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Revolutionizing lung cancer treatment: harnessing exosomes as early diagnostic biomarkers, therapeutics and nano-delivery platforms

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Abstract

Lung cancer, known for its high morbidity and mortality rates, remains one of the most critical health challenges globally. Conventional treatment options, such as chemotherapy and surgery, are often limited by high costs, significant side effects, and often yield a poor prognosis. Notably, recent research has shed light on the potential therapeutic roles of exosomes, which essentially influence lung cancer's development, diagnosis, treatment, and prognosis. Exosomes have been revealed for their exceptional properties, including natural intercellular communication, excellent biocompatibility, minimal toxicity, prolonged blood circulation ability, and biodegradability. These unique characteristics position exosomes as highly effective drug delivery systems, nanotherapeutics, and potential diagnostic and prognostic biomarkers in lung cancer. This review provides a comprehensive review of the physiological and pathological roles of exosomes in lung cancer, emphasizing their potential as innovative diagnostic biomarkers, therapeutics, and delivery platforms. By harnessing their unique properties, exosomes are poised to revolutionize the diagnosis and treatment of lung cancer, offering a promising avenue for more personalized and effective therapies.

Keywords Exosomes, Lung cancer, Diagonosis, Nanotherapeutics, Drug delivery

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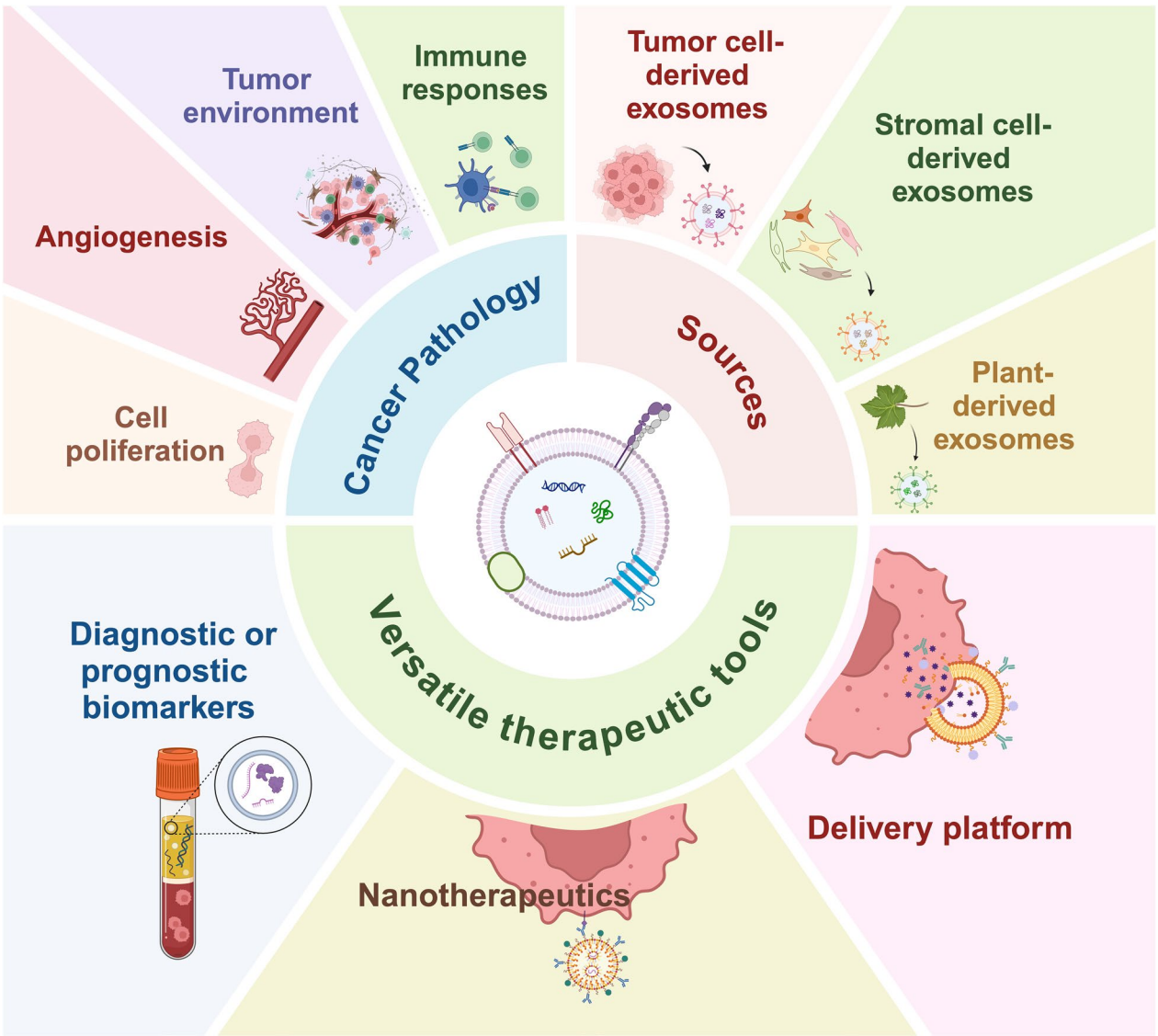
Graphical abstract



Introduction

Lung cancer, arising from the bronchial glands or mucosa, remains the leading cause of cancer-related mortality worldwide, with 2.48 million new cases reported in 2022, accounting for 12.4% of all cancer diagnoses globally [1, 2]. Small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) are two primary pathological subtypes of lung cancer, with NSCLC constituting 80–85% of cases [3]. Despite advancements in treatments such as surgery, chemotherapy, radiotherapy, immunotherapy, and targeted therapies, these approaches are often hindered by drug resistance, recurrence, and metastasis, resulting in poor survival rates. It is urgently needed to develop individualized strategies for the treatment of lung cancer.

Exosomes are nanovesicles composed of lipid bilayer membranes, which have emerged as key mediators in intercellular communication [4]. Derived from tumor, stromal, or plant cells, they transport bioactive substances, including proteins, mRNA, and miRNA, regulating gene and protein expression [5, 6]. Existing studies have indicated that exosomes play a pivotal role in various aspects of the tumor microenvironment (TME),

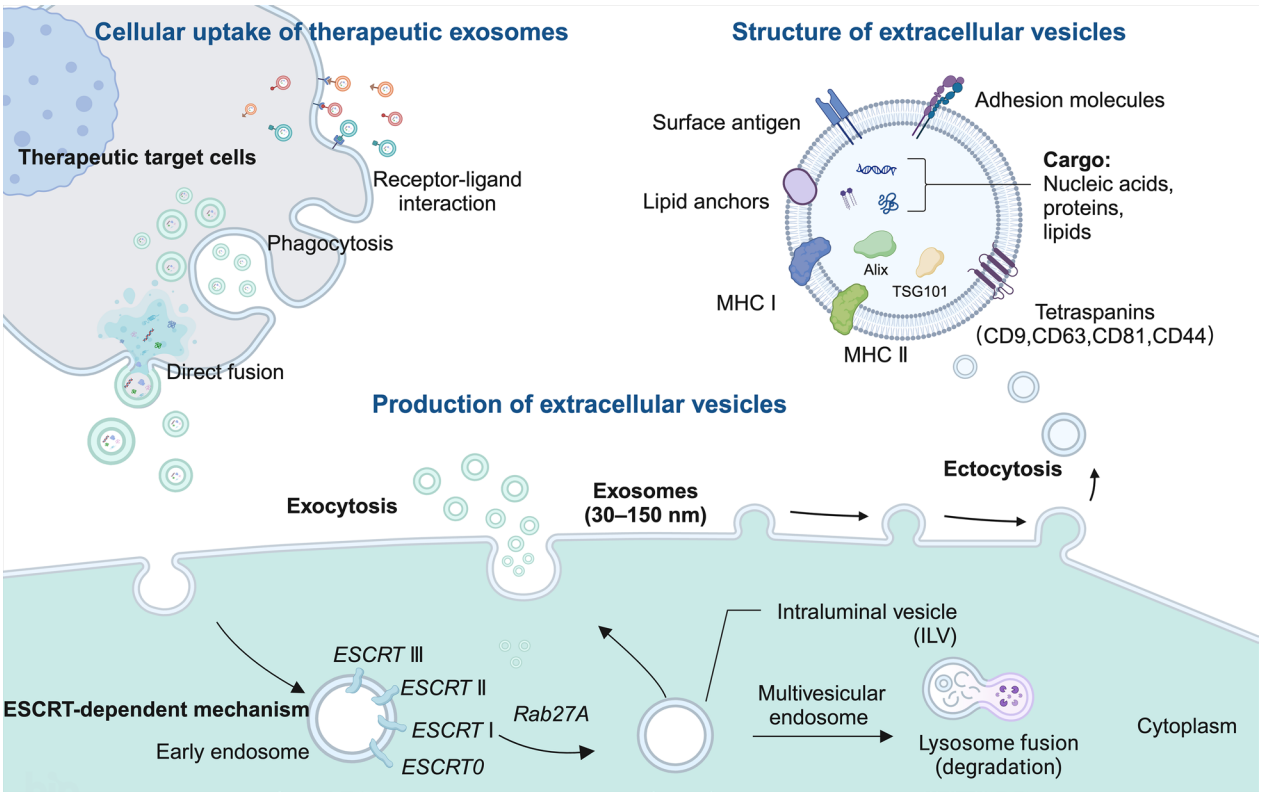


Fig. 1 The structure, production, and cellular uptake of exosomes

influencing lung cancer development, invasion, metastasis, immune regulation, angiogenesis, and chemotherapy resistance [7, 8]. Notably, exosomal components such as proteins and miRNA have demonstrated significant potential as biomarkers for early lung cancer diagnosis [9]. This potential was underscored in 2016 when exosome diagnostics introduced the pioneering liquid biopsy product, ExoDX Lung, enabling the sensitive, accurate, and real-time detection of EML4-ALK mutation in NSCLC patients through the isolation and analysis of exosome RNA from blood samples [10].

