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Review Article

Extracellular vesicles in the tumor microenvironment: Diverse origins, multifaceted functions, and emerging therapeutic opportunities

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ABSTRACT

As pivotal mediators in the tumor microenvironment (TME), extracellular vesicles (EVs) orchestrate intercellular communication by transferring bioactive cargo, including proteins, lipids, and nucleic acids. These highly heterogeneous EVs can exert profoundly divergent impacts on malignant progression and clinical treatment outcomes. Beyond their intrinsic biological roles, their natural capacity for cargo transfer also supports their development as next-generation engineered delivery platforms. Furthermore, specific subtypes of EVs or those carrying particular cargo are being pursued as both therapeutic targets for modulating pathogenic signaling and as noninvasive biomarkers for diagnosis and prognosis. Although modulation of EV-mediated pathways has shown promise in preclinical models, clinical translation remains hindered by insufficient target selectivity, off-target effects, and challenges in achieving scalable, standardized manufacturing. This review synthesizes current knowledge on EV heterogeneity and their diverse functions in modulating the TME, and further outlines a framework for emerging applications in clinical diagnostics and therapeutics.

Abbreviations

TME	Tumor microenvironment
EV	Extracellular vesicle
MVB	Multivesicular body
ECM	Extracellular matrix
TEV	Tumor-derived EV
sEV	Small extracellular vesicle
lEV	Large extracellular vesicle
ILV	Intraluminal vesicle
ESCRT	Endosomal sorting complex required for transport
TIL	Tumor-infiltrating lymphocyte
NK	Natural killer
DC	Dendritic cell
MDSC	Myeloid-derived suppressor cell
CTL	$CD8^+$ cytotoxic T lymphocyte
IFN-γ	Interferon-gamma
PD-1	Programmed death receptor 1
PD-L1	Programmed death ligand 1
ICAM-1	Intercellular adhesion molecule 1
TAM	Tumor-associated macrophage
Treg	Regulatory T cell
CAF	Cancer-associated fibroblast
EMT	Epithelial-to-mesenchymal transition
MTTP	Microsomal triglyceride transfer protein
ICB	Immune checkpoint blockade
CTLA-4	Cytotoxic T-lymphocyte antigen 4
TIM-3	T cell immunoglobulin and mucin-domain containing-3
NP	Nanoparticle
IR	Ionizing radiation
HS	heparan sulfate

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Introduction

The tumor microenvironment (TME) is a complex ecosystem of malignant cells, stromal cells, and acellular components that collectively orchestrate cancer progression. This progression is governed by intercellular communication networks mediating critical oncogenic processes, including immune evasion, angiogenesis, and metastasis. Extracellular vesicles (EVs) are pivotal components of these networks and facilitate communication through the transport of bioactive cargo.[1,2]

EVs are heterogeneous, membrane-enclosed particles generated via direct plasma membrane budding or the endosomal multivesicular body (MVB) pathway.[3,4] Their functional effects are dictated by cellular origin. Specifically, tumor-derived EVs (TEVs) disseminate pro-tumorigenic factors and drive malignant progression, immune cell-derived EVs exert context-dependent immunostimulatory or immunosuppressive functions, and stromal-derived EVs remodel the extracellular matrix (ECM) and help establish pre-metastatic niches.[5,6] Although certain EV subpopulations may limit tumor progression, a significant number of EVs are key mediators of clinical treatment resistance. The biogenesis routes, cellular sources, and cargo profiles that underlie this functional heterogeneity are summarized in Fig. 1.

Given their profound impact on oncology, certain EVs hinder immunotherapy, radiotherapy, chemotherapy, and novel targeted delivery systems. This impact on treatment outcomes has bifurcated research into the inhibition of pro-tumorigenic EV activity and the engineering of EVs as delivery platforms for therapeutic cargo. The former line aims to abrogate pro-tumorigenic EVs activity through developing small-molecule inhibitors of EV biogenesis and secretion or by repurposing existing drugs, thereby neutralizing EV-mediated signaling that drives therapeutic resistance. However, current inhibitors have limited clinical utility due to low target specificity and off-target effects. The latter strategy entails the engineering of EVs into precision delivery vehicles for chemotherapeutics, nucleic acids, or gene-editing systems. Beyond therapeutic applications, EVs are extensively investigated as noninvasive biomarkers for liquid biopsy to enable real-time monitoring of disease progression and treatment response. However, persistent technical and translational challenges remain for both applications, including optimization of cargo loading, engineering of tumor-specific targeting moieties, and development of scalable, standardized

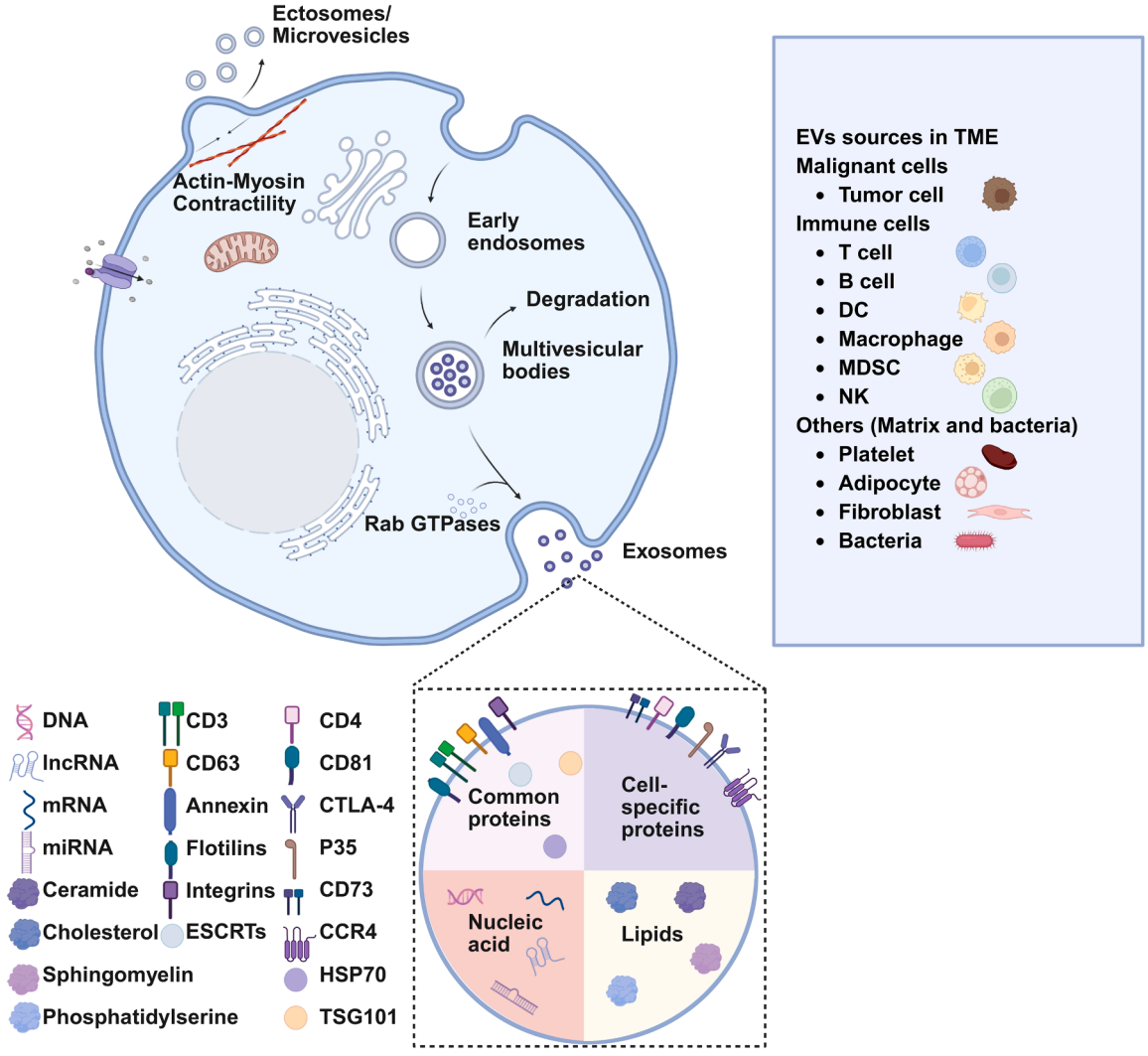

Fig. 1. EV Biogenesis and Diverse Cellular Sources in the TME. Biogenesis of lEVs and sEVs, along with their diverse cellular origins in the TME. lEV formation is driven by actin-myosin contractility at the plasma membrane. sEVs biogenesis depends on the ESCRT machinery and Rab GTPases, which cooperatively regulate endosomal maturation and intraluminal vesicle formation. EVs carry various bioactive cargo, including proteins (e.g., CD3, CD4, CD81, CD63, CD73, CCR4, CTLA-4, HSP70, TSG101, P35), nucleic acids (e.g., DNA, long non-coding RNA (lncRNA), messenger RNA (mRNA), microRNA (miRNA)), and lipids (e.g., ceramide, sphingomyelin, cholesterol, phosphatidylserine). Abbreviations: DC, dendritic cells; ESCRT, endosomal sorting complex required for transport; MDSC, myeloid-derived suppressor cells; NK, natural killer cells.

manufacturing protocols.

Collectively, EVs function as pivotal mediators within the TME communication network. They fundamentally shape tumor biology and therapeutic outcomes. Accordingly, current investigation principally encompasses the inhibition of pro-tumorigenic EV activity, the engineering of EVs as therapeutic delivery platforms, and their development as diagnostic biomarkers. Resolving the inherent technical and biological challenges is essential for clinical translation of EV-based strategies.

