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Review Article

# Exosomal LncRNAs and CircRNAs in lung cancer: Emerging regulators and potential therapeutic targets

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ABSTRACT

Lung cancer remains one of the most prevalent and lethal malignancies globally, characterized by high incidence and mortality rates among all cancers. The delayed diagnosis of lung cancer at intermediate to advanced stages frequently leads to suboptimal treatment outcomes. To improve the management of this disease, it is imperative to identify new, highly sensitive prognostic and diagnostic biomarkers. Exosomes, extracellular vesicles with a lipid-bilayer structure and a size range of 30–150 nm, are pivotal in intercellular communication and play significant roles in lung cancer progression. Non-coding RNAs (ncRNAs), including long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs), are highly prevalent within exosomes and play a crucial role in various pathophysiological processes mediated by these extracellular vesicles. Beyond their established functions in miRNA and protein sequestration, these ncRNAs are involved in regulating translation and interactions within exosomes. Numerous studies have highlighted the importance of exosomal lncRNAs and circRNAs in influencing epithelial-mesenchymal transition (EMT), angiogenesis, proliferation, invasion, migration, and metastasis in lung cancer. Due to their unique functional characteristics, these molecules are promising therapeutic targets and biomarkers for diagnosis and prognosis. This review provides a succinct summary of the formation of exosomal lncRNAs and circRNAs, clarifies their biological roles, and thoroughly explains the mechanisms by which they participate in the progression of lung cancer. Finally, we discuss the potential clinical applications and challenges associated with exosomal lncRNAs and circRNAs in lung cancer.

## 1. Introduction

Lung cancer remains a formidable global health challenge, representing one of the most prevalent and lethal malignancies worldwide. With over 2 million new cases and 1.8 million deaths reported in 2020 alone, lung cancer exacts a heavy toll on public health and underscores the urgent need for improved diagnostic and therapeutic strategies [1]. The disease is primarily categorized into two subtypes: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), comprising approximately 15 % and 85 % of cases, respectively [2,3]. In general, risk factors such as smoking, exposure to environmental pollutants, genetic predisposition, and pre-existing lung conditions contribute significantly to the development of lung cancer [4]. Despite advancements in diagnostic modalities, including serum tumor marker detection and low-dose computed tomography (LDCT), and therapeutic options spanning surgery, radiotherapy, chemotherapy, and targeted molecular therapies, the prognosis for lung cancer remains dismal, with limited improvements in patient survival rates and quality of life [3,5,6]. Consequently, there is an urgent need to investigate and develop innovative avenues for both diagnosis and treatment.

The emergence of extracellular vesicles (EVs), particularly exosomes, as pivotal mediators of intercellular communication, has garnered significant attention in the field of cancer research. Exosomes, one subtype of EVs and ranging in size from 30 to 150 nm, are nanosized membrane-bound vesicles released by cells into the extracellular environment [7–9]. These vesicles encapsulate a diverse array of bioactive molecules, including proteins, lipids, metabolites, and various nucleic acids, such as DNA, mRNAs, miRNAs, lncRNAs, and circRNAs. Notably, exosomes serve as vehicles for the transfer of these cargos between cells, facilitating the modulation of gene expression and biological activities in recipient cells [10–12]. Moreover, exosomes possess the ability to disseminate signals via bodily fluids, thereby influencing distant sites from the primary tumor and playing crucial roles in cancer metastasis and progression.

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Among the diverse cargo components of exosomes, lncRNAs and circRNAs have emerged as key players in cancer pathogenesis and progression. LncRNAs, exceeding 200 nucleotides in length, lack protein-coding capacity but exert regulatory functions by modulating gene expression at transcriptional, post-transcriptional, and epigenetic levels [13,14]. CircRNAs, characterized by their covalently closed loop structures, exhibit enhanced stability compared to linear RNAs and are involved in diverse cellular processes, including gene regulation, protein interaction, and cell signaling [15,16]. In the context of lung cancer, a growing body of evidence implicates exosomal lncRNAs and circRNAs as critical regulators of tumorigenesis, tumor growth, metastasis, and therapeutic resistance [17–28]. These non-coding RNAs functionally contribute to various hallmarks of cancer, including proliferation, invasion, angiogenesis, immune evasion, and drug resistance. Therefore, elucidating the roles of exosomal lncRNAs and circRNAs in lung cancer holds significant promise for identifying novel diagnostic biomarkers and therapeutic targets.

In this review, we aim to provide a comprehensive overview of the current understanding of exosomal lncRNAs and circRNAs in lung cancer. We will explore their roles as emerging regulators of lung cancer pathogenesis, metastasis, and therapy resistance, and discuss their potential utility in diagnosis and prognosis. By synthesizing existing knowledge in this field, we endeavor to shed light on new avenues for the diagnosis, treatment, and management of lung cancer, ultimately improving patient outcomes and quality of life.

## 2. Exosome dynamics: insights into biogenesis, key components, and diverse biological functions

Exosomes, nanoscale vesicles ranging from 30 to 150 nm, are intricately involved in cellular communication and contribute significantly to various physiological and pathological processes. The intravesicular components include proteins, lipids, DNA, miRNAs, lncRNAs, circRNAs, and other substances. MHC molecules (MHC-I/II), tetraspanins (CD9, CD63, CD81), transmembrane proteins (CD13, LAM1/2, PGRL) and other protein molecules are distributed on the membrane of exosomes (Fig. 1). In this section, we explore the intricate mechanisms underlying exosome biogenesis, highlighting the essential components and diverse biological functions that shape their role in cell-to-cell communication.

### 2.1. Biogenesis of exosomes: A complex journey

Exosomes originate from the inward budding of endosomes, resulting in the formation of multi-vesicular bodies (MVBs) [29,30]. The transformation of early endosomes into late endosomes, referred to as MVBs, sets the stage for exosome formation [31]. While most MVBs merge with lysosomes for degradation, others take an alternative route by fusing with the plasma membrane. This interaction, facilitated by the actin/microtubule cytoskeleton, allows exosomes to release their intraluminal vesicles (ILVs) into the extracellular environment [32]. Exosome biogenesis is a highly regulated process involving two distinct mechanisms: the classical endosomal sorting complex required for transport (ESCRT)-dependent pathway and the non-classical ESCRT-dependent pathways. The former involves over 30 proteins organized into four families (ESCRT-0, –I, –II, –III) and the ATPase VPS4, working synergistically to mediate ILV formation. The latter encompasses the ceramide-dependent sorting complex and the tetraspanin-mediated sorting pathway, featuring CD9, CD63, CD81, and TSPAN8 [33–38] (Fig. 1).