Exosomes also exhibit unique therapeutic advantages, including stability in biological fluids, biocompatibility, low immunogenicity, and potential for modification. They not only facilitate biological activity through their cargo but also serve as promising drug delivery vehicles [11–13]. Their dual functionality positions them as innovative tools for lung cancer treatment, offering opportunities for precision medicine [14, 15].

This review explores the biogenesis of exosomes and their multifaceted roles in lung cancer pathology. It further highlights their emerging applications as biomarkers, therapeutic agents, and drug carriers, providing a comprehensive overview of their potential to revolutionize lung cancer diagnosis and treatment.

Exosome biogenesis and its role in lung cancer pathology

The biogenesis of the exosomes

Exosomes are lipid bilayer vesicles, ranging from 30–150 nm in diameter, derived from late endosomes. They encompass a diverse range of biomolecules, including proteins, nucleic acids (DNA, mRNA, miRNA, non-coding RNA), and lipids [16]. Their biogenesis follows an ESCRT-dependent mechanism, involving four protein complexes (ESCRT-0 to −3) and Vps4, which drive the formation of multivesicular bodies that fuse with the plasma membrane to release exosomes [17, 18]. Exosomes mediate cell-to-cell communication through three mechanisms: (1) receptor-ligand interactions trigger fusion and release of contents into target cells, influencing gene transcription; (2) fusion with the cell membrane releases exosomal cargo into the cytoplasm; (3) exosomes are internalized via endocytosis. These complex mechanisms and the specificity of exosome uptake contribute to their diverse functions in intercellular signaling [19]. The structure, production, and cellular uptake of exosomes are shown in Fig. 1. (Created in https://BioRender.com).

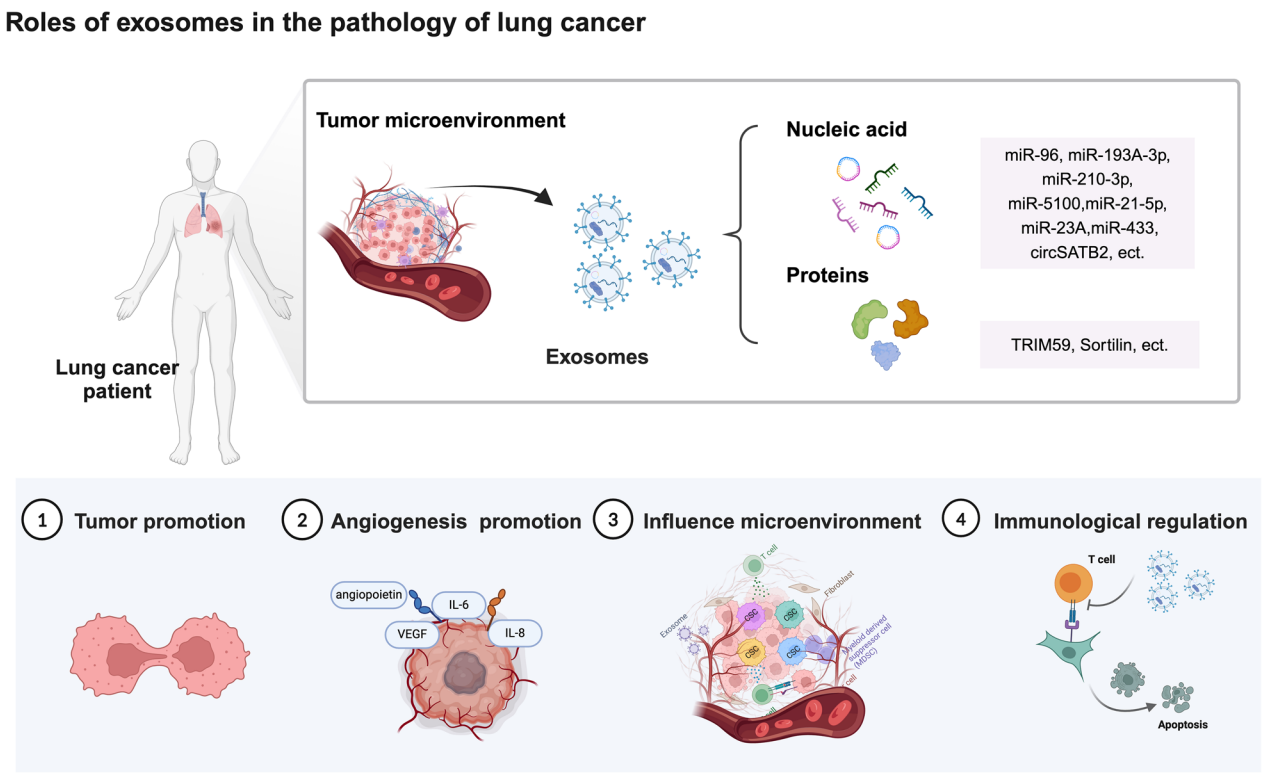


Fig. 2 The roles of exosomes in the pathology of lung cancer

Role of exosomes in lung cancer pathology

Exosomes play a critical role in lung cancer progression by promoting tumor growth, metastasis, immune evasion, and chemotherapy-radiotherapy resistance [15, 20–24]. The pathology of exosomes in the progress of lung cancer is summarized in Fig. 2. (Created in https://BioRender.com).

Exosomal miRNAs, such as miR-96, promote cell proliferation by targeting LMO7 [25], while miR-193A-3p, miR-210-3p, and miR-5100, derived from hypoxic bone marrow-derived mesenchymal stem cells (BMSCs), enhance metastasis by activating STAT3-induced epithelial-mesenchymal transition (EMT) [26–28]. Furthermore, exosomal miRNA-21-5p from blood schwann cells targets the metalloproteinase inhibitor RECK in tumor cells, facilitating their proliferation, migration, and invasion. CircRNAs in cancer cell exosomes, such as circSATB2, have also been found to promote the proliferation and invasion of NSCLC cells [29, 30]. Interestingly, some studies have revealed a new scene between tumor cells and macrophages: TRIM59 is directly transferred from cancer cells to macrophages through the exosomal, which promotes the degradation of ABHD5 proteasome, induces NLRP3 histone to activate the inflammatory body, and promotes the secretion of IL-1β, thereby promoting the proliferation and invasion of cancer cells [31].

While numerous studies highlight the role of exosomes in tumor metastasis and progression, further research is needed to fully elucidate their mechanisms of intercellular communication and their potential as therapeutic targets.

Exosomes also influence angiogenesis, a critical process for tumor growth and metastasis [32]. They regulate endothelial cell migration, phenotypic changes, and vascular sprouting by transmitting growth factors and angiogenin [33, 34]. Hypoxia-induced exosomal miR-23A enhances vascular permeability by targeting proline hydroxylases PHD1 and PHD2, leading to HIF-1α accumulation in endothelial cells and promoting lung cancer vascularization [35]. Additionally, the exosomal sorting protein Sortilin, derived from A549 cells, plays a key role in endothelial cell activation and migration, further driving angiogenesis in lung cancer [36].

The TME, composed of immune cells, blood vessels, extracellular matrix, fibroblasts, lymphocytes, and bone marrow-derived inflammatory cells, is heavily influenced by exosomes [37]. Exosomes regulate the behavior of fibroblasts and immune cells to support tumor growth and mediate metabolic reprogramming within the TME [38–40]. For example, exosomes from chemotherapy-resistant lung cancer patients remodel metabolism in a PKM2-dependent manner to sustain resistance [41].

