on metastasis	Reference
miR-92a-3p (CAFs)	CRC	Wnt/β-catenin	Enhances cancer stemness and EMT, as well as promotes chemoresistance	[54]
miR-92b-5p (tumor cells)	BC	MTSS1L	Regulates the migration, adhesion, and spreading of mammary epithelial cells	[55]
miR-181a-5p (highly metastatic CRC cells)	CRC	SOCS3	CRLM	[72]
miR-934 (CRC cells)	CRC	PTEN	Induces M2 macrophage polarization	[54]
miR-1247-3p (HCC cells)	HCC	B4GALT3	Promotes lung metastasis	[73]
miR-194/215 (pulmonary metastatic sites) 14	Osteosarcoma	MARCKS	Promotes lung metastasis	[74]
miR-17-5p and miR-21 (lung tumor cells)	Lung cancer	PTEN, PDCD4	Enhance bone metastasis by promoting osteoclastogenesis	[75,76]
miR-193a-3p, miR-210-3p, and miR-5100 (lung cancer cells)	Lung cancer	STAT3	Promote EMT and invasion	[62]
miR-345-5p (CAFs)	CRC	CDKN1A	Promotes metastasis	[63]
miR-301a-3p (tumor cells)	GC	PHD3	Promotes EMT	[64]
miR-16-5p (BMSC) 14	BC	EPHA1/NF-κB	Inhibits EMT and tumor growth	[65]
miR-421 (adipose-derived)	Not available	CBX7	Induces epigenetic changes to enhance metastasis	[66]

enhancing vascular permeability and acilitating tumor cell intravasation. For instance, Liang et al. have shown that EV-derived miR-423-5p from BC cells promotes angiogenesis via EFNA3/Akt signaling[69]. Conversely, BMSC-derived miR-126-3p carried by EVs in non-small cell lung cancer (NSCLC), inhibits VEGF-A/VEGFR-2/ERK signaling and targets PTPN9, reducing invasion and inducing apoptosis[70]. EV-derived mir-3174 from hepatocellular carcinoma (HCC) cells enhances vascular permeability and angiogenesis by targeting HIPK3 and inhibiting Fas/p53 signaling[71]. Hypoxia intensifies this effect; i.e., HIFs not only increase angiogenic cytokines but also regulate miRNA packaging, reinforcing angiogenic loops[71]. In addition, Yang et al. have reported that nasopharyngeal carcinoma EV-derived mir-205-5p targets the 3′UTR

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Table 2. EV-derived miRNAs involve in tumor angiogenesis

EVs-derived miRNA and source	Cancer type	Target	Effect on angiogenesis	Reference
miR-423-5p (BC)	BC	EFNA3	Activates the Akt pathway and promotes angiogenesis	[69]
miR-126-3p (BMSC)	NSCLC	PTPN9	Suppresses VEGF-A/VEGFR-2/ERK and induces apoptosis	[70]
miR-3174 (HCC)	Hepatocellular carcinoma	HIPK3	Inhibits Fas/p53 and promotes angiogenesis	[71]
miR-205-5p (NPC)	Nasopharyngeal carcinoma	DSC2	Activates EGFR/ERK, MMP2/9, and promotes angiogenesis	[72]
miR-1247-3p (tumor cells)	Bladder cancer	FOXO1	Increases VEGF and promotes angiogenesis	[73]
miR-155 (melanoma)	Melanoma	SOCS1	Activates JAK2/STAT3 and increases VEGFA, FGF2, MMP9	[74]
miR-210-3p (oral squamous cell carcinoma)	Oral squamous cell carcinoma	EFNA3	Activates PI3K/Akt and promotes angiogenesis	[75]
Unknown (oxidative stress-induced MSC)	Various tumors	Not specified	Promotes angiogenesis	[76]
miR-23a (lung cancer)	Lung cancer	PHD1, PHD2, ZO-1	Increases HIF-1α and vascular permeability	[77]
miR-522-3p (CAFs)	CRC	BMP5	Enhances angiogenesis and metastasis	[78]
miR-21-5p (circulating EVs)	CRC	KRIT1	Activates β-catenin and increases VEGFA	[79]
miR-92a-3p (retinoblastoma)	Retinoblastoma	KLF2	Promotes angiogenesis in HUVECs	[80]