### 2.2. Diversity in Exosome cargo: selective sorting and molecular composition

Exosomes exhibit remarkable heterogeneity owing to the involvement of various molecular substances, cell types, and cellular microenvironments at each stage of biogenesis. Depending on the cellular source, exosome biogenesis, cargo sorting and release occur through ESCRT-dependent or independent pathway. It selectively sorts nucleic acids, including DNA, mRNAs, miRNAs, tRNAs, lncRNAs, and viral RNA [39,40]. The number and type of nucleic acids in exosomes are the result of cells selective sorting. Generally, the complex components of exosomes, encompassing RNAs, lipids, metabolites, cytoplasmic and cell surface proteins, play a pivotal role in cell-to-cell communication.

### 2.3. Biological functions of exosomes: orchestrating cellular responses

Exosomes exert their biological effects through three main mechanisms: activating intracellular signaling pathways in target cells, completing intercellular information exchange via extracellular release

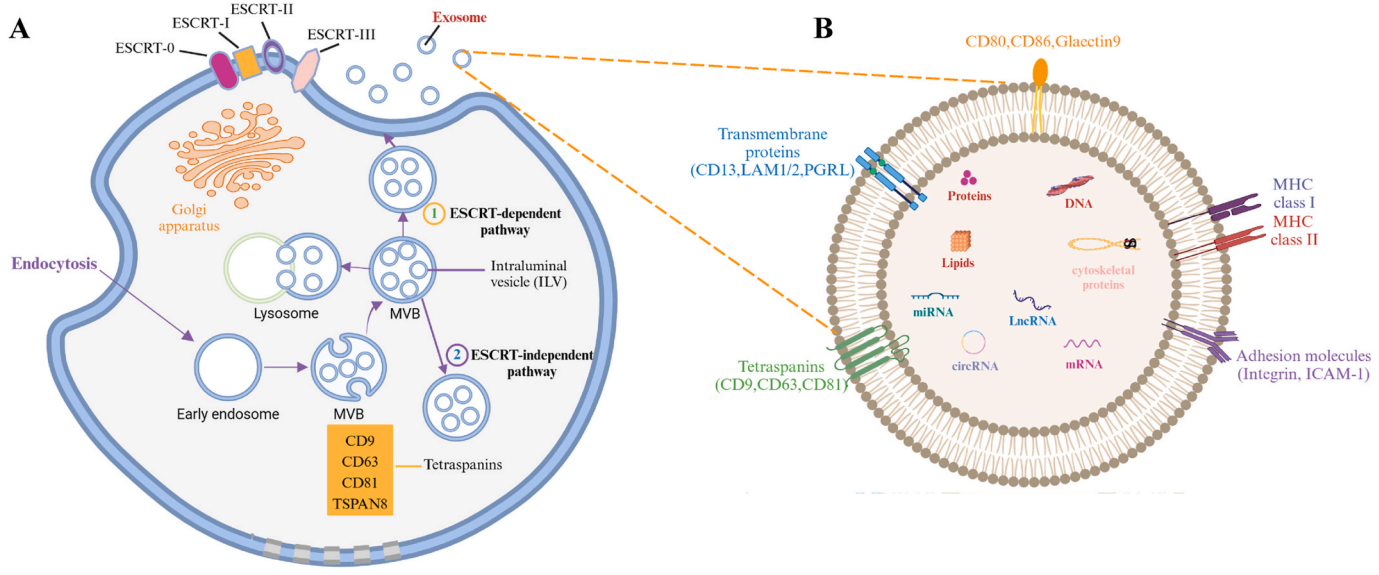


**Fig. 1.** The biogenesis and contents of exosomes. (A) Exosome biogenesis begins with inward depression of cell membrane, followed by the production of early endosome, which matureto form MVBs. Some MVBs develop into lysosomes. ILVs, the vesicles accumulating inside of MVBs, are released as exosomes by the fusion of MVBs with plasma membrane. The biogenesis of exosomes involves both ESCRT-dependent and ESCRT-independent pathways. (B) Exosomes are vesicle-like substances between 30 and 150 nm in diameter. The intravesicular components include proteins, lipids, DNA, miRNAs, lncRNAs, circRNAs, and other substances.

of biologically active components, and facilitating intercellular information exchange at the gene level through membrane fusion [41,42]. They actively contribute to cell differentiation, tumor immune response, tumor cell proliferation, migration, and invasion (Fig. 2) [43].

### *2.4. Clinical implications: exosomes in tumor microenvironment (TME) modulation*

Exosomes, ubiquitously released from various cells, can be found in bodily fluids such as blood, saliva, semen, milk, cerebrospinal fluid, and cell culture media. They play a crucial role in transmitting molecular information through autocrine, paracrine, and endocrine mechanisms [32]. Notably, tumor cell-derived exosomes (TEX) emerge as essential components of the tumor microenvironment (TME), influencing proliferation and migration rates of cancer cells. TEX modulate the TME, thereby affecting cancer cell response to radio- and chemo-therapies. In turn, tumor cells promote tumor progression by regulating the biogenesis, composition, and function of exosomes [11]. The reciprocal regulation between tumor cells and exosomes underscores their significance in tumor progression.

## 3. Insights into the exosomal LncRNAs and CircRNAs

LncRNAs, initially characterized in 2002, represent a class of RNA transcripts exceeding 200 nucleotides in length without protein translation capacity [44,45]. Functioning as pivotal players in diverse biological processes, lncRNAs exert regulatory effects at both transcriptional and post-transcriptional levels. CircRNAs, intricate covalently closed-loop structures comprised of single or multiple exons, primarily emanate from precursor mRNAs expressed by recognized protein-coding genes. These molecules influence transcription and post-translational modulation of parental genes, orchestrating various biological functions [46,47].

Both lncRNAs and circRNAs manifest in liquid biopsies such as blood, urine, and saliva, demonstrating distinctive expression patterns in tissues and cancers [16]. Numerous studies underscore the oncogenic potential of specific lncRNAs and circRNAs, contributing significantly to cancer development by steering cell cycle progression, proliferation, invasion, anti-apoptosis and metastasis [48]. Moreover, exosomal lncRNAs and circRNAs profoundly influence cellular responses to therapy by regulating drug efflux, cell survival pathways, and DNA damage repair mechanisms [49]. Perturbations in the levels or expression patterns of these exosomal transcripts correlate with therapy resistance, substantiating their role as predictive biomarkers and potential therapeutic targets. Strategic targeting of the implicated molecules or pathways promises more efficacious therapeutic strategies [50]. Beyond their diagnostic and therapeutic significance, exosomal lncRNAs and circRNAs emerge as potential drug delivery vehicles, facilitating precise modulation of gene expression by delivering specific lncRNAs or circRNAs to target cells [51].