Meanwhile, exosomes also contain immunostimulatory and immunosuppressive factors that regulate immune responses in the TME by modulating gene expression and signaling pathways in recipient cells [42]. NSCLC-derived exosomes can evade immune detection by inhibiting T cell activation, inducing regulatory T cells and myeloid suppressor cells, and impairing NK and CD8 + T cell function [43, 44]. Exosomal miR-433 has been shown to inhibit NSCLC tumorigenesis by increasing CD4 + T and CD8 + T cell infiltration [45]. Additionally, 80% of exosomes from lung cancer biopsies contain epidermal growth factor receptor (EGFR), which can induce tolerant dendritic cells (DC) and suppress tumor antigen-specific CD8 + T cells, leading to immune evasion [40, 46]. NSCLC-derived exosomal PD-L1 is related to the efficacy and prognosis of tumor immunotherapy and may become a new target for immunotherapy [47]. In conclusion, modulating the release of exosomes to alter the anti-tumor immune response in the TME is a potential strategy to enhance lung cancer immunotherapy efficacy.

Exosomes as versatile therapeutic tools for lung cancer

The treatments of NSCLC mainly include surgery, chemotherapy, radiotherapy, molecular targeted therapy (EGFR inhibitors, anaplastic lymphoma kinase (ALK) inhibitors, angiogenesis inhibitors), and immunotherapy [48, 49]. In addition, traditional Chinese medicine can be used as an adjunct treatment for NSCLC or can be used alone in the treatment of NSCLC, which has a significant impact on the survival, quality of life, and toxicity of patients [50]. Despite advancements in targeted molecular therapies, NSCLC continues to have high morbidity and mortality rates, highlighting the need for precision and personalized treatment approaches. Exosomes are now recognized as valuable tools for developing diagnostic methods and advancing therapeutic strategies [51].

Exosomes as diagnostic or prognostic biomarkers for lung cancer

It is of great significance for the diagnosis and treatment of lung cancer to find effective early screening methods [52]. At present, the main screening methods for lung cancer include chest X-ray, low-dose CT, sputum shedding cytology, bronchoscopy, and lung biopsy. Each of these methods has certain limitations in its current clinical application.

Exosomes, as key components of body fluid biopsy, can effectively reflect the characteristics of their parent [53, 54]. The proteins and nucleic acids they carry are similar to tumor cells and participate in the communication between tumor cells and host cells, with the advantages of repeatability and low cost [55]. Their stable lipid bilayer enables them to circulate under physiological conditions and withstand the harsh TME, ensuring high biological stability and long-term storage for detection purposes [56]. Additionally, exosomes have the advantages of less trauma, easy sample acquisition, and dynamic monitoring, making them highly promising as diagnostic markers for lung cancer. Figure 3 demonstrates the main screening methods for lung cancer, the benefits of exosomes in liquid biopsy, and the process of fluid biopsy. (Created in https://BioRender.com).

Studies have shown that exosomal proteins and nucleic acid derived from body fluids have strong potential as lung cancer biomarkers [57]. For instance, the researchers used an ultra-ex vitro method to isolate exosomes from the serum of SCLC patients and healthy individuals, and identified a panel of three serum exosomal miRNAs (miR-200b-3p, miR-3124-5p and miR-92b-5p) as diagnostic and prognostic markers for SCLC. Exosomes isolated from the plasma of NSCLC patients and healthy people can be used as biomarkers to achieve a non-invasive and repeatable detection method [58, 59] (Fig. 4). Some exosomal miRNAs, like miR-200b, are associated with PD-L1 expression and can influence tumor treatment responses. For instance, low expression of miR-200b correlates with poor prognosis in NSCLC and its negative correlation with PD-L1 suggests it may serve as a biomarker for PD-L1 expression and a predictor of immunotherapy efficacy [47].

In addition to miRNAs, circRNA also plays a large role in the diagnosis of lung cancer. Tang et al.proved that hypoxia-induced exosome circPLEKHM1 drives NSCLC metastasis by polarizing macrophages into M2 type. The results revealed a new mechanism by which cancer cells interact with macrophages in the tumor-hypoxic microenvironment to promote metastasis, highlighting the importance of exosomal circPLEKHM1 as a prognostic biomarker and therapeutic target for lung cancer metastasis [60]. Despite these promising findings, the clinical application of exosomes depends on their abundance, isolation techniques, and purity, with advancements in exosome separation technology being crucial for enhancing their clinical use [61].

Exosomes as nanotherapeutics for lung cancer therapy

Exosomes, primarily owing to their biocompatibility and immunologically inert nature, exhibiting considerable promise in therapeutic applications [62]. Studies have shown that targeting signaling pathways involved in tumor exosome secretion or production can effectively inhibit exosome release, thereby reducing carcinogenesis. Fabbri et al. demonstrated that GW4869, a neutral inhibitor of sphingomyelinase, blocks ceramide biosynthesis and inhibits exosome inward budding,

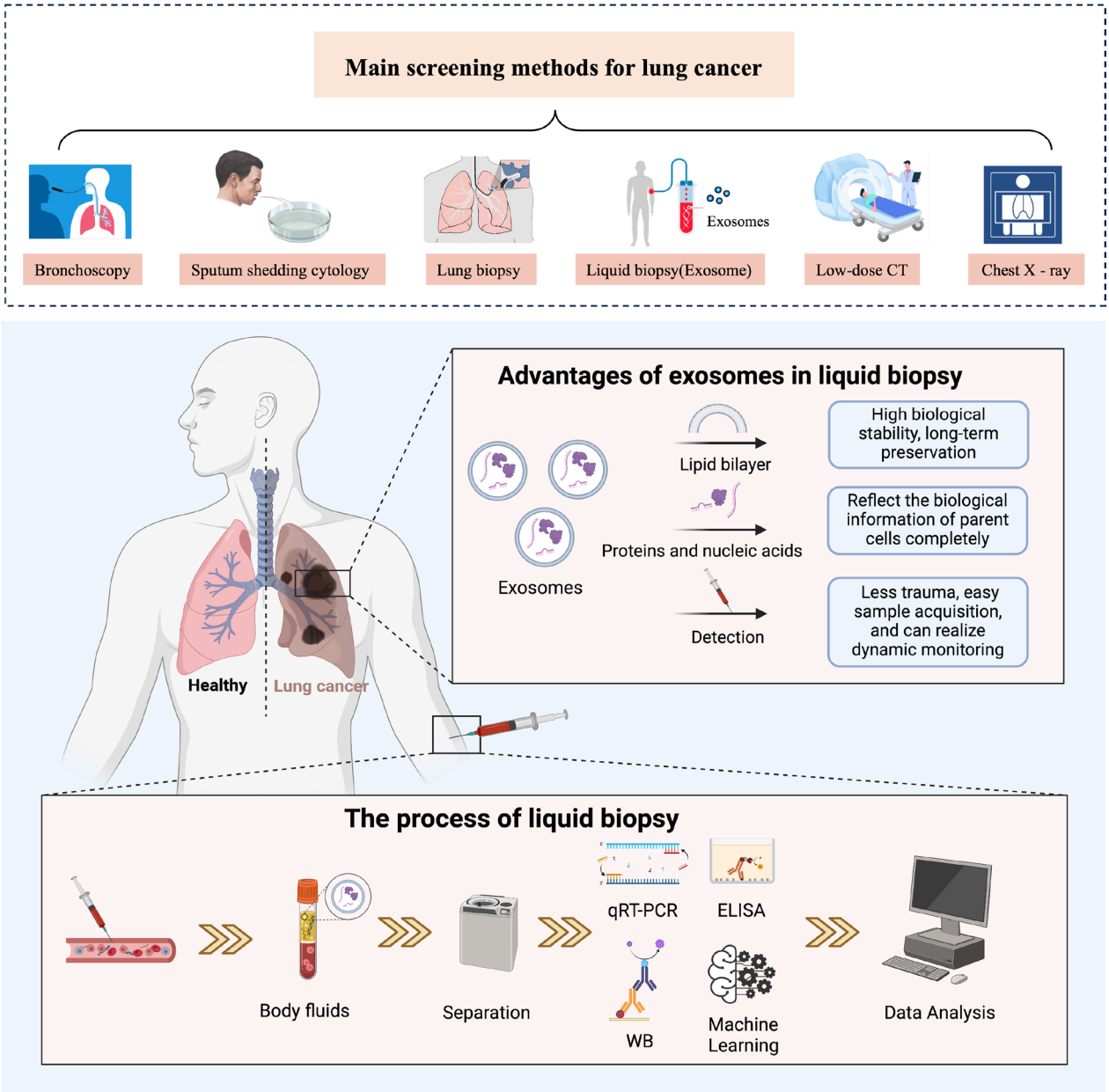


Fig. 3 The main screening methods for lung cancer, the benefits of exosomes in liquid biopsy, and the process of fluid biopsy

leading to reduced exosome production and decreased lung cancer metastasis [63]. Furthermore, exosomes can be further divided into tumor cell-derived exosomes (TDEs), stromal cell-derived exosomes (SDEs), and plant-derived exosomes (PDEs), which exhibit therapeutic potential in lung cancer treatment due to their bioactive components, such as proteins, lipids, and nucleic acids. Table 1 highlights the applications of exosomes as nanotherapeutics in lung cancer therapy [64].