of desmocollin-2 (DSC2) to activate EGFR/ERK signaling and MMP2/MMP9 expression, correlating with poor survival and metastasis[72]. Other examples include tumor-derived miR-1247-3p carried by EVs, which suppresses forkhead box protein O1 (FOXO1) and increases VEGF in bladder cancer[73]. Also, EV-derived miR-155 from melanoma cells reprograms fibroblasts into CAFs, driving VEGFA, FGF2, and MMP9 via SOCS1/JAK2/STAT3 signaling[74]. In oral squamous cell carcinoma, tEVs enriched with miRNA-210-3p promote cancer progression and trigger angiogenesis by targeting ephrin A3 (EFNA3) through the activation of the PI3K/Akt axis[75]. It has also been shown that EVs derived from oxidative stress-induced MSCs promote tumor progression and angiogenesis[76]. Hypoxia-regulated mir-23a, carried by EVs, suppresses prolyl hydroxylases 1 and 2 (PHD1/2), stabilizes HIF-1α, and reduces ZO-1, thereby increasing vascular permeability and angiogenesis in lung cancer[77]. EV-derived mir-522-3p from CAFs downregulates bone morphogenetic protein 5 (BMP5), leading to enhanced tumor growth, angiogenesis, and metastasis in CRC[78]. In CRC, circulating EV-derived miR-21-5p suppresses Krev interaction trapped protein 1 (KRIT1) and activates β-catenin signaling, elevating VEGFA and vascular permeability[79]. Additionally, EV-derived mir-

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92a-3p secreted by retinoblastoma cells contributes to angiogenesis in human umbilical vein endothelial cells (HUVECs) by targeting Krüppel-like factor 2 (KLF2) and plays an important role in retinoblastoma development[80]. Given their ability to simultaneously regulate multiple targets and pathways, miRNAs carried by EVs serve as master regulators of the tumor vasculature or neovascularization. Their stability in circulation and specificity in cellular targeting render them attractive candidates for biomarker development and therapeutic intervention[81]. Targeting EV communication or modulating the function of angiogenesis-related miRNAs holds promise for disrupting the vascular supply essential to tumor survival and spread.

3.4. Role of EV-derived miRNAs in shaping tumor-suppressive TME

EV-derived miRNAs play a critical role in TME. They can enhance immune evasion, the polarization of TAMs toward the immunosuppressive M2 phenotype, the MDSC function, and the establishment of pre-metastatic niches. Through the suppression of tumor suppressor genes and activation of oncogenic pathways such as PI3K/AKT/mTOR, JAK/STAT, and Wnt/β-catenin, EV-derived miRNAs help tumors manipulate their microenvironment to facilitate growth, metastasis, and therapy resistance (Table 3). For example, Otmani et al. have found that EV-derived miR-24-3p decreases AML T-cell survival by directly targeting DENN/MADD and indirectly altering NF-κB, p-JAK/STAT, and p-ERK pathways. It also promotes Treg development, suggesting a potential therapeutic target to restore antitumor T-cell function against AML blasts[41]. Given the significant role of MDSCs in the TME, Ren et al. have revealed that EV-associated mir-107 derived from GC cells is internalized by HLA-DR-CD33$^+$ MDSCs, inhibiting DICER1 and PTEN expression and activating the PI3K pathway, thereby facilitating MDSC expansion and activation[82]. TAMs, particularly the M2 subtype, exert immunosuppressive effects by releasing IL-10, TGF-β, and Arg-1, thus facilitating tumor progression. MiRNAs carried by EVs promote this polarization[83]. In this regard, miR-6794-5p suppresses SOCS1 and activates JAK1/STAT3, reducing M1/CD8$^+$ T cells and enhancing tumor migration, invasion, and stemness[84]. Moreover, EV-derived mir-519a-3p from GC cells accumulates in the liver, targeting dual specificity phosphatase 2 (DUSP2) in intrahepatic macrophages, activating MAPK/ERK signaling, promoting M2 polarization, and establishing a pre-metastatic niche[85]. Similarly, EV-derived mir-222-3p from epithelial ovarian cancer cells promotes M2 polarization via SOCS3/STAT3 activation[86]. In HCC, Hu et al. have demonstrated that EV-associated miR-21-5p derived from HCC cells promotes tumor progression by inducing specific protein 1 (SP1) expression and inhibiting X-box binding protein 1 (XBP1), facilitating M2 polarization, and correlating with advanced disease stages[87]. EV-derived mir-221-3p from M2-TAMs promotes osteosarcoma progression by modulating the SOCS3/JAK2/STAT3 axis[88]. In BC, EV-derived mir-148b-3p induces M2 polarization via targeting the TSC2/mTORC1 signaling pathway and thus, correlates with lymph node metastasis, late tumor stage, and worse prognosis of BC[89]. Additionally, miR-138-5p can also be delivered from BC cells to TAMs via EVs to downregulate lysine demethylase 6B (KDM6B) expression and inhibit M1 polarization, resulting in M2 polarization; these macrophages promote lung metastasis[90]. EV-derived mir-217 from human normal bladder stromal cells enhances bladder cancer