In summation, exosomal lncRNAs and circRNAs hold promise as potent biomarkers for cancer diagnostic and prognosis, with substantial potential for developing effective therapeutic strategies. Ongoing research and validation are imperative to unravel the functional roles of tumor-specific exosomal lncRNAs and circRNAs in diagnostic and therapeutic tumor mechanisms, paving the way for their therapeutic applications in precision medicine.

### *3.1. Roles and mechanisms of exosomal LncRNAs and CircRNAs in lung cancer*

Mounting evidence underscores the pivotal roles of exosomal lncRNAs and circRNAs in tumor progression, functioning as either oncogenes or suppressors [52,53]. These molecules facilitate key regulatory functions in cell-cell communication within the tumor microenvironment through mechanisms such as fusion, endocytosis, and receptor-mediated specific binding [54]. In lung cancer, exosomal lncRNAs and circRNAs significantly influence growth, invasion,

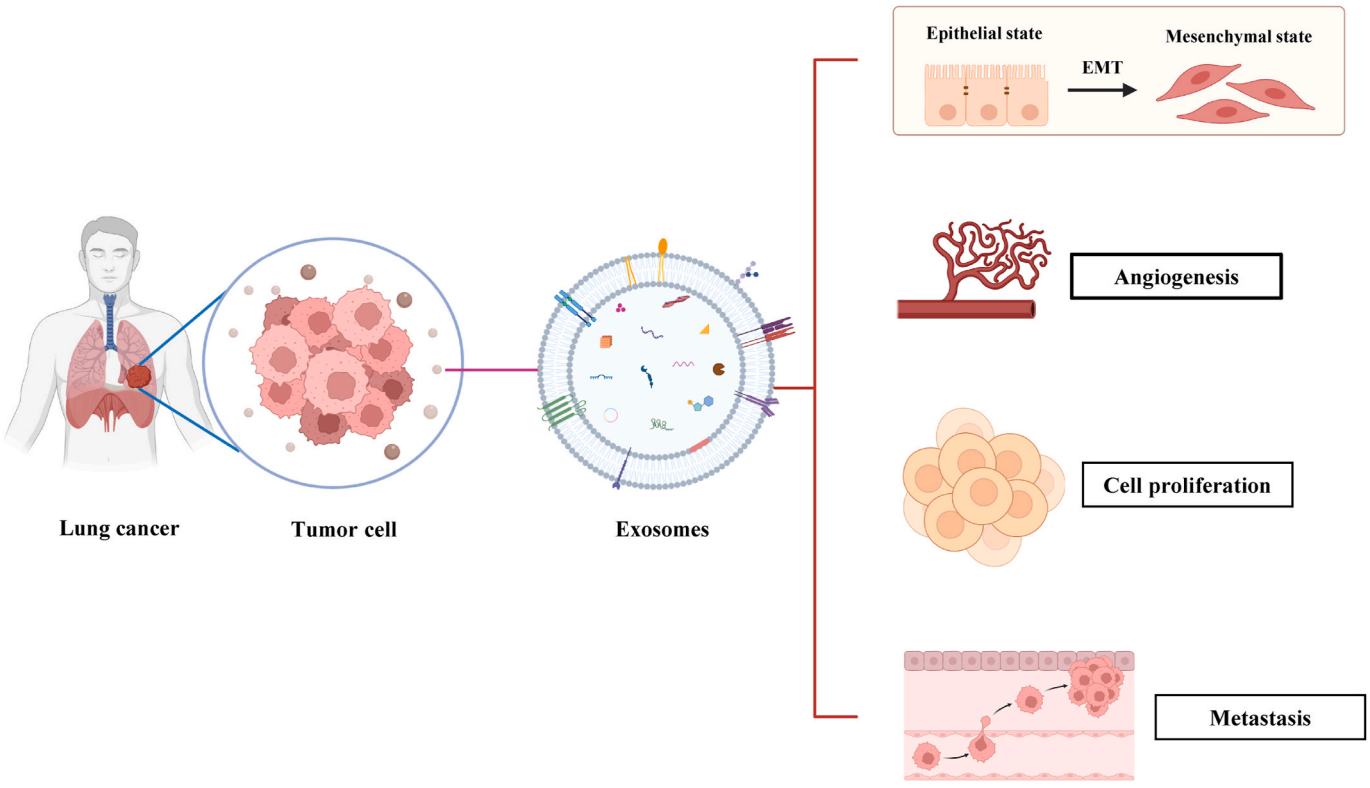


**Fig. 2.** Multiple functions of exosomes stem in the tumor and their contents in lung carcinogenesis. Exosomes derived from lung cancer cells participated in cell proliferation, metastasis, epithelial-mesenchymal transition (EMT), and angiogenesis.

metastasis, and angiogenesis by mediating cell-to-cell interactions and controlling signal transduction pathways [55]. This section focuses on elucidating the roles and mechanisms of exosomal lncRNAs and circRNAs in the pathogenesis and progression of lung cancer.

#### 3.1.1. Roles in proliferation, migration, and invasion

Cell proliferation, a cornerstone of human biological processes, is intricately linked to altered expression or activity of cell cycle-related proteins in lung cancer development [55]. Metastasis, the primary cause of treatment failure in advanced lung cancer, involves the invasion of tumor cells into surrounding tissues and eventual dissemination to distant organs through lymphatic and vascular circulation [56].

Studies reveal differential enrichment of lncRNAs and circRNAs in exosomes, with these exosomal transcripts regulating lung cancer proliferation, migration and invasion by altering the phenotype and function of recipient cells [57]. Notable examples include exosomal lncRNA FOXD3-AS1 promoting lung cancer cell proliferation, invasion and 5-fluorouracil resistance by upregulating ELAVL1 expression and activating the PI3K/Akt pathway [58]. Similarly, exosomal lncRNA LINC00662 and UFC1 accelerate proliferation, migration and invasion in non-small cell lung cancer through miR-320d/E2F1 pathway or binding to EZH2 to inhibit PTEN gene expression, respectively [59,60]. Additionally, exosome-transmitted lncRNA HOTAIR has been shown highly expressed in lung cancer cells, and enhances osteoclast differentiation by targeting TGF-β/PTHrP/RANKL axis [61]. It also promotes lung cancer occurrence and development through sponging miR-203 or regulating transportation [62,63]. Tumor-released exosomal HOTAIRM1 can be delivered to CAFs cells and promote progression of lung adenocarcinoma (LUAD) via regulating the expression of SPON2 [64]. Exosomal lncRNA lnc-MZT2A-5:1, highly expressed in AZD9291-resistant NSCLC cells, still facilitates the activation and migration of MRC-5 cells [65].

