International Journal of Nanomedicine

Dovepress
Taylor & Francis Group

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REVIEW

Harnessing EVs-ncRNA for Lung Cancer: From Oncogenic Pathways to Novel Diagnostic and Therapeutic Strategies

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Abstract: Extracellular vesicles (EVs), serving as pivotal mediators of intercellular communication within the tumor microenvironment (TME), exert substantial regulatory influence on lung cancer progression and treatment resistance through their cargo of non-coding RNA (ncRNA). This comprehensive review systematically delineates the biogenesis mechanisms of EVs-ncRNA and their dualistic biological functions in lung carcinogenesis. Pro-tumoral ncRNA are selectively packaged into EVs through specialized sorting mechanisms, subsequently activating oncogenic pathways to potentiate tumor proliferation, invasion, and angiogenesis. Conversely, tumor-suppressive ncRNA are depleted intracellularly via EV-mediated export, thereby attenuating their regulatory control over tumor-suppressive pathways. Notably, EVs-ncRNA derived from tumor stromal components—CAFs, TAMs and BMSCs—orchestrate immunosuppressive reprogramming through cross-regulatory networks, facilitating M2 macrophage polarization, T-cell exhaustion, and consequent therapeutic resistance. Clinically, EVs-ncRNA hold substantial promise as multifaceted biomarkers, enabling early detection, prognostic stratification, and dynamic monitoring of therapy resistance in malignancies. Moreover, their emerging roles as therapeutic carriers or molecular targets highlight transformative potential in precision oncology. Nevertheless, critical challenges persist, including heterogeneity resolution among EVs-ncRNA subpopulations, standardization of cross-species engineered EV production, and establishment of multi-omics dynamic monitoring systems. This synthesis provides a molecular foundation and translational framework for developing innovative diagnostic and therapeutic strategies in lung cancer management.

Keywords: EVs, exosome, ncRNA, lung cancer, NSCLC, TME

Introduction

Lung cancer remains the malignancy with the highest global incidence and mortality rates. According to the International Agency for Research on Cancer (IARC), over 2.5 million new cases were diagnosed worldwide in 2023, with approximately 85% classified as non-small cell lung cancer (NSCLC).[1] The dismal 5-year survival rate (<20%) is attributed to high rates of recurrence, metastasis, and therapeutic resistance. While advancements in early detection (eg, low-dose CT screening) and targeted therapies (EGFR-TKIs, ALK inhibitors) have improved prognosis, critical challenges persist, including chemotherapy insensitivity, suboptimal immunotherapy response rates, and heterogeneous resistance mechanisms.[1]

Emerging evidence highlights EVs as pivotal mediators of microenvironmental reprogramming in lung cancer.[2–4] EVs are membranous nanoparticles (30–1000 nm in diameter) categorized by biogenesis: (1) exosomes, derived from multivesicular body (MVB)-plasma membrane fusion via ESCRT-dependent/independent pathways; (2) microvesicles, formed through direct plasma membrane budding; and (3) apoptotic bodies, released during programmed cell death.[2–4] These vesicles transfer bioactive cargo (proteins, lipids, nucleic acids) to recipient cells, orchestrating key oncogenic processes.

ncRNAs, constituting 76–97% of the human genome, precisely orchestrate malignant phenotypes through epigenetic regulation, competing endogenous RNA (ceRNA) networks, and pathway activation.[5–8] MicroRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs) exhibit distinct regulatory hierarchies: miRNAs post-

Received: 13 March 2025
Accepted: 9 July 2025
Published: 14 July 2025

transcriptionally silence target mRNAs, lncRNAs scaffold chromatin-modifying complexes, circRNAs act as miRNA sponges via covalently closed structures. EVs selectively enrich ncRNA with dual functionalities: Pro-tumorigenic ncRNA (eg, HOTAIR, miR-1228-5p, circSATB2) drive epithelial–mesenchymal transition (EMT), angiogenesis, and immune evasion via Wnt/β-catenin and PI3K/AKT pathways. Tumor-suppressive ncRNA (eg, miR-130b-3p, circRABL2B) are depleted via EV-mediated export, derepressing oncogenic signaling. Deciphering the EVs-ncRNA interactome and its clinical translation potential offers transformative strategies to overcome current diagnostic and therapeutic limitations in lung oncology.

EVs and ncRNA

Classification and Formation Mechanism of EVs

EVs constitute a heterogeneous group of membrane-bound structures actively released by cells, classified into exosomes, microvesicles, and apoptotic bodies based on biogenesis pathways and physical characteristics. This section delineates the biogenesis mechanisms of exosomes and microvesicles, along with their regulatory networks (Figure 1).

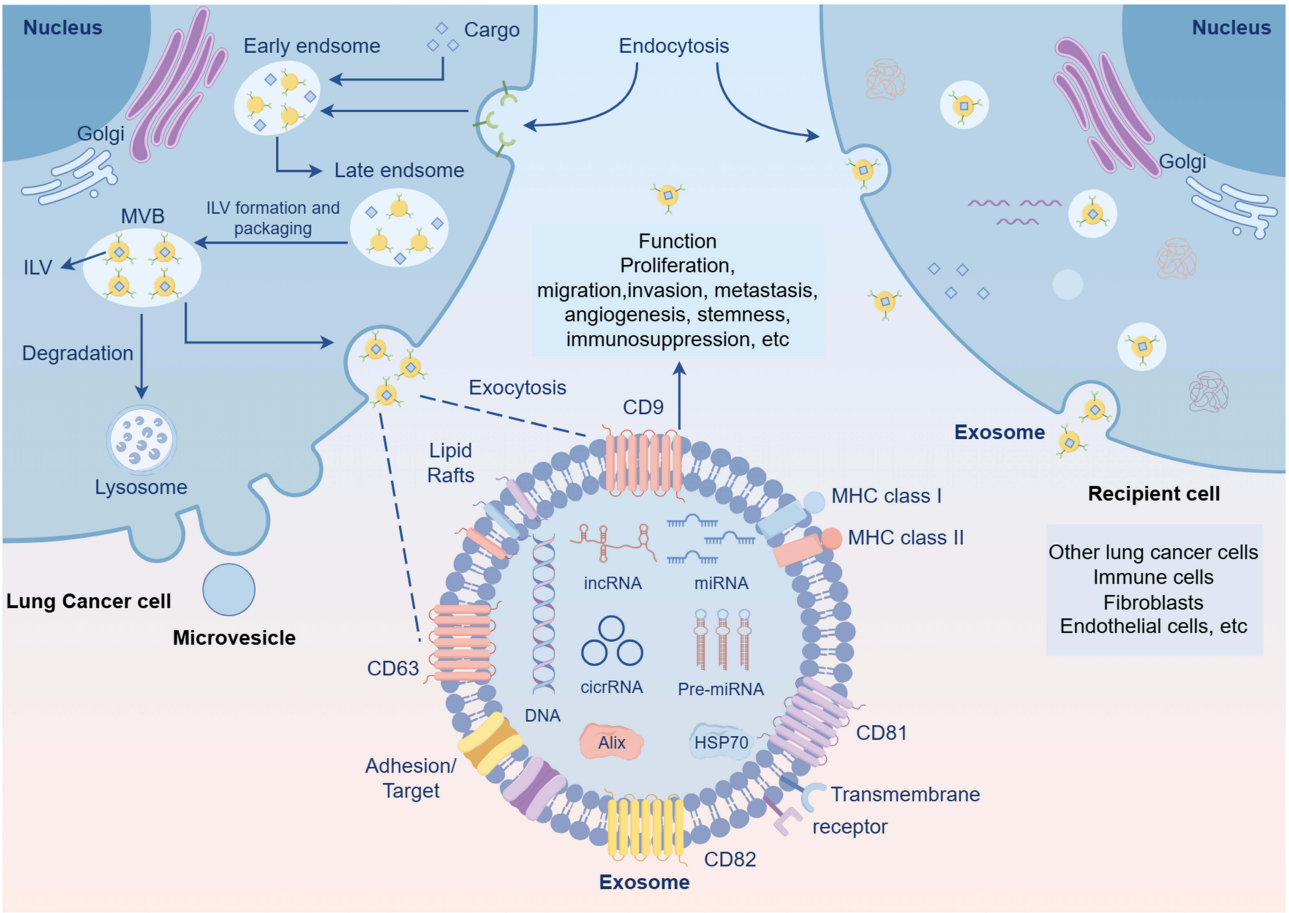

Figure 1 Biogenesis, secretion, transport, and functions of EVs-ncRNA in lung cancer cells. This figure illustrates the biogenesis of EVs in lung cancer cells, including the formation and packaging of MVBs and ILVs. Exosomes are released into the extracellular environment via exocytosis. These vesicles mediate intercellular communication through surface markers such as CD9, CD63, CD81, CD82, and lipid rafts. Their cargo includes various ncRNAs, such as lncRNAs, miRNAs, circRNAs and their precursors, as well as DNA and associated proteins (eg, Alix, HSP70). Exosomes can be taken up by nearby or distant recipient cells—including other lung cancer cells, immune cells, fibroblasts, and endothelial cells—modulating a range of biological functions. These functions involve key processes related to tumor progression, such as cell proliferation, migration, invasion, metastasis, angiogenesis, stemness maintenance, and immune suppression.

Exosomal Biogenesis

Exosomes originate from the endosomal pathway through dynamic regulation of MVBs. Their formation initiates when early endosomes generate intraluminal vesicles via inward membrane budding—a process primarily mediated by the Endosomal Sorting Complex Required for Transport (ESCRT). The sequential action of ESCRT subcomplexes orchestrates this process: ESCRT-0 recognizes ubiquitinated cargo proteins, ESCRT-I/II facilitates membrane curvature, and ESCRT-III executes membrane scission.[9] Emerging evidence highlights critical ESCRT-independent mechanisms, where tetraspanins (eg, CD63) cooperate with sphingomyelinase to promote ILV formation within lipid raft microdomains.[10] Mature MVBs exhibit divergent fates: lysosomal degradation of contents or plasma membrane fusion to release ILVs as exosomes.[10] Rab GTPases (eg, Rab27a/b) critically regulate exosomal trafficking and secretion.[4]

Microvesicle Biogenesis

Microvesicles arise directly through plasma membrane budding, requiring cytoskeletal reorganization. Elevated cytosolic calcium levels activate calpain proteases, triggering actin-filament disassembly and phospholipid asymmetry disruption with phosphatidylserine redistribution. Concurrent activation of the Rho/ROCK pathway induces myosin light chain phosphorylation, driving membrane contraction and vesicle shedding. Unlike exosomes, ARF6-mediated lipid remodeling predominantly governs microvesicle biogenesis, independent of ESCRT machinery.[2,10,11]

ncRNA Diversity and Biogenesis

ncRNAs are functional RNA molecules that do not encode proteins, playing critical roles in gene expression regulation, chromatin remodeling, and cell fate determination. Based on length and functional characteristics, they are categorized into lncRNAs, circRNAs, and miRNAs. Recent studies have uncovered diverse biogenesis mechanisms and functional associations.