Table 3. EV-derived miRNAs in TME remodeling

Mechanism	miRNA	Function/Target	Reference
Proliferation and metastasis	miR-519a-3p	Targets DUSP2; activates MAPK/ERK	[85]
	miR-221-3p	Targets SOCS3; activates JAK2/STAT3	[88]
	miR-107	Inhibits DICER1/PTEN, activates PI3K	[82]
M2 polarization and immunosuppression	miR-6794-5p	Inhibits SOCS1, activates JAK1/STAT3	[84]
	miR-222-3p	Targets SOCS3; activates STAT3	[86]
	miR-21-5p	Targets SP1; inhibits XBP1	[87]
	miR-148b-3p	Targets TSC2; activates mTORC1	[89]
	miR-138-5p	Targets KDM6B; inhibits M1, promotes M2	[90]
Immune evasion	miR-27a-3p	Enhances PD-L1 via PTEN inhibition	[92]
	miR-200a/miR-21-5p	Activates STAT1; increases PD-L1	[93]
	miR-24-3p	Targets DENN/MADD; alters NF-κB, p-JAK/STAT, p-ERK; promotes Treg	[41]

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proliferation and migration by targeting the Hippo-YAP pathway[91]. In terms of immunomodulation, EV-mediated PD-1/PD-L1 immunosuppression is pivotal for immune evasion. BC-derived EV-associated mir-27a-3p enhances PD-L1 expression in M2 macrophages via PTEN inhibition[92], while EV-derived mir-200a and miR-21-5p from CRC cells activate the STAT1 pathway to increase PD-L1 expression[93]. Understanding these regulatory mechanisms is essential for developing novel therapeutic strategies aimed at reprogramming the TME and restoring antitumor immunity.