Additionally, exosomal circRNAs display aberrant expression patterns in both lung cancer cells and tissues, playing a substantial role in the initiation, development, and progression of lung cancer. Further studies delineate the roles of exosomal circRNAs, such as circVMP1 and circKIF20B, in promoting cell proliferation and invasion in lung cancer. For instance, the transmission of circVMP1 via exosomes has been reported to promote non-small cell lung cancer progression by targeting the miR-524-5p-METTL3/SOX2 axis [66]. Exosome-derived circKIF20B binds to miR-615-3p, thereby regulating MEF2A and influencing the cell cycle, apoptosis, and mitochondrial oxidative phosphorylation (OXPHOS) [67]. These molecular alterations ultimately contribute to increased cell proliferation and invasion in lung cancer. Furthermore, tumor-related exosomal circSHKBP1 acts as a sponge for miR-1294, positively regulating PKM2. The upregulation of PKM2, in turn, enhanced the NSCLC cell proliferation, metastasis, glycolysis and accelerates macrophage polarization and recruitment [68]. These findings underscore the pivotal involvement of exosomal lncRNAs and circRNAs in lung cancer cell proliferation, metastasis, and invasion, revealing their potential as therapeutic targets.

#### 3.1.2. Roles in epithelial-mesenchymal transition (EMT)

Epithelial-mesenchymal transition orchestrates the transformation of epithelial cells into mesenchymal-like cells, acquiring stem cell-like characteristics. This process entails loss of cell polarity and adhesion properties and gain of motility properties, contributing to aggressive tumor cell phenotypes [69,70].

Exosomal lncRNAs and circRNAs emerge as master regulators of gene expression, regulating EMT in lung cancer. Noteworthy examples include lncRNA MALAT-1, modulating EMT through interactions with phosphoinositide 3-kinase (PI3K)/Akt and Wnt/β-catenin pathways. It also behaves like a sponge for microRNAs, preventing their interaction with target genes and promoting EMT [71]. Moreover, lncRNA PCAT6 knockdown has been observed to impede lung cancer cell proliferation, migration, invasion and macrophages M2 polarization. Mechanistically, PCAT6 is upregulated in non-small cell lung cancer. Macrophages M2 polarization is able to promote the metastasis and EMT process of NSCLC cells via regulating PCAT6/miR-326/KLF1 axis. Therefore, knockdown of PCAT6 is able to inhibit EMT process and lung cancer tumorgenesis [72].

Similar to lncRNAs, exosomal circRNAs also exert influence on cancer growth and EMT primarily by modulating the expression of miRNAs [73]. In a specific study, NSCLC cells are transfected with miR-5195-3p mimic to augment miR-5195-3p levels. Subsequent evaluation of epithelial and mesenchymal markers revealed an upregulation in the expression of mesenchymal markers, including N-cadherin, Vimentin, and β-catenin. These results suggest that elevated levels of miR-5195-3p induce EMT in lung cancer cells, with circERBB2IP identified as a sponge for miR-5195-3p [74]. Another investigation highlightes the downregulation of circZNF451 in lung cancer, triggering EMT by forming a complex with TRIM56 and FXR1 [75]. These findings accentuate the crucial involvement of exosomal lncRNAs and circRNAs in EMT induction, providing potential targets for mitigating lung cancer metastasis.

#### 3.1.3. Roles in angiogenesis

Tumor angiogenesis, a pivotal process in tumorigenesis, involves microvascular growth and the establishment of blood circulation orchestrated by tumor cells within the tumor microenvironment. This phenomenon is crucial for tumor progression, infiltration and metastasis [48]. In normal physiology, the delicate balance between pro-angiogenic and angiogenesis-inhibitory factors is disrupted during tumorigenesis, leading to aberrant vascular proliferation. The intricate process of tumor angiogenesis necessitates collaborative efforts between tumor cells, tumor stromal cells, and their secretory elements, including cytokines and extracellular vesicles [76].

Numerous investigations have reported the potential involvement of exosomal lncRNAs and circRNAs in tumor angiogenesis by regulating secreted factors, thereby impacting lung cancer development. For instance, exosomes released by NSCLC cells harbor elevate levels of lncRNA MFI2-AS1. This lncRNA upregulates the expression of NFAT5, a key angiogenesis-related protein in lung cancer, by binding to miR-107. Simultaneously, it inhibits the AKT signaling pathway in Human Umbilical Vein Endothelial Cells (HUVECs), thereby exerting an anti-angiogenic effect. Exosomes enriched with MFI2-AS1 suppress cell proliferation, tube formation, and promote apoptosis in HUVECs, collectively contributing to angiogenesis repression and diminished tumor metastasis [77]. Meanwhile, circ0008717 is observed increased expression in serum exosomes and tumor tissues from lung cancer patients. Functional assays assessing microtubule formation reveals that exosomal circ0008717 induces angiogenesis [78]. These findings elucidate the crucial roles of exosomal lncRNAs and circRNAs in angiogenesis, unveiling potential targets for anti-angiogenic therapy in lung cancer.

#### 3.1.4. Roles in drug resistance

While surgery, often coupled with chemotherapy or radiotherapy, remains a standard lung cancer treatment, the formidable challenges of side effects and drug resistance persist. Emerging evidence indicates that exosomal lncRNAs and circRNAs are influential modulators of lung cancer drug resistance. By transporting diverse drug-resistant biomolecules, these exosomal non-coding RNAs play critical roles in lung cancer development, metastatic recurrence, and chemotherapy resistance [42,79]. For instance, exosomal lncRNA FOXD3-AS1 enhances ELAVL1 expression, activating the PI3K/Akt pathway to fortify lung cancer cell proliferation, invasion, and 5-fluorouracil resistance [58]. Similarly, exosomal LOC85009 has been shown to inhibit docetaxel (DTX) resistance, proliferation, and autophagy while inducing apoptosis in DTX-resistant cells. Mechanistic studies reveal that LOC85009 sequesters ubiquitin-specific protease 5 (USP5), destabilizing upstream transcription factor 1 (USF1) protein and thereby inactivating ATG5

transcription. Thus, exosomal LOC85009 can inhibit DTX resistance through regulation of ATG5-induced autophagy via USP5/USF1 axis [80].