lncRNAs

lncRNAs are noncoding RNA molecules exceeding 200 nucleotides in length, orchestrating diverse biological processes including epigenetic regulation, chromatin remodeling, transcription, and post-transcriptional processing. While sharing transcriptional initiation mechanisms with mRNAs via RNA polymerase II, lncRNAs lack functional open reading frames. These versatile regulators modulate gene expression through distinct mechanistic pathways: 1. Chromatin scaffolding: Acting as molecular platforms to recruit chromatin-modifying complexes (eg, Xist-mediated recruitment of Polycomb Repressive Complex 2 during X-chromosome inactivation). 2. RNA-protein interplay: Influencing RNA stability and translational efficiency through direct interactions with mRNAs or proteins. 3. Nuclear architecture regulation: Driving the formation of subnuclear compartments (eg, NEAT1-mediated assembly of nuclear paraspeckles) to modulate spatial genome organization.[12–14]

circRNAs

circRNAs are a distinctive class of covalently closed, single-stranded noncoding RNAs generated via back-splicing, a mechanism that circularizes precursor RNAs by covalently linking a downstream 5' splice site to an upstream 3' splice site. This circular architecture eliminates free termini, rendering circRNAs inherently resistant to exonucleolytic degradation and conferring remarkable stability. Depending on their origin, circRNAs can be classified as exonic (EcircRNA), intronic (ciRNA), or exon-intron hybrids (EIciRNA). Their biogenesis is precisely regulated by trans-acting RNA-binding proteins (eg, QKI, HNRNPL) and cis-acting elements, such as flanking inverted repeat sequences (eg, Alu elements) that promote intramolecular base pairing. circRNAs exhibit versatile regulatory functions: (1) Serving as competitive endogenous RNAs (ceRNAs), they sequester miRNAs to derepress miRNA-targeted mRNAs (eg, CDR1as/ciRS-7 sponges miR-7); (2) Interacting with RNA polymerase II or transcription factors, they modulate transcription of parental genes; (3) Binding to and modulating protein activity, they influence cellular pathways (eg, circFOXO3 stabilizes p53 by blocking MDM2-mediated ubiquitination). Furthermore, recent advances demonstrate that subsets of circRNAs contain internal ribosome entry sites (IRES) capable of initiating cap-independent translation, producing functional micropeptides. For instance, circ-SHPRH-derived SHPRH-146aa inhibits glioma progression by antagonizing ubiquitin-mediated degradation of full-length SHPRH, underscoring their roles in oncogenic metabolic reprogramming.[15–17]

miRNA

Mature miRNA biogenesis involves a tightly regulated multi-step process. Initially, miRNA genes are transcribed by RNA polymerase II or III to produce primary miRNA transcripts (pri-miRNAs), which maintain characteristic 5' capping and 3' polyadenylation features.[18] Within the nucleus, the microprocessor complex – comprising Drosha endonuclease and DGCR8 cofactor – precisely cleaves pri-miRNAs to generate precursor miRNAs (pre-miRNAs).[19] Subsequent nuclear export is mediated by Exportin-5 through a Ran-GTP-dependent mechanism. Following cytoplasmic translocation, the RNase III enzyme Dicer typically processes pre-miRNAs into ~22 nucleotide miRNA duplexes. The functional guide strand is selectively incorporated into the RNA-induced silencing complex through its association with Argonaute proteins, enabling post-transcriptional regulation via partial complementarity with target mRNA 3' untranslated regions (3'UTRs).[18,19] Notably, alternative maturation pathways exist, as exemplified by miR-451 which bypasses Dicer processing and is directly cleaved by Argonaute2.[20]

Loading of ncRNAs in Lung Cancer EVs

The sorting mechanisms of ncRNAs into EVs involve multiple molecular regulatory pathways. Studies have demonstrated that RNA-binding proteins (RBPs) play pivotal roles in this process. Li et al revealed that methylated YBX1 protein specifically recognizes hY4 RNA fragments and facilitates their selective loading into EVs through coordinated interactions with EV biogenesis pathways. This methylation modification likely modulates YBX1's RNA-binding affinity, thereby influencing sorting efficiency.[21] Members of the hnRNP protein family exhibit distinct functional specialization in EVs-ncRNA sorting. Mechanistic studies show that hnRNPA2B1 interacts with the SIM domain of ALIX protein via SUMOylation, forming a molecular complex that mediates circTLCD4-RWDD3 loading into EVs. Notably, the SUMO2 modification at the K108 residue of hnRNPA2B1 critically determines binding specificity in this process.[22] A parallel regulatory mechanism governs miR-122-5p sorting, where hnRNPA2B1 achieves selective miRNA packaging through recognition of EXO-motif sequences.[23] The sorting machinery demonstrates remarkable RNA-protein synergy through structural coordination. CircTLCD4-RWDD3 employs a DNA-RNA triplex structure to recruit both hnRNPA2B1 and histone modification complexes, creating a three-dimensional platform that facilitates its own EV trafficking.[22] In miRNA sorting, SYNCRIP protein selectively enriches EV-associated miRNAs by recognizing specific sequence motifs (eg, GGAG). Post-translational modifications serve as critical regulatory switches in sorting processes.[24] SUMOylation of hnRNPA1 enhances its interaction with CAV1, driving bulk loading of pro-tumorigenic miRNAs into EVs.[25] This modification potentially alters protein subcellular localization or binding capacity. Similarly, the SUMOylation status of hnRNPA2B1 dynamically regulates its ALIX-binding affinity, thereby fine-tuning circRNA sorting efficiency.[22] Cellular state-dependent sorting mechanisms have been identified. Tumor cells exploit hnRNPK-mediated sorting of miR-4732-3p into fucosylated EVs to evade tumor-suppressive effects, suggesting microenvironmental adaptation strategies.[26] Current evidence establishes EVs-ncRNA sorting as an integrated process governed by multi-layered regulatory networks involving RNA-protein interactions, post-translational modifications, and membrane trafficking machinery. While these findings advance our understanding of EV-mediated intercellular communication, key questions remain regarding RBP crosstalk (synergistic/antagonistic interactions) and the precise determinants of sorting specificity (Table 1).

The Dual Role of EVs-ncRNA in Lung Cancer

EVs-ncRNA exhibit a "double-edged sword" effect in lung cancer pathogenesis. On one hand, these ncRNAs can act as signaling molecules to promote cancer cell proliferation, invasion, metastasis, and drug resistance. Conversely, certain ncRNAs demonstrate tumor-suppressive properties by inhibiting cancer growth and migration. This section comprehensively summarizes the dual regulatory roles of EVs-ncRNA (including miRNAs, lncRNAs, and circRNAs) in proliferation, invasion, metastasis, and drug resistance across NSCLC (squamous and adenocarcinoma subtypes) and small cell lung cancer (SCLC), offering novel insights and challenges for lung cancer diagnosis and therapeutic development.

Table 1 Key Molecular Mechanisms Governing ncRNA Sorting Into EVs in Lung Cancer

Mechanistic Overview	Critical RBPs	Interacting Partners	Regulatory Mode	Target RNA Type	Functional Impact	Reference
Methylated YBX1 recognizes hY4 RNA fragments with sequence specificity	YBX1	EV biogenesis machinery	K3/K7 methylation enhances RNA binding	miRNA hY4F	Directional sorting of oncogenic RNAs into EVs	[21]
SUMOylated hnRNPA2B1 coordinates circRNA sorting	hnRNPA2B1	ALIX (SIM domain)	SUMO2 modification at K108 strengthens binding	circTLCD4-RWDD3	Enhanced metastatic potential via circRNA release	[22]
EXO-motif recognition drives miRNA selection	hnRNPA2B1	RNA hairpin motifs (eg, CGAG)	Sequence-specific EXO-motif binding	miR-122-5p, miR-21	Selective enrichment of pro-tumorigenic miRNAs	[23]
Triplex DNA-RNA structure-dependent sorting	hnRNPA2B1	Histone modification complex	RNA tertiary structure-driven recruitment	circTLCD4-RWDD3	Stabilizes RNA and boosts EV packaging	[22]
SYNCRIP-mediated GGAG motif recognition	SYNCRIP	miRNA consensus sequences	RNA motif recognition (GGAG loop)	GGAG-containing miRNAs	Reprograms EV-miRNA cargo for immune evasion	[24]
SUMOylated hnRNPA1-CAV1 collaboration	hnRNPA1	Caveolin-1 (CAV1)	SUMOylation enhances CAV1 interaction	Pro-metastatic miRNAs	Bulk miRNA export to suppress antitumor immunity	[25]
Fucosylated EV sorting of tumor-suppressive miRNAs	hnRNPK	Fucosylation enzymes	Glycosylation-dependent RNA exclusion	miR-4732-3p	Immune-editing by suppressing tumor suppressor RNAs	[26]

Roles of EVs-ncRNA in Lung Cancer Progression and Metastasis

Roles of EVs-miRNA in Lung Cancer Progression and Metastasis

Wu et al identified significant enrichment of miR-1228-5p in plasma exosomes from SCLC patients compared to healthy volunteers, correlating with tumor size, distant metastasis, and advanced staging. Functionally, exosomes derived from miR-1228-5p-high cells markedly enhanced lung cancer cell proliferation and migration, mechanistically attributed to suppression of a metastasis-regulating tumor suppressor gene DUSP22.[27] In NSCLC, miR-744 exhibits tumor-suppressive effects by targeting SUV39H1, which represses Smad9 expression, thereby alleviating BMP4-driven NSCLC progression. Paradoxically, low miR-744 levels in NSCLC-derived EVs result in elevated SUV39H1, Smad9 inhibition, and subsequent BMP4 upregulation.[28] Similarly, miR-4732-3p exerts tumor-suppressive effects in NSCLC by inducing G2/M arrest through regulation of the MFSD12/AKT/p21 axis. However, its expression is notably reduced in tumor tissues, a phenomenon linked to the "exosomal escape" theory. This mechanism involves NSCLC cells selectively packaging miR-4732-3p into EVs for extracellular release, thereby reducing intracellular levels of this tumor-suppressive miRNA and enabling tumor cell survival.[26] The tumor suppressor hY4F inhibits tumor progression by downregulating the MAPK/NF-κB signaling pathway. Consistent with the exosomal escape theory, hY4F is selectively packaged into EVs, thereby reducing its intracellular levels in NSCLC cells and facilitating tumor survival.[21] In Ras-driven NSCLC, syntenin-1 upregulation enhances small EV (sEV) secretion. miRNA profiling revealed Ras/syntenin-1-dependent sEV enrichment of miR-494-3p, which promotes tumor proliferation, migration, and angiogenesis by targeting PTPN12 and activating EGF/VEGF signaling.[29] Notably, TME dynamics involve bidirectional EV interactions—tumor cells may internalize EVs carrying tumor-suppressive factors, highlighting the complexity of EV-mediated regulation (Figure 2) (Table 2).

