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REVIEW

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Exosomes promote pre-metastatic niche formation in lung cancer

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Abstract

Lung cancer is a major cause of cancer-related mortality worldwide. Distant metastasis is the primary driver of poor prognosis, and the formation of the pre-metastatic niche (PMN) represents a critical early event in this process. Tumor cells remodel the microenvironment of distant organs by releasing various factors, including exosomes, which create a favorable environment for the colonization and growth of circulating tumor cells (CTCs). Exosomes carry diverse molecular cargos including proteins, RNAs, and lipids, and they play a pivotal role in PMN formation. They modulate several microenvironmental components, including immune cells, endothelial cells, and fibroblasts, by promoting immune evasion, angiogenesis, and extracellular matrix remodeling, thereby enhancing the metastatic potential of cancer cells. This review systematically discusses how distinct lung cancer-derived exosomes (LCDEs) subpopulations contribute to PMN formation, emphasizing how the heterogeneous molecular cargos they carry facilitate metastasis through immune suppression, angiogenesis, and matrix remodeling. It also highlights efforts to understand the cellular origins of LCDEs and how this influences their functional specificity. Unlike existing reviews, we establish the first functional classification system for LCDEs based on their niche-modulating actions, and rigorously evaluate their clinical potential as both biomarkers and therapeutic vehicles. We further provide a critical appraisal of technical limitations in exosome-based applications. These insights advance the translational development of LCDE-targeted strategies.

Keywords Lung cancer, Exosomes, Pre-metastatic niche, Metastasis, Biomarkers and therapy

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Introduction

Despite advances in targeted therapies and immunotherapy, metastatic lung cancer remains a formidable clinical challenge, with 5-year survival rates below 20%. In 2022, approximately 2.5 million new lung cancer cases were reported globally, and about 1.8 million deaths, making it one of the leading causes of cancer-related mortality [1].The process of cancer metastasis is complex and multifaceted, involving the spread of cancer cells to distant organs via the blood or lymphatic systems [2]. This concept was first framed by Paget's classical "seed and soil" hypothesis, which emphasized that metastasis depends not only on cancer cell properties but also on the microenvironment of target organs. Building on this concept, the PMN theory proposes that primary tumors can actively condition distant sites prior to cell arrival, establishing a supportive microenvironment for colonization [3]. This paradigm was first demonstrated by Kaplan et al., who showed that tumor-secreted factors can initiate niche formation even before tumor cell dissemination [4]. Among these tumor-derived factors, exosomes have emerged as key mediators in PMN formation. These nanoscale vesicles carry diverse and heterogeneous cargos (proteins, RNAs, lipids) and are released by various cell types within the tumor microenvironment, including cancer cells, fibroblasts, and immune cells [5].

In this review, we focus on LCDEs, which act as molecular messengers between tumor cells and distant organs. This creates a favorable microenvironment for the dissemination and colonization of cancer cells [5]. Numerous studies have shown that LCDEs carry lung cancer-specific molecular signals, such as integrins, miRNAs, and proteins, and also modulate the microenvironment by targeting cells in specific organs, thereby promoting distant metastasis of lung cancer cells. LCDEs likely act as permissive factors, cooperating with local microenvironmental cues (e.g., hypoxia, cytokines) to fully establish PMN. For example, miR-21a, rich in LCDEs, induces the expansion of myeloid suppressor cells (MDSCs), inhibits the function of effector T cells and natural killer (NK) cells, and enhances the immune escape ability of tumors by down-regulating the expression of programmed death protein 4 (PDCD4) [6]. In addition, the potential application of LCDEs in the early diagnosis of lung cancer has garnered widespread attention, and their unique advantages as drug delivery vehicles have opened new avenues for anti-tumor therapy [7]. Unlike previous reviews that primarily catalogued exosomal components, this work systematically organizes LCDEs into functionally defined subgroups based on their niche-modulating actions. By classifying LCDEs as immune suppressors, angiogenic activators, and stromal remodelers, we establish a unified framework that directly links molecular mechanisms to clinical applications—a critical advance beyond descriptive cargo analyses. We further assess their clinical relevance as diagnostic biomarkers and therapeutic carriers, while addressing the current limitations posed by their heterogeneity and unresolved cellular origins.

Background of lung cancer exosomes

Extracellular vesicles(EVs)are a broad term that refers to all vesicles released by cells into the extracellular space, including exosomes, microvesicles, and apoptotic bodies. Exosomes, which are a subtype of EVs, specifically refer to vesicles with a diameter of 30–150 nm [8]. In this review, we use the term 'exosomes' to refer to the 30–150 nm EVs isolated by standard methods (e.g., differential ultracentrifugation or size-exclusion chromatography), consistent with common usage in clinical and translational studies. While strictly defined exosomes originate from multivesicular bodies (MVBs), the cited literature may include studies of broader EV populations due to technical limitations in exosome-specific isolation. Their membrane structure is similar to that of the cell membrane, primarily composed of a phospholipid bilayer, which provides them with high physical and chemical stability. This stability allows exosomes to maintain their integrity during transport, ensuring the biological activity of their contents, and enabling them to circulate in body fluids for extended periods. Key lipid components, such as cholesterol and ceramide, are crucial for the structural integrity and functionality of exosomes. Cholesterol is involved in regulating the fluidity and stability of the exosomal membrane. It facilitates the fusion of MVBs with the cell membrane, which is essential for the efficient release of exosomes. Ceramide, on the other hand, plays a key role in the formation of intraluminal vesicles (ILVs) within MVBs by promoting membrane curvature [9]. This is critical for cargo loading into exosomes, including RNA, proteins, and lipids, which are necessary for their biological functions.

Exosomes are formed via endocytosis, resulting in the formation of MVBs, which subsequently release the exosomes into the extracellular space through fusion with the cell membrane [10]. The process includes the cell membrane forming an early endosome through endocytosis, which matures into an MVB, and during this maturation, the membrane invaginates to produce ILVs, which are exosomes [11]. This formation is regulated by the endosomal sorting complexes required for transport (ESCRT) and other protein complexes [12, 13]. During MVB formation, cell-specific substances are selectively loaded into ILVs via either the ESCRT-dependent or -independent pathways or lipid raft pathways. The mature MVB then fuses with the cell membrane, releasing the exosomes [14]. As shown in Fig. 1, cells produce exosomes through a series of pathways. During MVB