3.5. Role of EV-derived miRNAs in shaping tumor chemoresistance within the TME

Drug resistance is a major challenge in cancer therapy, leading to relapse and poor outcomes. EV-derived miRNAs, secreted by tumor and stromal cells, play a central role in this process by reprogramming recipient cells through gene regulation and signaling modulation. EV-derived miRNAs can drive chemoresistance through different pathways, which we will survey in the following. EV-derived miRNAs inhibit apoptosis and protect cancer cells from drug-induced cell death through the downregulation of pro-apoptotic regulators such as BAX, Bak1, and CASP9. For example, CAF-derived miR-103a-3p carried by EVs reduces Bak1 and mediates cisplatin resistance in lung cancer[94], while EV-derived mir-210 from cancer stem cells (CSCs) promotes gemcitabine resistance in pancreatic cancer by activating mTOR signaling[95]. In addition, Zhao et al. have reported that doxorubicin-resistant BC cells exhibit upregulated EV-derived mir-181b-5p, which transfers a drug-resistant phenotype by downregulating p53/p21 levels, inhibiting doxorubicin-induced G1 arrest, and decreasing Bcl-2-associated transcription factor 1 (BCLAF1) expression[96]. Additionally, Fang et al. have shown that CAF-derived EV-associated mir-106b plays a crucial role in inducing gemcitabine resistance in pancreatic cancer by directly targeting tumor protein p53 inducible nuclear protein 1 (TP53INP1)[97]; and activating survival pathways such as PI3K/AKT/mTOR, JAK2/STAT3, and Wnt/β-catenin, often through targeting tumor suppressors like PTEN, SOCS5/6, or programmed cell death factor 4 (PDCD4). These pathways enhance cell proliferation, survival, and resistance to chemotherapy-induced stress[98]. Moreover, Deng et al. have found that EV-derived mir-424-5p, derived from Cisplatin (DDP)-resistant cells, significantly contributes to NSCLC development and DDP resistance by downregulating SOCS5 and SOCS6, thereby activating the JAK2/STAT3 and PI3K/AKT pathways[99]. EV-derived miRNAs promote cancer stemness by upregulating stemness-related pathways (e.g., NOTCH, EZH2/STAT3, YAP/Hippo) and downregulating inhibitors such as NUMB endocytic adaptor protein (NUMB) and Dickkopf 3 (DKK3), thereby helping maintain a population of drug-tolerant persisted cells[100]. Yang et al. have shown that in BC, chemotherapy with doxorubicin[101] and paclitaxel induces release of miR-378a-3p/miR-378d, which activate WNT and NOTCH pathways via targeting DKK3 and NUMB, thereby sustaining stemness and resistance[101]. In addition, EV-derived miRNAs remodel the immune microenvironment by promoting M2 macrophage polarization, increasing Treg expansion, and suppressing $CD8^+$ T-cell function, ultimately contributing to immunotherapy resistance and the establishment of an immunosuppressive niche. For instance, tumor-secreted miR-208b has been shown to drive oxaliplatin resistance and Treg expansion in CRC by targeting PDCD4[102]. Similarly, miR-588 promotes M2 macrophage polarization in DDP-resistant GC through partial targeting of cylindromatosis (CYLD)[103], while miR-221/222 reshape the TME and induce tamoxifen resistance in BC by targeting P27 and ERα[104]. Furthermore, EV-derived miRNAs enhance metabolic rewiring in cancer cells by both promoting glycolysis through the regulation of pyruvate dehydrogenase E1 subunit alpha 1 (PDHA1) and reducing ferroptosis sensitivity via the suppression of ACSL4, thereby enabling the cells to adapt metabolically under drug pressure. For example, EV-derived miR-21-5p enhances cisplatin resistance and promotes glycolysis in ovarian cancer by regulating PDHA1[105], while EV-derived mir-214-3p from GC cells suppresses Acyl-CoA synthetase long chain family member 4 (ACSL4) to inhibit ferroptosis, reducing sensitivity to Apatinib as an angiogenesis inhibitor[34]. Also, EV-derived miRNAs alter drug metabolism by regulating key enzymes, including cytidine deaminase and deoxycytidine kinase (DCK), which are essential for the bioactivation and degradation of chemotherapeutic agents. For instance, macrophage-derived EVs containing miRNA-365 promote gemcitabine resistance in pancreatic ductal adenocarcinoma (PDAC) by stimulating cytidine deaminase activity[106]. Collectively, EV-derived miRNAs from tumor cells, CAFs, CSCs, and immune cells can transform drug-sensitive cells into resistant phenotypes. Beyond being mediators of resistance, they hold strong potential as predictive biomarkers and therapeutic targets to overcome treatment failure across cancer types.

4. Therapeutic strategies and effects of EV-derived miRNAs in cancer treatment

EV-derived miRNAs have emerged as crucial modulators in cancer therapy, offering strategies to reverse tumor progression by regulating oncogenic