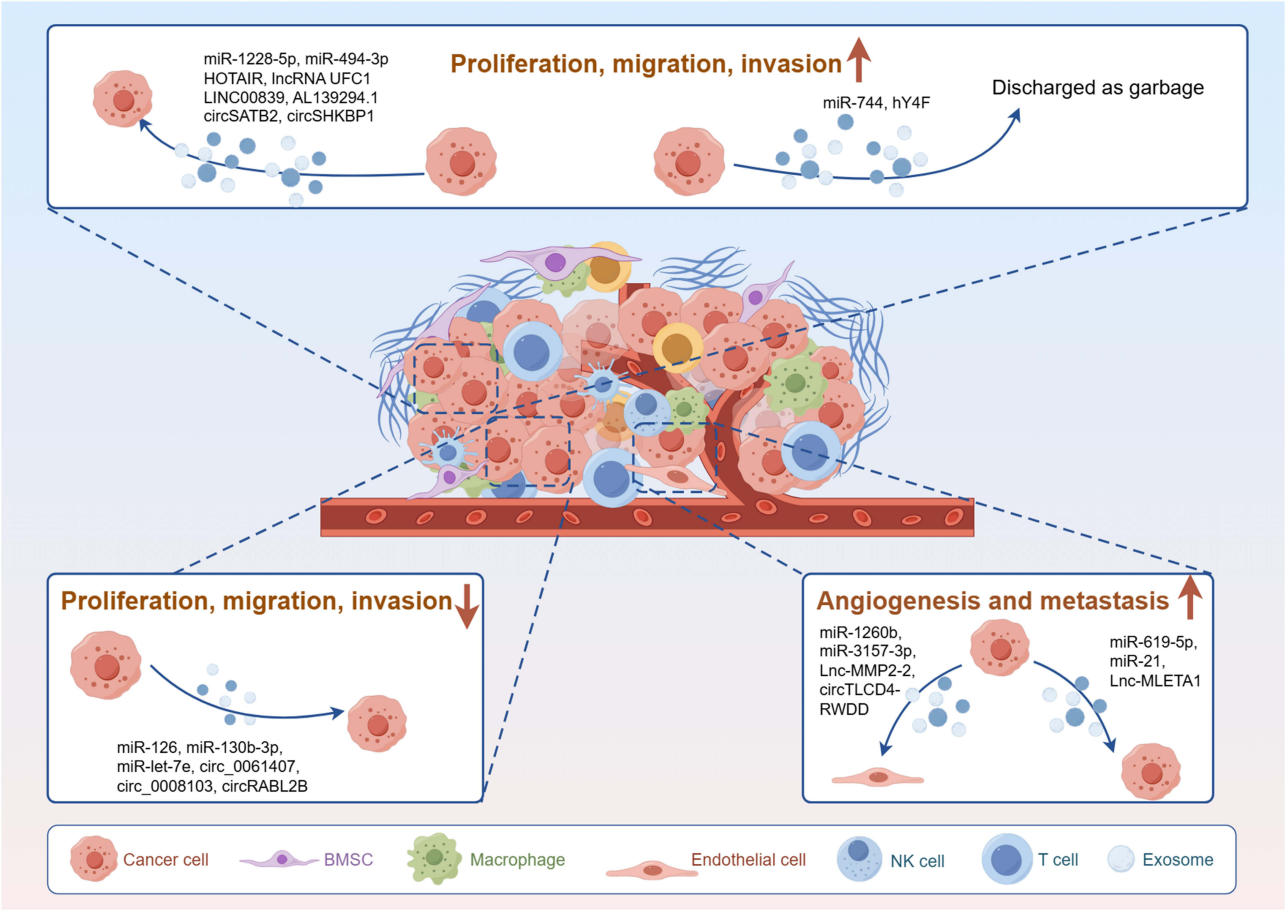

Figure 2 Functional roles of EVs-ncRNA in the lung cancer tumor microenvironment. This figure illustrates the diverse functional roles of EVs-ncRNA within the lung cancer tumor microenvironment. EVs-ncRNA derived from different cell types regulate the behavior of both tumor cells and microenvironmental cells—including BMSCs, macrophages, endothelial cells, NK cells, T cells, and others—thereby influencing processes such as tumor cell proliferation, migration, invasion, angiogenesis, and metastasis. Some ncRNAs (eg, miR-1228-5p, miR-494-3p) promote tumor progression, while others (eg, miR-126, miR-130b-3p) inhibit tumor development; certain ncRNAs are also expelled from cells as "waste". In addition, EVs-ncRNAs contribute to tumor-associated angiogenesis and distant metastasis.

Angiogenesis, the formation of new blood vessels from pre-existing vasculature, is pivotal for tumor growth and metastasis by providing oxygen/nutrient supply, facilitating hematogenous dissemination, and secreting pro-invasive factors.[62,63] NSCLC cell-derived exosomes exhibit heterogeneous pro-metastatic capacities. miRNA profiling of metastasis-prone exosomes identified miR-619-5p and miR-1260b as key mediators: miR-619-5p targets RCAN1.4 (a metastasis suppressor in NSCLC cells), while miR-1260b suppresses HIPK2 in endothelial cells (HUVECs) to drive metastasis.[30,31] Ma et al discovered miR-3157-3p as the most abundant miRNA in plasma exosomes from NSCLC patients, particularly elevated in metastatic cases. NSCLC-derived exosomal miR-3157-3p enhanced HUVEC proliferation, migration, tube formation, angiogenesis, and vascular permeability by targeting TIMP2 and KLF2.[32] In brain metastasis models, EVs from metastatic NSCLC cell spheres enriched with miR-21 activated ERK/STAT3 signaling in non-metastatic cells, increasing their metastatic potential. Combined inhibition of ERK (via Ulixertinib) and miR-21 silencing synergistically suppressed lung tumorigenesis and brain metastasis in xenografts, suggesting promising combinatorial therapeutic strategies[33] (Figure 2) (Table 2).

While EVs-miRNAs are well-documented drivers of tumor progression, emerging evidence highlights their dual role as tumor suppressors in lung cancer. A deeper exploration of these tumor-inhibitory EVs-miRNAs is critical for comprehensively understanding lung carcinogenesis. Below, we summarize key mechanisms by which specific EVs-miRNAs counteract malignancy: For instance, miR-126 and miR-let-7e are downregulated in serum-derived exosomes from NSCLC patients. Functional studies reveal that exosomes loaded with miR-126 mimics suppress NSCLC cell

Table 2 Roles of EVs-ncRNA in Lung Cancer Progression and Metastasis

EV-ncRNA Type	ncRNA	Role in Cancer	Key Mechanism	References
miRNAs	miR-1228-5p	Pro-tumorigenic	Targets DUSP22 → Promotes proliferation and metastasis in SCLC	[27]
	miR-744	Pro-tumorigenic	Low EVs-miR-744 levels → SUV39H1↑ → Smad9↓ → BMP4↑ → Drives NSCLC progression	[28]
	miR-4732-3p	Pro-tumorigenic	Low miR-4732-3p reduces G2/M arrest induced by MFSD12/AKT/p21 axis	[26]
	miR-494-3p	Pro-tumorigenic	Targets PTPN12 → Activates EGF/VEGF signaling → Enhances angiogenesis and metastasis	[29]
	miR-619-5p	Pro-metastatic	Targets RCAN1.4 → Promotes NSCLC metastasis	[30]
	miR-1260b	Pro-metastatic	Targets HIPK2 in endothelial cells → Facilitates metastasis	[31]
	miR-3157-3p	Pro-angiogenic	Targets TIMP2/KLF2 → Enhances angiogenesis, vascular permeability, and metastasis	[32]
	miR-21	Pro-metastatic	Activates ERK/STAT3 → Promotes brain metastasis	[33]
	miR-126	Tumor-suppressive	Targets ITGA6 → Induces apoptosis and cell cycle arrest	[34]
	miR-let-7e	Tumor-suppressive	Targets SUV39H2/LSD1/CDH1 axis → Inhibits the metastasis	[35]
	miR-130b-3p	Tumor-suppressive	Targets DEPDC1 → Inhibits proliferation and induces apoptosis	[36]
	miR-338-3p	Tumor-suppressive	Targets CHL1 → Inhibits MAPK signaling → Suppresses tumor growth	[37]
lncRNAs	HOTAIR	Pro-tumorigenic	Promotes NSCLC proliferation and migration (mechanism unclear)	[38,39]
	lncRNA UFC1	Pro-tumorigenic	Recruits EZH2 → PTEN promoter H3K27me3 → Silences PTEN → Enhances tumor growth	[40]
	LINC00839	Pro-tumorigenic	Sponges miR-17-5p → Activates TLR4/NF-κB; regulates NF-κB p65 nuclear translocation	[41]
	AL139294.1	Pro-tumorigenic	Sponges miR-204-5p → Activates Wnt5a/NF-κB2 signaling → Drives NSCLC progression	[42]
	Lnc-MLETA1	Pro-metastatic	Sponges miR-186-5p/miR-497-5p → Upregulates EGFR/IGF1R → Enhances metastasis	[43]
	lncRNA-SOX2OT	Pro-metastatic	Targets miR-194-5p/RAC1 axis → Promotes bone metastasis via osteoclast differentiation	[44]
	lnc-MMP2-2	Pro-metastatic	Sponges miR-1294 → EPB41L5↑ → Increases BBB permeability → Facilitates brain metastasis	[45]
	Linc01703	Tumor-suppressive	Enhances CD81+ EV secretion → Inhibits immune cell infiltration → Suppresses LUAD metastasis	[46]
circRNAs	circSATB2	Pro-tumorigenic	Sponges miR-326 → Upregulates FSCN1 → Promotes NSCLC invasion and proliferation	[47]
	circSHKBP1	Pro-tumorigenic	Sponges miR-1294 → PKM2↑ → Enhances glycolysis and M2 macrophage polarization	[48]
	circTLCD4-RWDD3	Pro-metastatic	Activates PROX1 → Promotes lymphangiogenesis and lymph node metastasis	[22]
	circ_0061407 circ_0008103	Tumor-suppressive	Inhibits NSCLC proliferation, migration, and invasion via exosomal transfer	[49]
	circRABL2B	Tumor-suppressive	Inhibits integrin β4/pSrc/p53 signaling → Reduces stemness and enhances drug sensitivity	[50]

(*Continued*)

https://doi.org/10.2147/IJN.S528115

Table 2 (Continued).

