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Exosome therapeutics for non-small cell lung cancer tumorigenesis

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Abstract

Non-small cell lung cancer (NSCLC) remains an ongoing health concern, with poor treatment options and prognosis for many patients. Typically, individuals with lung cancer are detected at the middle and terminal stages, resulting in poor medical results due to lack of initial diagnosis and treatment. So, finding the initial specific and effective therapy options for lung cancer is necessary. In addition, exosomes are generally small lipid vesicles with a diameter in the nanometer range that are created and released by different cell types. Exosomes have therapeutic potential through delivering bioactive compounds including microRNAs, siRNAs, and therapeutic proteins to tumor cells, modifying the tumor microenvironment, and promoting anti-tumor immune responses. In recent years, exosome-based therapy has become known as an appropriate approach for NSCLC treatment. This review offers an overview of the possibility of exosome-based therapy for NSCLC, with an emphasis on mechanisms of action, preclinical research, and current clinical trials. Preclinical studies have shown that exosome-based therapy can decrease tumor growth, metastasis, and drug resistance in NSCLC models. Furthermore, ongoing clinical trials are looking at the safety and efficacy of exosome-based therapies in NSCLC patients, offering important insights into their translational prospects. Despite promising preclinical evidences, significant obstacles remain, including optimizing exosome isolation and purification techniques, standardizing production strategies, and developing scalable manufacturing processes. Overall, exosome-based therapy shows significant promise as a novel and various methods for treating NSCLC, with the potential to enhance patient outcomes and evolution cancer treatment.

Keywords Lung cancer, NSCLC, NSCLC treatment, Exosome, Exosome-based therapy

Introduction

Lung cancer remains a main driving cause of mortality and morbidity in both sexes around the world [1]. The two kinds of lung cancer are known as small cell lung cancer and non-small cell lung cancer (NSCLC). NSCLC has been further classified into three distinct types: adenocarcinoma, squamous-cell carcinoma, and large-cell carcinoma [2]. The etiology of lung cancer is not yet clear. Smoking and air pollution are two main risk factors. Also, occupational exposures as asbestos have crucial roles in the development of lung cancer [3].

NSCLC is usually treated through surgery, radiation therapy, chemotherapy, targeted therapy and

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immunotherapy. Treatment options vary depending on the type and stage of the cancer. Surgery is the main treatment for stage I to IIIA NSCLC, while stage IIIB to IV patients are treated with radiation or chemotherapy due to tumor metastasis. The 5-year survival rate of NSCLC is poor, ranging from 68% for patients with IB to 0–10% for patients with IVA and IVB [4].

Exosomes are a type of small extracellular vesicles (with a diameter ranging from 30 to 100 nm) that contain many bioactive compounds, including proteins, nucleic acids (including RNA and DNA molecules), and lipids [5]. The exosome composition is saved from destruction, making it more stable than nucleic acids and protein in human body fluids [6]. Exosomes contain abundant biological content that may be transported across cells, allowing them to fulfill various functions in both normal and disease states. Tumor-derived exosomes promote the progression of metastasis in lung cancer by augmenting cancer cell expansion and migration, facilitating angiogenesis and epithelial–mesenchymal transition (EMT), and simultaneously inhibiting immune response [7].

Many studies have revealed the significance of exosomes in stimulating tumorigenesis and progression. For instance, exosomes are implicated in chemotherapy resistance in lung cancer. Exosomes that were derived from a lung cancer cell line that was resistant to cisplatin (A549) exhibited different contents, which suggests that exosomes play a role in promoting cisplatin resistance [8].

The immunogenicity and molecular delivery function of exosomes as cell-derived nano vesicles make them a promising option for cancer immunotherapy [9]. Therefore, there are emerging opportunities in the exosome field that could be helpful for the diagnosis and treatment of cancers. This review aims to provide a comprehensive understanding of the role of exosomes in the tumor microenvironment (TME) of non-small cell lung cancer (NSCLC), particularly their impact on tumorigenesis, metastasis, immune modulation, and potential therapeutic applications. By synthesizing the latest research on exosome biology and their influence on cancer progression, this study seeks to highlight emerging opportunities for diagnostic advancements and innovative treatment strategies for NSCLC.