The biogenesis and uptake of EVs

EVs are lipid bilayer-bound particles released from cells. Per 2023 International Society for Extracellular Vesicles (ISEV) guidelines, they are classified into small EVs (sEVs; <200 nm) and large EVs (lEVs; >200 nm).[7] ISEV discourages the use of historically prevalent terminology, such as "exosomes" (derived from multivesicular bodies [MVBs]) and "ectosomes" or "microvesicles" (derived from the plasma membrane), when insufficient evidence confirms their subcellular origins.[7–9] Nevertheless, many studies still refer to sEVs as "exosomes" and lEVs as "microvesicles".[10–12] Throughout this manuscript, the term "sEVs" is used in place of "exosomes", and "lEVs" is used in place of "microvesicles" to align with current nomenclature.

EV biogenesis occurs through two primary pathways: intraluminal vesicle (ILV) formation within MVBs and direct plasma membrane budding.[8,13,14] ILVs are generated via inward budding of early endosomes, which subsequently mature into MVBs. Fusion of these MVBs with the plasma membrane leads to the release of sEVs.[9,15] sEV secretion is regulated by both endosomal sorting complex required for transport (ESCRT)-dependent and ESCRT-independent pathways, the latter mediated in part by sphingolipid ceramide.[16–19] Emerging evidence indicates that radiation-induced stress stimulates sEV release primarily via the accumulation of free arachidonic acid. This accumulation promotes endosomal sorting and spermidine synthase secretion.[20] Collectively, lipid metabolism and signaling form the core regulatory network for ESCRT-independent biogenesis. Cellular stress, including endoplasmic reticulum stress, viral infection, and mitochondrial damage, can activate these pathways to drive aberrant EV secretion.

Recipient cells internalize EVs via clathrin-mediated endocytosis, caveolin-dependent endocytosis, macropinocytosis, and phagocytosis.[21–24] Physical dimensions and membrane compositions explicitly dictate the cellular entry machinery.[8,22,25,26] Smaller vesicles preferentially undergo clathrin- or caveolin-mediated endocytosis. Larger vesicles tend to employ alternative internalization routes to accommodate their size.[27–30] However, the underlying regulatory mechanisms remain to be fully elucidated. Beyond physical dimensions, specific membrane lipid compositions profoundly modulate cellular uptake. Phosphatidylserine deficiency reduces uptake and prolongs systemic circulation.[31] Conversely, cholesterol depletion induces structural deficits that actively enhance vesicle internalization.[32] Extravesicular domains of proteins such as integrins essentially facilitate initial contact with recipient cells.[33,34] Despite these structural insights, investigations into EV transport kinetics remain conspicuously scarce.[22,35] It is essential to rigorously elucidate the precise mechanisms that dictate the biogenesis and selective uptake of distinct EV subpopulations across dynamic physiological and pathological states within the TME.

EV heterogeneity and functional diversity in the TME

The TME is a complex ecosystem comprising distinct cellular and non-cellular components. Its cellular compartment includes malignant cells, stromal cells such as fibroblasts, and a diverse immune cell infiltrate (e.g., tumor-infiltrating lymphocytes (TILs), natural killer (NK) cells, macrophages, dendritic cells (DCs), and myeloid-derived suppressor cells (MDSCs)), while the non-cellular milieu consists of the extracellular matrix, soluble factors, and microbial communities.[36–38] Released by these components, EVs function as critical mediators of intercellular communication. They orchestrate fundamental TME processes through the horizontal transfer of bioactive cargo. These EVs reflect their cellular origin and regulate immune modulation, angiogenesis, matrix remodeling, and metastasis (Fig. 2). This section delineates the functional pleiotropy of EVs originating from this complex cellular landscape (Table 1),[39–89] with their specific roles in therapeutic resistance and sensitization deferred to subsequent discussion.

Tumor-derived EVs: dual regulators of the malignant progression

The TME dynamically regulates the biogenesis and composition of EVs (Fig. 3).[90] Tumor cells exhibit heightened EV secretion compared to their non-malignant counterparts.[91,92] TME-specific stressors such as hypoxia, acidic pH, and genomic instability directly drive this elevated production.[66,93,94] Furthermore, TME-modulating factors including leptin, estrogen, and TGF-β further stimulate TEV release,[95–97] which concurrently alters their cargo composition. Consequently, genetic ablation of TEV biogenesis in preclinical models enhanced anti-tumor immunity with robust T-cell infiltration and response.[67,68]

TEVs modulate the tumor immune microenvironment to favor tumor growth through multifaceted mechanisms, including direct suppression of cytotoxic immune cell proliferation and effector functions, modulation of antigen presentation by DCs and other antigen-presenting cells, and regulation of myeloid cell activity (e.g., macrophage polarization and MDSC recruitment).[67,98] These effects collectively establish an immunosuppressive TME that limits immune cell infiltration and dampens anti-tumor responses. Specifically, TEVs inhibit $CD8^+$ cytotoxic T lymphocyte (CTL) function and infiltration in carcinomas.[70,99,100] TEVs also promote CTL exhaustion and senescence by dysregulating their metabolic pathways.[101,102] Similarly, TEVs abrogate the cytotoxic capacity of NK cells through the targeted downregulation of the activating receptor NKG2D.[103,104] TEVs additionally modulate antigen presentation by DCs. TEVs derived from Lewis lung carcinoma or 4T1 breast cancer cells explicitly block the differentiation of myeloid precursor cells into $CD11c^+$ DCs.[105] Beyond direct lymphocyte suppression, TEVs initiate broad myeloid cell reprogramming. They drive M2-like macrophage polarization in multiple tumor types, including colorectal cancer, gastric cancer, renal cell carcinoma, and non-small-cell lung cancer.[106–109] Paradoxically, specific TEVs subpopulations induce M1-like macrophages to promote tumor migration via $THBS1^+$ sEVs in oral squamous cell carcinoma.[110,111] Despite the prevailing paradigm of TEVs as pathogenic agents, certain subpopulations exhibit distinct immunostimulatory properties. These specific vesicles carry tumor-associated antigens to stimulate DC maturation. This maturation subsequently activates CTL responses.[112,113] In colorectal cancer models with lung metastasis, specific TEVs reduce the proportion of regulatory T-cell proportion and suppress tumor growth.[114] This functional dichotomy underscores the dualistic nature of TEV-mediated TME regulation, which appears critically dependent on tumor type and microenvironmental context. A deeper understanding of this duality is essential for elucidating the regulatory mechanisms governing their opposing functions and for the future development of EV-based therapeutics.

Immune cell-derived EVs: orchestrators of the tumor immune landscape

The initial modulation of the TME by TEVs establishes a reciprocal dialogue with resident immune populations to dictate tumor initiation and immune surveillance.[115,116] Immune cell-derived EVs participate in bidirectional exchange and transport molecular cargo that reflects the lineage and activation status of the parent cells. These immune cell-derived EVs exert dichotomous effects on malignancy. They either foster an immunosuppressive microenvironment to accelerate disease progression or amplify immune responses to drive tumor regression. Through continuous molecular transfer, both immune cell-derived EVs