EV-ncRNA Type	ncRNA	Role in Cancer	Key Mechanism	References
Non-Tumor Cell EVs	CAF-derived miR-369/miR-20a	Pro-tumorigenic	Activate MAPK/PI3K-AKT pathways → Promote proliferation and cisplatin resistance	[51,52]
	CAF-derived OIP5-AS1	Pro-tumorigenic	Sponges miR-142-5p → Upregulates PD-L1 → Suppresses immune response	[53]
	CAF-derived miR-19a	Pro-tumorigenic	Targets ZMYND11 → Upregulates c-Myc → Promotes proliferation	[54]
	TAM-derived miR-501-3p/circFTO	Pro-tumorigenic	Target WDR82 and miR-148a-3p/PDK4 → Promote proliferation and migration	[55,56]
	TAM-derived miR-155/miR-196a-5p	Pro-metastatic	Promote migration, invasion, and EMT	[57]
	TAM-derived circEML4	Pro-tumorigenic	Interacts with ALKBH5 → Alters SOCS2 m6A modification → Activates JAK-STAT pathway	[58]
	BMSC-derived miR-21-5p	Pro-tumorigenic	Downregulates PTEN/PDCD4/RECK → Enhances tumor growth and M2 polarization	[59]
	BMSC-derived miR-144	Tumor-suppressive	Targets CCNE1/CCNE2 → Inhibits NSCLC proliferation	[60]
	Osteocyte-derived miR-99b-3p	Tumor-suppressive	Maintains tumor dormancy → Reduces bone metastasis	[61]

proliferation, migration, and invasion by targeting ITGA6, inducing cell cycle arrest and apoptosis.[34] Similarly, miR-let-7e exerts anti-tumor effects via the SUV39H2/LSD1/CDH1 axis.[35] The tumor-suppressive miR-130b-3p, which is also reduced in NSCLC serum exosomes, directly binds to the 3'UTR of DEPDC1 to inhibit its expression, thereby blocking NSCLC cell proliferation and migration while promoting apoptosis. Notably, normal bronchial epithelial cells (BEAS-2B) secrete exosomes enriched with miR-130b-3p, which are transferred to NSCLC cells to exert these inhibitory effects.[36] Additionally, miR-338-3p, highly expressed in exosomes from both NSCLC serum and normal lung epithelial cells, suppresses tumor growth by targeting CHL1 and inhibiting MAPK signaling, ultimately inducing apoptosis in co-cultured lung cancer cells.[37] These findings underscore the therapeutic potential of harnessing tumor-suppressive EVs-miRNAs to counteract oncogenic signaling networks in lung cancer (Figure 2) (Table 2).

Roles of EVs-lncRNA in Lung Cancer Progression and Metastasis

Compared to adjacent non-tumor tissues and serum from healthy volunteers, HOTAIR levels are markedly elevated in NSCLC tissues, patient serum, and serum-derived exosomes. Exosomes carrying highly expressed HOTAIR significantly enhance NSCLC cell proliferation and migration, though the precise mechanisms remain to be elucidated.[38,39] Similarly, lncRNA UFC1 is upregulated in NSCLC tumor tissues, serum, and serum-derived exosomes. Mechanistically, lncRNA UFC1 binds to EZH2, facilitating its accumulation at the PTEN promoter to induce H3K27 trimethylation and suppress PTEN expression. Exosomal transfer of lncRNA UFC1 to recipient cells perpetuates this oncogenic axis, driving tumor proliferation, migration, and invasion.[40] In lung adenocarcinoma, exosome-enriched LINC00839 promotes tumor progression via dual mechanisms: in the cytoplasm, it acts as a molecular sponge for miR-17-5p, activating the TLR4/NF-κB pathway to enhance malignant behaviors; in the nucleus, LINC00839 interacts with PTBP1 to regulate nuclear translocation of NF-κB p65, thereby modulating transcription of downstream oncogenes.[41] Serum EV profiling identified AL139294.1 as the most significantly upregulated lncRNA in NSCLC patients. AL1392941 sponges miR-204-5p, relieving its suppression of BRD4 and subsequently activating Wnt5a and NF-κB2 signaling to fuel NSCLC progression.[42] Comparative sequencing of exosomes derived from high- and low-metastatic NSCLC cells identified Lnc-MLETA1 as a metastasis-associated lncRNA. Mechanistically, Lnc-MLETA1 sponges miR-186-5p and miR-497-5p to upregulate EGFR and IGF1R expression, thereby enhancing the migratory and metastatic capacities of lung cancer cells.[43] Furthermore, NSCLC-derived EVs-lncRNA critically regulate organ-specific metastasis. For instance, exosomal lncRNA-SOX2OT is enriched in peripheral blood from NSCLC patients with bone metastasis. It drives osteoclast differentiation and bone metastasis by targeting the miR-194-5p/RAC1 axis in tumor cells and the TGF-β/pTHrP/RANKL pathway in osteoclasts.[44] Increased blood–brain barrier (BBB) permeability is a hallmark of lung cancer brain metastasis.[64] TGF-β1-high NSCLC-derived exosomes disrupt BBB integrity by delivering lnc-MMP2-2, which sponges miR-1294 to de-repress EPB41L5, thereby enhancing vascular permeability and facilitating brain metastasis[45] (Figure 2) (Table 2).

Intriguingly, Linc01703 also suppresses tumor metastasis by modulating the release of CD81-positive EVs. Specifically, in vivo studies have demonstrated a significant inhibitory effect of Linc01703 on lung cancer metastasis, whereas it has no apparent impact on the proliferation or invasion of LUAD cells in vitro. This suggests that Linc01703 may exert its anti-metastatic effects by modulating other cell types within the TME, with changes in immune cell populations being the most plausible factor. Mechanistically, Linc01703 enhances the interaction between Rab27a, SYTL1, and CD81, thereby promoting the secretion of CD81-positive EVs. These EVs, in turn, inhibit the infiltration of immune cells within the TME, ultimately impeding LUAD metastasis[46] (Figure 2) (Table 2).

Roles of EVs-circRNA in Lung Cancer Progression and Metastasis

Zhang et al identified circSATB2 as highly expressed in NSCLC tissues, cells, and cell-derived exosomes. By sponging miR-326, circSATB2 upregulates FSCN1 to promote NSCLC cell proliferation, migration, invasion, and aberrant proliferation of normal bronchial epithelial cells.[47] Similarly, exosomal circSHKBP1 is elevated in NSCLC, enhancing tumor cell proliferation, migration, invasion, stemness, and macrophage M2 polarization. Mechanistically, circSHKBP1 sponges miR-1294 to upregulate PKM2, driving glycolysis in NSCLC cells via HIF-1α-dependent pathways.[48] Lymph node metastasis, a predominant route of NSCLC dissemination, is facilitated by exosomal circTLCD4-RWDD3. This

circRNA is internalized by lymphatic endothelial cells, activating PROX1 transcription to promote lymphangiogenesis and lymph node metastasis, as validated in both cellular and animal models[22] (Figure 2) (Table 2).

In terms of tumor suppression, circ_0061407, circ_0008103, and circRABL2B are downregulated in the serum of NSCLC patients. Upregulation of circ_0061407 and circ_0008103 inhibits the proliferation, migration, and invasion of NSCLC cells. Moreover, exosomes carrying circ_0061407 and circ_0008103 are transferred to recipient cells, where they also suppress proliferation, migration, and invasion.[49] circRABL2B interacts with YBX1 to inhibit MUC5AC, thereby suppressing the integrin β4/pSrc/p53 signaling pathway, reducing stemness, and enhancing sensitivity to erlotinib[50] (Figure 2) (Table 2).

ncRNA From Non-Tumor Cellular EVs in Lung Cancer Progression and Metastasis

Within the intricate TME of lung cancer—comprising vascular cells, immune cells, fibroblasts, extracellular matrix, and signaling molecules—EVs released by non-tumor stromal cells critically orchestrate tumor initiation, progression, and metastasis. Cancer-associated fibroblasts (CAFs), characterized by their α-smooth muscle actin (α-SMA)-positive "activated" phenotype, secrete EVs loaded with miR-369 and miR-20a into NSCLC cells. These miRNAs activate MAPK signaling via NF1 targeting[51] and PI3K/AKT signaling via PTEN suppression, respectively, enhancing tumor proliferation, migration and invasion.[52] Comparative sequencing of CAF and normal fibroblast (NAF)-derived exosomes revealed elevated levels of lncRNA OIP5-AS1 in CAF exosomes. Upon internalization by lung cancer cells, OIP5-AS1 acts as a ceRNA by sponging miR-142-5p, downregulating its expression and upregulating PD-L1, thereby suppressing PBMC-induced apoptosis and promoting immune evasion.[53] Beyond CAFs, Yu Fujita et al established lung fibroblasts (LFs) from idiopathic pulmonary fibrosis (IPF) and non-IPF lung tissues. They demonstrated that IPF-derived LF EVs promote lung cancer cell proliferation by transferring miR-19a to suppress ZMYND11 signaling, mechanistically leading to c-Myc oncoprotein upregulation.[54] Notably, this study was limited to in vitro validation, lacking in vivo or clinical confirmation.

Macrophages exhibit a complex dual role in tumorigenesis, capable of both suppressing and promoting cancer progression. Within the TME, tumor-associated macrophages (TAMs) are predominantly polarized into pro-tumor M2 phenotypes by cytokines secreted from cancer cells.[65,66] M2 macrophage-derived EVs drive lung cancer progression through distinct mechanisms. miR-501-3p directly targets WDR82 to enhance tumor proliferation, while circFTO activates the miR-148a-3p/PDK4 axis to promote migration.[55,56] In metastatic NSCLC, M2 macrophage-derived EVs enriched with miR-155 and miR-196a-5p critically facilitate tumor cell migration, invasion, and EMT.[57] Cigarette smoke, a major lung cancer risk factor, exacerbates M2 macrophage infiltration in NSCLC tissues. EVs from smoke-polarized M2 macrophages further accelerate tumor progression. For instance, circEML4 within these EVs interacts with ALKBH5, inducing its cytoplasmic redistribution. This interaction alters m6A modifications of SOCS2, as revealed by m6A-seq and RNA-seq analyses, ultimately activating the JAK-STAT signaling pathway to fuel tumorigenesis.[58]

Cancer stem cells (CSCs), a subpopulation within tumors characterized by self-renewal and multilineage differentiation capacity, play a pivotal role in tumor progression. Wang et al identified that lncRNA Mir100hg is upregulated in lung cancer stem cells (LLC-SD) and can be transferred via exosomes to non-stem Lewis lung carcinoma cells. In recipient cells, Mir100hg directly targets miR-15a-5p and miR-31-5p, thereby elevating global glycolytic activity and enhancing metastatic potential through metabolic reprogramming.[67] Another key stem cell type in the TME, bone marrow-derived mesenchymal stem cells (BMSCs), plays a crucial role in lung cancer progression. Under hypoxic conditions, BMSC-derived EVs enriched with miR-21-5p downregulate the expression of tumor suppressor genes PTEN, PDCD4, and RECK in lung cancer cells. This results in significantly enhanced tumor growth, increased cancer cell proliferation, elevated intratumoral angiogenesis, and promotion of M2 macrophage polarization in vivo.[59] Furthermore, under hypoxic conditions, BMSC-derived EVs can deliver miR-193a-3p, miR-210-3p, and miR-5100 into lung cancer cells. This transfer activates STAT3 signaling and increases the expression of mesenchymal markers, thereby promoting cancer cell invasion and EMT.[68] Schwann cells (SCs), recognized as primary glial cells of the peripheral nervous system, are frequently detected within various solid tumors. In the context of NSCLC, SC-derived exosomal miRNA-21 has been shown to promote the proliferation, motility, and invasiveness of human lung cancer cells by targeting RECK, a matrix metalloproteinase inhibitor, within the tumor cells. Furthermore, in mouse xenograft models, SC exosomes and specifically their contained hsa-miRNA-21-5p enhanced the growth and lymph node metastasis of human lung cancer

cells in vivo.[69] Bronchoalveolar lavage fluid-based EV analysis identified miR-1246b as a novel oncogenic miRNA targeting FGF14, driving ERK phosphorylation, EMT, and metastasis in NSCLC[70] (Figure 2) (Table 2).