TDEs as nanotherapeutics

TDEs are capable of conveying regulatory signals that modulate cellular behaviors imparting considerable versatility, particularly within the domain of therapeutic interventions in cancer [6, 76]. Studies have demonstrated that TDEs can modulate immune responses and serve as potential therapeutic tools. Fu et al. demonstrated that the CAR-containing exosomes express a high level of cytotoxic molecules as tumor attackers, reducing toxicity risk and offering potential as an "off-the-shelf"

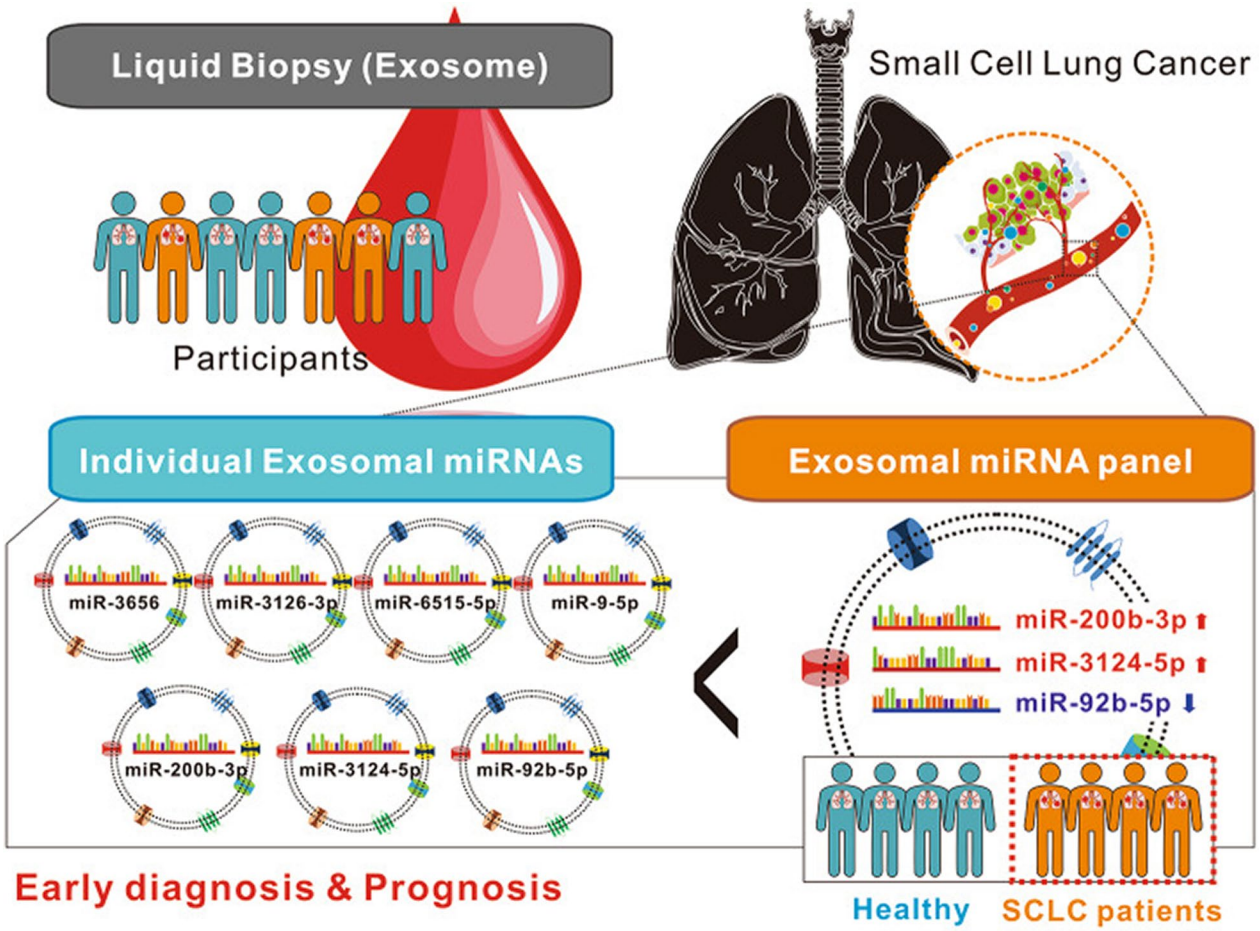


Fig. 4 Specific exosomal miRNA, (miR-200b-3p, miR-3124-5p, and miR-92b-5p) may be used as diagnostic and prognostic markers for SCLC [58]

treatment [65]. Similarly, Wang et al. found that exosomes derived from 3LL tumor cells modified by CD40L gene enhanced antigen presentation and immunogenicity, exerting potent anti-tumor effects [67]. Exosomal miRNAs from tumor cells are closely associated with cancer progression. For example, cisplatin-induced accumulation of miR-29a-3p in lung tumor exosomes downregulates type I collagen expression, thereby inhibiting lung metastasis (Fig. 5) [68].

Additionally, exosomes can mediate the transfer of drug resistant-related molecules between cancer cells, thereby mediating the tolerance of antineoplastic drugs. Studies have shown that cisplatin can induce NSCLC cells to produce two kinds of exosomes enriched in APE1p33-Exo and APE1p37-Exo, but only APE1p33-Exo has complete DNA repair activity. These results suggest that NSCLC may develop drug resistance through APE1p33-Exo-mediated DNA repair [66]. Xie et al. demonstrated that exosome-mediated transmission of circVMP1 promoted NSCLC progression and DDP resistance by targeting the miR-524-5p-METTL3/SOX2 axis [77]. TDEs also include p-glycoproteins from their donor cells, which can effectively bind to drug-sensitive recipient cells and transfer functional p-glycoproteins to the latter, and are critical in signaling pathways that induce drug resistance in recipient cells [78].

SDEs as nanotherapeutics

Exosomes secreted by stromal cells, such as BMSCs, cancer-associated fibroblasts, and human umbilical cord mesenchymal stem cells (HUCMSCs), significantly influence the TME by promoting tumor progression, modulating immune responses, and offering therapeutic opportunities [79].

BMSCs-derived exosomes have been shown to inhibit NSCLC proliferation, migration, and invasion while promoting apoptosis by upregulating miR-193a and downregulating LRRc1 [69]. The enhanced expression of let-7 in stromal-derived exosomes has also been identified as beneficial for NSCLC therapy [80]. Moreover, Xie's team has shown that exosomes derived from HUCMSCcan carry miR-320a and inhibit the growth of lung cancer

Table 1 Exosomes as nanotherapeutics for lung cancer

Classification	Donor cells	Cargo	Exosomes function	Molecular mechanisms
Tumor cell-derived	Car-T	CAR	Reducing the risk of toxicity	Don't express Programmed cell PD1 [65]
Tumor cell-derived	Lung cancer cells	APE1P33	Increasing cisplatin resistance	Enhancing DNA base excision repair [66]
Tumor cell-derived	3LL tumor cells	CD40L	Inhibiting tumor growth	Inducing DCs maturation and the secretion of IL12, promoting the proliferation of tumor antigen-specific CD4 + cells proliferation and the cytotoxic T lymphocyte response [67]
Tumor cell-derived	Lewis lung cancer cells	miR-29a-3p	Inhibiting colony formation, invasion, and proliferation as well as metastasis and tumorigenesis of LC cells	Reducing the secretion of collagen I [68]
Stromal cell-derived	BMSCs	miR-193a	Increasing apoptosis, and inhibiting colony formation, proliferation, invasion, migration, and tumor growth	Reducing LRRC1 level [69]
Stromal cell-derived	HUCMSC	miR-320a	Inhibiting the growth of lung cancer cells	Sox4/Wnt/β-Catenin axis [70]
Plant-derived	Ginger	miRNA, proteins, lipids	Inhibiting early tumorigenesis	Reducing the level of cyclin D1mRNAs [71]
Plant-derived	Lemon	miRNA, proteins, lipids	Suppressing tumor growth	Activating TRAIL-mediated apoptotic cell processes [72]
Plant-derived	Edible tea flowers	miRNA, proteins, lipids	Promoting apoptosis and inhibiting lung metastasis	ROS generation and microbiota modulation [73]
Plant-derived	Brucea javanica	miRNA, proteins, lipids	Inhibition of tumor cell growth and metastasis	Regulating PI3K/Akt/mTOR signaling pathway and promoting ROS/ CAPase-mediated apoptosis [6]
Plant-derived	Ginseng	miRNA, proteins, lipids	Inhibiting tumor progression and regulating tumor-associated macrophages	Silencing the c-MYC [74]
Plant-derived	Grapefruit	lipid	Inhibiting tumor growth	Tumor targets, enhance the ERP effect [75]

cells through the Sox4/Wnt/β-Catenin axis. This illustrates the potential of exosomes expressing miR-320a as a treatment for lung cancer [70]. Furthermore, Li et al. showed that Exo-MiR-613 reversed cisplatin resistance in NSCLC cells by down-regulating the expression of GJA1, TBP, and EIF-4E in TC [81]. These findings underscore the dual roles of stromal exosomes in offering avenues for therapeutic intervention.