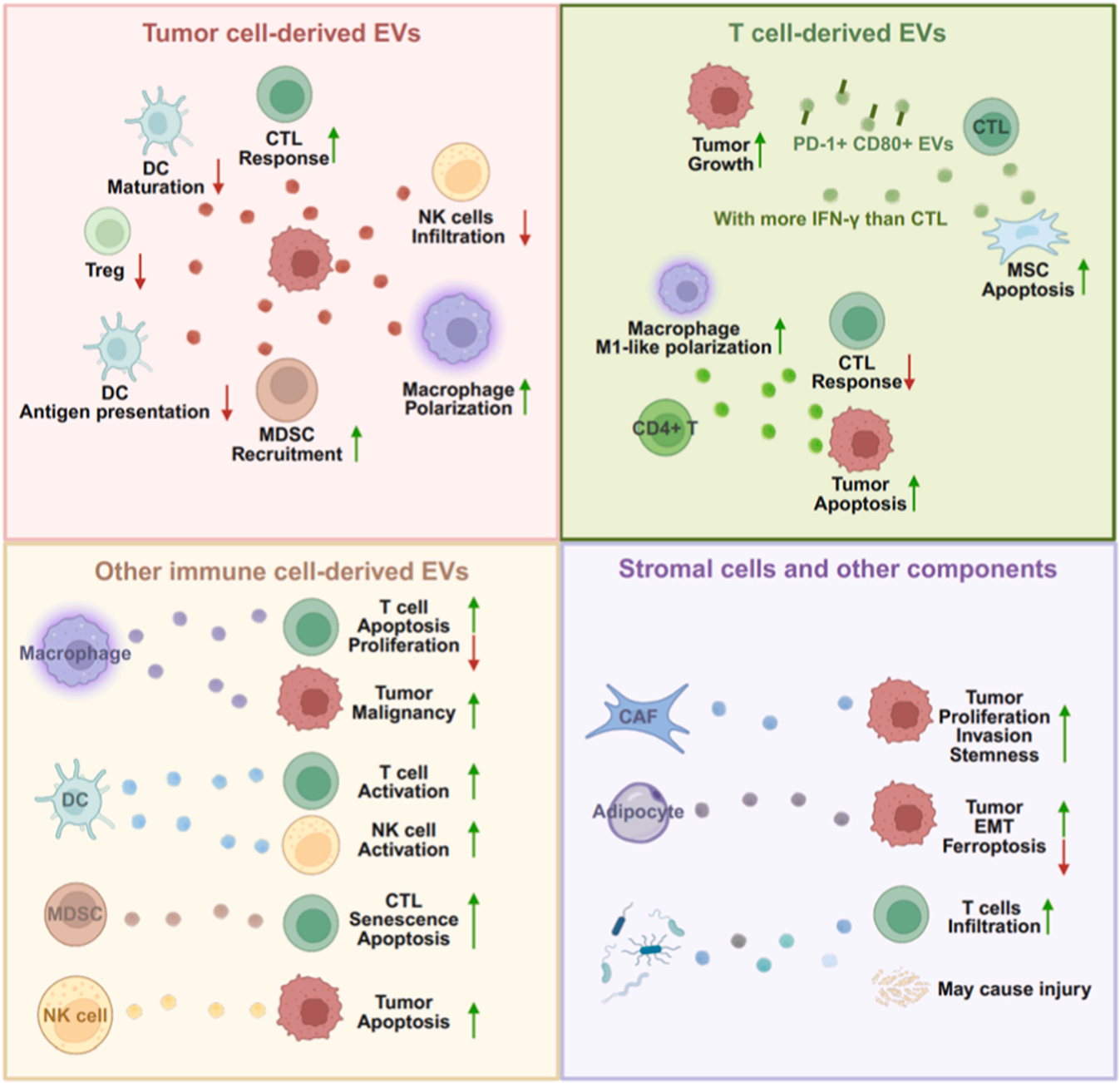

Fig. 2. EV-Mediated Intercellular Communication within the TME. EVs act as critical messengers mediating communication between tumor cells, immune cells, and stromal cells to establish a dynamic network within the TME. These EV-dependent interactions shape the TME by regulating processes including immune evasion, metabolic reprogramming, and therapeutic resistance, thereby modulating tumor progression and treatment outcomes. Abbreviations: CAF, cancer-associated fibroblast; CTL, cytotoxic T lymphocyte; DC, dendritic cells; EMT, epithelial-to-mesenchymal transition; MDSC, myeloid-derived suppressor cell; MSC, mesenchymal stem cell; NK, natural killer cell.

and TEVs engage their respective recipient cells to establish an intricate communication network within the TME.

T cells-derived EVs

CTLs mediate antitumor immunity through the T-cell receptor-mediated recognition of peptide-MHC class I (pMHC) complexes on target cells.[117] These lymphocytes concurrently secrete EVs with highly multifaceted functions.[118] Interestingly, the biogenesis of these EVs is activation phase-dependent: early-phase stimulation predominantly generates EVs via ESCRT-independent mechanisms, while late-phase responses shift to ESCRT-dependent production.[119] Under robust antigen stimulation, CTL-derived EVs exhibit significantly higher IFN-γ enrichment than the parent cells[77] Critically, under weak or absent antigen stimulation, interleukin-12 (IL-12) reprograms CTL-derived sEVs to activate bystander naïve $CD8^+$ T cells antigen-independently to trigger IFN-γ and granzyme B production, thereby enhancing their tumor killing effect in immunotherapy and chronic virus infection.[120]

Distinct CTL EVs subtypes manifest profound functional heterogeneity. For instance, EVs with immunological checkpoint receptor programmed death receptor 1 (PD-1) from activated CTLs and $CD4^+$ T cells could enhances the killing capacity of CTLs, thus suppressing tumor proliferation and enhance anti-tumor immunity.[78] Conversely, PD-1 and CD80 double-positive sEVs from activated T cells elevate programmed death ligand 1 (PD-L1) and intercellular adhesion molecule 1 (ICAM-1)

Table 1
EV heterogeneity and their diverse functions in modulating TME.

Exosome Cargos		Origin of EVs	Cancer Type	Impact on Cancer	Reference
LncRNA	SNHG3	CAFs	Colorectal cancer	Facilitates cancer proliferation	39
	RP11-161H23.5		Pancreatic ductal adenocarcinoma	Promotes cancer immune evasion	40
miRNA	hsa-mir-24-1 hsa-miR-103b hsa-miR-127	Tumor	Oral squamous cell carcinoma	Causes lymph node metastasis and an adverse prognosis	41
	miR-105		Metastatic breast cancer	Destroys tight junctions and the integrity of natural barriers against metastasis; induces metastasis and vascular permeability in distant organs	42
	miR-21-5p	Macrophage	Hypoxic head and neck squamous cell carcinoma	Promotes angiogenesis and growth	43
	miR-155-5p		Colorectal cancer	Induces cancer cells' migration and invasion	44
	miR-101-3p		Ovarian cancer	Promotes tumor progression and $CD8^+$ T cell apoptosis	45
	miR-155 miR-196a-5p		Non-small cell lung cancer	Promotes tumor metastasis	46
	miR-501-3p		Pancreatic ductal adenocarcinoma	Promotes tumor formation and metastasis	47
	miR-223		Breast cancer	Promotes tumor invasion	48
	miR-16-5p miR-342-3p miR-24-3p miR-92a-3p	NK cell	Various cancer cells	Detected	49
	let-7b-5p		Pancreatic cancer	Inhibits tumor growth	
	miR-146b miR-23a		Various cancer cells	Targets genes related to oncogenic processes and then enhances NK cytotoxic capacity against tumor cells.	50
	miR-345-5p	CAFs	colorectal cancer	Promotes cancer progression and metastasis	51
	miR-34b-5p			Facilitates tumor cell proliferation	39
	miR-21		Multiple myeloma	Promotes angiogenesis of cancer	52
			Pancreatic cancer	Triggers stemness maintenance; Promotes gemcitabine resistance	53
	miR-1-3p		Breast cancer	Inhibits tumor cell viability, invasion, migration, and epithelial-to-mesenchymal transition; Suppresses cancer progression and metastasis	54
	miR-10a-5p		Cervical squamous cell carcinoma	Promotes angiogenesis and tumorigenicity	55
	miR-1228-3p		Hepatocellular carcinoma	Promotes proliferation, migration, invasion; Strengthens the chemoresistance	56
	miR-331-3p		Pancreatic cancer	Accelerates proliferation, migration, and invasion	57
	miR-3173-5p		Pancreatic ductal adenocarcinoma	Inhibits ferroptosis; Promotes gemcitabine chemoresistance	58
	miR-876-3p		Oral squamous cell carcinoma	Decreases cisplatin resistance	59
	miR-503-5p	Adipocyte	triple-negative breast cancer	Reverses cancer progression	60
	miR-23a miR-23b		Hepatocellular carcinoma	Strengthens chemoresistance	61
	miR-10a-5p	MDSC	Experimental Sjögren's syndrome	Inhibits the generation of B cells and eventually alleviates cancer progression	62
circRNA	circCRIM1	Adipocyte	Triple-negative breast cancer	Reverses cancer progression	60
DNA	Bacteroidia DNA	Bacteria	Renal cell carcinoma	Serves as a biomarker for renal cell carcinoma	63
Proteins	TGF-β type II receptor (TβRII)	Tumor	Breast cancer	Initiates tumor cell EMT Enhances cancer stemness Increases metastasis	64
	CUB-domain containing protein 1 (CDCP1)		Metastatic prostate cancer	Promotes osteoclast formation Detects bone metastasis of prostate cancer	65
	phosphatase and tensin homolog (PTEN)		Cholangiocarcinoma	PTEN deficiency impairs lysosome biogenesis to facilitate exosome secretion and cancer metastasis	66
	NSMASE2		Prostate cancer	RAB27A and NSMASE2 affect the content of PD-L1 in the secreted EVs, and promote tumor growth through the suppression of the immune system	67
	Rab27a		Prostate cancer		
			Pancreatic cancer	Rab27 knockout attenuated the inhibitory effect of TEVs on Meso-CAR T cells, thereby improving the efficacy of CAR T treatment	68
	CD63		Prostate cancer	Induces strong platelet activation leading to thrombosis	69
	PD-L1		Colorectal cancer	Promotes tumor immune evasion by upregulating PD-L1 expression in tumor-associated macrophages	70
		Macrophage	Non-small cell lung cancer	Inhibits the proliferation and function of $CD8^+$ T cells Suppresses tumor's anti-tumor immunity	71
		Platelet	Non-small cell lung cancer	Serves as a prognostic biomarker	72
	FasL	NK cell	Melanoma	Induces apoptosis	73
	DNAX Accessory Molecule (DNAM-1; CD226)		Myeloid leukemia	Enhances cytotoxic activity against cancer cells; potentially involved in immune responses against tumors	51
	NK Lytic-Associated Molecule (NKLAM)		Breast cancer	Inhibits proliferation, induces caspase-mediated apoptosis and tumor cell death	74
	Granzyme A Granzyme H	Adaptive immune cells / NK cell	Various cancer cells	Contributes to cell death in cancer cells Cytotoxicity	51,74–77

(*continued on next page*)

Table 1 (*continued*)

Exosome Cargos		Origin of EVs	Cancer Type	Impact on Cancer	Reference
	Granzyme B Perforin				
	PD-1	Adaptive immune cells	Various cancer cells	Inhibits tumor growth Boosts anti-tumor immunity Accelerates tumor growth and reduces lifespan Diminishes the effectiveness of anti-PD-1 immunotherapy	78,79
	CD80		Melanoma	Contributes to systemic immunosuppression Converts tumors to an immunologically cold phenotype	79
	DOCK7	Macrophage	Colorectal cancer	Regulates cholesterol metabolism	80
	NEAT1		Ovarian cancer	NEAT1 sponged miR-101-3p to increase ZEB1 and PD-L1 expression Promotes tumor progression	45
	MHC I and MHC II	DC / NK cell	Various cancer cells	Facilitates peptide presentation and T cell activation	74,81,82
	GPR84	MDSC	B16-OVA melanoma	Induces T-cell senescence Immunosuppresses MDSCs	83
	FOSL1	CAFs	Colorectal cancer	Promotes colorectal cancer cell proliferation, stemness, and chemo-resistance	84
	Secretory leukocyte protease inhibitor (SLPI)		Ovarian cancer	Facilitates cell proliferation, migration, invasion, and adhesion.	85
	microsomal triglyceride transfer protein (MTTP)	Adipocyte	Colorectal cancer	Serves as an inhibitor of ferroptosis Reduces sensitivity to chemotherapy	86
	IL-12 IL-13 IL-1Ra IL-4 C-X-C motif chemokine 5 (LIX) (TNF)-α IL-2 IL-7 L-selectin Thymic stromal lymphopoietin (TSLP)	MDSC	Various cancer cells	Induces hyperactivation or exhaustion of $CD8^+$ T cells Elevates reactive oxygen species (ROS) production, leading to activation-induced cell death in $CD8^+$ T cells.	87
	IFN-γ	Adaptive immune cells	Various cancer cells	Participates in EV-induced apoptosis in cancer cells	77
		NK cell		Enhances immune response against tumors Inhibits tumor growth	50
	IL6	CAFs	Salivary adenoid cystic carcinoma (SACC)	Promotes EMT	88
Lipids	Fatty acids	Adipocyte	Melanoma	Stimulates fatty acid oxidation	89

in tumor cells. This molecular reprogramming restricts anti-PD-1 immunotherapy efficacy.[79] In inflammatory settings, activated CTLs package CD73 into released EVs. Subsequent adenosine signaling directly suppresses T cell effector functions.[121] Furthermore, EVs derived from $CD4^+$ T cells enhance STING pathway responsiveness to cGAMP. This targeted molecular reprogramming shifts tumor-associated macrophages (TAMs) toward pro-inflammatory M1-like phenotypes to potentiate anti-tumor immunity.