Beyond their pro-tumor roles, EVs released by other cell types within the TME can also contribute to tumor suppression. For instance, BMSC-derived exosomes containing miR-144 inhibit NSCLC proliferation by targeting CCNE1 and CCNE2[60] Furthermore, osteocytes, when sensing mechanical stimulation (eg, from exercise), release sEVs containing miR-99b-3p. These sEVs inhibit NSCLC cell proliferation and maintain a dormant state, thereby reducing bone metastasis.[61] This observation suggests that moderate exercise may have a role in preventing NSCLC bone metastasis (Figure 2) (Table 2).

In summary, EVs-ncRNA play complex and dynamic dual roles in lung cancer progression and metastasis. On the one hand, tumor cells and other cells within the TME (such as fibroblasts and macrophages) release EVs carrying specific ncRNA that activate oncogenic signaling pathways and inhibit tumor suppressor gene function. This drives the proliferation, invasion, angiogenesis, and distant metastasis of lung cancer cells. These ncRNAs may synergistically promote malignant progression by modulating key signaling networks, epigenetic modifications, or remodeling the TME. On the other hand, some EVs-ncRNA exert tumor-suppressive effects by targeting oncogenic pathways, inducing cell cycle arrest or apoptosis, and enhancing treatment sensitivity. However, these inhibitory ncRNA are fewer in number in lung cancer, which seems to align with the objective pattern of continuous tumor progression. This bidirectional regulatory mechanism not only reveals the complexity of lung cancer progression but also provides a theoretical basis for developing dynamic monitoring strategies and targeted interventions based on EVs-ncRNA. For example, modulating the release or delivery of specific ncRNA to balance the interplay between pro-cancer and anti-cancer signals may open up new avenues for lung cancer treatment.

Role of EVs-ncRNA in Therapeutic Resistance

EVs-ncRNA in Chemoresistance

Common chemotherapeutic agents for lung cancer include platinum-based compounds (eg, cisplatin, carboplatin), taxanes (eg, paclitaxel, docetaxel), antimetabolites (eg, pemetrexed, gemcitabine), vinca alkaloids (eg, vinorelbine), and topoisomerase inhibitors (eg, etoposide, irinotecan). These drugs inhibit tumor proliferation and metastasis by disrupting DNA replication, impeding cell division, or interfering with microtubule function. Combination chemotherapy regimens are frequently employed in lung cancer to enhance therapeutic efficacy.[71,72] This section explores how tumor-derived EVs mediate chemoresistance in lung cancer through diverse mechanisms.

Platinum agents are first-line treatments for NSCLC, and extensive research has focused on their resistance mechanisms. EVs-ncRNA associated with platinum resistance have been identified using three approaches: (1) comparing EVs from conventional NSCLC cells versus platinum-resistant cell lines, (2) analyzing EVs from NSCLC patient tissues versus platinum-resistant tumor tissues, and (3) profiling EVs from serum of NSCLC patients versus those with platinum resistance. Comparative analyses revealed that CircVMP1 and miR-100–5p are significantly upregulated in platinum-resistant NSCLC cell lines and their secreted exosomes. These ncRNAs are transferred via exosomes to sensitive NSCLC cells, where CircVMP1 sponges miR-524-5p to upregulate methyltransferase-like 3 and SOX2, while miR-100–5p directly suppresses mTOR expression, collectively promoting chemoresistance.[73,74] Conversely, CircSH3PXD2A is downregulated in SCLC chemoresistant cell lines. Overexpression of CircSH3PXD2A in EVs suppresses chemoresistance, proliferation, and metastasis in SCLC by sequestering miR-375-3p to enhance YAP1 expression.[75] In cisplatin-resistant NSCLC tissues, exosomal miR-4443 is elevated and drives resistance by inhibiting METTL3-mediated m6A modification of FSP1.[76] Serum-derived EVs from platinum-resistant NSCLC patients exhibit elevated Circ0014235 and miR-425-3p. Circ0014235 promotes cisplatin resistance via the miR-520a-5p/CDK4 axis,[77] while c-Myc transcriptionally activates miR-425-3p, which induces autophagy-mediated resistance by targeting AKT1.[78] Similarly, plasma exosomal miR-92b-3p is upregulated in SCLC patients and enhances chemoresistance by suppressing PTEN to activate the AKT pathway.[79] Notably, CAF-derived exosomal miR-20a promotes NSCLC cisplatin resistance by inhibiting PTEN and activating PI3K/AKT signaling.[52] Additionally, M2 macrophage-derived exosomal miR-3679-5p stabilizes c-Myc by targeting NEDD4L, enhancing aerobic glycolysis and cisplatin resistance.[80]

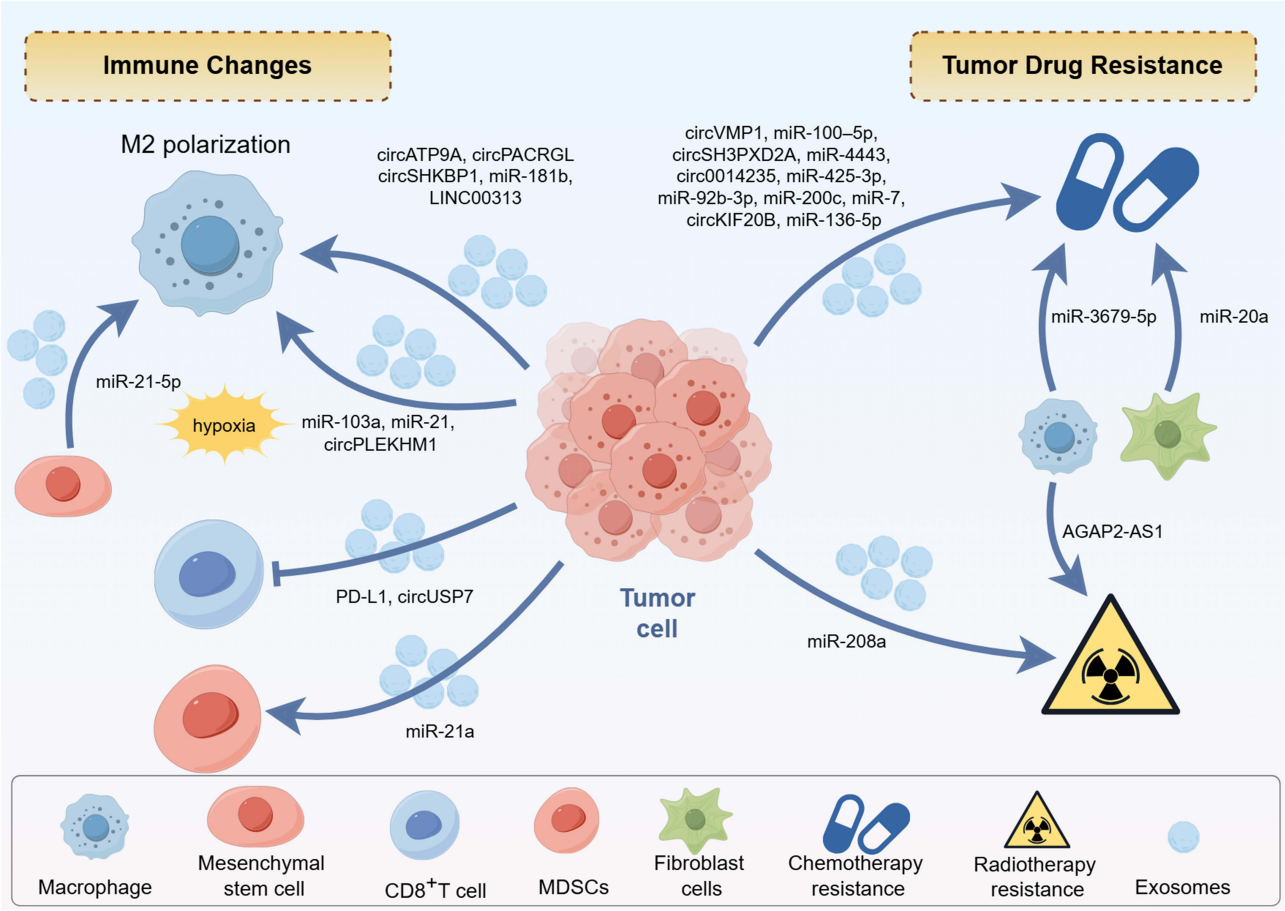

Figure 3 EVs-ncRNA regulate the immune microenvironment and drug resistance mechanisms in lung cancer. This figure highlights the roles of EVs-ncRNAs in immune regulation and therapy resistance in lung cancer. Tumor cell-derived EVs-ncRNAs can induce macrophage polarization toward the M2 phenotype and modulate the behavior of $CD8^+$ T cells, MDSCs, and fibroblasts, thereby contributing to immune suppression and tumor immune evasion. Specific ncRNAs—such as circATP9A and circSH3PXD2A—participate in immune regulation. In addition, EVs-ncRNAs (eg, miR-3679-5p, AGAP2-AS1) can mediate resistance to chemotherapy and radiotherapy, promoting tumor cell survival and malignant progression.

Gefitinib, a first-generation EGFR-TKI, is a frontline therapy for EGFR-mutant NSCLC. Comparative EV miRNA profiling between EGFR-mutant PC9 cells and wild-type CL1-5 cells identified the miR-200 family (particularly miR-200a and miR-200c) as enriched in gefitinib-sensitive plasma EVs. Exosomal miR-200c sensitizes cells to gefitinib by suppressing STAT3/AKT phosphorylation, inhibiting EMT, and activating caspase-3/9-dependent apoptosis.[81] Conversely, exosomal miR-7 from PC9 cells reverses gefitinib resistance by binding YAP.[82] Clinically, low serum exosomal CircKIF20B correlates with gefitinib resistance; CircKIF20B sponges miR-615-3p to upregulate MEF2A, restoring gefitinib sensitivity by modulating apoptosis and mitochondrial OXPHOS.[83] Furthermore, plasma exosomal miR-136-5p from anlotinib-resistant NSCLC cells activates AKT via PPP2R2A suppression, driving cell proliferation and resistance[84] (Figure 3).