The expression level of hsa_circ_0002130 is elevated in osimertinib-resistant NSCLC cells, and in vitro experiments demonstrate that deletion of hsa_circ_0002130 suppresses osimertinib resistance. Mechanistic findings suggest that hsa_circ_0002130 regulates GLUT1, HK2 and LDHA by targeting miR-498. The inhibitory effects of hsa_circ_0002130 deletion on osimertinib resistance can be reversed by downregulating miR-498 [81]. Additionally, exosomal circ_PIP5K1A is overexpressed in NSCLC tissues, serum samples, and cells. Knockdown of exosomal circ_PIP5K1A inhibits the proliferation, migration, and invasion of NSCLC cell while enhancing apoptosis and cisplatin sensitivity. Mechanistic experiments have shown that circ_PIP5K1A positively regulated ABCC1 expression by sponging miR-101 [82]. Exosome-transmitted circVMP1 fosters non-small cell lung cancer progression and cisplatin resistance by targeting the miR-524-5p-METTL3/SOX2 axis. This intricate mechanism involves miR-524-5p indirectly regulating SOX2 expression by interacting with its methyltransferase METTL3 and directly regulating SOX2 expression by binding to its 3′UTR. Furthermore, DDP-resistant NSCLC cells-derived exosomal circVMP1 endow DDP sensitivity to DDP-sensitive cells [66]. Exosomal circKIF20B curtails gefitinib resistance and impedes cell proliferation by orchestrating the cell cycle, promoting apoptosis, and diminishing OXPHOS through the circKIF20B/miR-615-3p/MEF2A axis in NSCLC. Through its binding to miR-615-3p, circKIF20B can regulate MEF2A, thereby influencing the cell cycle, apoptosis, and mitochondrial OXPHOS. Upregulating exosomal circKIF20B expression in recipient cells restores sensitivity to gefitinib [67]. Together, strategies regulating the expression level of exosomal lncRNAs and circRNAs present therapeutic potential for overcoming drug resistance.

#### 3.1.5. Roles in immune regulation

Numerous investigations have delved into the intricate effects of exosomes on the immune system, exploring their interactions with key players such as dendritic cells (DCs), macrophages, and T-regulatory cells [83]. Beyond these interactions, exosomes have been implicated in orchestrating anti-tumor immune responses, particularly in modulating Natural Killer (N.K.) cells, thereby influencing tumor progression. Tumor-derived exosomes function as paracrine messengers, shuttling pro-inflammatory signals or immunosuppressive agents. For instance, the predominance of exosomal circUSP7 secretion by NSCLC cells contributes to immunosuppression by inducing CD8 T cell dysfunction, leading to resistance against anti-PD1 immunotherapy [84]. This highlights circUSP7 as a potential therapeutic target for NSCLC patients. Hong et al. found that NSCLC cell secreted PD-L1 inactivates $CD8^+$ T cells by activating extracellular and intracellular pathways mediated cell death to facilitate immune evasion. Knock-down circ-CPA4 inhibits intracellular and extracellular PD-L1 by targeting let-7 miRNA. Thus, circ-CPA4/let-7 miRNA/PD-L1 axis regulates cell growth, stemness, drug resistance and immune evasion in NSCLC [85]. Meanwhile, a notable upregulation in CCNB1 expression is observed in non-responders, correlating with the *cis*-regulation of exosomal lnc-CENPH-1 and lnc-CENPH-2. The pivotal factor contributing to primary resistance to immunotherapy is identified as the exosomal lnc-ZFP3-3-TAF1-CCNB1 pair. In additional, IL6R is downregulated in the responders following treatment, suggesting that IL6R may be used as an effective target for future immunotherapy [86]. Therefore, exosomal lnc-ZFP3-3-TAF1-CCNB1 pair and IL6R might be key factors predicting efficiency of immunotherapy.

Further investigations reveal the regulatory roles of exosomal lncRNAs and circRNAs in macrophage polarization. For example, circFARSA, upregulated in NSCLC tissues, is transported to macrophages by exosomes. Exosomal circFARSA activates PI3K/AKT signaling in macrophages, promoting M2 polarization and enhancing EMT and metastasis in NSCLC cells [87]. Similarly, NSCLC exosomal lncRNA FGD5-AS1 promotes M2 macrophage polarization through the MicroRNA-944/MACC1 axis, fostering NSCLC migration, invasion, and metastasis [88]. In conclusion, mature immune cells' ability to uptake antigens and promote immune function is influenced by exosomal lncRNAs and circRNAs. These molecules play indispensable roles in immune regulation within the context of lung cancer, offering potential targets for therapeutic intervention. Refer to Table 1 for the latest research on exosomal lncRNAs and circRNAs in lung cancer [89–99].

### 3.2. Potential clinical applications of exosomal LncRNAs and CircRNAs in lung cancer

Early detection is pivotal for the survival of lung cancer patients. Tumor-derived exosomes, obtainable from ascites fluid, urine, pleural effusions, and serum of patients, offer a valuable resource for isolation. Evaluation of exosomes derived from lung tumors holds promise for the development of noninvasive diagnostic approaches, facilitating the monitoring of disease progression, therapeutic effectiveness, and resistance mechanisms. The cargo encapsulated within these exosomes even serves as a representative snapshot of the tumor status. Notably, exosomal lncRNAs and circRNAs extracted from bodily fluids and blood emerge can present promising opportunities for clinical applications, including diagnosis and prognosis.

Multiple studies have demonstrated a close correlation between lung cancer-derived exosomal lncRNAs and circRNAs with TNM stage, tumor volume, survival rates, and poor prognosis in lung cancer. The expression profiles of exosomal lncRNAs and circRNAs at different stages exhibit heightened sensitivity and specificity, rendering them promising dual-purpose diagnostic and prognostic biomarkers for lung cancer. For instance, cancer-associated exosomal lncRNA LINC01614 enhances glutamine uptake in lung adenocarcinoma. Clinically, elevated LINC01614 expression in cancer-associated fibroblasts (CAFs) correlated with increased glutamine influx and poor prognosis in patients with lung adenocarcinoma, positioning exosomal lncRNA LINC01614 as a prognostic tool in LUAD [104]. Another investigation highlighted that exosomal LOC85009 mediates resistance to docetaxel via the USP5/USF1 axis. Notably, exosomes containing LOC85009 induce autophagy and are associated with an unfavorable prognosis, revealing their potential role as prognostic indicators [80]. Furthermore, exosomes derived from highly metastatic lung cancer cells are observed to enhance the migration and invasion of lung cancer cells with lower metastatic potential. Elevated levels of lnc-MLETA1 in these exosomes are identified in lung cancer patients, indicating its potential as a prognostic indicator for metastatic lung cancer [105].