$CD4^+$ T helper cells represent a heterogeneous population central to adaptive immunity.[122,123] Their functions include facilitation of essential helper signals for cytotoxic $CD8^+$ T cell activation, induction of dendritic cell maturation, and release of anti-tumor cytokines such as IFN-γ.[124,125] $CD4^+$ T cell EVs also effectively enhance B cell responses,[126] which execute antigen presentation and antibody production, thereby focusing immune responses on cognate antigens to support both T cell responses and innate mechanisms.[127] Conversely, $CD4^+$ regulatory T cells ($CD4^+$ Tregs), as a subtype of $CD4^+$ T cells, suppress $CD4^+$ and $CD8^+$ T-cell proliferation.[128] $CD4^+$ Treg-derived EVs could inhibit the proliferation of T cells in a dose-dependent manner.[129] These EVs downregulate CD80 and MHC class II expression on DCs while suppressing cytokine production (e.g., IL-12),[130] thereby impairing DC-mediated T cell activation. However, the functional contributions of $CD4^+$ T cell-derived EVs within the TME remain poorly characterized and warrant further investigation. Collectively, T cell-derived EVs exhibit context-dependent regulation of tumor progression. Functional outcomes are strictly determined by their cellular origin, molecular cargo, and recipient cell characteristics. However, the precise molecular mechanisms governing this spatiotemporal regulation and its relative dominance in tumor evolution remain to be further explored.

Natural killer cell-derived EVs

NK cells act as principal effectors of innate immunity to mediate surveillance against malignant transformation.[131,132] The anti-tumor activity of NK-EVs is multifaceted, primarily mediated by the delivery of potent cytotoxic payloads. These EVs inherit parental CD56 and NKG2D to exert robust cytotoxicity against tumor and senescent cells.[133,134] Pre-stimulation with cytokines such as IL-15 enhances the loading of perforin and granzyme B into NK-EVs. Concurrently, the surface expression of death ligands, notably FasL and TRAIL, engages cognate death receptors on tumor cells, thereby amplifying caspase-dependent cell death pathways in models of hepatocellular carcinoma and B-cell lymphoma.[75,76,135] The endocytic uptake of NK cell-derived EVs by tumor cells triggers mitochondrial oxidative damage, leading to the suppression of malignant progression.[136] The distinct miRNA cargo of NK-EVs targets highly specific oncogenic pathways. NK-EV-delivered miR-186 inhibits neuroblastoma growth by targeting TGF-β signaling, while let-7b-5p suppresses pancreatic cancer cell proliferation by downregulating the cell cycle regulator CDK6.[49,137] Beyond direct malignant cytotoxicity, NK-EVs orchestrate a broader anti-tumor immune response to reverse the immunosuppressive TME. They specifically drive the polarization of monocytes toward pro-inflammatory M1 macrophages. They simultaneously enhance the antigen-presenting capabilities of DCs. This secondary cellular reprogramming bolsters adaptive immunity to improve T-cell activation and function.[138,139]

Suboptimal biodistribution severely impedes the current clinical translation of NK-EVs. Suboptimal biodistribution severely impedes the

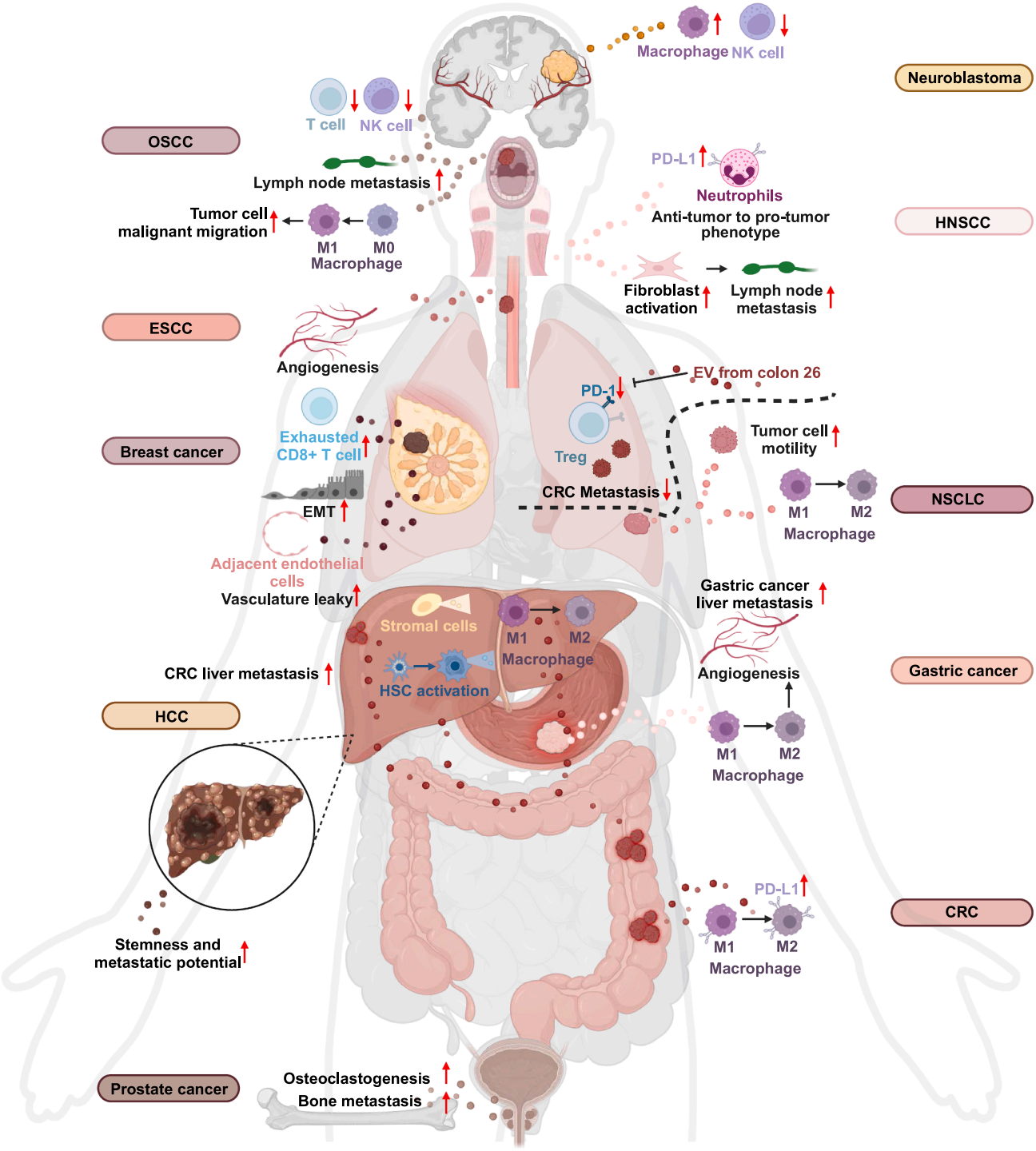

Fig. 3. The Multifaceted Roles of TEVs in Cancer Pathogenesis. TEVs orchestrate key aspects of cancer pathogenesis, including tumor progression, immune modulation, and pre-metastatic niche formation. TEVs suppress cytotoxic immune cells (e.g., NK cells, $CD8^+$ T cells) and promote M2-like macrophage polarization to foster an immunosuppressive environment. In certain contexts, they can also activate M1-like macrophages. Furthermore, TEVs facilitate lymphatic metastasis, vascular leakage, the EMT, and the acquisition of cancer stem cell properties. Abbreviations: BC, breast cancer; CRC, colorectal cancer; EMT, epithelial-to-mesenchymal transition; ESCC, esophageal squamous cell carcinoma; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancer; OSCC, oral squamous cell carcinoma; PC, prostate cancer; TEV, tumor-derived extracellular vesicle.

clinical translation of NK-EVs. After systemic administration, unmodified vesicles predominantly accumulate in the liver and spleen, while only a marginal fraction reaches tumors, thereby limiting therapeutic efficacy.[133] Therefore, future research must prioritize engineering these vesicles for enhanced tumor targeting, and fully elucidate their functional effects on non-malignant recipient cells and the subsequent impact on the TME.