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signaling pathways. Currently, two main therapeutic approaches exist to modulate key signaling pathways driving cancer progression: (1) depleting oncogenic miRNAs or inhibiting their function in tumor cells, and (2) delivering tumor-suppressor miRNAs via engineered EVs to restore antitumor activity or trigger immune response. In the first approach, several strategies have been described: (i) anti-miRNA oligonucleotides, (ii) miRNA sponges, (iii) small molecule inhibitors, (iv) miRNA masking, and (v) blocking EVs transfer and sorting. These strategies prevent miRNA-mediated suppression of tumor suppressors. For example, miR-221/222 sponges restore ERα and PTEN expression in tamoxifen-resistant BC, reducing cell proliferation and migration[107]. Circular miRNA decoys, such as CM21D targeting miR-21, induce apoptosis and inhibit proliferation in glioblastoma and CHO-engineered cells[108,109]. Small molecule inhibitors, like fluoroquinolone derivatives, suppress miR-21 activity[110], while miRNA-masking antisense oligonucleotides protect target mRNAs from oncogenic miRNAs[111]. Blocking EV secretion (for example, by knockdown of Rab27a) retains onco-miRNAs intracellular, promoting apoptosis and suppressing tumor growth[112]. In the second approach, EV-mediated delivery of tumor-suppressor miRNAs restores antitumor signaling, inhibits proliferation, invasion, and metastasis, and modulates the immune microenvironment. Similarly, miRNA mimic technologies and gene therapy strategies, whether via transient expression or stable integration, have demonstrated significant efficacy in restoring tumor-suppressor functions and modulating antitumor pathways. Recently, Yuen et al. have developed a therapeutic strategy for treating PDAC, using tumor suppressors miR-15a and miR-194 mimics combined with gemcitabine. These modified miRNA-mimics induce cell-cycle arrest, apoptosis, and inhibit PDAC growth[32]. EV-derived mir-101 and miR-22 inhibit proliferation and metastasis in osteosarcoma by targeting BCL6 and Twist1[113,114]. miR-122-3p, miR-181c, and miR-665 suppress growth and metastasis in BC, CRC, and osteosarcoma, respectively[115-117]. miR-92b-3p inhibits angiogenesis and invasion by targeting SOX4 in ovarian cancer[118]. Human BMSC overexpressing miR-16-5p suppresses proliferation, migration, and invasion in CRC while enhancing apoptosis by downregulating integrin α2 (ITGA2)[119]. EV-derived mir-99b-5p from MSCs inhibits tumor proliferation in CRC[120]. Similarly, in liver cancer, miR-99b re-educates TAMs toward an antitumor M1 phenotype, enhancing immune surveillance and inhibiting M2 polarization by targeting κB-Ras2 and/or mTOR[121]. Moreover, EV-associated miR-375 derived from human umbilical cord MSCs targets enabled homolog and suppresses proliferation, invasion, migration, and tumor sphere formation in esophageal squamous cell carcinoma[122]. EV-derived mir-124a acts as an anti-glioma agent by silencing Forkhead box A2, causing intracellular lipid accumulation and increasing overall survival in glioma models[123]. EV-derived mir-433, by targeting TMED5 and the WNT/β-catenin pathway, promotes apoptosis, suppresses tumor growth, enhances CD4/CD8 T-cell infiltration into the TME, and reduces DDP resistance in NSCLC[124]. Also, EV-derived miR-145-3p enhances autophagy by targeting the histone deacetylase 4 (HDAC4), leading to the upregulation of BCL2L11 and inhibition of mTORC1, thereby restoring bortezomib sensitivity in myeloma cells[125]. In the context of T-cell immune responses, Li et al. have reported that EV-derived miR-16-5p from M1 macrophages inhibits GC progression by regulating PD-L1[126]. Similarly, EV-derived mir-16-5p inhibits lung adenocarcinoma development by downregulating PD-L1[127]. Overall, EV-derived miRNAs represent versatile tools for cancer therapy. Depletion of oncogenic miRNAs or delivery of tumor-suppressor miRNAs can inhibit tumor growth, metastasis, angiogenesis, and chemoresistance. Engineering EVs to carry specific miRNAs, combined with small molecule inhibitors, provides promising avenues for personalized cancer treatment. Continued optimization and clinical translation of these strategies may enhance the efficacy of current therapies and offer novel options for refractory cancers.

5. CONCLUSION

miRNAs from EVs are pivotal regulators in cancer biology. These small ncRNAs encapsulated within EVs mediate communication between tumor cells and the TME, including endothelial cells, fibroblasts, and immune cells. By modulating signaling pathways, EV-derived miRNAs influence tumor growth, angiogenesis, metastasis, epithelial-to-mesenchymal transition, immune evasion, and therapy resistance. They reprogram gene expression in recipient cells, fostering a microenvironment that supports tumor progression. EV-derived miRNAs also have dual roles: tEVs typically promote malignancy, whereas those from stromal or immune cells suppress or regulate tumors, underscoring their context-dependent function. Their stability in body fluids and selective packaging make EVs promising biomarkers for cancer diagnosis, prognosis, and treatment monitoring. Furthermore, their functional significance offers therapeutic potential, either by disrupting their biogenesis/secretion or modulating activity in recipient cells, paving the way for RNA-based strategies in precision oncology.

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DECLARATION

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Generative AI and AI-assisted technologies
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Authors' contributions
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