Other studies highlight the diagnostic potential of serum exosomal circRNAs, such as circSATB2 and hsa_circ_0069313, showing high sensitivity and specificity in discriminating benign and malignant lung cancers, serving as both diagnostic and prognostic markers. CircSATB2 exhibited upregulation in serum exosomes of lung cancer patients, with an area under the receiver operating characteristic curve (ROC) of 0.685. Additionally, lung cancer patients with elevated circSATB2 expression display shorter free survival, suggesting its potential as a marker for poor prognosis in lung cancer [100]. Hsa_circ_0069313 expression is also significantly higher in the NSCLC group compared to healthy, pneumonia, and benign lung tumor groups. And survival curve analysis also reveals shorter survival in lung cancer patients with high expression of serum exosomal hsa_circ_0069313 compared to those with low expression, suggesting its slightly higher sensitivity and specificity in discriminating benign and malignant lung cancer [106]. Furthermore, exosomal circRNAs like hsa_circ_0001492, hsa_circ_0001439, and hsa_circ_0000896 exhibit promising diagnostic sensitivity and specificity in lung adenocarcinoma patients [107].

These findings underscore the potential reliability of exosomal lncRNAs and circRNAs as diagnostic and prognostic biomarkers for lung cancer, enhancing the accuracy of treatment strategies. Additional exosomal lncRNAs and circRNAs with diagnostic and prognostic

**Table 1**
The role of exosomal lncRNAs and circRNAs in the occurrence and progression of lung cancer.

| Application in lung cancer | Exosomal component | Expression | Function/Role in lung cancer | Target/Mechanism | References |
|---|---|---|---|---|---|
| Proliferation, migration and invasion | LncRNA FOXD3-AS1 | Up-regulated | promotes proliferation, invasion and 5-fluorouracil resistance. | upregulates ELAVL1 expression and activates PI3K/Akt pathway | [58] |
| | LINC00662 | Up-regulated | promotes proliferation, invasion, and migration.<br>inhibits apoptosis and cell cycle arrest of NSCLC cells. | modulates miR-320d/E2F1 axis | [59] |
| | LncRNA UFC1 | Up-regulated | promotes NSCLC cell proliferation, migration and invasion. | inhibits PTEN expression to promote NSCLC progression by EZH2-mediated epigenetic silencing | [60] |
| | LncRNA HOTAIR | Up-regulated | promotes osteoclast differentiation and bone metastasis. | targets TGF-β/PTHrP/RANKL pathway | [61] |
| | LncRNA HOTAIR | Up-regulated | promotes progression of the lung cancer cell cycle and the occurrence of EMT. | enhances lung cancer occurrence and development through sponging miR-203 | [63] |
| | HOTAIRM1 | Up-regulated | promotes the migration and invasion of NSCLC cells. | adsorb miR-328-5p to up-regulates the expression of SPON2 in CAFs | [64] |
| | Lnc-MZT2A-5:1 | Upregulated | promotes the activation and migration of MRC-5 cells. | – | [65] |
| | CircVMP1 | Up-regulated | promotes the proliferation, migration and invasion of NSCLC cells. | regulates miR-524-5p-METTL3/SOX2 axis | [66] |
| | CircKIF20B | Up-regulated | alters the cell cycle, apoptosis, and mitochondrial OXPHOS. | bounds to miR-615-3p for regulating the MEF2A | [67] |
| | CircSHKBP1 | Up-regulated | enhances the NSCLC cell proliferation, metastasis, glycolysis. | sponges for miR-1294, positively regulating PKM2 | [68] |
| | LINC01356 | Up-regulated | enhances invasion ability of a lung cancer cell line in an in vitro BBB model. | regulates the expression of the junction proteins Occludin, Claudin and N-cadherin | [89] |
| | LINC00273 | Up-regulated | facilitates LUAD cell migration and invasion. | regulates Hippo/YAP pathway by LATS2 ubiquitination | [90] |
| | Lnc-MMP2-2 | Up-regulated | increases blood-brain barrier permeability. | via the miRNA-1207-5p/EPB41L5 axis | [91] |
| | CircSATB2 | Up-regulated | facilitates proliferation, invasion, and migration in lung cancer cells. | promotes fascin homolog 1, actin-bundling protein 1 (FSCN1) expression via miR-326 in lung cancer cells | [100] |
| | LncRNA-SOX2OT | Up-regulated | modulates osteoclast differentiation and stimulated bone metastasis. | targets the miRNA-194-5p/RAC1 signalling axis and TGF-β/pTHrP/RANKL signalling pathway in osteoclasts. | [101] |
| Angiogenesis | MFI2-AS1 | Up-regulated | promotes migration and tube formation of HUVECs in vitro.<br>promotes sangiogenesis in vivo. | regulates the miR-107/NFAT5/AKT axis | [77] |
| | Circ_0008717 | Up-regulated | promotes cell growth, mobility and angiogenesis in NSCLC. | promotes cell tumorigenicity through microRNA-1287-5p/P21-activated kinase 2 (PAK2) axis | [78] |
| | LncRNA GAS5 | Down-regulated | inhibits HUVECs proliferation and tube formation and increases their apoptosis. | regulates PTEN, PI3K, and AKT by binding miR-29-3p with PTEN. | [102] |
| | LincRNA-p21 | Up-regulated | promotes angiogenesis and metastasis. | – | [103] |
| Drug resistance | lncRNA FOXD3-AS1 | Up-regulated | promotes cell proliferation, invasion and 5-fluorouracil resistance. | upregulates ELAVL1 expression and activates PI3K/Akt pathway | [58] |
| | CircVMP1 | Up-regulated | promotes NSCLC progression and DDP resistance. | targets miR-524-5p-METTL3/SOX2 axis | [66] |
| | CircKIF20B | Down-regulated | inhibits gefitinib resistance and cell proliferation | bounds to miR-615-3p for regulating the MEF2A | [67] |
| | LOC85009 | Up-regulated | inhibits DTX resistance, and apoptosis in DTX-resistant cells | regulates ATG5-induced autophagy via USP5/USF1 axis | [80] |
| | Hsa_circ_0002130 | Up-regulated | promotes osimertinib resistance | targetes miR-498 to regulate GLUT1, HK2 and LDHA | [81] |
| | Circ_PIP5K1A | Up-regulated | promotes cisplatin resistance | regulates ABCC1 expression by sponging miR-101 | [82] |
| | LncRNA MSTRG.292666.16 | Up-regulated | is associated with osimertinib resistance. | – | [94] |
| | LncRNA H19 | Up-regulated | induces erlotinib resistance of sensitive cells. | targets miR-615-3p to regulate ATG7 expression | [95] |
| | LncRNA SNHG7 | Up-regulated | enhances docetaxel resistance of LUAD cells. | induces autophagy and macrophage M2 polarization | [96] |
| | LncRNA UCA1 | Up-regulated | promotes gefitinib resistance. | targets FOSL2 by Sponging miR-143 | [97] |
| | LncRNA MEG3 | Up-regulated | promotes cancer progression and enhances Cisplatin chemoresistance | targets miR-15a-5p to mediate CCNE1 expression | [98] |
| | CircDNER | Up-regulated | enhances paclitaxel resistance. | sponges miR-139-5p to regulate ITGB8 expression | [99] |
| Immune regulation | CircUSP7 | Up-regulated | induces -$CD8^+$ T cell dysfunction and anti-PD1 resistance. | regulates the miR-934/SHP2 axis | [84] |
| | CircCPA4 | Up-regulated | promotes intracellular and extracellular PD-L1 by targeting let-7 miRNA. | regulates circ-CPA4/let-7 miRNA/PD-L1 axis | [85] |
| | Lnc-ZFP3-3-TAF1-CCNB1 | Up-regulated | inhibits the maturation of DCs and target for anti-PD-1 therapy. | regulates the expression of IL6R to active STAR3 pathway | [86] |
| | CircFARSA | Up-regulated | promotes M2 polarization. | regulates PTEN ubiquitination activated PI3K/AKT signaling | [87] |
| | LncRNA FGD5-AS1 | Up-regulated | promotes M2 macrophage polarization. | regulates the MicroRNA-944/MACC1 axis | [88] |