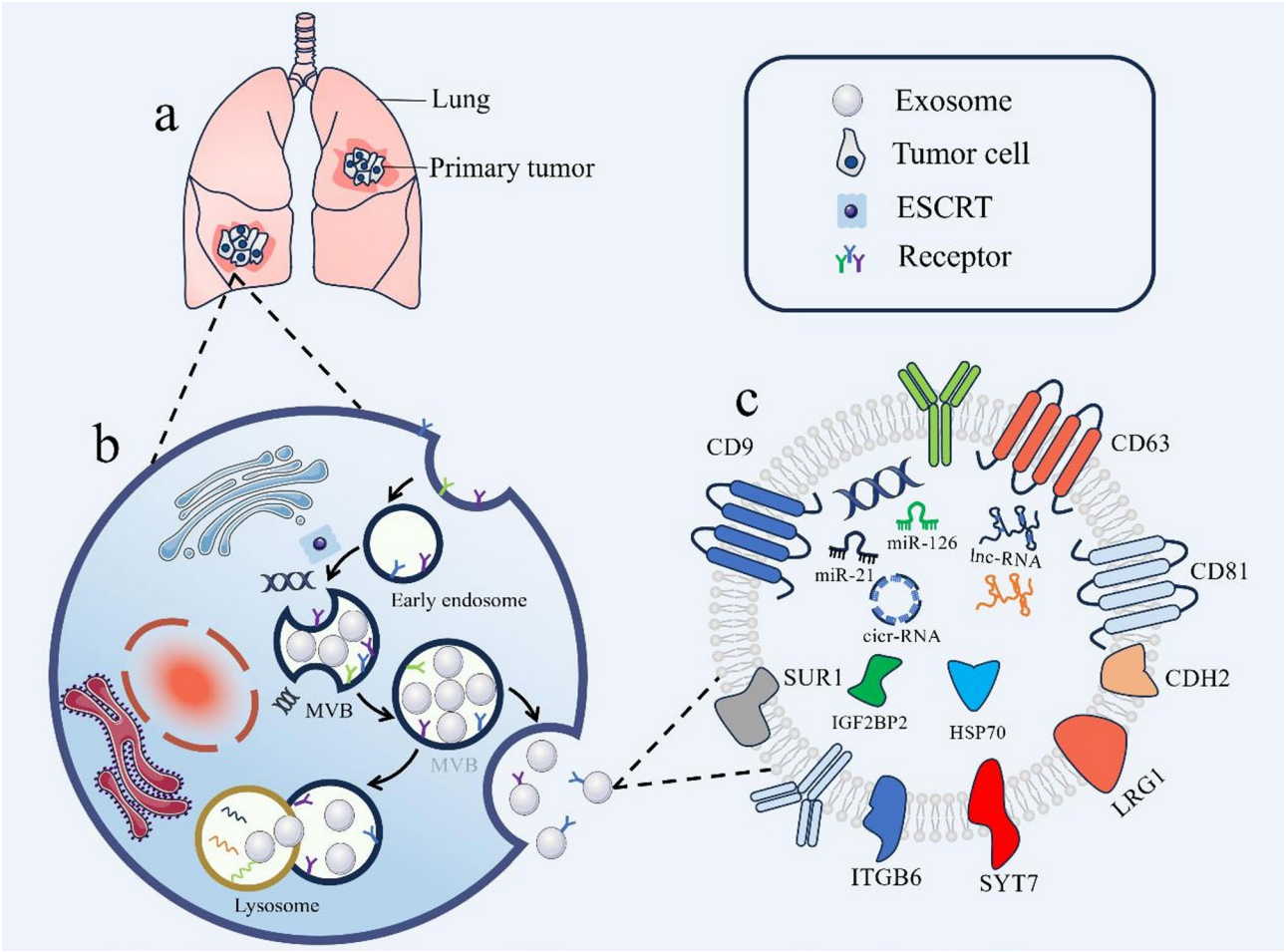

Fig. 1 Formation and composition of LCDEs. (**a**) Primary tumor of lung cancer. (**b**) LCDEs are produced by tumor cells. The cell membrane buds inward to form an early endosome and then releases it through the fusion of MVB with the membrane or fuses with lysosomes for internal degradation. (**c**) The composition of LCDEs

formation, cell-specific substances are selectively loaded into ILVs via either the ESCRT-dependent or -independent pathways or lipid raft pathways. The mature MVB then fuses with the cell membrane, releasing the exosomes [15]. In lung cancer, tumor-associated cells communicate with the surrounding microenvironment and distant organs by secreting exosomes. Receptor cells in the distal microenvironment internalize these exosomes through receptor-mediated endocytosis or membrane fusion. The exosomes carry signaling molecules and bioactive substances (such as miRNAs, proteins, etc.), which are transferred to the target cells and activate specific signaling pathways. This signaling transmission induces functional changes in the target cells, further promoting the formation of the PMN and creating a favorable microenvironment for tumor cell metastasis. As shown in Fig. 1, LCDEs exhibit unique molecular characteristics, such as membrane proteins (Alix, TSG101), small GTPases (Rab family proteins), tetraspanins (CD9, CD63, CD81), tumor-associated antigens (e.g., CA125, CEA), and glycoproteins (e.g., LRG1) [16–22]. These small molecules participate in the interaction between exosomes and target cells, ensuring that exosomes specifically target certain cell types in distant organs, thus influencing their behavior.

Exosome origin exhibits significant heterogeneity, primarily arising from tumor cells, immune cells, cancer-associated fibroblasts (CAFs), and other cell types [23]. This heterogeneity plays varying roles in different subtypes of lung cancer and the metastatic process. For example, exosomes secreted by lung cancer cells are often enriched in specific miRNAs (such as miR-23a and miR-130a), which promote tumor immune evasion by influencing PMN [24]. In addition, immune-suppressive cells such as MDSCs can further enhance tumor immune evasion by transferring immune evasion-related factors (such as PD-L1) through exosomes [25]. CAFs, as a major component of the lung cancer microenvironment, secrete exosomes enriched with pro-metastatic factors such as TGF-β, which promote matrix remodeling and

tumor cell migration by stimulating fibroblast differentiation into CAFs [26]. These heterogeneously sourced exosomes work synergistically to promote the formation of the PMN and provide a favorable microenvironment for lung cancer metastasis. For example, exosomal integrin α3β1 in lung squamous cell carcinoma binds to brain tissue, significantly enhancing the brain metastatic ability of tumor cells [27]. This heterogeneity also provides opportunities for researchers to develop specific biomarkers and therapeutic targets. By detecting specific molecules carried by exosomes, one can infer the type and functional state of the originating cells, offering potential directions for disease diagnosis and targeted therapy [28].

PMN refers to a specific microenvironment established in the target organ through various mechanisms before CTCs reach the metastatic site, which favors the colonization and growth of CTCs [5]. This concept was first proposed by Lyden et al. [3]. In recent years, with continuous research, scientists have gradually uncovered the complex mechanisms involved in its formation and explored its role in tumor metastasis [29]. Tumor cells can remodel the microenvironment of target organs remotely through the secretion of exosomes, tumor-derived secretory factors (TDSFs), and the recruitment of bone marrow-derived cells (BMDCs), creating favorable conditions for tumor cell colonization [30]. Studies on lung cancer have found that LCDEs play a significant role in the formation of the PMN. The establishment of PMN involves various cellular and molecular processes, such as immune suppression, angiogenesis, and matrix remodeling, which collectively promote the formation of a suitable metastatic environment. In this context, we will focus on the role of LCDEs in these mechanisms and reveal their critical impact on the metastatic microenvironment during the preparation of distant organs.