Tumor-associated macrophages subsets-derived EVs

TAMs constitute a prominent and functionally plastic immune cell population within the TME that critically regulates disease progression.[71,140] M1-polarized TAMs typically exert anti-tumor effects through

the expression of pro-inflammatory factors. Conversely, M2-polarized TAMs inherently support tumor growth via the production of angiogenic and pro-metastatic factors. The polarization state of the parental macrophage strictly determines the functional capacity of the resulting TAM-derived EVs.[80,141]]. These specific vesicles establish a critical feedback loop within the TME. M2-polarized TAMs release EVs to entrench and amplify the initial immunosuppressive milieu established by TEVs. These secondary vesicles induce CTL apoptosis, enhance Treg activity, and promote severe T-cell exhaustion.[45,142] Mechanistically, these specific EVs directly inhibit CTL proliferation and function via the targeted transfer of surface PD-L1 to recipient cells.[71] Beyond direct immune suppression, M2-TAM-derived EVs serve as potent feedback vectors for oncogenic microRNAs. These specific vesicles deliver miR-589-3p to facilitate aggressive tumor cell proliferation in ovarian cancer. Similarly, EVs containing miR-21-5p actively stimulate endothelial angiogenesis in head and neck squamous cell carcinoma.[43,143] However, the traditional discrete M1 and M2 classification represents a significant oversimplification. Recent single-cell transcriptomic atlases reveal ubiquitous co-expression of M1 and M2 signature genes across most human cancers.[144,145] These findings indicate a continuous spectrum of macrophage activation states rather than fixed phenotypes. A refined molecular classification of TAM subtypes is therefore imperative. The comprehensive profiling of EV cargo offers a highly promising strategy for resolving this complex spatiotemporal heterogeneity.

Dendritic cells-derived EVs

DCs bridge innate and adaptive immunity to initiate antigen-specific responses.[146] DC-derived EVs retain robust immunological capacity to enhance targeted $CD4^+$ T-cell and CTL responses and concurrently activate NK cells within the TME.[147,148] The therapeutic potential of allogeneic DC-derived EVs possess immense therapeutic potential. They orchestrate a multifaceted anti-tumor response to reverse TEV-induced tolerance, mediate immediate effector functions, and promote durable T-cell memory to prevent tumor recurrence.[149] DC-derived sEVs inherently carry essential antigen-presentation machinery and costimulatory molecules within a stable lipid bilayer. This structural integrity establishes them as an ideal platform for therapeutic development.[81,150] Current research primarily focuses on the bioengineering of DC-derived as advanced nano-delivery systems that co-load tumor-associated antigens with potent immunomodulators such as XCL1 or STING agonists to maximize downstream T-cell priming and recruitment.[151,152] Significant challenges impede widespread clinical application. Future efforts must enhance cargo loading efficiency of DC-derived EVs and establish robust manufacturing processes that preserve product immunogenicity to unlock their full therapeutic potential.

Other immune cells derived EVs in TME

Myeloid-derived suppressor cells (MDSCs) are a population of pathologically-activated and heterogeneously immature myeloid cells that orchestrate a potent immunosuppressive TME.[153] EVs derived from MDSCs recapitulate this immunosuppressive function to drive immune evasion.[87] These EVs directly impair the activity of CTLs through multiple mechanisms. Specifically, MDSC-derived sEVs induce CTL senescence through p53-mediated DNA damage in B16-OVA tumor models.[83] Conversely, in 4T1 breast cancer models, these EVs trigger CTL apoptosis via reactive oxygen species cargo.[87] The inherent heterogeneity and plasticity of MDSCs complicate precise delineation of their EV-mediated functions. EVs from granulocytic MDSCs promote transdifferentiation of monocytic MDSCs into M2-like macrophages by transferring miR-93-5p and suppressing STAT3 signaling, a process that exacerbates colitis-associated colorectal carcinogenesis.[154] Elucidating the distinct functional roles of EVs from specific MDSC subsets therefore remains a critical area of investigation.

Platelets mediate lymphocyte, neutrophil, and monocyte recruitment to inflammatory sites.[155] Platelet-derived EVs function as pleiotropic agents in physiological homeostasis and disease pathogenesis.[156,157] Their functional repertoire encompasses regulation of vascular biology,[158] modulation of immunity, and promotion of cancer progression via metastatic dissemination.[159] Platelet-derived $PD\text{-}L1^+$ lEVs were identified as prognostic and predictive biomarkers in non-small cell lung cancer.[72] Paradoxically, elevated levels of these shed $PD\text{-}L1^+$ lEVs correlated with improved survival. Conversely, high levels of platelet-associated PD-L1 confer a poor prognosis to establish immunotolerant pre-metastatic niches.[160] This striking dichotomy underscores that the biological function of PD-L1 is not absolute. It is instead dictated by its molecular context and carrier. The underlying mechanisms remain poorly elucidated. Future investigations must dissect the upstream pathways within the TME to elucidate the selective release of these pro-response lEVs from platelets. This mechanistic insight is a prerequisite for resolving their contradictory roles and harnessing their clinical potential.

Stromal and microbial-derived EVs: architects of the tumor niche

The stromal compartment of the TME consists of cancer-associated fibroblasts (CAFs), vascular cells, adipocytes, and ECM proteins, which collectively drive tumor progression.[115] These components not only provide structural scaffolding but also mediate intercellular communication, a process in which EVs function as crucial mediators. Additionally, recent advances in sequencing technologies reveal that the intratumoral microbiota contributes to tumorigenesis and progression through multiple mechanisms.[161] EVs derived from these resident microbes represent another axis of TME modulation. Collectively, EV-mediated communication from stromal and microbial sources regulate TME architecture, promotes immune evasion, and dictates metabolic reprogramming.

Cancer-associated fibroblasts-derived EVs

CAFs represent a predominant stromal component in the TME, activated from precursors like normal fibroblasts or mesenchymal stem cells through signals such as TGF-β and IL-6.[162] EVs derived from CAFs modulate hallmark cancer processes by transferring distinct molecular cargos.[52] Current evidence establishes a pro-tumorigenic role for CAF-EVs. CAF-EVs promote tumor progression and therapy resistance by impairing cell death pathways in pancreatic and oral cancers.[53,58,59] They drive malignancy by delivering oncogenic miRNAs that enhance stemness or activate pro-survival signaling in ovarian and colorectal cancers.[51,84,163] Furthermore, CAF-EVs orchestrate angiogenesis and the epithelial-to-mesenchymal transition (EMT) through Hedgehog and JAK2/STAT3 signaling.[55,88] Nevertheless, this pro-tumorigenic function is not absolute, as a subset of studies reveals a tumor-suppressive capacity. EVs carrying miR-1-3p inhibit breast cancer viability and EMT,[54] while those delivering the lncRNA DACT3-AS1 have been demonstrated to suppress proliferation and migration in gastric cancer cells.[164] This functional dichotomy suggests that the ultimate biological impact of CAF-EVs is determined not by their origin alone, but by the specific molecular composition of their cargo. The emerging understanding of profound CAF heterogeneity, revealed by single-cell sequencing to comprise distinct subtypes with specialized functions.[165,166] This heterogeneity provides a compelling framework for the observed functional variability. The mechanisms by which distinct CAF subtypes govern EV cargo selection remain largely undefined. This represents a critical focus for future investigation.

Adipocyte-derived EVs

Under pathological conditions such as obesity, adipocytes mediate systemic metabolic and inflammatory disorders via EV secretion.[167–169]]. This intercellular communication axis has emerged as a critical driver of oncogenesis. Adipocyte-derived EVs promote malignancy by modulating multiple cancer hallmarks. They facilitate invasion and metastasis by delivering cargo such as ECM1 to upregulate matrix-degrading enzymes[170] or by inducing EMT.[171]

Adipocyte-derived EVs also potently drive metabolic reprogramming and therapy resistance. They remodel mitochondrial networks and stimulate fatty acid oxidation in melanoma cells to enhance migration,[89] and transfer proteins like microsomal triglyceride transfer protein (MTTP) to suppress ferroptosis, thereby conferring oxaliplatin resistance in colorectal cancer.[86] Despite this accumulating mechanistic evidence, a critical knowledge gap persists. The precise mechanisms by which the obese state quantitatively and compositionally remodels the adipocyte-derived EVs secretome to modulate metabolic crosstalk within the TME remain fundamentally unresolved. Defining this mechanistic linkage is therefore a central objective, as it may unveil novel therapeutic vulnerabilities for intercepting obesity-related cancer progression.

Bacteria-derived EVs: mediators in host-microbe crosstalk

Bacteria are established residents within the TME of various cancers. Their functional roles in modulating immune activity, metastasis, and drug metabolism have been extensively reviewed.[172–176] Beyond secreted metabolites, bacterial EVs have emerged as pivotal mediators in this host-microbe crosstalk.[7,177] According to ISEV guidelines, bacteria release EVs that include outer membrane vesicles (OMVs) from Gram-negative organisms.[178] For terminological consistency, this review primarily uses the term "EV", with specific references to OMVs where appropriate. Bacteria-derived EVs exhibit a functional dichotomy, exerting both pro- and anti-tumoral effects contingent on their bacterial origin. For instance, *Fusobacterium nucleatum*-derived EVs fuse with colorectal cancer cells to facilitate intratumoral colonization of this bacterium.[179] which in turn accelerates tumor progression.[143] *Streptococcus pneumoniae*-derived EVs disrupt epithelial integrity and thereby contribute to bacterial pathogenicity.[180] Clinical data support this pro-tumoral association. Elevated levels of bacterial DNA from phyla such as *Bacteroidia* within serum EVs correlate with inferior immunotherapy outcomes in renal cell carcinoma patients.[63] Conversely, bacteria-derived EVs from commensal or other specific bacteria frequently elicit robust anti-tumor immunity. OMVs from *Klebsiella pneumoniae* induce a broad antitumor T cell response,[181] while those from *Escherichia coli, Akkermansia muciniphila*, and *Parabacteroides distasonis* suppress tumor growth by enhancing the infiltration and activation of CTLs.[182–184] This immunomodulatory capacity holds therapeutic promise. *E. coli* OMVs and *Bifidobacterium*-derived EVs synergize with anti-PD-1 checkpoint blockade to induce tumor remission.[179,185,186] Nevertheless, significant technical challenges severely limit the characterization of their specific functional roles. Isolating and distinguishing bacteria-derived EVs from host-derived vesicles remains technically demanding. Consequently, the mechanisms governing bacteria-derived EVs release and their downstream impact on tumorigenesis remain poorly defined. Future research must elucidate these processes. This will determine whether bacteria-derived EVs are primary drivers of bacteria-mediated oncogenesis, a critical step for developing novel therapeutic strategies such as vaccines targeting intratumoral microbes.[187]