The role of exosomes in NSCLC tumor microenvironment (TME)

It is evident that cells in all species with multiple cells, including tumors, must interact with each other in order to regulate development and enhance their ability to adapt and operate in their environment. The TME has a significant role in both the beginning and subsequent stages of tumor formation. Certain malignant characteristics of a tumor cannot be expressed without the significant interaction between tumor cells and their surrounding environment [10].

In order to rich potential therapeutics and overcome the low efficiency of immunotherapy and drug resistance, increasing research is focusing on the lung TME. Vascular structures, immune and inflammatory cells, extracellular matrix (ECM), and cancer-associated fibroblasts (CAFs) are key components of the TME [11, 12]. Tumor-derived exosomes (TDEs) are essential mediators of many processes in the TME and carry a significant amount of information and molecules that facilitate intercellular communication and participate in tumor growth, angiogenesis, invasion, and immune escape [13] (Table 1; Fig. 1).

It is known that tumor cells release more exosomes than normal cells and also the surface of TDE contains membrane proteins such as Epidermal growth factor receptor (EGFR), CD317, CD91, in conjunction with possibly PD-L1, which could be a potential tumor marker [14, 15]. Overall, NSCLC development is a complicated and long-term process driven by various factors and

Table 1 Some exosomal cargos and their biological roles in NSCLC tumorigenesis

Exosomal cargo	Target	Function	Ref.
miR-1247-3p	B4GALT3	An elevated level lead to lung metastasis via activating β1-integrin NF-κB signaling.	[84]
miR-512	TEAD4 mRNA	Decrease in the cell proliferation.	[85]
miR-9	SOCS5	Activation of the JAK-STAT pathway that facilitates endothelial cell migration and tumor angiogenesis.	[86]
circ_0008717	miR-1287-5p	Enhances tumorigenesis via miR-1287-5p/P21-activated kinase 2 (PAK2) axis in NSCLC.	[87]
miR-660-5p	KLF9	miR-660-5p significantly promotes proliferation, migration, and invasion in NSCLC.	[88]
miR-619-5p	RCAN1.4	Promotion of the angiogenesis, proliferation and metastasis in NSCLC cells.	[89]
OSER1-AS1	miR-433-3p/Smad2	Enhanced OSER1-AS1 expression was significantly associated with lymph node metastasis in patients with NSCLC.	[90]
miR-494	PTEN	Activation of Akt/eNOS pathway and promotes angiogenesis.	[91]
miR-103a	PTEN	miR-103a transfers to monocytes, increases polarization of immunosuppressive M2 type macrophages.	[92]
miR-582-3p	PTEN	miR-582-3p targets SFRP1 and induces malignant behaviors in cancer cells.	[93]

Abbreviations: B4GALT3: β-1,4-galactosyltransferases III; NF-κB: Nuclear factor-κB; SOCS5: Suppressor of cytokine signalling 5; RCAN1: Regulator of calcineurin 1; OSER1-AS1: OSER1 antisense RNA 1; SFRP1: Secreted frizzled-related protein 1