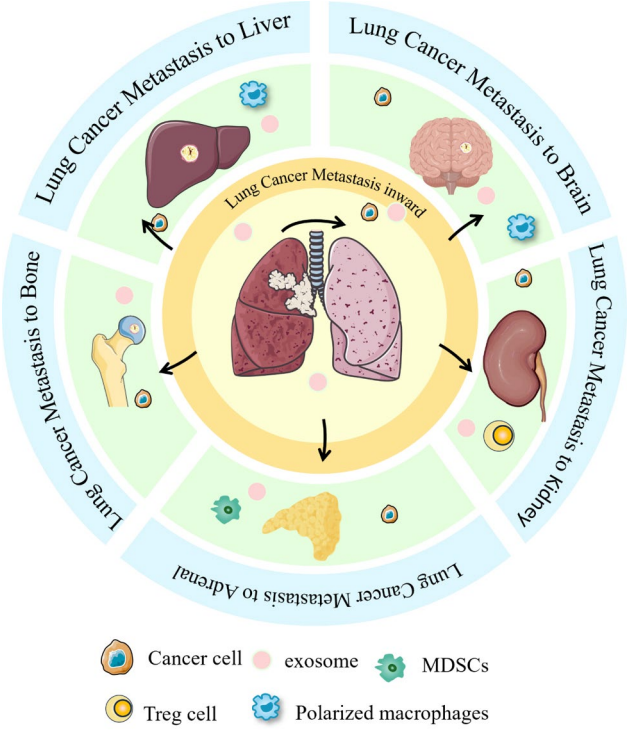

Fig. 2 Metastatic Cascade: From Primary Tumor to Distal Colonization

Mechanisms by which exosomes promote PMN formation

The metastatic cascade governed by LCDEs represents a dynamic, multi-organ pathological progression that unfolds through four critical phases (Fig. 2). Primary tumor cells actively release LCDEs bearing distinctive molecular markers such as integrins and miRNAs, which then disseminate systemically through circulation. These vesicles employ surface molecules, including ITGA3/ITGB1, to achieve organ-specific homing to target sites (liver, brain, bone, etc.). Upon reaching destination organs, LCDEs remodel local microenvironments through paracrine mechanisms, ultimately establishing a functional PMN that provides the necessary conditions for subsequent circulating tumor cell retention, extravasation, and proliferation. The following discussion will focus on how LCDEs coordinate this process through three fundamental mechanisms - immune evasion, angiogenic induction, and stromal reconstruction - while exploring relevant therapeutic targeting approaches.

This figure illustrates the metastatic cascade of lung cancer, highlighting the process of cancer cell dissemination from the primary lung tumor to various distal sites, including the liver, brain, bone, adrenal, and kidneys, as well as the potential spread inward within the lung itself. The diagram emphasizes the role of different components in metastasis: cancer cells, exosomes, MDSCs, Treg cells, and polarized macrophages. These cells and their interactions contribute to the complex process of tumor metastasis, aiding in the establishment of secondary cancer sites in distant organs.

Exosomes cause immunosuppression within the PMN

The immune system is a crucial defense line against tumor metastasis. Under normal conditions, immune cells such as CD8 + T cells, monocytes, and NK cells can generate anti-tumor effects, thus preventing tumor spread [29]. However, to evade immune surveillance, exosomes produced by lung cancer-associated cells can promote the transformation of normal immune cells into states that support tumor growth through a variety of mechanisms. These include inhibiting CD8 + T cells and NK cells, recruiting and activating suppressive immune cells (such as MDSCs, Tregs, and TANs) [31], and, more importantly, inducing macrophage polarization towards the M2 phenotype. Activated M2 macrophages further reinforce the immunosuppressive microenvironment

by secreting immunosuppressive factors like IL-10 and TGF-β. These cells migrate to metastatic sites, collectively creating an immunosuppressive microenvironment that facilitates tumor metastasis. In this process, exosomes play a critical role [32].

MDSCs are a heterogeneous population of immunesuppressive cells. During tumorigenesis, LCDEs regulate immune responses by recruiting MDSCs, thus promoting the formation of the PMN (Fig. 3a). For example, in the liver, MDSCs mediate immune suppression via tumor necrosis factor receptor-2 (TNFR-2), thereby promoting PMN formation [25]. Studies have shown that the number of MDSCs is significantly increased in lung cancer patients. miR-21a, enriched in LCDEs, induces the expansion of MDSCs by downregulating the expression of PDCD4, a mechanism that has been validated in mouse tumor models [6]. The accumulated MDSCs also secrete exosomes. miR-143-3p targets the 3' untranslated region (UTR) of integral membrane protein 2B (ITM2B), inhibiting its expression and thereby activating the PI3K/Akt signaling pathway. This pathway is critical for maintaining the immunosuppressive microenvironment and supporting tumor cell survival [33]. Research shows that Aggregated MDSCs further enhance the immunosuppressive microenvironment by secreting S100A8/A9 proteins. S100A8/A9 binds to pattern recognition receptors such as RAGE and TLR4, promoting the production of inflammatory mediators like serum amyloid A (SAA), which further attracts CD11b + MDSCs to migrate to pre-metastatic sites, enhancing local immune suppression [34]. Recent studies have also found that LCDEs, by interacting with fibroblasts, activate S100A10 from the S100 protein family, inducing lung fibroblasts to secrete chemokines like CXCL1 and CXCL8, thus promoting MDSC recruitment [35]. Furthermore, polymorphonuclear MDSCs (PMN-MDSCs) are significantly increased in the peripheral blood of cancer patients, and these cells directly inhibit the cytotoxic functions of NK cells, weakening the immune system's anti-tumor capacity and accelerating tumor progression [36].

T cells play a crucial role in tumor immunity as the primary effector cells of the adaptive immune system. However, LCDEs evade immune surveillance by regulating T cell function (Fig. 3a), with the upregulation of programmed cell death ligand 1 (PD-L1) being particularly critical. PD-L1 promotes immune escape and metastasis by inhibiting the activation of CD8 + T cells. In NSCLC tissues, the high expression of circ-CPA4 upregulates PD-L1 in exosomes by inhibiting miRNA-let-7, thereby suppressing T-cell function in the microenvironment [37]. Similarly, high expression of miR-C190 in lung cancer cells reduces the inhibition of PD-L1 mRNA by