potential are presented in Table 2 [60,102,103,108–123].

## 4. Challenges and future directions

Despite the burgeoning progress in understanding the roles of exosomal lncRNAs and circRNAs in lung cancer, several challenges and avenues for future research remain. Efficient and standardized methods for the extraction and identification of exosomes are lacking, leading to variability in experimental techniques and discrepancies across studies. Therefore, standardization efforts are crucial to validate the clinical significance of exosomal lncRNAs and circRNAs as biomarkers in lung cancer. Additionally, the functional characterization of the active molecules carried by exosomes remains ambiguous. Although numerous studies have identified dysregulated exosomal lncRNAs and circRNAs in lung cancer, a comprehensive understanding of their functions is imperative. Unraveling their precise roles in cellular processes, signaling

**Table 2**
Exosomal lncRNAs and circRNAs as biomarker for lung cancer.

| Exosomal biomarker | Exosome sources | Expression(oncogene/suppressor) | Diagnostic performance | Clinical significance | References |
|---|---|---|---|---|---|
| LncRNA UFC1 | Serum | Upregulated in NSCLC patients | AUC = 0.794; sensitivity of 73.3 %; specificity of 74.1 % | Diagnosis | [60] |
| MFI2-AS1 | Serum | Higher in NSCLC patients | | Diagnosis | [77] |
| Lnc-ZFP3-3-TAF1-CCNB1 pair | Plasma | Up-regulated in NSCLC patients | – | Predictive biomarker | [86] |
| LncRNA GAS5 | Serum | Prominently lower in the NSCLC group; Lower Exo-GAS5 expression was associated with larger tumor size and advanced TNM stage | Exo-GAS5 (AUC = 0.857, sensitivity = 85.94 %, specificit = 70.00 %)<br>CEA + Exo-GAS5(AUC = 0.929, sensitivity = 89.06 %, specificit = 90.00 %) | Diagnosis | [102] |
| LincRNA-p21 | Plasma | Higher in blood from the tumor-draining vein and associated with shorter time to relapse and shorter overall survival | The 6, 12, 24, and 36 months showed an AUC of 0.639, 0.737, 0.686, and 0.632 | Prognosis | [103] |
| Hsa_circ_0069313 | Serum | Up-regulated in NSCLC patients | AUC = 0.749 | Diagnosis | [106] |
| Hsa_circ_0001492<br>Hsa_circ_0001439<br>Hsa_circ_0000896 | Serum | Up-regulated in LUAD patients | AUC = 0.783<br>AUC = 0.783<br>AUC = 0.799 | Diagnosis | [107] |
| LncRNA RP11-510M2.10 | Serum | Lower in malignant group than control group | Sensitivity of 95 %; specificity of 90 %; AUC of 0.918 | Early diagnosis | [109] |
| LncRNA LUCAT1 | Serum | Higher in LUAD patients | AUC of 0.852; sensitivity of 84.45 %; specificity of 77.38 %; | Early diagnosis | [110] |
| Linc00917 | Serum | Upregulated in stage III/IV than in stage I/II NSCLC patients; high expression level of exosomal LINC00917 was significantly associated with shorter OSs among all participating NSCLC patients, as well as stage III/IV NSCLC patients. | AUC of 0.811 for all NSCLC patients; 0.773 for Stage I/II NSCLC patients and 0.907 for Stage III/IV NSCLC patients | Prognosis | [111] |
| Linc01125 | Serum | Higher in NSCLC patients than healthy donors and tuberculosis patients;<br>Patients with advanced T stages expressed more exosomal linc01125 than those with T1/T2 stages | AUC = 0.662 | Prognosis | [112] |
| LncRNA RP5-977B1 | Serum | Significantly upregulated in NSCLC patients; high expression is closely related with worse prognosis | AUC = 0.8899 | Diagnosis; prognosis | [113] |
| LncRNA SCIRT | Serum | Upregulated in lung cancer patients and correlated with the advanced stage of disease | – | Diagnosis; prognosis | [114] |
| LncRNA H19 | Serum | Upregulated in patients with erlotinib resistance | AUC of 0.799; sensitivity of 70 %; specificity of 85.71 % | Erlotinib therapy | [116] |
| LncRNA TBILA | Serum | Upregulated in NSCLC patients and associated with tumor size; | combined diagnostic value: AUC = 0.853; sensitivity of 91.4 %; specificity of 80.7 % | Diagnosis | [117] |
| LncRNA AGAP2-AS1 | Serum | Upregulated in NSCLC patients; linked to lymph node metastasis and TNM stage | combined diagnostic value: AUC = 0.853; sensitivity of 91.4 %; specificity of 80.7 % | Diagnosis | [117] |
| LncRNA SOX2-OT | Serum | Upregulated in LSCC patients and correlated with tumor size, TNM stage, and lymph node metastasis | AUC = 0.815; sensitivity of 76 %; specificity of 73.17 % | Diagnosis | [118] |
| LncRNA SNHG15 | Serum | Upregulated in NSCLC patients and closely associated with poor differentiation, positive lymph node metastasis and advanced TNM stage | combined with CEA, AUC of 0.915, sensitivity of 92.3 % and specificity of 76.2 % for the detection of NSCLC | Prognosis | [119] |
| LncRNA MALAT1 | Serum | Highly expressed in NSCLC patients; associated with tumor stage and lymphatic metastasis | – | Prognosis | [120] |
| HOTAIR | Serum | Significantly higher in NSCLC patients. | AUC = 0.821, sensitivity = 0.889 and specificity = 0.783;<br>Exosomal HOTAIR expression associated with lymphatic metastasis and TNM staging | Diagnosis | [121] |
| Lnc-FRAT1-5<br>Lnc-SRY-11<br>Lnc-RNASE13-1<br>Lnc-RP11-80A15.1.1–2<br>Lnc-ARL6IP6-4<br>Lnc-DGKQ-1 | Urine | Upregulated in NSCLC patients<br>Down-regulated in NSCLC patients | – | Diagnosis | [122] |
| CircSATB2 | Serum | Up-regulated in NSCLC patients | AUC of lung cancer patients = 0.660; AUC of metastatic lung cancer patients = 0.797 | Diagnosis | [123] |