Exosomes derived from both tumor and stromal cells are integral to the pathophysiology of lung cancer. Tumor exosomes primarily drive oncogenesis, immune evasion, and drug resistance, while stromal exosomes influence the TME and provide therapeutic potential. This duality has positioned exosomes as promising candidates as diagnostic tools, therapeutic agents, and drug delivery systems in the treatment of lung cancer.

PDEs as nanotherapeutics

Increasingly studies have shown that PDEs also have great potential in the therapeutic application of lung cancer [82, 83]. These exosomes, derived from sources such as ginseng [20, 84], brucea javanica [6], strawberry [85], ginger [86], carrot [87], honeysuckle [88], and grape [89], have been identified as efficient regulators of gene expression [85, 90, 91]. Meanwhile, extensive studies have shown that miRNAs in PDE can play a certain regulatory role in the human body across species [20, 86].

Exosomes extracted from ginger can inhibit early tumorigenesis to a certain extent by reducing proinflammatory cytokines and inhibiting the proliferation and apoptosis of intestinal epithelial cells [71]. In addition, citrus lemon-derived exosomes are able to inhibit in vivo tumor development in chronic myeloid leukemia through tumor targeting, oxidative stress reduction, and promoting cell apoptosis by inducing TNF-related apoptosis-inducing ligands [72]. Similarly, edible tea flower-derived exosomes can increase intracellular ROS content, cause mitochondrial damage, arrest the cell cycle, and exert anti-proliferation, anti-migration, and anti-invasion effects on cancer cells in vitro (Fig. 6) [73]. Ginseng-derived exosomes exhibit strong targeting effects and stability against tumors [74], while grape-derived exosomes could not only be used as a biosafe and non-toxic nanocaptor, but also prolong the circulation in

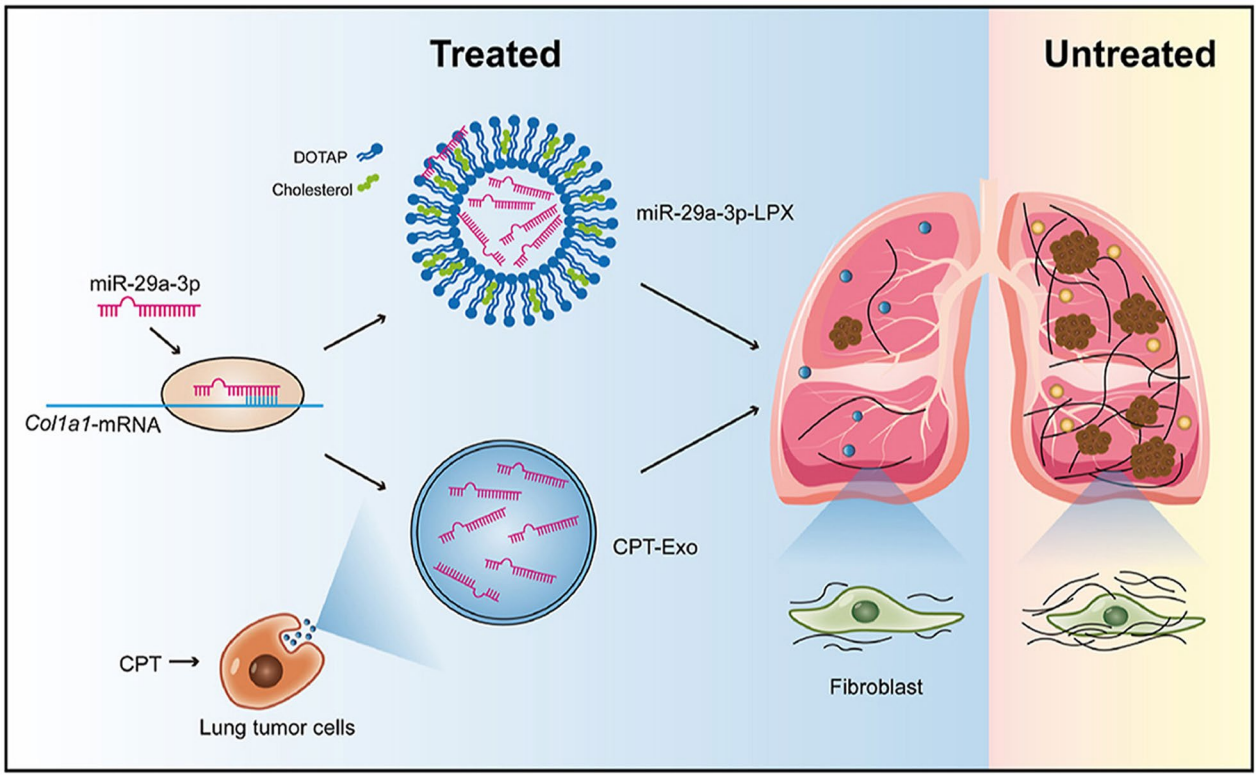


Fig. 5 MiR-29a-3p delivered by TDEs inhibits tumor cell colonization in the lung by reducing the production of fibroblast-derived type I collagen [68]

tumors, enhance the ERP effect, and successfully inhibit tumor growth [75]. Besides these advances, clinical trials are underway to explore PDEs for drug delivery, cancer treatment, and other applications [92]. For instance, a clinical trial (NCT01668849) was conducted to evaluate the potential of grape-derived exosomes in preventing oral mucositis caused by chemoradiation therapy for head and neck cancer. However, the results remain unavailable [93].

PDEs possess significant advantages such as natural abundance, smaller particle size, higher biocompatibility, higher stability, longer biological half-life, and higher tissue penetration. With the development of genetic engineering and nanotechnology, PDEs hold great promise for revolutionizing cancer therapy by offering targeted, efficient, and less toxic treatment options, thereby aligning with the principles of precision medicine [94, 95].

Exosomes as the delivery platform for lung cancer therapy

Currently, many drug delivery systems such as polymers, liposomes, and stem cells, which have been developed for the treatment of lung cancer, have some limitations in terms of toxicity, immunogenicity, and size [96]. In contrast, exosomes offer superior biocompatibility, low immunogenicity, minimal toxicity, biodegradability, and strong penetration ability. The presence of conspecific adhesion molecules on the exosome membrane enables better homologous targeting, stability in circulation, and the ability to direct membrane fusion with cells [97–99]. Collectively, these characteristics position exosomes as promising carriers for drug transport [100].

Experiments have proved that exosomes are indeed an ideal drug carrier, which can carry chemical drugs, nucleic acid drugs, and plant extracts by active (ultrasound, electrical stimulation, or freeze–thaw cycle) or passive (co-incubation method) methods [101], and further applied to drug delivery systems for various diseases [102]. Exosomes can transport various types of cargo, including DNA, RNA, lipids, metabolites, and proteins. Exosomes as drug delivery systems for delivering various therapeutic agents are listed in Table 2.