EVs-ncRNA in Resistance to Other Therapies

Radiotherapy employs high-energy radiation to damage tumor DNA and induce apoptosis. Post-radiotherapy serum profiling revealed elevated miR-208a, which is transferred via exosomes to promote radioresistance by targeting p21 and activating AKT/mTOR signaling.[85] Additionally, M2 macrophage-derived exosomal AGAP2-AS1 enhances radioresistance by downregulating miR-296 and upregulating NOTCH2[86] (Figure 3).

In summary, EVs-ncRNA mediate therapy resistance in lung cancer through multifaceted mechanisms: (1) Epigenetic regulation: acting as miRNA sponges (eg, circVMP1/miR-524-5p-METTL3 axis) or modulating m6A modifications (eg, miR-4443-METTL3/FSP1 axis) to drive drug resistance-associated gene expression; (2) Signaling pathway dysregulation: disrupting PTEN/PI3K/AKT, Hippo/YAP, and apoptosis/autophagy pathways (eg, miR-92b-3p/20a/136-5p targeting

the PTEN-PPP2R2A-AKT hub, circSH3PXD2A sponging miR-375-3p to activate YAP1) to promote cell survival and therapeutic evasion; (3) Tumor microenvironment remodeling: EVs-ncRNA from stromal cells (eg, CAF-derived miR-20a, M2 macrophage-delivered AGAP2-AS1/miR-296-NOTCH2 axis) enhance adaptive resistance by reprogramming the immunosuppressive niche; (4) Intercellular propagation: horizontal transmission of resistance phenotypes via EVs (eg, circ0014235/miR-520a-5p-CDK4 axis, miR-7-YAP crosstalk) from resistant to sensitive cells; (5) Metabolic reprogramming: sustaining aerobic glycolysis and energy metabolism (eg, miR-3679-5p-NEDD4L-c-Myc axis) to fuel therapeutic resilience. Collectively, these mechanisms position EVs-ncRNA as central orchestrators of drug resistance in lung cancer, establishing a theoretical foundation for developing targeted delivery systems and combination therapies to overcome therapeutic failure.

EVs-ncRNA-Mediated Remodeling of the Tumor Immune Microenvironment

In lung cancer, EVs-ncRNA secreted by tumor cells or stromal components are internalized by immune cells, reprogramming their functionality and phenotypic states. This process drives immunosuppressive microenvironmental alterations—such as M2 macrophage polarization and $CD8^+$ T cell exhaustion—that collectively foster tumor progression.

Macrophage Polarization

NSCLC-derived EVs-ncRNA orchestrate macrophage M2 polarization through diverse mechanisms. For instance, circATP9A interacts with the HuR protein in NSCLC cells, forming an RNA-protein complex that upregulates NUCKS1, thereby activating PI3K/AKT/mTOR signaling to enhance tumor progression. Importantly, circATP9A-containing EVs further induce M2 macrophage polarization, though the precise mechanism remains uncharacterized.[87] circPACRGL in exosomes binds IGF2BP2 in THP-1 macrophages, stabilizing YAP1 to dysregulate Hippo signaling and promote M2 polarization.[88] Notably, trans-3,5,4′-trimethoxystilbene suppresses circPACRGL levels in NSCLC, highlighting its therapeutic potential.[88] In vivo, circSHKBP1-enriched exosomes enhance M2 macrophage infiltration into tumors. Co-culture experiments reveal that circSHKBP1 augments glycolysis in THP-1 macrophages, suppressing M1 polarization while favoring M2 differentiation.[48] miR-181b, upregulated in NSCLC serum-derived exosomes, is transferred to macrophages, activating the miR-181b/JAK2/STAT3 axis to reinforce M2 polarization.[89] Exosomal LINC00313 sponges miR-135a-3p, derepressing STAT6 to drive M2 polarization.[90]

Hypoxia, a defining characteristic of the TME in solid malignancies, drives pro-tumorigenic cellular crosstalk through EV-mediated communication.[91] Hypoxic NSCLC cells release EVs enriched with miR-103a, miR-21, and circPLEKHM1, which respectively suppress PTEN/activate AKT-STAT3, downregulate IRF1, and enhance OSMR translation via PABPC1-eIF4G interaction, collectively inducing M2 polarization.[92–94] Hypoxia-primed mesenchymal stem cell EVs deliver miR-21-5p to macrophages, reducing PTEN and activating AKT-STAT3[59] (Figure 3) (Table 3).

T Cell Dysregulation

T lymphocytes play pivotal roles in immune surveillance by recognizing and eliminating abnormal host cells, including infected and malignant cells. Within TME, distinct T cell subsets exhibit divergent immunological functions: $CD8^+$ cytotoxic T lymphocytes (CTLs) serve as primary effector cells in antitumor immunity, directly targeting and lysing neoplastic cells through MHC class I-mediated antigen recognition. $CD4^+$ helper T cells function as immune modulators, mediating their functions through cytokine secretion to orchestrate and modulate the activities of other immune components, thereby amplifying antitumor responses. Regulatory T cells (Tregs) – primarily characterized by the $CD4^+CD25^+Foxp3^+$ phenotype – paradoxically facilitate tumor immune evasion. These immunosuppressive cells constrain effector T cell activation and functionality through multiple mechanisms, creating an immunotolerant niche favorable for tumor progression. The intricate interplay among T cell populations creates a dynamic equilibrium in tumor immunity, where protective immune responses and tumor-promoting immunosuppression coexist. This duality underscores the complexity of developing immunotherapeutic strategies that must simultaneously enhance effector functions while mitigating regulatory suppression.[99–101] In NSCLC: circ-CPA4 acts as a sponge for let-7 miRNAs, upregulating PD-L1 to promote tumor growth, migration, EMT, and cisplatin resistance. $PD\text{-}L1^+$ exosomes from NSCLC cells impair $CD8^+$ T cell cytotoxicity in co-culture systems, enhancing immune evasion.[95] circUSP7 suppresses IFN-γ,

Table 3 EVs-ncRNA-Mediated Remodeling of the Tumor Immune Microenvironment

Immune Component	EVs-ncRNA	Key Mechanism	Impact on Immune Microenvironment	References
Macrophage Polarization	circATP9A	Mechanism unclear	Promotes M2 polarization, tumor progression	[87]
	circPACRGL	Binds IGF2BP2 to stabilize YAP1 and activate Hippo signaling	Promotes M2 polarization	[88]
	circSHKBP1	Enhances glycolysis in macrophages; inhibits M1 polarization	Enhances M2 infiltration, suppresses M1 polarization	[48]
	miR-181b	Activates JAK2/STAT3 axis via exosomal transfer	Promotes M2 polarization	[89]
	LINC00313	Sponges miR-135a-3p to upregulate STAT6	Promotes M2 polarization	[90]
	miR-103a	Reduces PTEN → activates AKT/STAT3	Promotes M2 polarization and metastasis	[92]
	miR-21	Targets IRF1 to suppress its expression	Promotes M2 polarization	[93]
	circPLEKHM1	Promotes OSMR translation via PABPC1-eIF4G interaction	Promotes M2 polarization and metastasis	[94]
	miR-21-5p (BMSC)	Downregulates PTEN → activates AKT/STAT3	Promotes M2 polarization	[59]
T cell Dysfunction	circ-CPA4	Sponges let-7 miRNA → upregulates PD-L1	Suppresses CD8+ T cell cytotoxicity; promotes EMT	[95]
	circUSP7	Sponges miR-934 → upregulates SHP2	Inhibits IFN-γ/TNF-α secretion; induces anti-PD1 resistance	[96]
	miR-3200-3p	Targets DDB1 → activates DCAF1/GSTP1 → induces ROS-dependent Treg senescence	Paradoxically promotes tumor growth via VEGFR2 override	[97]
MDSC Expansion	miR-21a	Suppresses PDCD4 → activates IL-6/STAT3	Expands MDSCs; enhances tumor growth	[98]

TNF-α, granzyme B, and perforin production in $CD8^+$ T cells by sequestering miR-934, thereby upregulating SHP2 and conferring anti-PD1 resistance.[96] miR-3200-3p in NSCLC EVs targets DDB1, inhibiting DCAF1/GSTP1 to induce ROS-mediated Treg senescence. However, NSCLC-expressed VEGFR2 counteracts this effect, sustaining Treg activity to fuel progression[97] (Figure 3) (Table 3).

Myeloid-Derived Suppressor Cells (MDSCs)

Lewis lung carcinoma-derived exosomes deliver miR-21a to myeloid cells, suppressing PDCD4 and driving IL-6/STAT3-mediated MDSC expansion. Depleting exosomal miR-21a or overexpressing PDCD4 reverses this protumorigenic effect. Human NSCLC exosomes similarly induce monocyte-to-MDSC differentiation in vitro[98] (Figure 3) (Table 3).

EVs-ncRNA significantly impact tumor progression by remodeling the lung cancer immune microenvironment. Future research should prioritize the following directions: (1) Investigating how EVs-ncRNA derived from lung cancer cells or stromal cells regulate diverse immune cell populations within the TME. (2) Exploring functional heterogeneity of ncRNAs across distinct EV subpopulations (eg, exosomes, microvesicles). (3) Deciphering dynamic regulatory networks mediated by ncRNAs among immune cells, tumor cells, and stromal cells. (4) Integrating single-cell spatiotemporal omics with multi-omics technologies to resolve microenvironmental heterogeneity and temporal evolution, offering novel insights into immunotherapy resistance mechanisms. (5) Elucidating mechanisms underlying immune cell-specific uptake of lung cancer EVs by analyzing interactions between EV "molecular barcodes" (eg, integrins, PD-L1, glycosylation patterns) and immune cell receptors. These insights will provide transformative perspectives for developing precision immunotherapies in lung cancer.

EVs-ncRNA in Lung Cancer: Clinical Applications

EVs-ncRNA demonstrate multidimensional clinical potential in lung cancer diagnosis and treatment. As liquid biopsy biomarkers in diagnostics, the vesicular encapsulation of these RNAs preserves molecular integrity, enabling reliable detection of cancer-specific miRNA, lncRNA, and circRNA expression profiles in blood or bronchoalveolar lavage fluid. This approach facilitates non-invasive early-stage screening, with subclinical lesion identification preceding conventional imaging modalities. In pathological staging, EVs-ncRNA levels dynamically mirror TME evolution, exhibiting strong correlations with metastatic aggressiveness. For prognostic evaluation, EV-encapsulated ncRNAs serve as independent prognostic factors for overall survival, reflecting chemotherapy resistance patterns and metastatic potential. Therapeutically, EVs-ncRNA possess dual utility as both molecular targets and drug delivery vectors, pioneering novel paradigms for personalized treatment.

EVs-ncRNA as Biomarkers in Lung Cancer Management

Current research evaluating EVs-ncRNA biomarkers follows a tiered framework: Level 1: Investigations solely utilizing in vitro cell experiments to explore candidate biomarkers. Level 2: Validation studies combining cellular models with clinical samples (tissues/plasma). Level 3: Clinically oriented approaches employing plasma/EV-derived sequencing data, corroborated by experimental models. The third-tier methodology currently represents the most clinically translational strategy for biomarker development. With advancing technologies, novel high-throughput platforms are anticipated to further refine biomarker discovery pipelines. This section additionally synthesizes optimized protocols for EV isolation (eg, differential ultracentrifugation, size-exclusion chromatography, microfluidics) and ncRNA detection methodologies (next-generation sequencing, digital PCR, nanostring profiling), emphasizing standardization challenges in clinical implementation.