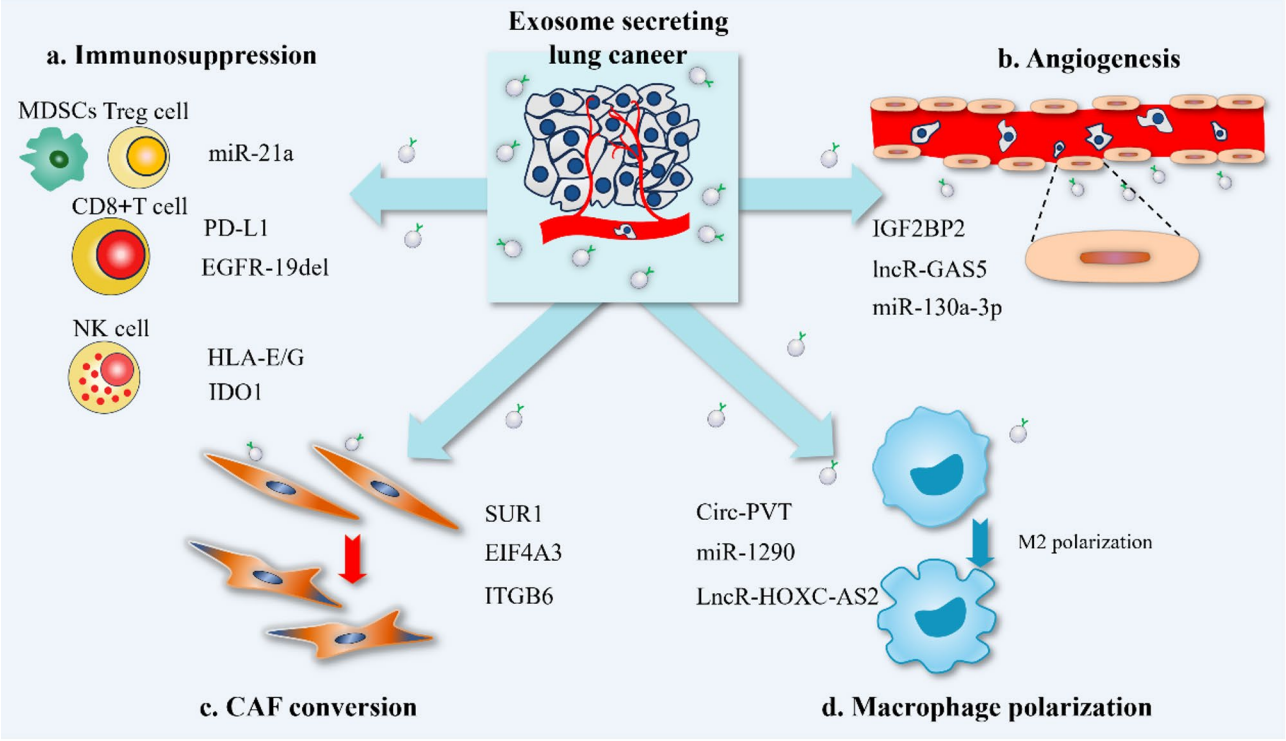

Fig. 3 Impact of LCDEs on target cells during PMN formation. (**a**) LCDEs induced the accumulation of MDSCs and Tregs and inhibited the functions of T cells and NK cells by releasing miR-21a, PD-L1, EGFR-19del, HLA-E/G, IDO1. (**b**) LCDEs can induce angiogenesis by releasing IGF2B2P, LncR-GAS5, and miR-130a-3p in endothelial cells. (**c**) LCDEs convert fibroblasts into CAFs by releasing SUR1, EIF4A3, and CD155. (**d**) LCDEs regulate macrophage polarization by releasing Circ-PVT, miR-1290, LncR-HOXC-AS2.

adsorbing specific miRNAs, thereby exerting a similar effect [38]. Additionally, bioinformatics analysis has revealed that the transmembrane protein integrin α2 (ITGA2) can also upregulate PD-L1 expression, further enhancing the tumor's immune evasion ability [39]. Exosomal PD-L1, as a key factor in tumor immune escape, holds potential as a clinical marker for predicting tumor metastasis and immune therapy response. A study analyzing serum samples from 120 NSCLC patients found significantly elevated exosomal PD-L1 levels [40]. Another study found a significant correlation between exosomal PD-L1 expression and lymph node metastasis positivity [41]. In summary, serum exosomal PD-L1 not only serves as a quantitative marker for PD-L1 status but may also help predict the patient's response to anti-PD-1 immunotherapy [42].

PD-L1 inhibits T cell immune responses through the PD-1/PD-L1 signaling pathway. When PD-L1 binds to PD-1 on the surface of T cells, the tyrosine phosphatase SHP-2 is recruited to the cytoplasmic domain of PD-1. This inhibits the phosphorylation of the PI3K/AKT and MAPK signaling pathways, thereby suppressing T cell proliferation, activation, and survival [43]. Furthermore, the PD-L1/PD-1 interaction also affects TCR signaling, phosphorylating the immunoreceptor tyrosine-based inhibitory motif (ITIM) and immunoreceptor tyrosine-based switch motif (ITSM), which further recruit SHP-1 and SHP-2. This hinders the activation of the PI3K/AKT/mTOR pathway, generating a similar suppressive effect [44]. Additional studies have shown that PD-L1 can activate the Wnt/β-catenin signaling pathway, leading to increased expression of β-catenin and its downstream target genes, such as Axin2, Snail1, and fibronectin, which in turn promote the production of T cell immune suppressive factors [45].

In addition to directly inhibiting T cell function through PD-L1, LCDEs also impact T cell immune defense through other mechanisms. Studies have shown that EGFR-19del present in exosomes can effectively transfer to the surface of dendritic cells, inhibiting CD8 + T cell activation and leading to poor responses to PD-1/PD-L1 blockade in these patients [46]. Furthermore, circUSP7 in LCDEs can suppress the secretion of anti-tumor factors, such as interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), granzyme B, and perforin by CD8 + T cells, further weakening their anti-tumor functions [47]. Another study found that LCDEs regulate the interaction between CCL1 + lung fibroblasts and CCR8 + Tregs, promoting the differentiation and accumulation of Tregs, thereby reinforcing the immune suppressive effect within the tumor microenvironment [48].

NK cells are a critical component of the immune system, capable of recognizing and killing lung cancer cells. The number and activity of NK cells are closely associated with the severity, metastasis, and prognosis of lung cancer [49]. NK cells regulate their anti-tumor function through the expression of various activating receptors (such as NKG2D, NKp46, NKp30) and inhibitory receptors (such as NKG2A, Ly49I) [50–53]. However, in the lung cancer metastatic microenvironment, under the influence of LCDEs, the expression of inhibitory receptors on NK cells increases, while activating receptors are downregulated, which is closely related to the tumor's immune escape mechanism (Fig. 3a). Research has shown that IDO1 upregulates the expression of ADAM10 through the IDO1-Kyn-AhR signaling pathway, thereby inhibiting the expression of NKG2D ligands, which ultimately leads to significant impairment of NK cell function [54]. Moreover, through immunofluorescence analysis of samples from 84 lung cancer patients and confirmation in a mouse lung metastasis model, it was demonstrated that the high expression of HLA-E and HLA-G on the surface of LCDEs serves as ligands for the NK cell inhibitory receptors CD94/NKG2A and immunoglobulin-like transcript molecule 2 (ILT2). These molecules inhibit NK cell activation and further weaken their anti-tumor function [55].