pathways, and intercellular communication will shed light on the mechanisms underlying lung cancer progression. Integrating functional analysis with clinical data will bolster our ability to harness these molecules for diagnostic and therapeutic applications. Advancements in multi-omics technologies offer opportunities for comprehensive profiling of molecular alterations in lung cancer. Integrating multi-omics data with exosomal lncRNA and circRNA profiles can unveil intricate networks and provide a holistic understanding of tumorigenesis and progression. This integrative approach holds promise for identifying robust biomarkers and therapeutic targets, thereby informing personalized treatment strategies. Furthermore, the translation of the therapeutic potential of exosomal lncRNAs and circRNAs into clinical settings presents formidable challenges. Overcoming hurdles such as achieving efficient and targeted delivery of therapeutic exosomal RNAs necessitates advancements in drug delivery technologies. Concerns regarding off-target effects, immunogenicity, and long-term safety must be adequately addressed before the routine implementation of exosome-based therapies in clinical practice.

Additionally, exosomal miRNAs have been identified as key drivers of NSCLC progression and metastasis by targeting tumor suppressors. However, the involvement of lncRNAs and circRNAs in targeted therapy pathways remains largely unexplored. A recent study shed light on the exchange of exosomes between tumor cells and TAMs, revealing a pivotal role in promoting lung adenocarcinoma metastasis through the Hippo pathway [90]. This underscores the significance of investigating exosomal lncRNAs and circRNAs as potential therapeutic targets for NSCLC, akin to the pivotal role played by miRNAs. Moreover, the utilization of small interfering RNAs (siRNAs) designed to target specific lncRNAs and circRNAs, delivered via exosomes to lung cancer cells, offers a promising strategy. These siRNAs aim to diminish the expression of oncogenic lncRNAs or circRNAs, thereby intervening in lung cancer progression. Alternatively, modifying exosomes to load anti-cancer lncRNAs and circRNAs presents another avenue for therapeutic intervention. The multifaceted properties of exosomes, including their biocompatibility, targeting capabilities, and potential for specific cargo loading, position them as promising vehicles for drug delivery in cancer treatment. Consequently, exosomal lncRNAs and circRNAs emerge as leading candidates for early diagnosis and prognosis of lung cancer.

Nevertheless, further research and clinical trials are imperative to fully harness the diagnostic and therapeutic potential of exosomal lncRNAs and circRNAs in lung cancer management. With continued investigation, these biomolecules hold promise not only for early screening and treatment but also for predicting treatment efficacy and assessing prognosis. Thus, a concerted effort towards comprehensive exploration and validation is essential to realize the clinical utility of exosomal lncRNAs and circRNAs in the diagnosis and treatment of lung cancer.

## 5. Conclusion

Exosomes, minute extracellular vesicles encapsulating cytoplasmic proteins and RNA within phospholipid bilayers, serve as crucial messengers in intercellular communication across diverse cellular landscapes. Particularly within the context of lung cancer, these nano-sized vesicles intricately orchestrate the tumor microenvironment, modulating immunomodulation, angiogenesis, therapy resistance, and metastasis through autocrine and paracrine signaling cascades. Central to this dynamic interplay are exosomal lncRNAs and circRNAs, whose involvement in lung cancer progression illuminates their potential as pivotal diagnostic, prognostic, and therapeutic targets. These molecular entities actively partake in the cardinal hallmarks of cancer, spanning proliferation, migration, invasion, epithelial-mesenchymal transition, angiogenesis, and immune regulation. The aberrant expression patterns of specific exosomal lncRNAs and circRNAs among lung cancer patients underscore their clinical relevance, positioning them as promising candidates for precision medicine interventions. Noteworthy attributes of exosomal lncRNAs and circRNAs include their robust enrichment and enduring presence within exosomes, rendering them stable and informative biomarkers. They exhibit discriminative capabilities, effectively distinguishing between healthy individuals and patients, discerning early-stage malignancies from advanced ones, and delineating recurrent cases from non-recurrent ones. Moreover, their diagnostic prowess manifests in superior sensitivity and specificity, underscoring their potential as reliable indicators for clinical stratification and monitoring in lung cancer management.

## Data availability

No data was used for the research described in the article.

## CRediT authorship contribution statement

**Xia Li:** Writing – original draft, Project administration, Methodology, Investigation, Conceptualization. **Yunbing Wu:** Validation, Investigation, Data curation. **Yue Jin:** Writing – review & editing, Validation, Investigation, Formal analysis, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None.

## Abbreviations

| | |
|---|---|
| ncRNAs | non-coding RNAs |
| lncRNAs | long noncoding RNAs |
| MALAT1 | metastasis-associated lung adenocarcinoma transcript 1 |
| circRNAs | circular RNAs |
| EMT | epithelial-mesenchymal transition |
| ESCRT | endosomal sorting complex required for transport |
| TEX | tumor cell-derived exosomes |
| ILVs | intraluminal vesicles |
| MVBs | multi-vesicular bodies |
| EVs | extracellular vesicles |
| ROC | receiver operating characteristic curve |
| LUAD | lung adenocarcinoma |

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