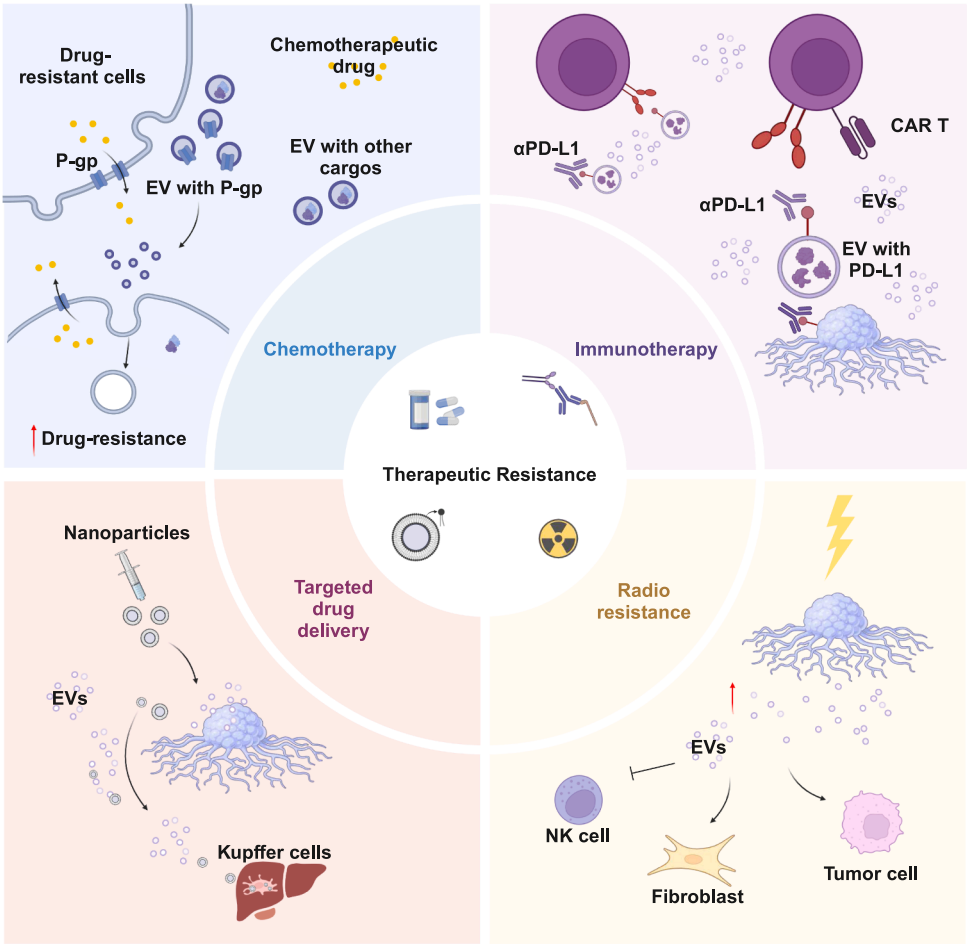

Fig. 4. EV-Mediated Mechanisms of Therapeutic Resistance. EVs mediate resistance to chemotherapy, radiotherapy, and immunotherapy through diverse mechanisms. They promote tumor cell survival, modulate anti-tumor immune responses, and transfer resistance-conferring cargo (e.g., drug efflux pumps, signaling molecules) to recipient cells. Understanding these pathways is critical for developing strategies to overcome therapeutic failure. Abbreviations: P-gp, P-glycoprotein; αPD-L1, anti-programmed death-ligand 1 antibody.

EV-mediated therapeutic resistance in the TME

Beyond their heterogeneous origins within the TME, EVs govern intercellular communication and mediate resistance to therapies such as immunotherapy, chemotherapy, and radiotherapy by transferring bioactive molecules (Fig. 4). This functional diversity serves as a direct driver of therapeutic resistance by integrating multi-layered defense strategies. Such diversity manifests through: (1) Cargo heterogeneity, where the simultaneous transfer of decoys (e.g., surface PD-L1), efflux pumps (e.g., P-gp), and survival-promoting miRNAs allows EVs to physically neutralize drugs while molecularly reprogramming recipient cells; (2) Origin heterogeneity, enabling cross-talk between tumor cells and stromal constituents (e.g., CAFs, adipocytes) to foster a collaborative pro-resistant niche; and (3) Mechanistic versatility, which bridges the gap between different treatment modalities, allowing EV subpopulations to elicit resistance to multiple therapies concurrently.

EVs compromise immunotherapy efficacy through decoy-mediated checkpoint evasion and targeted T-cell fratricide

Immune checkpoint blockade (ICB) reinvigorates anti-tumor immunity through the targeted inhibition of specific regulatory pathways including PD-1/PD-L1, cytotoxic T-lymphocyte antigen 4, and mucin-domain containing-3 (TIM-3).[188,189] However, TEVs act as prominent drivers of clinical resistance to compromise therapeutic efficacy. Surface PD-L1-expressing TEVs mediate immune evasion through two principal routes. Certain vesicle subpopulations function as systemic decoys to reduce therapeutic antibody bioavailability through direct physical binding. Other TEV populations engage the PD-1 receptor to deliver profound inhibitory signals. This engagement delivers an inhibitory signal that induces T-cell exhaustion and apoptosis, a mechanism contributing to immune evasion even in the presence of anti-PD-1 antibodies. This direct immunosuppressive action, independent of PD-L1 on the tumor cell surface, represents a significant pathway for resistance.[190–194] Adhesion molecules including ICAM-1 on the surface of PD-L1$^+$ TEVs structurally stabilize the vesicle-lymphocyte interaction to enhance direct binding to target T cells.[195,196] Genomic knockout or pharmacological inhibition of EV secretion effectively restores ICB sensitivity. The specific reduction of exosomal PD-L1 levels similarly increases overall therapeutic efficacy.[197–201] Beyond PD-L1, EVs with other immune checkpoint molecules also contribute to an immunosuppressive TME.[202] For instance, glioblastoma-derived sEVs carry CTLA-4, which impairs the function of multiple immune effectors, including CD8$^+$ T cells, CD4$^+$ T cells, and NK cells.[203] Similarly, TIM-3$^+$ EVs facilitate M2 macrophage infiltration, further suppressing anti-tumor immunity.[204] Consequently, EVs carrying ICB molecules contribute to poor treatment responses. Further investigation is warranted to elucidate their underlying mechanisms in therapeutic resistance.

Chimeric antigen receptor (CAR) T cell therapy, a form of adoptive cell transfer, faces similar challenges from TEVs. In models of pancreatic ductal adenocarcinoma, EVs bearing both PD-L1 and tumor-associated antigens impair CAR-T cell infiltration and function. Conversely, the blockade of TEV secretion or the specific inhibition of PD-L1 enhances the antitumor activity of CAR T cells.[68] Furthermore, TEVs with high PD-L1 expression from chronic lymphocytic leukemia patients induce profound CAR T cell exhaustion.[205] These findings identify a potent systemic mechanism for treatment failure in hematological malignancies. The direct relationship between circulating PD-L1$^+$ vesicle levels and CAR-T cell efficacy across large solid tumor patient cohorts remains to be rigorously validated. EVs can also play a stimulatory role. EVs that present self-antigens can activate CAR-T cells. Neuroblastoma-derived EVs display the CAR targets GPC2 and GD2 and directly activate cognate CAR T cells.[206] This functional dichotomy underscores the complex bidirectional role of EVs in modulating CAR-T therapy. Therefore, a deeper understanding of the selective inhibition of immunosuppressive EVs and the concurrent exploitation of immunostimulatory EVs thus constitutes a promising frontier for enhancing the efficacy of cellular immunotherapies.

EVs hamper the efficacy of chemotherapy through drug efflux and survival signaling

Chemotherapeutic agents paradoxically stimulate the secretion of TEVs, which in turn mediate therapy resistance and metastasis.[207–209] The resistance is conferred through multiple mechanisms. One primary pathway is the intercellular transfer of the P-glycoprotein efflux pump from resistant to sensitive cells, a mechanism that actively reduces intracellular drug accumulation.[210–214] Beyond direct drug efflux, EVs from diverse origins in TME carry other specific molecular cargo that undermines treatment efficacy. For instance, CAF-derived EVs deliver miRNA-1228-3p to promote sorafenib resistance, while EVs from the aggressive CAF-P subtype confer cisplatin resistance.[56,59] Similarly, adipocyte-derived sEVs reduce chemosensitivity by transferring MTTP, which subsequently suppresses ferroptosis.[86] Consequently, the therapeutically inhibiting certain EV secretion sensitizes tumors to chemotherapy and mitigates treatment-associated toxicities.[215]

The therapeutic challenges posed by EVs also extend to direct interference with drug delivery platforms. Although significant progress has been made in NP-based drug delivery, its efficacy is often compromised by TEVs. These vesicles can sequester therapeutic NPs in circulation and redirect them toward clearance organs, such as the liver. This redirection limits the accumulation of NP-encapsulated drugs at the tumor site.[216] Paradoxically, EVs from various sources, including TEVs, exhibit exceptional drug delivery properties. They maintain structural stability and possess superior biocompatibility, targeting ability, and lower toxicity compared to traditional carriers like liposomes. The engineering of EV-based delivery platforms that exploit these advantages is discussed subsequently.