Recent studies have further demonstrated that LCDEs can stimulate T cells to produce interleukin-22 (IL-22), which subsequently induces tumor cells to express CD155. CD155 inhibits NK cell function by facilitating the internalization of the activation receptor CD226 on NK cells [56]. Although previous research has highlighted the critical role of NK cells in lung cancer immunity, studies on NK cell activation, particularly regarding their activating and inhibitory receptors, are still underdeveloped. Advancing this research may be pivotal for enhancing NK cell-mediated immunity and improving lung cancer prognosis.

Macrophages, as a crucial component of the tumor microenvironment, exhibit two polarization phenotypes: M1 pro-inflammatory and M2 anti-inflammatory [57]. Studies have shown that tumor-associated macrophages (TAMs) primarily exhibit the M2 phenotype, and the cytokines they secrete, such as IL-4 and IL-6, enhance the tumor's invasive abilities [58]. LCDE-mediated macrophage polarization is a key step in the formation of the PMN. Long non-coding RNAs (lncRNAs) in exosomes play a critical role in regulating macrophage polarization. LncRNA-HOXC-AS2 in LCDEs binds to STAT1, inhibiting the activation of the STAT1/SOCS1 and STAT1/CIITA signaling pathways, thereby inducing macrophages to polarize towards the M2 phenotype [59]. Additionally, LncRNA-00313 increases STAT6 expression by adsorbing miR-135a-3p, further promoting M2 polarization [60]. Another study showed that LncRNA-00963 regulates STAT6, increasing the expression of the M2 macrophage marker CD206, while

decreasing the expression of the M1 macrophage marker HLA-DR, reinforcing the M2 polarization trend [61]. In addition to lncRNAs, circular RNAs (circRNAs) in LCDEs also play significant roles in macrophage polarization. For example, circ-PLEKHM1 enhances the PABPC1-eIF4G interaction, promoting the translation of OSMR mRNA and activating the JAK/STAT3 signaling pathway, which induces macrophages to polarize towards the M2 phenotype [62].Circ-0001715 adsorbs miR-205-5p to upregulate TREM2, further promoting M2 macrophage polarization [63]. Another study indicated that circ-PVT1 promotes M2 polarization by targeting the miR-124-3p/EZH2 axis [64]. These circRNAs play diverse roles in M2 macrophage formation through various regulatory mechanisms. Furthermore, miRNAs also play key roles in exosome-mediated regulation of macrophage polarization. miR-1290 in LCDEs significantly promotes M2 polarization by targeting SOCS3 [65]. miR-21 enhances M2 polarization by targeting IRF1 [66]. Additionally, miR-19b-3p promotes M2 polarization through the PTPRD/STAT3 pathway, and this polarized state can be feedback-regulated through exosomal lncRNA-00273 in lung adenocarcinoma metastasis, forming a positive feedback loop [67]. These miRNAs demonstrate the bidirectional regulatory capacity of exosomes in macrophage polarization, reshaping the tumor microenvironment by both inhibiting anti-tumor pathways and enhancing tumor-promoting pathways.

Table 1 The role of exosomes in immunosuppression of lung cancer

Exosomal contents	Related genes or pathway	Effect	Ref.
miR-21a	PDCD4	Induced MDSCs	[6]
S100A8/A9	RAG、TLR4	Induced MDSCs	[34]
S100A10	CXCL1、 CXCL8	Induced MDSCs	[35]
PD-L1	miRNA- let-7	T cells inhibition	[37]
PD-L1	sPD-L1	T cells inhibition	[38]
PD-L1		T cells inhibition	[39]
circUSP7	IFN-γ、TNF-α、Granzyme B、Perforin	T cells inhibition	[47]
IDO1	IDO1-Kyn-AhR	NK cells inhibition	[54]
LncR-HOXC	SOCS1/CIITA	Macrophage M2 polarization	[59]
LncR-00313	STAT6	Macrophage M2 polarization	[60]
LncR-00963	STAT6	Macrophage M2 polarization	[61]
circ-PLEKHM1	JAK/STAT3	Macrophage M2 polarization	[62]
circ-0001715	TREM2	Macrophage M2 polarization	[63]
circ-PVT1	miR-124-3p	Macrophage M2 polarization	[64]
circ-ADRM1	MMP14	Macrophage M2 polarization	[71]
miR-129	SOCS3/STAT3	Macrophage M2 polarization	[65]
miR-21	IRF1	Macrophage M2 polarization	[66]
miR-19b-3	PTPRD/STAT3	Macrophage M2 polarization	[67]
miR-146a	TRAF-6、IRAK-1	Inhibition of M1 polarization	[68]

Exosomes also inhibit M1 macrophage polarization. For example, miR-146a in LCDEs targets TRAF-6 and IRAK-1 to suppress M1 macrophage polarization, thereby reducing the anti-tumor activity of tumor-associated macrophages (TAMs) [68]. Although most exosome components promote M2 macrophage polarization, certain molecules have shown inhibitory effects on M2 polarization. For instance, miR-770 targets MAP3K1 to prevent macrophage polarization towards the M2 phenotype, subsequently inhibiting the invasion of NSCLC cells [69]. This finding offers a new approach to enhancing anti-tumor immunity by inhibiting M2 polarization. In addition to regulating gene expression, LCDEs further enhance tumor immune evasion by altering macrophage metabolic pathways. Research has shown that LCDEs bind to Toll-like receptor 2 (TLR2) on the surface of macrophages, activating the NF-kB signaling pathway, which enhances macrophage glycolysis by increasing the expression of glucose transporter 1 (GLUT-1) and subsequently increasing lactate production [70]. Lactate, as a metabolic byproduct, promotes the expression of PD-L1 on macrophage surfaces through the NF-kB pathway. High PD-L1 expression inhibits T cell activity, further exacerbating tumor immune evasion. This metabolic regulation mechanism provides a novel pathway for tumor cells to evade host immune surveillance and offers potential targets for future immune-metabolic therapies.

In conclusion, lung cancer cells regulate the immune system strategically through the release of exosomes, suppressing the anti-tumor responses of effector immune cells while recruiting and activating suppressive immune cells to establish an immunosuppressive tumor microenvironment. These mechanisms underscore the pivotal role of exosomes in tumor immune evasion and metastasis, suggesting the potential of molecules such as PD-L1 and miR-21a as therapeutic targets. Further investigation of these mechanisms will not only advance our understanding of how tumors evade immune surveillance but also provide a critical basis for the development of new immunotherapy strategies, thereby enhancing treatment outcomes and improving patient prognosis (Table 1).

Exosomes promote angiogenesis in the PMN

Angiogenesis plays a critical role in tumor development and metastasis. By remodeling the microenvironment of distal organs, tumor angiogenesis provides essential

support for tumor cell survival and proliferation. Specifically, angiogenesis supplies oxygen and nutrients to tumor cells, facilitates the clearance of metabolic waste, and provides pathways for tumor cells to enter the circulatory system, thereby promoting their dissemination [72]. LCDEs modulate several angiogenesis-related signaling pathways by carrying a range of bioactive molecules such as miRNA, lncRNA, and proteins, which stimulate endothelial cell proliferation and migration. This process upregulates pro-angiogenic factors and downregulates inhibitory factors, significantly altering the microenvironment of the target organ. These changes create favorable conditions for tumor cell colonization and growth, ultimately resulting in the formation of the PMN [18] (Fig. 3b).