Exosomes for chemical medicine delivery

Exosomes have demonstrated significant potential in delivering chemotherapeutic drugs such as paclitaxel (PTX), doxorubicin (DOX), and gemcitabine (GEM) for lung cancer treatment, which can effectively improve the inhibitory effect of chemotherapeutic drugs on tumor growth and the selectivity of targeting tumor sites [114]. Li et al. loaded GEM into pancreatic cancer cell-derived

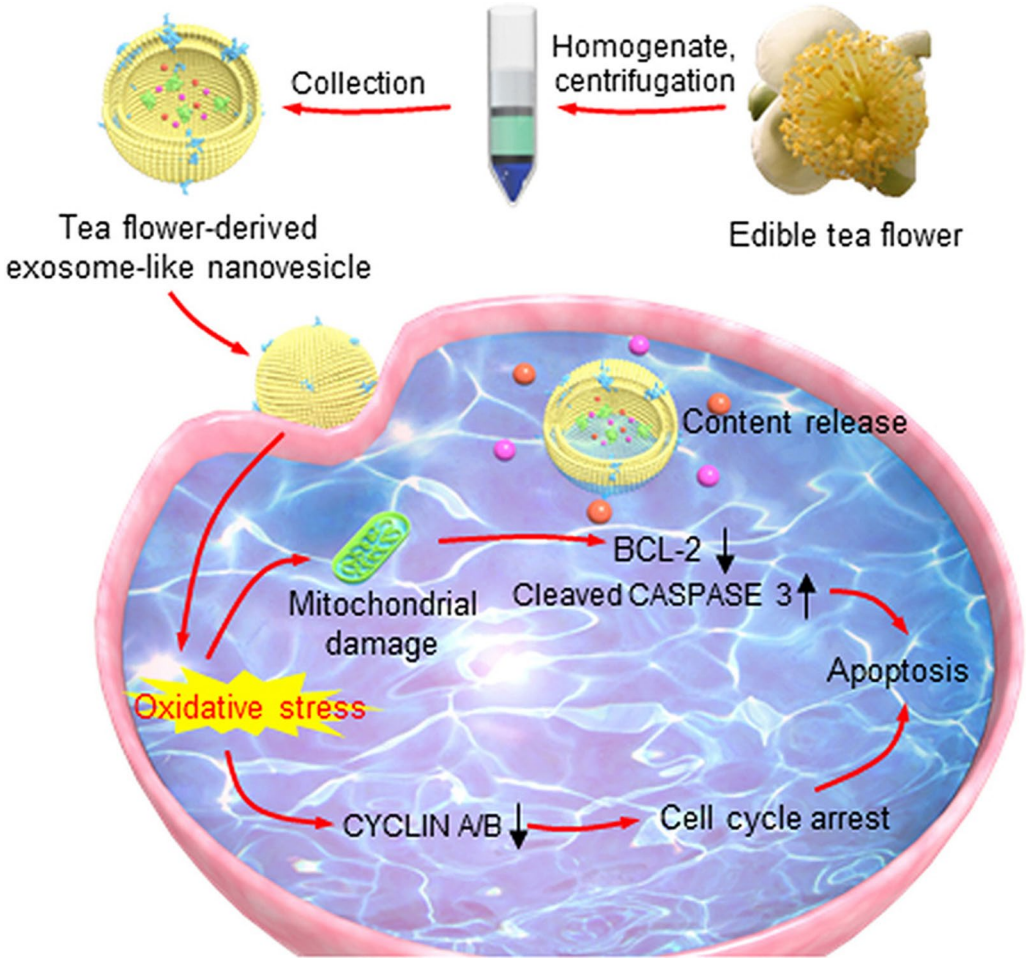


Fig. 6 The anti-proliferation, pro-apoptosis, and anti-migration and invasion effects of edible tea flowers derived-exosome in vitro [73]

exosomes using incubation and sonication methods. The results showed that the cytotoxicity of GEM is significantly increased, which could significantly inhibit the tumor growth and prolong the survival of tumor-bearing mice in a dose–effect relationship, while the damage to normal tissues was small [113]. Zheng et al. proposed a novel therapeutic strategy to target lung cancer in situ by aerosol inhalation of PTX-loaded CAR-Exos. Through the active recognition and passive inhalation movement of CAR-Exos, the treatment has shown better anti-tumor effects than free PTX. This strategy not only provides a nanocarrier to promote the efficacy of anticancer drugs but also reduces the adverse effects of current clinical PTX chemotherapy in NSCLC [115].

The membranes of exosomes can be modified by a variety of innovative methods to be used for NSCLC treatment [116]. Tian et al. developed exosomes from mouse immature dendritic cells (ImDC) fused with αv integrin-specific IRGD peptide to promote tumor targeting. These exosomes, loaded with Dox via electroporation, demonstrated specific delivery to tumor tissues, effectively inhibiting tumor growth without significant toxicity, highlighting their clinical potential for targeted drug delivery [111]. Akhil et al. invented an exosome-gold nanoparticle (Exo-GNP) drug delivery system for the treatment of lung cancer. This system linked Dox to Exo-GNP via a pH-cleavable bond, resulting in preferential cytotoxicity to tumor cells, reduced toxicity to normal tissues, and improved therapeutic efficacy [112]. Similarly, Zhu et al. designed hybrid nanovesicles by co-extruded CAR-T cell-derived exosomes and lung-targeting liposomes, which can rapidly accumulate in the lung and were targeted to MSLN-positive tumor cells. After lysis of the cells, PTX induced immunogenic cell death and attracted more infiltrating lymphocytes to the tumor tissue, while PD-L1 blockade reduced the depletion of infiltrating T cells, enhancing anti-tumor response. These hybrid nanocapsules with cascade targeting capability may enable precise delivery of chemotherapeutic drugs and amplify immunogenic cell death effects, thereby

Table 2 Exosomes as drug delivery systems for therapeutic agents

Exosomes donor	Cargo	Loading method	Delivery method	Therapeutic effects
MSC	miR-146b	Electroporation	Intra-tumor injection	Reduced glioma xenograft growth in brain tumors [103]
HEK	Let-7a miRNA	Transfection	Intravenous injection	Deliver miRNA to EGFR-expressing breast cancer cells [104]
HEK	IL-12	Electroporation	Inhalation	Promote immune response, inhibit lung cancer, and prevent recurrence [105]
MDA-MB-231	miRNA-126	Incubation	Intravenous injection	Inhibiting the proliferation and migration of A549 lung cancer cells and had a good lung homing effect [106]
CAR-T cells	Paclitaxel	Stirring	Intravenous injection	Better cell lysis and prolonged survival of tumor-bearing mice [107]
HL60 cells	Piceatannol	Incubation	Intraperitoneal (i.p.) injection	Alleviated acute lung inflammation/injury and sepsis induced by LPS [108]
RAW 264.7	Paclitaxel	Sonication	Intravenous injection	Possessed high loading capacity, profound ability to accumulate in cancer cells, and high anticancer efficacy in a mouse model of pulmonary metastases [109]
HEK	Doxorubicin	Incubation	Intravenous injection	Highly efficient targeting and Dox delivery, significant tumor growth inhibition [110]
ImDCs	Doxorubicin	Electroporation	Intravenous injection	Tumor growth was inhibited without significant toxicity [111]
H1299 and YRC9 cells	Doxorubicin	Co-incubated	N/A	Preferential cytotoxicity towards cancer cells and minimal activity on non-cancerous cells [112]
Panc-1	Gemcitabine	Incubation and sonication	Intravenous injection	Significantly suppressed tumor growth with prolonged survival in a dose–response manner [113]

further reducing side effects and promoting anti-tumor responses (Fig. 7) [107].

Exosomes for miRNAs and mRNAs delivery

miRNA and mRNA replacement therapy has become a promising therapeutic strategy for the treatment of malignant tumors [117]. Clinical studies have shown that tumor cells can release exosomes containing miRNAs and mRNAs, which can be taken by recipient cells [118, 119], highlighting exosomes as a natural RNA drug delivery system [116]. Cheng's team loaded IL-12 mRNA into human embryonic kidney cell (HEK)—derived exosomes (HEK-Exo) by electroporation to generate IL-12 mRNA-loaded exosomes (IL-12-Exo). The nanosystem can be inhaled for local lung administration, which promotes IFNγ-mediated immune activation, systemic immunity, and immune memory in a mouse model of lung cancer, successfully inhibits lung cancer and prevents tumor recurrence. Studies have shown that after inhalation administration of IL-12-Exo, its biodistribution in the TME of lung cancer is better than that of liposome loaded with IL-12 mRNA, and has the smallest systemic toxicity (Fig. 8) [105].

Mark Katakowski et al. demonstrated that exosomes derived from miR-146b-expressing MSCs could significantly reduce glioma xenograft growth in a rat model of primary brain tumors [103]. Ohno et al. showed that exosome modified with GE11 targeting peptide can deliver let-7a miRNA to EGFR-expressing xenograft breast cancer tissues in RAG2^{-}/.$^{-}$ mice [104]. Huifang Nie et al. demonstrated that breast cancer cell-derived exosome (BCExo) can be specifically internalized by NSCLC cells through a specific interaction between highly expressed integrin β4(located on the exosome) and cancer cell surfactant protein C. They found that BCExo loaded with miRNA-126 significantly inhibited the proliferation and migration of A549 lung cancer cells by blocking the PTEN/PI3K/AKT signaling pathway [106].