EVs-ncRNA as Diagnostic Biomarkers for Lung Cancer

The investigation of EVs-miRNAs constitutes the predominant focus in this research domain. We present a chronological synthesis of studies identifying distinct EV-associated miRNAs through varied stratification approaches. In 2013, Cazzoli et al pioneered the use of circulating exosomal miRNAs as noninvasive biomarkers, developing a two-step plasma assay for lung cancer screening.[102] Their study employed qRT-PCR to profile 742 miRNAs across 30 training and 105 validation samples, identifying a 4-miRNA panel (miR-378a, miR-379, miR-139-5p, and miR-200b-5p) that distinguished pulmonary nodules (adenocarcinomas/granulomas) from healthy smokers with 97.5% sensitivity and 72% specificity (AUC=0.908). A subsequent 6-miRNA diagnostic subpanel differentiated malignant from benign nodules (76% AUC). The 2017 Jin cohort systematically identified stage I NSCLC-specific miRNAs through sequencing of 46 patients and 42 controls.[103] Eleven upregulated and thirteen downregulated miRNAs characterized LUAD, while LSCC exhibited six upregulated and eight downregulated species. Validated biomarkers included miR-181-5p/miR-30a-3p (LUAD-specific) and miR-10b-5p/miR-15b-5p (LSCC-specific), achieving AUCs of 0.936 and 0.911, respectively. Key NSCLC-associated miRNAs (let-7 family, miR-21, miR-24) corroborated sequencing reliability. Yang et al (2021) demonstrated multiclass discriminatory capacity of EV-miRNAs across NSCLC subgroups.[104] Combinatorial biomarkers attained exceptional performance: miR-205-5p/miR-199a-5p discriminated NSCLC from nonsmokers (AUC=0.993), while miR-497-5p/miR-22-5p distinguished NSCLC from smokers (AUC=0.953). For COPD-NSCLC differentiation, miR-27a-3p combined with miR-106b-3p/miR-361-5p yielded AUC=0.870. Recent studies emphasize ultrasensitive detection. Zheng et al (2022) developed the CirsEV-miR model using five plasma sEV miRNAs (eg, miR-101-3p, miR-150-5p), achieving AUC=0.920 in training cohorts while maintaining diagnostic efficacy for ≤1 cm nodules.[105] Zhang et al (2023) identified exosomal miR-1290 (upregulated) and miR-29c-3p (downregulated) with pooled AUC=0.947 for early detection, outperforming CEA and demonstrating NSCLC-SCLC discriminative capacity (AUC=0.810–0.842).[106]

EV-lncRNA biomarkers show comparable potential. In 2019, Li et al investigated the potential of tumor-derived exosomal lncRNA GAS5 (Exo-GAS5) as a diagnostic biomarker for early-stage NSCLC.[107] Their study revealed significant downregulation of serum Exo-GAS5 in NSCLC patients compared with healthy controls, showing negative correlations with tumor size and TNM staging. The combination of Exo-GAS5 with carcinoembryonic antigen (CEA)

achieved an AUC of 0.929 in ROC curve analysis, while Exo-GAS5 alone demonstrated an AUC of 0.822 for distinguishing stage I NSCLC patients. Building on this methodology, Tao et al (2020) identified elevated expression of TBILA and AGAP2-AS1 in serum exosomes from NSCLC patients, with positive correlations observed between these lncRNAs and tumor progression parameters including tumor size, lymph node metastasis, and TNM stage.[108] Both TBILA and AGAP2-AS1 exhibited robust diagnostic performance across histological subtypes and early-stage NSCLC when used individually. The diagnostic accuracy was further enhanced through combined analysis with the serum tumor marker Cyfra21-1. Advancing the technical landscape, Pedraz-Valdunciel et al (2022) optimized methodologies for plasma exosomal circRNA analysis using the nCounter platform, identifying eight upregulated circRNAs in NSCLC patients.[109] Through machine learning algorithms, they established a 10-circRNA signature capable of distinguishing lung cancer from controls with an AUC of 0.86, thereby validating the platform's feasibility for multiplexed circRNA profiling in clinical samples. Most recently, Zhu et al (2023) characterized the diagnostic utility of exosomal circHIPK3 in lung cancer, demonstrating its significant upregulation in patient plasma alongside concurrent downregulation of miR-637.[110] The circHIPK3 biomarker achieved an AUC of 0.897 in diagnostic ROC analysis, while mechanistic investigations suggested functional involvement of the circHIPK3/miR-637 axis in lung carcinogenesis (Table 4).

Table 4 EVs-ncRNAs as Diagnostic Biomarkers for Lung Cancer

Types of EVs-ncRNAs	Types of Body Fluids	Methods for Extracting EVs-ncRNAs	Screening Methods	Diagnostic Markers	References
miRNA	Plasma	ExoRNeasy	Quantitative RT-PCR	Early diagnosis: (miR-378a, miR-379, miR-139-5p and miR-200b-5p) Lung adenocarcinoma and granuloma (miR-151a-5p, miR-30a-3p, miR-200b-5p, miR-629, miR-100 and miR-154-3p)	[102]
miRNA	Plasma	Ultrafiltration method, magnetic beads and mirVana reagent kit	miRNA sequencing and quantitative RT-PCR	LUAD: (miR-181-5p, miR-30a-3p, miR-30e-3p and miR-361-5p) LSCC: (miR-10b-5p, miR-15b-5p and miR-320b)	[103]
miRNA	Serum	Total Exosome RNA & Protein Isolation Kit	Quantitative RT-PCR	NSCLC: (miR-23a and miR-let7i)	[111]
miRNA	Plasma	miRCURY Exosome Serum/Plasma Kit and miRNeasy Mini Kit	Quantitative RT-PCR	NSCLC and healthy non-smokers: (miR-205-5p and miR-199a-5p) NSCLC and healthy smokers: (miR-497-5p and miR-22-5p) NSCLC and stable COPD participants: (miR-27a-3p, miR-106b-3p and miR-361-5p)	[104]
miRNA	Plasma	Polyethylene glycol-based 3D Medicine isolation reagent and miRNeasy	miRNA sequencing and quantitative RT-PCR	Distinguish between benign and malignant nodules: (let-7b-3p, miR-101-3p, miR-125b-5p, miR-150-5p and miR-3168)	[105]
miRNA	Plasma	Ultracentrifugation and TRIzol LS Reagent	miRNA sequencing and quantitative RT-PCR	Diagnosis of early lung cancer and differentiation between NSCLC and SCLC: (miR-1290 and miR-29c-3p)	[106]

(*Continued*)

Table 4 (Continued).

Types of EVs-ncRNAs	Types of Body Fluids	Methods for Extracting EVs-ncRNAs	Screening Methods	Diagnostic Markers	References
circRNA	Plasma	Polyethylene glycol (PEG) precipitation method and TRIzol LS Reagent	Quantitative RT-PCR	Lung Cancer: Circ HIPK3	[110]
circRNA	Plasma	Ultracentrifugation or the miRCURY Exosome Serum/Plasma Kit and TRIzol LS Reagent	nCounter	NSCLC: (circFAM13B, circADAM22, circUBXN7, circZCCHC6, circITGAX, circRDH11, circEPB41L2, circCLK1, circFARSA, circPIK3R1)	[109]
LncRNA	Serum	Exosome Kit and TRIzol LS Reagent	Quantitative RT-PCR	NSCLC: lncRNA GAS5	[107]
LncRNA	Serum	Exosome Kit and TRIzol LS Reagent	Quantitative RT-PCR	NSCLC: lncRNA TBILA and AGAP2-AS1	[108]

EVs-ncRNA as Prognostic Markers in Lung Cancer

Early investigations predominantly focused on plasma vesicle-associated miRNA profiling. In 2011, Silva et al employed TaqMan low-density array technology to analyze vesicle-bound miRNAs in NSCLC patient plasma, identifying significant downregulation of let-7f, miR-20b, and miR-30e-3p.[112] Notably, let-7f and miR-30e-3p levels demonstrated discriminative capacity across disease stages and correlated with disease-free survival (DFS) and overall survival (OS). Subsequent studies explored specific EV-miRNA functional roles and clinical relevance. Shu et al (2018) revealed through deep sequencing and qRT-PCR validation that elevated exosomal miR-425-3p associates with platinum-based chemotherapy resistance and shortened progression-free survival (PFS) in NSCLC patients.[113] Mechanistically, miR-425-3p enhances autophagy via AKT1 targeting, correlating with reduced treatment responsiveness in tumor tissues. Peng et al (2020) investigated plasma exosomal miRNA profiles in EGFR/ALK-negative advanced NSCLC patients undergoing immune checkpoint inhibitor therapy, identifying significant upregulation of hsa-miR-320d, hsa-miR-320c, and hsa-miR-320b in progressive disease cohorts, suggesting their predictive potential for immunotherapy response.[114] Concurrent downregulation of T-cell suppressor hsa-miR-125b-5p during treatment correlated with enhanced T-cell functionality and improved clinical outcomes. Han et al (2021) further identified EV-derived HOTTIP as a recurrence predictor in surgically treated NSCLC patients.[115] Song et al demonstrated EV-associated miR-184 and miR-3913 involvement in osimertinib resistance mechanisms, providing novel insights into therapeutic resistance management.[116] Recent advancements by Sanchez-Cabrero et al (2023) linked plasma miR-124 levels with early-stage NSCLC recurrence and mortality, potentially mediated through KPNA4 and SPOCK1 interactions.[117] Petracci et al found that combined analysis of cell-free and EV-derived miRNAs significantly enhanced prognostic performance compared to single-source analyses, identifying TGF-β/SMAD, NOTCH, and PI3K pathway-associated miRNA signatures.[118] Serrano et al reported elevated baseline EV miR-30c levels correlating with prolonged recurrence-free survival (RFS) and OS in locally advanced NSCLC patients undergoing chemoradiotherapy.[119] Experimental validation confirmed miR-30c delivery via direct transfection or EV encapsulation suppressed cellular autophagy. These collective findings underscore the emerging potential of EVs-ncRNA in NSCLC prognosis, though large-scale multicenter validation and mechanistic investigations remain imperative.