MiRNAs in exosomes play a critical role in the regulation of angiogenesis. For instance, miR-130a-3p promotes angiogenesis in tumors by upregulating RAC1 and NRP2, which activate the PI3K/Akt signaling cascade [73]. Similarly, miR-4739 promotes angiogenesis in tumor cells and endothelial cells by targeting APC2 and DKK3 within the Wnt/β-catenin signaling pathway [74]. Additionally, miR-23a enhances vascular permeability and further promotes the dissemination of lung cancer by inhibiting the tight junction protein ZO-1 [24]. Other key miRNAs include: miR-619-5p, which promotes angiogenesis by inhibiting RCAN1.4 and enhances the proliferation and metastasis of NSCLC cells [75]; miR-141, which promotes endothelial cell proliferation, migration, and lumen formation by targeting KLF12 [76]; and miR-210, which activates the JAK2/STAT3 signaling pathway in fibroblasts, leading to increased expression of pro-angiogenic factors such as MMP9, FGF2, and VEGF [77]. Together, these miRNAs synergistically enhance the angiogenic capacity of lung cancer and create a favorable microenvironment for distant metastasis.

In addition to miRNAs, long non-coding RNAs (lncRNAs) in exosomes also play a role in this process. In NSCLC, lncRNA-MFI2-AS1 functions as a competing endogenous RNA for miR-107, counteracting its inhibition of NFAT5, which activates the PI3K/AKT signaling cascade and promotes angiogenesis and tumor metastasis [78]. Similarly, lncRNA-GAS5 competitively binds to miR-29-3p, increasing the expression of PTEN, which further enhances the PI3K/AKT signaling pathway, thereby supporting tumor angiogenesis and dissemination [79].

Exosomes also carry a variety of pro-angiogenic proteins. For example, the m6A methylation reader protein IGF2BP2 increases the stability of FLT4 mRNA through m6A modification, activating the PI3K/Akt signaling cascade, thereby enhancing angiogenesis and accelerating tumor metastasis [80]. This highlights the critical role of IGF2BP2 in regulating angiogenesis by stabilizing the expression of transcripts. In small cell lung cancer (SCLC), Profilin 2 promotes tumor cell proliferation and migration through exosomes, while activating the Smad2/3 and pERK signaling pathways, further enhancing angiogenesis [81]. Similarly, LRG1 in exosomes from NSCLC enhances endothelial cell proliferation and angiogenesis through the TGF-β signaling pathway [82]. Additionally, SYT7 in exosomes transfers CEP55-containing molecules to HUVECs, activating the mTOR signaling pathway and promoting angiogenesis [83]. In lung adenocarcinoma, Cadherin-2 (CDH2) regulates HIF-1α/VEGF-mediated angiogenesis by activating the MAPK/ERK and MAPK/JNK signaling pathways [84]. MORC2 upregulates VEGF expression and activates the Wnt/β-catenin signaling pathway, further driving tumor angiogenesis and enhancing tumor stem cell characteristics [85]. The proteins carried by exosomes synergize through multiple signaling pathways, significantly driving the angiogenesis process in tumors. Future research should further investigate the specific mechanisms of action of these proteins to develop more precise anti-angiogenesis therapeutic strategies.

Although certain molecules in the tumor microenvironment exert anti-angiogenic effects, lung cancer exosomes promote angiogenesis by downregulating these inhibitors. For instance, the well-known anti-angiogenic factor HIPK2 is directly targeted by miR-1260b, which reduces HIPK2 expression and subsequently enhances the angiogenic capacity of HUVECs [86]. Similarly, TIMP2 and KLF2 are inhibitors of tumor angiogenesis, and miR-3157-3p promotes angiogenesis in HUVECs by targeting the 3' UTRs of these factors, while also enhancing the migration and invasion of NSCLC cells [87]. Another study demonstrates that miR-197-3p significantly promotes the proliferation, angiogenesis, and migration of HUVECs by targeting both TIMP2 and TIMP3 [88].

In summary, exosomes released by lung cancer cells play a critical role in the formation of PMN by carrying various miRNAs, lncRNAs, and proteins that regulate multiple angiogenesis-related signaling pathways. Although several anti-angiogenesis agents are already available, these therapies remain inadequate due to the powerful pro-angiogenic capacity of tumor cells. Therefore, future research should further investigate these molecular mechanisms and develop targeted therapies directed against key signaling pathways and pro-angiogenic factors, particularly through combination therapies that target multiple critical pathways, in order to more effectively prevent tumor metastasis and progression (Table 2).

Table 2 The role of exosomes in angiogenesis of lung cancer

Exosomal contents	Relevant pathways or targets	Effect	Ref.
miR-130a-3p	PI3K/Akt	FpA reduction	[73]
miR-4739	Wnt/β-catenin	Vascular epithelial cell proliferation	[74]
miR-23a	ZO-1	HIF-1α accumulation	[24]
miR-619-5p	RCAN1.4	Promoting angiogenesis	[75]
miR-141	KLF12	Increased microvascular density	[76]
miR-210	JAK2/STAT3	Increased angiogenesis factors	[77]
lncRNA- MFI2-AS1	PI3K/AKTNFAT5	Increased NFAT5	[78]
lncRNA-GAS5	PTEN	Inhibited serine/threonine kinase 1 (AKT) phosphorylation	[79]
IGF2BP2	PI3K-Akt	Promoting angiogenesis	[80]
Profilin 2	Smad2/3、PERK	Promoting endothelial cell formation	[81]
LRG1	TGF-β	Promoting angiogenesis	[82]
SYT7	mTOR	Increased CEP55	[83]
CDH2	MAPK/ERK、MAPK/JNK	HIF-1α/VEGF accumulation	[84]
MORC2	Wnt/β-catenin	Increased VEGF	[85]
miR-1260	HIPK2	Promoting angiogenesis	[86]
miR-3157-3	TIMP/KLF2	Increased VEGF/MMP2/MMP	[87]
miR-197-3p	TIMP2、TIMP3	Promoting angiogenesis	[88]

Exosomes promote stromal remodeling at PMN

During tumor metastasis, the remodeling of the extracellular matrix (ECM) is a crucial process that supports the expansion, invasion, and spread of tumor cells. Tumor cells regulate ECM remodeling by releasing various signaling molecules, especially exosomes, which create a favorable microenvironment for tumor colonization at distant sites. Functionally, they reprogram stromal cells within the PMN, including CAFs and pericytes [89]. As important messengers between tumor cells and distant organs, LCDEs carry molecules that, by altering the structure and function of the ECM, promote matrix degradation, collagen fiber remodeling, and fibroblast activation, thus contributing to tumor metastasis.