The clinical application of exosomes in lung cancer therapy

It is worth noting that as of August 2024, 89 clinical studies worldwide have explored the use of exosomes in cancer, of which lung cancer treatment accounts for 18, representing a high proportion of all major cancers, as shown in Table 3 (https://clinicaltrials.gov). The majority of ongoing clinical trials are leveraging the genetic information contained within exosomes to enable early screening for lung cancer, predict treatment efficacy, and prevent recurrence. Notably, the Gustave Roussy and Curie institutes have advanced an immunotherapeutic approach for lung cancer. This method involves the use of metronomic cyclophosphamide (mCTX) followed by

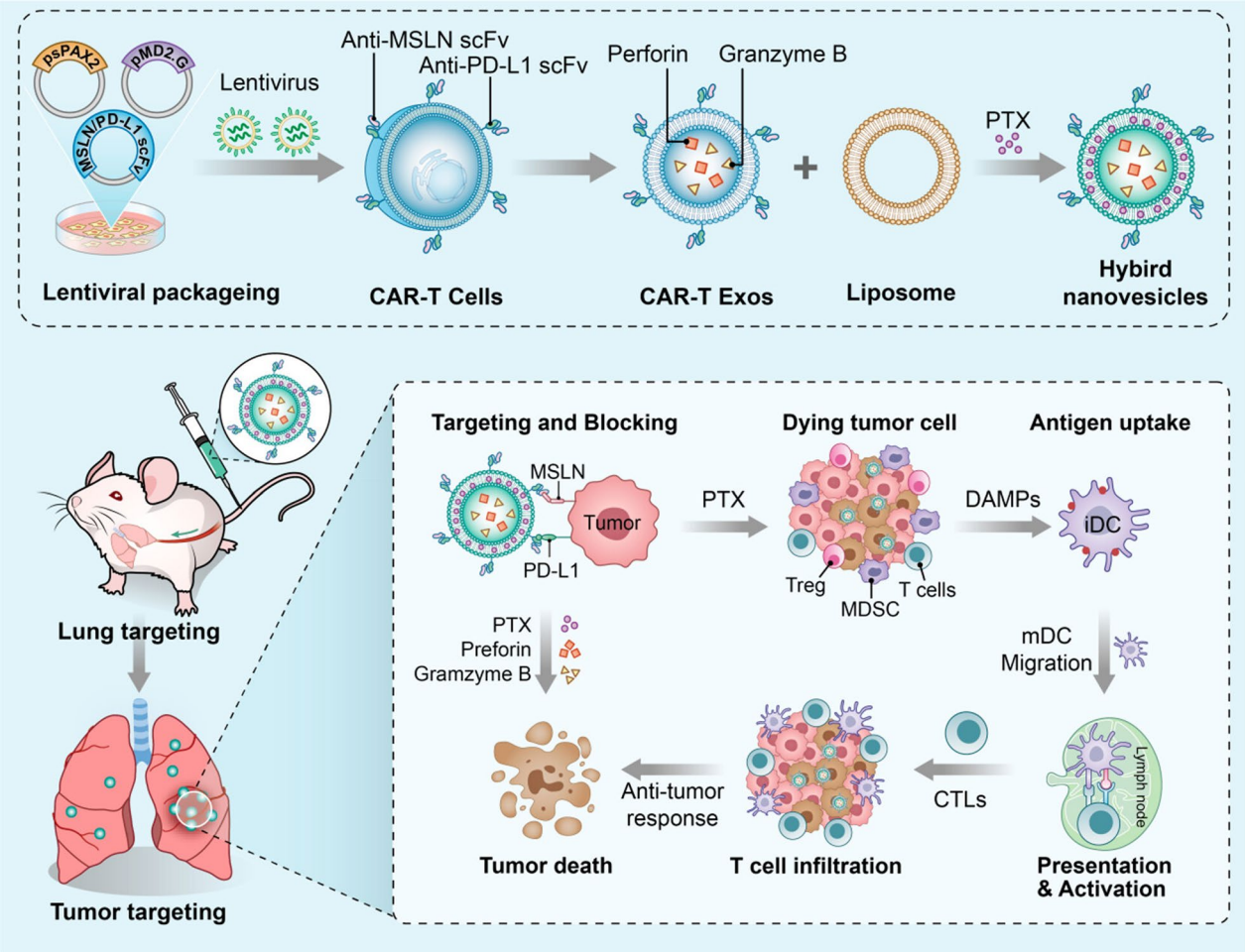


Fig. 7 Schematic of hybrid nanovesicles of bispecific CAR-T cell-derived exosomes and liposomes for lung cancer therapy [107]

vaccinations utilizing tumor antigen-loaded dendritic cell-derived exosomes (Dex). The mCTX treatment serves to inhibit Treg cells, thereby restoring the effector functions of T and NK cells. Concurrently, Dex exosomes are capable of activating specific immune responses. This study has progressed to a Phase II Trial, underscoring the vast potential of exosomes in the treatment of lung cancer [120].

Clinical research on PDEs has primarily focused on their potential as drug delivery vehicles and therapeutic agents. For instance, clinical trials have explored the encapsulation of chemotherapeutic agents, such as curcumin and paclitaxel, within grape- (NCT01294072) and ginger-derived (NCT01668849) exosomes for enhanced delivery and efficacy in cancer treatment. Unfortunately, as of now, there is no clinical evidence supporting the use of PDEs in lung cancer treatment. The clinical application of exosomes faces challenges related to production, storage, and application efficiency [121]. Standardizing industry protocols for isolation, purification, and quality control is critical to ensuring consistency and reliability in production. Preservation techniques such as cryopreservation, freeze-drying, and spray-drying are vital for extending shelf life and maintaining biological activity [122]. Meanwhile, increasing research has focused on modifying the surface of PDEs with functional ligands, such as antibodies and peptides, to improve cellular uptake and enhance their therapeutic potential [123].

Discussions and conclusions

The potential of exosomes in lung cancer therapy is promising, given their diverse biological cargo, including proteins and nucleic acids, which influence intercellular communication and modulate crucial physiological

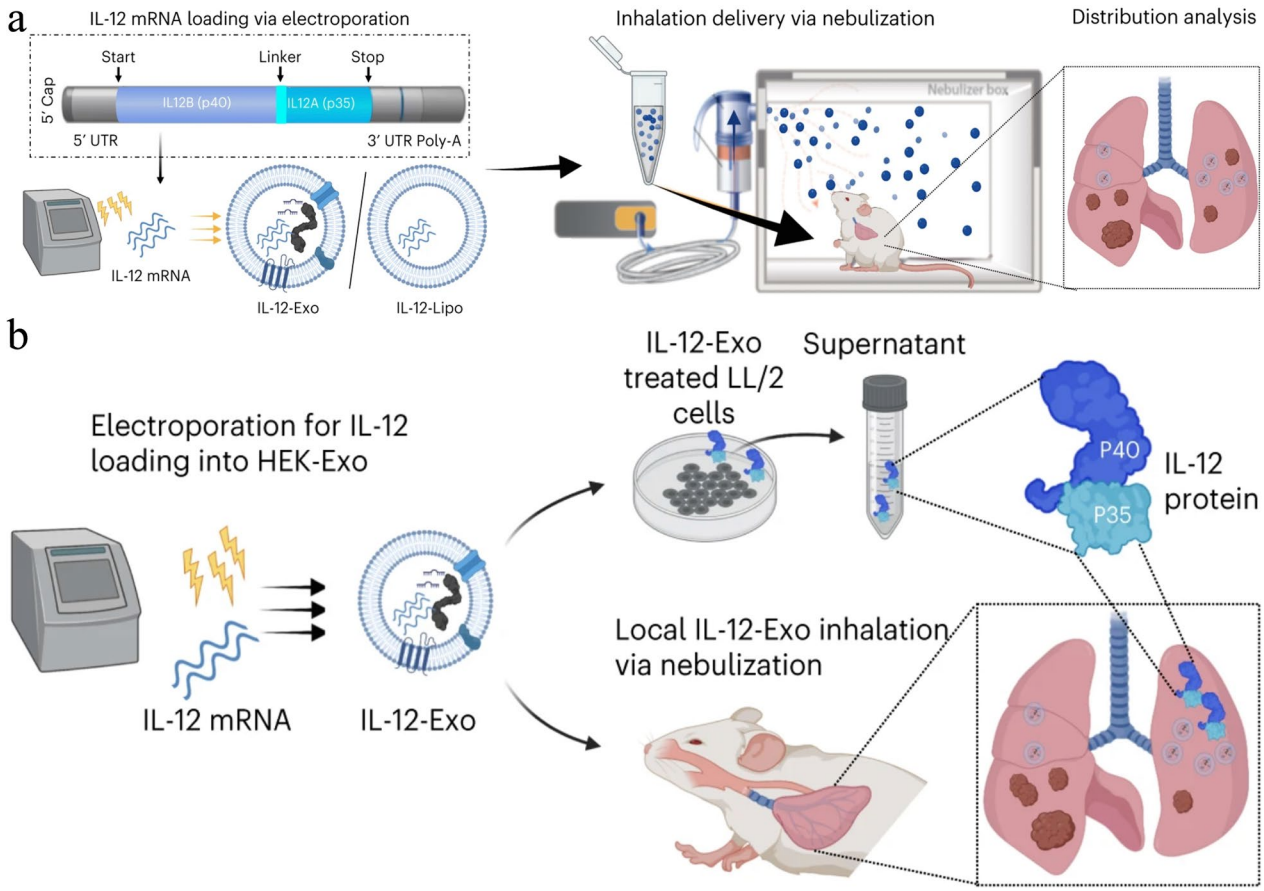


Fig. 8 IL-12 mRNA was loaded into HEK-Exo by electroporation to generate an exosome loaded with IL-12 mRNA, IL-12-Exo, which was locally administered to the lungs by inhalation. **a** Schematic diagram of IL-12-Exo and atomized inhalation into the lungs of LL/2 tumor-bearing mice. **b** Schematic diagram of IL-12 expression evaluation in vitro (24 h) and in vivo (1 and 3 days) [105]