EVs promote radioresistance through DNA repair activation and antioxidant delivery in TME

Ionizing radiation (IR) drives adaptive radioresistance and tumor recurrence by remodeling the TME through metabolic reprogramming, augmented cancer stem cell self-renewal, and dysregulated cell cycle and DNA repair pathways.[217] This resistance of radiotherapy is centrally mediated via EVs. Irradiated tumor cells secrete EVs that orchestrate a pro-survival niche. IR-upregulated heparan sulfate (HS)$^+$CD44v3$^+$ TEVs activate fibroblasts to support cancer stem-like cell expansion in breast cancer.[218] TME stressors amplify this mechanism. Hypoxic conditions induce secretion of miR-152-3p-laden TEVs that abrogate apoptosis and DNA damage to confer radioresistance in cervical cancer.[219] Hypoxia-induced GRP78-enriched TEVs transfer a radioresistant phenotype by enhancing recipient cell migration and viability in head and neck cancer.[220] Stromal constituents are incorporated into this EV-mediated network. CAF-derived sEVs deliver miR-93-5p to augment colorectal cancer cell proliferation and inhibit radiation-induced apoptosis.[221] Prostate cancer stromal sEVs carrying IL-8 activate AMPK-mediated autophagy to promote radioresistance.[222] lEVs from radioresistant glioma stem cells enriched with nicotinamide phosphoribosyltransferase drive proliferation in recipient cell,[223] These findings establish a complex, EV-mediated signaling network as the mechanistic foundation of adaptive radioresistance. Inhibition of these EV axes is therefore a therapeutic strategy to overcome radioresistance and enhance radiotherapy outcomes.

EVs as therapeutic targets, delivery vehicles, and clinical biomarkers in oncology

EV heterogeneity within the TME determines their dual oncogenesis roles and mediates clinical therapy resistance. This functional dichotomy establishes the inhibition of pro-tumorigenic EV biogenesis,

release, and cellular uptake as a rational therapeutic strategy. Concurrent with these inhibitory strategies, the superior biocompatibility and intrinsic transport capacity of beneficial vesicles establish their advantages over synthetic nanoparticles as delivery platforms. Bioengineering of these natural carriers enables the loading of small-molecule therapeutics or gene-editing tools to achieve targeted tumor accumulation and promote tumor regression (Fig. 5). EVs also possess clinical utility as noninvasive biomarkers. Liquid biopsies utilizing circulating vesicles yield diagnostic molecular signatures and circumvent invasive tissue sampling. Recent progress in multi-omics and single-vesicle analytics facilitates biomarker discovery although the standardization of isolation and characterization protocols remains essential. The subsequent sections systematically examine these investigative avenues.

Therapeutic targeting of EV dynamics

The most direct approach to countering EV-driven therapeutic resistance lies in the systematic disruption of the intercellular communication network. These networks sustain the oncogenic dialogue within the TME. At the level of biogenesis and release, pharmacological inhibition of the ceramide-dependent pathway employs imipramine or GW4869 to reduce EV secretion. Imipramine further exerts additional antitumor effects through the induction of apoptosis and the impairment of DNA repair.[101,224–227] Concurrently, compounds such as neticonazole and manumycin-A target the ESCRT machinery to deplete the TME of pathogenic vehicles.[228-230] Modulation of regulatory networks including the Ras and Rab GTPase pathways further addresses EV-mediated signaling.[230] Genetic ablation of the master regulator Rab27a suppresses EV release and limits tumor progression.[215,231,232] Pharmacological agents such as Nexinhib20 and MEK inhibitors therefore serve as strategic intercepts to restore treatment sensitivity.[233–237] Intervention at the uptake level is equally critical to shield target cells from the systemic impact of tumorigenic EVs.[238,239] Specific inhibitors of endocytic pathways arrest the cellular internalization process through distinct mechanisms. Amiloride disrupts macropinocytosis to curb tumor growth.[240,241] Genistein and its analogue AXP107-11 inhibit caveolae-mediated endocytosis to enhance clinical efficacy.[242–244] Chlorpromazine targets clathrin-mediated endocytosis to reduce hypoxia-induced EV uptake and promote lymphocyte activity.[245,246] Beyond endocytic blockade, heparin physically obstructs EV-cell interactions to mitigate the immunosuppressive effects of myeloma-derived vesicles.[247–250] Despite preclinical promise, clinical translation remains hindered by poor specificity, suboptimal pharmacokinetics, and the lack of robust validation for repurposed EV-targeting

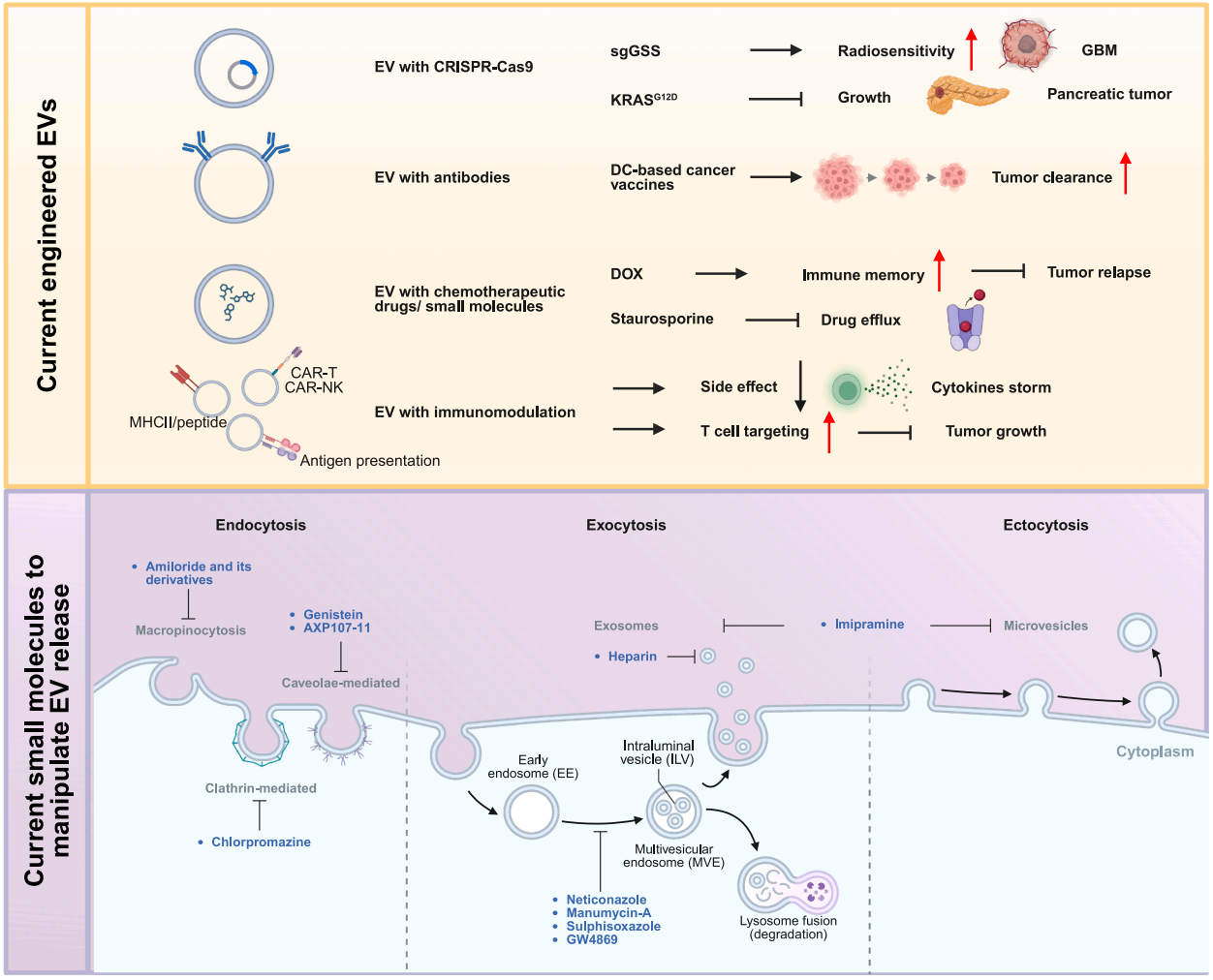

Fig. 5. Current Strategies for Manipulating EVs and Applications of Engineered EVs. Current strategies for manipulating EVs focus on inhibiting their biogenesis, release, and uptake through both novel small-molecule inhibitors and repurposed FDA-approved drugs. While new compounds targeting specific EV pathways are being developed, drug repurposing offers distinct advantages, including established safety profiles and faster clinical translation. Engineered EVs are potent therapeutic platforms, especially for cancer. Their natural biocompatibility and targeting make them effective at delivering drugs, proteins, and gene-editing tools like CRISPR-Cas9. In immunotherapy, immune-cell-derived or immunomodulatory-decorated EVs boost antitumor responses and sensitize tumors to radiotherapy. Controlling natural EV pathways and using engineered EVs constitute a comprehensive strategy for EV-based treatments.

therapeutics (Table 2).[201,230,244,251–269] This challenge necessitates the development of targeted delivery systems or environment-sensing peptides to achieve tumor-specific disruption of EV activity.

EVs as therapeutic delivery vehicles

The intrinsic stability and efficient cellular entry of EVs position these vesicles as an ideal platform for precision drug delivery. Researchers are therefore repurposing them as biocompatible carriers with an innate capacity for molecular transport.[270] According to ISEV guidelines, "EV mimetics" encompasses EV-like particles derived from cell disruption, synthetic assembly, or liposomal fusion.[7] To refine the efficacy of cell-based therapies, EVs derived from immune effector cells such as CAR-T or NK cells serve as cell-free agents. These vehicles retain potent anti-tumor activity and successfully circumvent systemic toxicity.[271,272] Furthermore, EVs are engineered to transport fragile payloads including p53 proteins, CRISPR-Cas9 systems, and microRNAs.[40,270,273–275] The encapsulation of small-molecule drugs such as doxorubicin or paclitaxel improves pharmacokinetic profiles and minimizes off-target effects.[276–278] Advanced biomimetic systems further enhance tumor-targeting capabilities.[279,280] Nevertheless, the absence of standardized production protocols and the lack of complete

Table 2
Comprehensive translational landscape of pharmacological agents targeting the release and uptake of extracellular vesicles.