Activation of MMPs

Tumor matrix remodeling often involves the degradation of the extracellular matrix (ECM), with matrix metalloproteinases (MMPs) playing a critical role in this process. LCDEs promote the secretion of MMPs by regulating the polarization of tumor-associated macrophages (TAMs) towards the M2 phenotype. Studies have shown that MMP-2 and MMP-9, secreted by M2 macrophages, are the primary enzymes responsible for ECM degradation. These enzymes can hydrolyze collagen and other matrix components, facilitating tumor cell invasion and metastasis [90]. For example, exosomal miR-106b targets PTEN, increasing the expression of MMP-2 and MMP-9, thus accelerating ECM degradation and providing space for tumor cell invasion [91].

Fibroblasts convert to CAF

CAFs are crucial reprogrammed stromal cells within the tumor microenvironment, extensively involved in cancer initiation, extracellular matrix remodeling, tumor progression, and the formation of PMN [89]. Lung cancer cells secrete exosomes to convert quiescent fibroblasts into CAFs, maintaining their tumorigenic phenotype through activation of signaling pathways. This process is regarded as a key step in stromal remodeling during tumor metastasis [92] (Fig. 3c). CAFs secrete numerous pro-tumor factors in the tumor microenvironment, such as TGF-β, stromal-derived factor-1α (SDF-1α), S100A4, fibronectin, and matrix metalloproteinases (MMPs), playing essential roles in matrix remodeling and tumor cell migration [93, 94]. Although these molecules have distinct biological functions, they act synergistically to facilitate the formation and progression of PMN in the local microenvironment.

Studies have demonstrated that ITGB6 within LCDEs plays a pivotal role in tumor progression by activating the KLF10 positive feedback loop and enhancing TGF-β signaling, which induces the conversion of normal stromal fibroblasts into CAFs [26]. Similarly, in NSCLC, SUR1 reduces the levels of let-7a-5p in exosomes, further activating the TGF-β pathway and promoting CAF formation [95]. Additionally, through co-culture assays using exosomes from lung cancer patients and MRC5 cells, researchers discovered that EIF4A3 in LCDEs activates the MyD88/NF-κB pathway by stabilizing lncRNA-AGAP2-AS1 expression, thereby further enhancing CAF activation [96]. These findings indicate that exosomes serve as crucial communication mediators between cancer cells and stromal cells, facilitating fibroblast oncogenic transformation via multiple signaling pathways.

In addition to the molecular mechanisms described above, LCDEs promote the expression of CAF markers, such as α-smooth muscle actin (α-SMA) and fibroblast activation protein (FAP), in NIH/3T3 fibroblasts, driving

Table 3 The role of exosomes in matrix remodeling of lung cancer

Exosomal contents	Related genes or pathway	Effect	Ref.
ITGB6	KLF10/TGF-β	Converting fibroblasts to CAFs	[26]
SUR1	let-7a-5p/TGF-β	Converting fibroblasts to CAFs	[95]
miR-106b	PTEN	Increasing MMP-2/9	[91]
EIF4A	MyD88/NF-κB	Converting fibroblasts to CAFs	[96]

their transformation into CAFs [77]. If the conversion of fibroblasts into CAFs could be inhibited, or even reversed back to quiescent fibroblasts, it would significantly inhibit the stromal remodeling of PMN. This strategy offers a novel therapeutic approach for blocking tumor metastasis and may represent a crucial breakthrough in future anti-cancer therapies.

In summary, LCDEs can release a variety of molecules, including miRNAs, circRNAs, and LncRNAs, which induce macrophage polarization toward the M2 phenotype through multiple pathways such as STAT1, STAT3, STAT6, and JAK, thereby facilitating the formation of tumor PMN. Based on this mechanism, future therapeutic strategies may aim to enhance anti-tumor immune responses by promoting M1 polarization and inhibiting M2 polarization of macrophages. For example, one study developed engineered exosomes (I3E) that carry a CRISPRi system to specifically silence the PI3Kγ gene, while a TAM-specific peptide (CRV) on the surface enables targeted delivery, ultimately promoting the polarization of M2 macrophages to M1 macrophages and activating the host's anti-tumor immune response [97]. While current therapeutic approaches targeting macrophage polarization remain limited, further understanding of exosome regulatory mechanisms may lead to breakthroughs in lung cancer immunotherapy (Table 3).

Exosomes as biomarkers and therapeutic applications in lung cancer

In recent years, as the understanding of exosomes has advanced, LCDEs have garnered widespread attention for their biological functions and natural ability to carry bioactive molecules from donor cells, playing a significant role in the occurrence, diagnosis, treatment, and LCDEs is of lung cancer [9]. The cargo carried by LCDEs, including miRNAs and proteins, is considered a promising non-invasive tool for early diagnosis, prognosis, and treatment, as it provides key information about signaling pathways involved in tumor biology. Additionally, LCDEs contribute to tumor cell resistance and the formation of PMN, offering new directions for clinical exploration and application.

Exosomes as biomarkers in lung cancer diagnosis

In lung cancer diagnosis, LCDEs are being explored as potential biomarkers. Various protein, glycoprotein, and nucleic acid markers have been identified as promising [98]. For instance, specific proteins such as CKAP4, CXCR4, and GCC2 are highly expressed in the serum of lung cancer patients. CKAP4 shows a positivity rate of 19.6% in lung cancer patients, compared to 6.5% in healthy controls, but its low sensitivity limits its clinical utility as a single biomarker [99]. Similarly, the diagnostic sensitivity of exosome GCC2 is 90%, with a specificity of 75%, indicating that it should be used alongside other markers to improve diagnostic accuracy [100]. As research progresses, the potential of various proteins continues to be uncovered. For example, FGB, FGG, and VWF are closely linked to the early diagnosis and prognosis of NSCLC, while proteins like CFHR5, C9, and MBL2 may help assess lung cancer metastasis, especially CFHR5, which is significantly correlated with patient survival [101]. PD-L1 is significantly elevated in lung cancer patients, and its expression level is notably associated with lymph node metastasis. Quantitative detection of PD-L1 may also help predict patients' responses to anti-PD-1 immunotherapy [41]. Although RNA biomarkers are more complex to detect, some, such as LncRNA-RP5-977B1, have shown high diagnostic potential, with an AUC value of 0.8899 [102]. Future research should focus on optimizing RNA biomarker detection technologies to enhance their clinical feasibility and effectiveness.