processes such as cell proliferation, migration, invasion, metastasis, and apoptosis. Exosomes offer crucial diagnostic and prognostic insights through liquid biopsy, presenting a transformative approach to lung cancer monitoring and treatment. As adept therapeutic agents and delivery vehicles, exosomes demonstrate advantages such as prolonged blood circulation time, superior biocompatibility, and enhanced targeting capabilities. These features improve drug efficacy, minimize toxicity, and overcome drug resistance. Notably, PDEs, due to their natural origin and composition, evade immune detection, and enhance bioavailability, demonstrating considerable therapeutic potential in lung cancer therapy. These advancements position exosomes as pivotal in shaping the future of lung cancer treatment, with the promise of improved patient outcomes. However, despite these advancements, challenges and limitations persist in their application for lung cancer therapy.

Due to the limited ability of exosomes alone to treat tumors, engineered exosomes can be used as a targeted delivery carrier for anticancer drugs, so that the treatment can be directly, accurately, and efficiently delivered to lung tumors. It can be further combined with functional peptides, small molecule drugs, and some new materials to improve its stability and targeting, and can be combined with other methods such as chemotherapy or immunotherapy to enhance the therapeutic effect of exosomes on tumors. Most importantly, the development of biomimetic or biomimetic exosomes provides clues for exosome-based drug delivery platforms in the clinical stage.

Despite these advancements, challenges such as the scalable production of exosomes, quantification of their cargo, and standardization of analytical methods persist. There are still no clear means, and there are still many different opinions on how to choose the appropriate

Table 3 The clinical trials of exosomes

NCT Number	Title	Conditions	Treatment	Last Update Posted	Exosome functions
NCT06342427	Stomach Cancer Exosome-based Detection (DESTINEX)	Gastric Cancer Metastatic to Lung	Diagnostic Test: DESTINEX	2024.7.8	Early diagnosis of stomach cancer
NCT02869685	Consistency Analysis of PD-L1s in Advanced NSCLC Tissues and in Plasma Exosomes Before and After Radiotherapy (RadImm02)	NSCLC	Radiation: radiotherapy	2024.2.23	Reflecting the information of tumor tissues
NCT06026735	NSCLC With Central Nervous System Metastasis	Lung Cancer With Central Nervous System Metastasis	Other: lung cancer with brain /leptomeningeal metastasis	2023.9.7	Predicting lung cancer metastasis and bioindicators of treatment effect
NCT04939324	Molecular Profiling of Exosomes in Tumor-draining Vein of Early-staged Lung Cancer (ExOnSite-Pro)	Lung Cancer	Biological: Blood samples at 2 sites: peripheral vein and tumor-draining vein	2023.4.10	Prognostic biomarkers of lung cancer relapse
NCT03108677	Circulating Exosome RNA in Lung Metastases of Primary High-Grade Osteosarcoma	Lung Metastases	Other: Blood samples	2023.10.3	Detecting the lung metastases
NCT05101655	Construction of Microfluidic Exosome Chip for Diagnosis of Lung Metastasis of Osteosarcoma	Pulmonary Metastases	N/A	2022.11.15	Detecting the lung metastases
NCT05587114	Comparison of Various Biomarkers Between Peripheral and Pulmonary Blood	Lung Cancer	Diagnostic Test: frozen blood plasma samples	2022.10.19	Early diagnosis of lung cancer
NCT04529915	Multicenter Clinical Research for Early Diagnosis of Lung Cancer Using Blood Plasma Derived Exosome	Lung Cancer	Diagnostic Test: Exosome sampling	2021.12.30	Early diagnosis of lung cancer
NCT03830619	Serum Exosomal Long Noncoding RNAs as Potential Biomarkers for Lung Cancer Diagnosis	Lung Cancer	Diagnostic Test: frozen blood plasma samples	2021.11.22	Early diagnosis of lung cancer
NCT04499794	The Study of Exosome EML4-ALK Fusion in NSCLC Clinical Diagnosis and Dynamic Monitoring	Untreated Advanced NSCLC Patients	Drug: ALK inhibitor	2020.8.5	NSCLC diagnosis and efficacy monitoring
NCT04427475	Prediction of Immunotherapeutic Effect of Advanced NSCLC	NSCLC Patients	Drug: pabolizumab Drug: nafulizumab	2020.6.11	Predicting the therapeutic effect of NSCLC on anti-PD-1 / PD-L1
NCT04315753	Circulating and Imaging Biomarkers to Improve Lung Cancer Management and Early Detection (SMAC-2)	Lung Cancer	Other: LDCT (Low Dose CT)	2020.3.20	Early diagnosis of lung cancer
NCT05218759	Exosomes Detection for the Prediction of the Efficacy and Adverse Reactions of Anlotinib in Patients With Advanced NSCLC	NSCLC	Drug: Anlotinib	2020.2.1	Predicting the efficacy or risk of serious adverse
NCT04629079	Improving the Early Detection of Lung Cancer by Combining Exosomal Analysis of Hypoxia With Standard of Care Imaging (LungExoDETECT)	Lung Cancer	N/A	2020.11.16	Early diagnosis of lung cancer

Table 3 (continued)

NCT Number	Title	Conditions	Treatment	Last Update Posted	Exosome functions
NCT03228277	Olmutinib Trial in T790M (+) NSCLC Patients Detected by Liquid Biopsy Using BALF Extracellular Vesicular DNA	NSCLC	Drug: Olmutinib	2019.8.28	Evaluating the efficacy of Olmutinib(Olita®)
NCT04182893	Clinical Study of ctDNA and Exosome Combined Detection to Identify Benign and Malignant Pulmonary Nodules (ctDNA)	Pulmonary Nodules	Diagnostic Test: ctDNA and Exosome Combined Detection	2019.12.2	Early diagnosis of lung cancer
NCT03542253	Combined Diagnosis of CT and Exosome in Early Lung Cancer	Early Lung Cancer	Procedure: Surgery	2018.5.31	Early diagnosis of lung cancer
NCT01159288	Trial of a Vaccination With Tumor Antigen-loaded Dex(CSET 1437)	Lung Cancer	Biological: Dex2	2018.3.29	The immunotherapy of lung cancer

exosomes for lung cancer treatment. Looking forward to the future, there is increasing evidence that exosomes have transformation potential, and exosomes as clinical drugs for the treatment of lung cancer are around the corner.

Abbreviations

SCLC	Small cell lung cancer
NSCLC	Non-small cell lung cancer
TME	Tumor microenvironment
EMT	Epithelial-mesenchymal transition
BMSCs	Bone marrow-derived mesenchymal stem cells
DC	Dendritic cells
EGFR	Epidermal growth factor receptor
ALK	Anaplastic lymphoma kinase
TDEs	Tumor cell-derived exosomes
SDEs	Stromal cell-derived exosomes
PDEs	Plant-derived exosomes
HUCMSCs	Human umbilical cord mesenchymal stem cells
ImDC	Immature dendritic cells
PTX	Paclitaxel
Dox	Doxorubicin
GEM	Gemcitabine
Exo-GNP	Exosome-gold nanoparticle
HEK	Human embryonic kidney cell
HEK-Exo	Human embryonic kidney cell-derived exosomes
IL-12-Exo	IL-12 mRNA-loaded exosomes
BCExo	Breast cancer cell-derived exosome
Dex	Dendritic cell-derived exosomes
mCTX	Metronomic cyclophosphamide

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Author contributions
LH-Peng conceived and designed the review topic and writing scheme. QY-Xiao, MH-Tan, and G-Yan performed the literature sorting, wrote the original draft, and edited the manuscript; LH-Peng and QY-Xiao revised the manuscript; All authors have read and approved the final manuscript.

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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
We agree on the publication of any human face that might be detected in the images contained in this article. All authors have read the journal policies and submit this manuscript in accordance with thosepolicies. All authors agree to publish.

Competing interests
The authors declare no competing interests.

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