Pharmacological Agent	Mechanism of Action	Preclinical Efficacy	Toxicology and Adverse Effects	Clinical Stage	Translational Challenges in EV Inhibition	Ref
Imipramine	Acid sphingomyelinase (aSMase) inhibitor	Reduces EV secretion; synergizes with retinoic acid to induce apoptosis and impairs DNA repair and exerts additional antitumor effects	Cytotoxic at elevated concentrations	Approved (Antidepressant)	Narrow therapeutic index; off-target systemic effects	251–253
GW4869	Inhibits ceramide-dependent pathway (neutral sphingomyelinase inhibitor)	Arrests tumor growth and significantly enhances anti-PD-L1 antibody efficacy in breast cancer models; suppresses autocrine-regulated proliferation in murine melanoma; reduces cell viability in prostate cancer cells under hypoxic conditions	Elicits local inflammation and depletes resident macrophages in vivo	Preclinical	Suboptimal pharmacokinetics; poor specificity; hydrophobic nature requires specific nanoplatforms (e.g., HA-based) for in vivo delivery	201, 254–256
Neticonazole	Targets ESCRT machinery	Depletes pathogenic EVs from TME, suppresses intestinal dysbacteriosis-induced tumorigenesis of colorectal cancer	Dose-dependent cytotoxicity at elevated concentrations	Preclinical	Undefined molecular mechanisms and potential off-target effects *in vivo*	257,258
Manumycin-A	Inhibits nSMase and ESCRT machinery; blocks Ras/Raf/ERK1/2 signaling	Suppresses secretion in castration-resistant prostate cancer (CRPC) cells	Well-tolerated in preclinical models	Preclinical	Target pleiotropy	230,253
Nexinhib20	Interferes with the RAB27A-JFC1 complex	Inhibits EV release and restores treatment sensitivity	Cytotoxicity	Preclinical	Compensatory pathways bypass RAB27A blockade	256,259
U0126	Noncompetitive inhibitor of MEK1 and MEK2 (MAPKK family)	Reduces lEV release from stimulated monocytic cell lines and macrophages	Interference with essential normal cell physiology	Preclinical	Suboptimal pharmacokinetic profile	260,261
Amiloride& Dimethyl amiloride (DMA)	Disrupts macropinocytosis	Curbs tumor growth	Long-term administration may induce electrolyte imbalances; exhibits cytotoxicity at elevated concentrations	Approved (Antihypertension)	Target pleiotropy	251,261, 262
Ketoconazole	Inhibits EVs through downstream ERK signaling; Downregulates RAB27A, Alix, and nSMase2	Dose-dependent decrease of exosomes in cancer cells, acts as an adjunctive therapy enhancing sunitinib efficacy in renal cell carcinoma	Hepatic toxicity	Approved (Prostate Cancer)	Target pleiotropy	256,263
Tipifarnib	Farnesyl transferase inhibitor; downregulates RAB27A, Alix, and nSMase2	Selectively decreases EV release in prostate cancer cells; induces apoptosis	Dose-limiting myelosuppression	Phase II/III (Oncology)	Efficacy isolated to specific cell lines	253,263, 264
Genistein	Inhibits caveolae-mediated endocytosis	Enhances clinical efficacy	Cytotoxicity	Phase II (Oncology)	Target pleiotropy; low *in vivo* bioavailability	265–267
AXP107-11	Inhibits caveolae-mediated endocytosis	Enhances clinical efficacy	No additive toxicity in combination with gemcitabine	Phase Ib/Iia	Target pleiotropy	244
Chlorpromazine	Targets clathrin-mediated endocytosis	Reduces hypoxia-induced EV uptake; promotes lymphocyte activity	Dose-dependent neurotoxicity	Approved (antipsychotic medication)	Target pleiotropy	268
Heparin	Physically obstructs EV-cell interactions.	Mitigates immunosuppressive effects of myeloma-derived vesicles, attenuates tumor proliferation and invasion by efficiently inhibiting TEV secretion in melanoma models	Heparin-induced thrombocytopenia	Approved (Anticoagulants)	High dosages required for EV inhibition may elevate bleeding risks	256,269

biodistribution data currently impede clinical translation. Establishing rigorous validation standards is therefore essential for transforming this pathological mechanism into a reliable therapeutic asset.[28]

EVs as clinical biomarkers

The functional diversity and cargo heterogeneity of EVs furnish a multi-dimensional data source for non-invasive diagnostics. The analysis of disease-specific cargo in liquid biopsies enables clinicians to bypass the inherent limitations of static tissue sampling. These molecular profiles capture the dynamic nature of tumor evolution and reflect metastatic potential.[281–283] Specific EV biomarkers such as acyl-CoA dehydrogenase medium chain and circLPAR1 demonstrate significant diagnostic and prognostic value.[284–286] EVs also serve as critical tools for monitoring immunotherapy responses through the quantification of EV-associated PD-L1 levels. Circulating PD-1$^+$ EVs are similarly linked to therapeutic resistance.[287–290] Decoding these complex circulating biomarkers empowers clinicians to identify resistance at its earliest stages.[291] This detection allows for strategic intervention prior to overt clinical failure (Table 3). However, a lack of methodological standardization and patient heterogeneity severely impede the clinical translation of EV-based liquid biopsies. Overcoming these obstacles requires standardized approaches that harness the inherent molecular cargo of EVs to enable high-resolution profiling and guide precision oncology.

Challenges and perspectives

EVs have emerged as pivotal regulators of intercellular communication within the TME to orchestrate fundamental processes such as tumor progression, metastasis, and therapeutic resistance. The translational potential of EVs in oncology encompasses therapeutic targeting, engineered delivery, and biomarker development. However, the clinical realization of this potential is critically constrained by the profound biological heterogeneity of EVs. The functional effects of EV populations are dictated by their cellular origin and microenvironmental context a complexity that generates distinct subsets with potentially opposing biological functions. Therefore, a central challenge in therapeutic targeting is to distinguish and selectively inhibit pathological EV signaling without disrupting physiological processes. For EV-based delivery platforms, this heterogeneity complicates biodistribution, necessitates rigorous standardization of manufacturing, and impedes reliable dosage regimens. Similarly, the diagnostic and prognostic utility of EV biomarkers remains limited until the release patterns and molecular signatures of disease-specific subsets are fully characterized. Overcoming these challenges requires prioritizing the deconstruction of EV heterogeneity as the foundational objective for future TME-focused EV research. At the molecular level, single-vesicle multi-omics resolves individual vesicle heterogeneity. Concurrently, high-resolution biomechanical analyses must delineate how membrane tension, elasticity, curvature, and lipid raft architecture govern specific entry pathways. These comprehensive profiling efforts directly inform advanced isolation techniques to yield high-purity, subtype-specific EVs. Subsequent functional validation using TME-mimetic models definitively links these isolated phenotypes to biological function. To synthesize these multidimensional datasets, artificial intelligence and machine learning-driven algorithms will facilitate the identification of context-specific EV subsets. This strategic integration accelerates preclinical-to-clinical translation. To ensure broad reproducibility, standardized experimental protocols and international collaboration remain essential prerequisites. Such collaborative foundations empower future investigations to establish robust clinical correlations between EV cargo profiles and therapeutic outcomes across large patient cohorts. This rigorous framework could directly bridge the gap between fundamental EV biology and viable clinical strategies.

Conclusion

EVs occupy a paradoxical yet coherent position in cancer biology. These vesicles concurrently orchestrate tumor progression, metastasis, and therapeutic resistance, yet exert specific anti-tumorigenic functions. This functional duality underpins their translational potential as therapeutic targets, delivery platforms, and diagnostic biomarkers. However, persistent biological and methodological barriers severely constrain clinical translation. These profound limitations encompass insufficiently characterized heterogeneity, unresolved biogenesis and cargo sorting mechanisms, inconsistent isolation protocols, inherent clinical safety concerns, and the absence of harmonized guidelines. These deficits demand rigorous biological research, advanced methodologies, and the comprehensive elucidation of context-specific EV functions. The prioritized deconstruction of EV heterogeneity and the resolution of these translational hurdles could bridge the gap between foundational biology and clinical realization.

Ethics approval and consent to participate

This review complies with the relevant ethical guidelines for human and animal research. No human or animal studies were included, and ethical approval is therefore not applicable.

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CRediT authorship contribution statement

Zhanghao Li: Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Jinfang Zhang:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Huiyi**

Table 3
Clinical Translation Status of EV Biomarkers.

EV Biomarker	Clinical Utility	Molecular Indication	Limitations of Detection / Implementation	Ref
Acyl-CoA dehydrogenase medium chain	Diagnostic and prognostic	Disease-specific tumor cargo	Method standardization; inter-cohort heterogeneity	284
circLPAR1	Diagnostic and prognostic	Disease-specific tumor cargo		286
EV-associated PD-L1	Monitoring immunotherapy responses	Quantifiable circulating signals		287, 288
Circulating PD-1$^+$ EVs	Proactive identification of therapeutic resistance	Circulating signals prior to overt clinical failure		289, 290

Guan: Writing – review & editing, Writing – original draft, Investigation. **Wei Yang:** Writing – review & editing, Writing – original draft. **Wing Ho Chan:** Investigation. **Nanxi Li:** Investigation. **Chuanxin Zhong:** Investigation. **Ge Zhang:** Investigation. **Sifan Yu:** Investigation. **Aiping Lyu:** Writing – review & editing, Supervision, Conceptualization. **Jin Liu:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that no competing interests exist, and all authors have read and strictly complied with the journal's policy on the disclosure of conflicts of interest.

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