Exosome detection technologies have been continually advancing, primarily including electrochemical, immunoassay, and spectroscopic techniques. While these methods have demonstrated good sensitivity and specificity in laboratory settings, their clinical application still faces challenges. Electrochemical biosensor technology has shown promising potential for precise exosome detection, with studies utilizing electrochemical sensors to identify exosomal PD-L1 from lung cancer and achieving accurate detection [103]. However, electrochemical methods are complex to operate and cost-prohibitive, which limits their large-scale clinical adoption. Spectroscopic techniques, such as Surface-Enhanced Raman Spectroscopy (SERS), have exhibited exceptional performance in exosome capture and analysis, although their clinical application remains in the exploratory phase [104]. Immunoassay techniques, such as ELISA and Western Blot (WB), have been employed to detect specific markers, such as calnexin, in exosomes from the serum of lung cancer patients [105]. Surface Plasmon Resonance (SPR)-based detection methods have also proven highly effective in detecting exosomal TF-Ag-α, with an accuracy exceeding 95% in lung cancer diagnosis [106]. Additionally, PCR technology has been used to quantify lncRNA in EpCAM-specific exosomes, which

can differentiate between benign and malignant lung cancer [107]. Despite these advancements, further optimization of these technologies is required for clinical application, particularly to enhance their ease of use and detection efficiency.

Exosomes in lung cancer therapy

In terms of treatment, exosome-based strategies are also emerging. Due to their natural homing effects and excellent biomolecule-carrying capacity, exosomes have become promising drug delivery vehicles [108]. Similarly, exosomes are regarded as efficient drug carriers because of their inherent properties and ability to carry large biomolecules [7]. Techniques such as electroporation can be employed to load exosomes with chemotherapeutic drugs or RNA molecules, and modifications can enhance their targeted delivery accuracy. For instance, engineered exosomes derived from chimeric antigen receptor T cells (CAR-T) have been used as drug delivery vehicles, reducing tumor volume and extending survival in lung cancer mouse models [109]. Exosomes can also carry specific RNA molecules, such as siRNA and miRNA, to target and silence key genes in cancer cells [110]. For example, researchers loaded miRNA-126 into exosomes and intravenously injected them into lung cancer mice, significantly inhibiting the proliferation and migration of A549 lung cancer cells [111].

Limitations and challenges

Although LCDEs have shown great potential in the diagnosis and treatment of lung cancer, their clinical application still faces numerous challenges and limitations. First, the heterogeneity of exosomes is a major issue. As exosomes originate from various cell types, such as tumor cells and immune cells, their composition and function exhibit high variability, leading to significant differences in their specificity and sensitivity across different patients and tumor types. This increases the difficulty in early diagnosis and treatment [23]. Therefore, the variability of exosomes between different patients and tumor types may result in differing specificity and sensitivity as biomarkers [112].

Second, the separation and purification techniques for exosomes remain a bottleneck for their clinical application. While current methods such as ultracentrifugation, immunoaffinity, and size-exclusion chromatography are effective in laboratory settings, they face challenges in clinical practice, such as low efficiency, high cost, and complexity [113]. Moreover, although exosomes have good biocompatibility and cell membrane penetration capabilities, their drug-loading efficiency is relatively low, and their targeting ability is limited [114]. The targeting delivery capacity of exosomes is influenced by their membrane surface markers and the tumor microenvironment, which limits the precise delivery of drugs to tumor cells and affects the treatment outcome [115]. Another challenge is the role of exosomes in treatment resistance. Tumor cells transfer drug resistance information through exosomes, enhancing their resistance to chemotherapy and further exacerbating treatment failure [116]. For example, circVMP1 promotes cisplatin resistance in non-small cell lung cancer by targeting the miR-524-5p-METTL3/SOX2 axis [117]. In addition, exosomes can mediate the excretion of chemotherapy drugs. The main mechanisms include enhancement of drug efflux pumps, transport of miRNA and mRNA, regulation of antioxidant enzymes, and transmission of resistance information between cells [118]. This phenomenon of resistance transmission presents a significant challenge for exosomes as a therapeutic tool, requiring in-depth research to overcome this issue and improve treatment efficacy.

In conclusion, although exosomes demonstrate great potential in the diagnosis and treatment of lung cancer, their clinical application faces a range of challenges, including heterogeneity, limitations in separation technologies, drug-loading efficiency, and treatment resistance. To fully translate exosomes into effective clinical tools, breakthroughs are urgently needed in both technical and biological aspects. With further research into exosome biology and advancements in technology, it is expected that these limitations will be overcome, enabling the widespread application of exosomes in precision medicine.

Clinical application of exosomes

Currently, SOB100 is the only exosome-based lung cancer treatment project that has entered clinical phase I. This genetically engineered exosome expresses HLA-G nanobodies on its surface and is designed to target drug delivery to the tumor microenvironment. It was approved by the FDA for clinical phase I trials in March 2025. However, no supporting literature or subsequent reports have been published to date. Other studies, such as the inhalable IL-12 mRNA exosome developed by Columbia University and the TMTP1 peptide-modified exosome delivery system developed by Harbin Medical University, are still in preclinical stages [119, 120]. Although most research remains in preclinical stages, the potential for exosome application in lung cancer treatment is still vast. Future studies should focus on optimizing exosome production and separation processes, developing standardized clinical application procedures, and exploring combined therapies to further enhance treatment efficacy and patient survival rates.

Conclusion and perspectives

LCDEs play a critical role in the formation of the pre-metastatic niche, acting as messengers between primary tumors and distant organs. Through their diverse molecular cargos—comprising miRNAs, lncRNAs, and proteins—LCDEs facilitate immune evasion, angiogenesis, and extracellular matrix remodeling, which significantly contribute to the metastatic spread of cancer cells. Understanding the molecular mechanisms underlying these processes not only enriches our knowledge of lung cancer metastasis but also presents promising avenues for developing exosome-targeted therapies.

Despite the promising potential of exosomes, several challenges remain. The heterogeneity of exosomes across different patients and tumor types complicates their use as reliable diagnostic or therapeutic tools. Moreover, limitations in exosome isolation techniques and low drug-loading efficiency hinder their broader clinical application. The ability of exosomes to mediate drug resistance also presents a formidable obstacle to treatment success.

Future research should focus on overcoming these barriers. This includes advancing the molecular characterization of exosomes, developing standardized methods for exosome isolation and drug loading, and investigating their role in treatment resistance. Additionally, the development of exosome-based liquid biopsy techniques holds immense promise for non-invasive cancer detection. Combining exosome-targeted therapies with existing treatment strategies, such as immunotherapy and anti-angiogenesis treatments, could further enhance treatment efficacy and improve patient survival. As exosome-based therapies continue to evolve, they have the potential to play a pivotal role in the precision treatment of lung cancer, offering a path towards more effective and personalized treatment options.

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Author contributions
Y.Z. and M.Z. were responsible for the conception and design of the study, as well as for obtaining funding and supervising the overall project.X.G., X.Z., and Y.L. contributed to data acquisition, performed data analysis, and participated in interpretation of the results.Q.Z. and D.W. assisted in data collection and provided technical support.Z.W. and Y.Z. contributed to the critical revision of the manuscript for important intellectual content.W.P., X.G., and X.Z. drafted the initial manuscript.All authors reviewed and approved the final version of the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This declaration is not applicable as the study does not involve human or animal subjects.

Competing interests
The authors declare no competing interests.

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