Therapeutic Applications of EVs-ncRNA in Lung Cancer

EVs-ncRNA demonstrate unique translational advantages as novel therapeutic carriers in lung cancer management. Xu et al developed a folate-modified milk-derived exosome delivery system that effectively reverses EGFR-TKI resistance through targeted delivery of c-Kit siRNA, mediated by mTOR pathway suppression and cancer stem cell regulation.[120]

This natural vesicle-based strategy overcomes immunogenicity limitations of synthetic nanoparticles while enhancing tumor-specific accumulation via folate receptor-mediated active targeting. In addressing multidrug resistance, Huang et al pioneered the use of kiwifruit-derived cationic-free vesicles as siRNA carriers, leveraging their intrinsic surface properties for EGFR-specific binding to inhibit T790M mutation-driven resistance pathways in vitro models.[121] Compared with synthetic vectors, these plant-derived vesicles exhibit superior biocompatibility and transmembrane transport efficiency, offering novel perspectives for oral gene therapeutics. Critical advancements in production scalability have been achieved by Kim et al, who established an acoustic shock wave-induced loading technology enabling efficient packaging of KRASG12C mutation-specific siRNA into exosomes, generating 10^12 particles per treatment cycle to overcome industrial-scale manufacturing challenges.[122] For metastatic disease management, Wang et al designed a lung-tropic miRNA-126 delivery system mimicking native exosomal homing properties, demonstrating 68% reduction in pulmonary metastases through dual modulation of VEGF/VEGFR2 signaling axis in vivo.[123] This organotropic vector minimizes off-target effects associated with systemic administration, providing precision solutions for metastatic lung cancer. Microenvironment modulation strategies employing miRNA-497-engineered exosomes exhibit synergistic anti-angiogenic effects in 3D microfluidic models through simultaneous targeting of tumor cells and vascular endothelial cells.[124] EVs have emerged as versatile platforms for tumor-targeted therapy by delivering photothermal agents or photosensitizers to achieve precise tumor accumulation, followed by localized activation of photothermal therapy (PTT) or photodynamic therapy (PDT) under laser irradiation at specific wavelengths. For instance, a recent study demonstrated that near-infrared radiation could induce tumor cells to secrete HSP70-overexpressing EVs decorated with tellurium nanoparticles (Te@EVsHSP70), which not only mediated tumor ablation via PTT but also enhanced antigen cross-presentation and dendritic cell maturation, thereby synergizing photothermal and immune-activating effects.[125] Simultaneously, EVs have been utilized in green synthesis strategies to develop multifunctional nanocomposites, such as popcorn-like gold nanostructures loaded with doxorubicin (EV-Au-DOX). These platforms leverage near-infrared-triggered photothermal effects and controlled drug release to achieve a tumor suppression rate of up to 98.6% while minimizing systemic toxicity.[126] Furthermore, to address challenges in tumor-specific accumulation of small-molecule photothermal agents, researchers engineered CDH17 nanobody-functionalized EVs (CR@E8-EVs) to deliver cresyl violet (CR) dye. These engineered EVs enabled precise tumor-targeted delivery guided by photoacoustic imaging and robust photothermal conversion for effective tumor growth inhibition.[127] Collectively, these advancements highlight how EV-based smart delivery systems overcome limitations of conventional therapies, paving the way for integrated photothermal-chemotherapy, immunomodulation, and theranostic applications in precision oncology.

The multi-target action mechanism effectively counteracts adaptive resistance arising from tumor evolution. Despite these advancements, clinical translation requires resolution of critical challenges including carrier standardization and pharmacokinetic optimization. Current evidence reveals substantial heterogeneity in exosomes derived from different individuals, necessitating establishment of standardized quality assessment protocols as a prerequisite for clinical implementation. Future directions should emphasize intelligent vector design, multi-omics-guided personalized regimens, and exosome-based treatment monitoring technologies to accelerate the transition of EVs-ncRNA therapies from preclinical research to clinical practice.

Advances in EVs-ncRNA Detection Technologies for Lung Cancer

Recent years have witnessed diversified technological developments in EVs-ncRNA as liquid biopsy biomarkers for lung cancer. A digital microfluidics-based workstation integrating RT-qPCR achieved "sample-to-answer" detection of EVs-miRNAs, with optimized droplet manipulation algorithms enhancing sensitivity for miR-486-5p and miR-21-5p to clinically applicable levels, demonstrating an AUC of 0.89 in ROC curve analysis.[128] To improve throughput, researchers developed a quadruple supramolecular dendrimer-zirconium metal-organic framework biosensor coupled with engineered erythrocytes, enabling EV enrichment within 30 minutes and achieving a miR-155 detection limit of 2.03 fM.[129] In surface plasmon resonance imaging, gold-silver heterostructured DNA probes enhanced signal response through multivalent hybridization, allowing simultaneous detection of four NSCLC-associated miRNAs (miR-21, miR-378) with two-order-of-magnitude sensitivity improvement over conventional ELISA.[130] For low-abundance targets, CRISPR-Cas13a nanoprobes combined with thermophoretic accumulation enabled visual detection of A549 exosomal miR-205 at 5×10^6 particles/mL without nucleic acid amplification.[131] Multianalyte detection systems represent a critical breakthrough, exemplified by DNA linker-

metal-organic framework-modified paper platforms performing cascaded signal amplification for concurrent measurement of three lung cancer-related miRNAs (let-7b, miR-21) across six orders of magnitude.[132] Yoon-Bo Shim et al developed a p53 protein-hydrazine bioconjugate-based exosomal miRNA array sensor specifically detecting lung cancer, validating the clinical relevance of exosomal miRNA-21, miRNA-155, miRNA-205, and let-7b in recurrence monitoring, progression-free survival prediction, and diagnosis.[133] Absolute quantification advancements include multicolor fluorescent chip-based digital PCR utilizing droplet partitioning for EV-lncRNA enumeration, significantly improving sensitivity and precision in molecular diagnostics.[134] Integrated detection systems combining EV isolation with nucleic acid analysis achieved synchronous EGFR protein and miR-21 detection through aptamer-modified magnetic beads, enhancing early-stage diagnosis specificity to 87%.[135] Preprocessing innovations substantially improved sensitivity: ultracentrifugation-size exclusion chromatography hybrid protocols enabled efficient EV recovery from 0.5 mL plasma, tripling miRNA detection efficiency via membrane fusion probes.[136] Engineered erythrocyte-based isolation strategies minimized genomic DNA contamination through anucleate cell utilization,[129] while exhaled breath condensate EV capture technology provided novel respiratory tract-derived specimens for local microenvironment studies.[136]

Current technological advancements manifest two predominant trends: 1) deep integration of micro/nanofabrication with molecular probes, exemplified by 40% reduction in detection time through coordinated optimization of digital microfluidics and rapid PCR reagents;[128] 2) simultaneous profiling of tumor-derived exosomal protein-miRNA pairs to enhance diagnostic efficiency and accuracy.[137] Future development priorities include standardization of detection protocols, optimization of trace sample processing, and creation of cross-platform data integration models to accelerate clinical translation of EVs-ncRNA detection technologies.

Summary and Outlooks

This study comprehensively summarizes the molecular mechanisms and clinical implications of EVs-ncRNA in the initiation, progression, and therapeutic resistance of lung cancer. Key findings include: EVs selectively package oncogenic or tumor-suppressive ncRNAs through sorting mechanisms such as SUMOylation of hnRNPA2B1 and methylation of YBX1, thereby regulating critical pathways (eg, Wnt/EGFR) and remodeling the TME (eg, promoting M2 macrophage polarization and CD8+ T cell exhaustion). Clinically, multi-ncRNA diagnostic models (eg, EVs-miR-21 and EVs-miR-1290) demonstrate high diagnostic accuracy (AUC > 0.9), while EVs-circTLCD4-RWDD3 is strongly associated with lymph node metastasis. Therapeutically, engineered EVs delivering siRNA or tumor-suppressive miRNAs (eg, folate-modified carriers reducing drug resistance by 60%) and strategies targeting EVs-ncRNA sorting pathways (eg, Rab27a inhibition) show promise in blocking metastatic signaling.

However, translating these discoveries into clinical practice faces significant challenges. First, the heterogeneity of EVs and the functional complexity of their ncRNA cargo limit reproducibility. For instance, distinct EV subpopulations (exosomes, microvesicles) exhibit marked differences in ncRNA content and activity, and individual EVs may simultaneously harbor pro- and anti-tumor components, complicating standardized detection and therapeutic targeting. Second, scalable manufacturing and quality control remain critical bottlenecks for engineered EV therapies. Current isolation methods (eg, ultracentrifugation) suffer from low efficiency and batch-to-batch variability, while synthetic EV production struggles with high costs and inconsistent drug-loading efficiency. Furthermore, regulatory pathways for EVs-ncRNA diagnostics and therapeutics remain undefined. Key hurdles include the absence of unified potency criteria (eg, ncRNA copy number thresholds per EV), insufficient long-term safety data (eg, immunogenicity and off-target effects of engineered EVs), and unclarified synergistic mechanisms with conventional therapies (chemotherapy, immunotherapy).

Future advancements demand multidisciplinary collaboration. Single-EV sequencing integrated with spatial multi-omics could unravel ncRNA interaction networks. Technological innovations such as microfluidic EV sorting and cell-free synthetic platforms may enhance production scalability, while surface modifications (eg, PD-L1 antibody conjugation) could improve tumor-targeting precision. Establishing globally recognized EVs-ncRNA detection standards and regulatory frameworks will accelerate clinical translation, enabling early-phase trials for SUMOylation inhibitors and EVs-siRNA combination strategies. Although EVs-ncRNA research is reshaping lung cancer management, overcoming the intertwined challenges of heterogeneity, standardization, and regulatory alignment remains essential to bridge the gap between mechanistic discovery and precision intervention.

Abbreviations

EVs, Extracellular vesicles; TME, tumor microenvironment; ncRNA, non-coding RNA; CAFs, Cancer-associated fibroblasts; TAMs, Tumor-associated macrophages; BMSCs, Bone marrow-derived mesenchymal stem cells; IARC, International Agency for Research on Cancer; NSCLC, Non-small cell lung cancer; MVB, Multivesicular body; miRNAs, MicroRNAs; lncRNAs. Long non-coding RNAs; circRNAs, Circular RNAs; ESCRT, Endosomal Sorting Complex Required for Transport; ceRNAs, endogenous RNAs; IRES, internal ribosome entry sites; pri-miRNAs, primary miRNA transcripts; pre-miRNAs, precursor miRNAs; 3'UTRs, 3' untranslated regions; RBPs, RNA-binding proteins; SCLC, small cell lung cancer; sEV, small EV; BBB, blood–brain barrier; α-SMA, α-smooth muscle actin; NAF, normal fibroblast; LFs, lung fibroblasts; IPF, idiopathic pulmonary fibrosis; CSCs, Cancer stem cells; SCs, Schwann cells; CTLs, Cytotoxic T Lymphocytes; Tregs, Regulatory T cells; MDSCs, Myeloid-Derived Suppressor Cells; CEA, carcinoembryonic antigen; DFS, disease-free survival; OS, overall survival; PFS, progression-free survival; RFS, recurrence-free survival; PTT, photothermal therapy; PDT, photodynamic therapy.

Acknowledgments

We extend our gratitude to Figdraw for their assistance with the figures in this paper.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by basic scientific research project of Education Department of Liaoning Province (LJ212410159084).

Disclosure

The authors declare no conflict of interest.

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