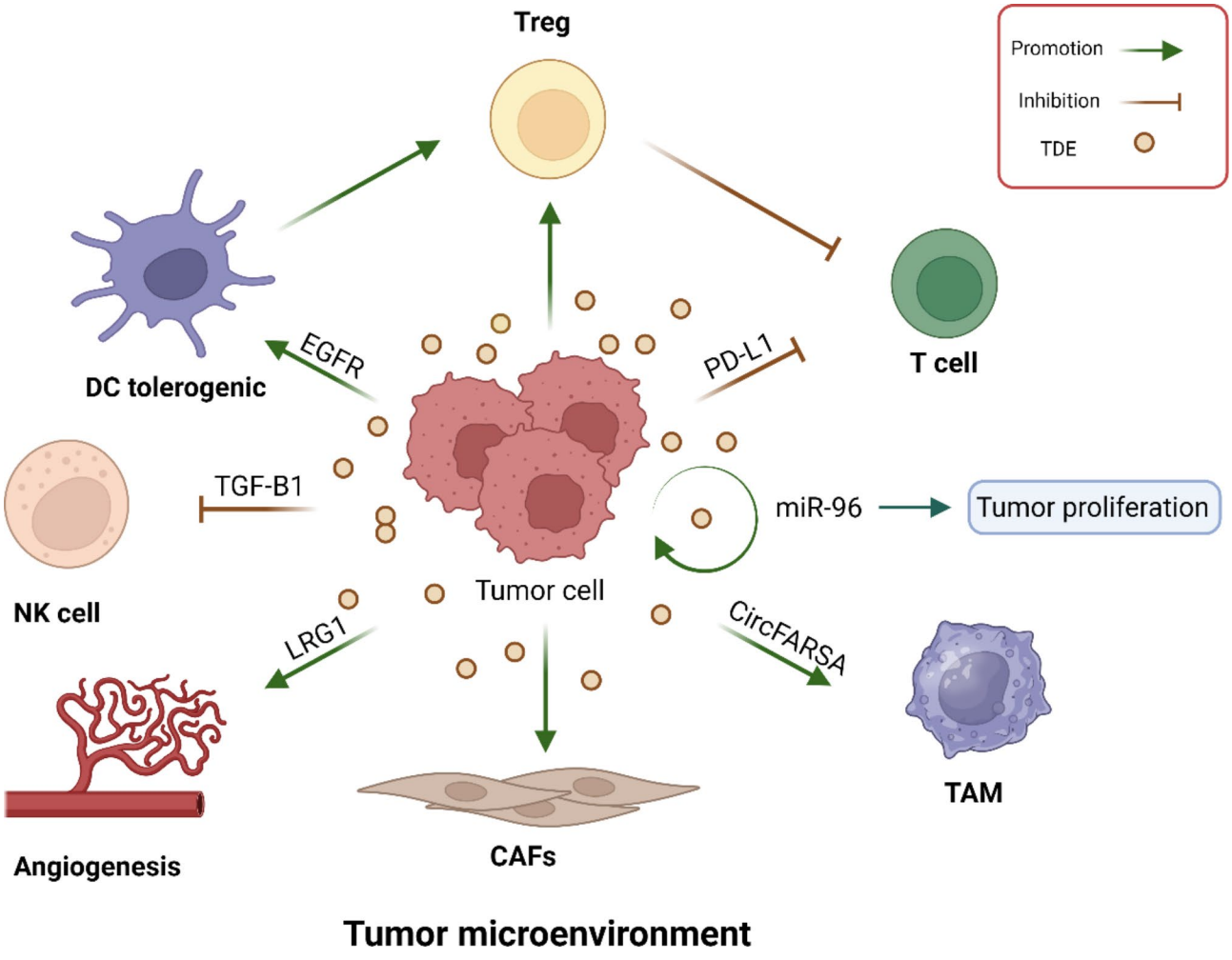

Fig. 1 TDEs play an important role in inhibiting the immune response against lung cancer and stimulating tumor expansion. This figure illustrates the multifaceted roles of TDEs in NSCLC, focusing on immune modulation, tumor proliferation, and metastasis. TDEs can induce the polarization of macrophages towards the M2 phenotype, enhance cancer associated fibroblasts expansion, and promote regulatory T-cell (Treg) differentiation. These exosomes carry immune-suppressive molecules, such as PD-L1, and affect immune surveillance by reducing the activity of cytotoxic T lymphocytes (CTLs). CAF, Cancer Associated Fibroblasts; TAM, Tumor Associated Macrophage

mechanisms. Exosomes produced by lung cancer cells play an important function in facilitating intercellular communication [16].

Immunomodulation

The immunological response refers to the combination of innate and adaptive immunity. Immunomodulation is the process by which various components, such as proteins, lipids, and RNAs influence the responses. Tumor cell elements in cancer create intricate networks that enable immunomodulation and suppress the body's adaptive immune response against cancer cells [17, 18]. TDEs, which have diverse and often contrasting immune-related functions, are currently receiving attention in relation to tumourigenesis. Specifically, they play a role in cancer immune surveillance and tumor escape, contributing to tumor progression [19]. Exosomes promote angiogenesis, directly suppress the anti-tumor responses of cytotoxic T lymphocytes (CTLs) and natural killer cells (NKs), and activate immune suppressor cell subsets, leading to a loss of tumor immune surveillance [20]. Additionally, tumor vesicles appear to induce the generation, development, and inhibitory function of the regulatory T cell (Treg) subsets [21]. TDEs also contain immunosuppressive signaling compounds like death receptor ligands (FasL, TNF-related apoptosis-inducing ligand (TRAIL)), checkpoint receptor ligands (PD-L1), prostaglandin E2 (PGE2), inhibitory cytokines (interleukin-10 (IL-10) and tumor growth factor- β1 (TGF-β1)), and ecto enzymes participating in the adenosine pathway (CD39 and CD73) which play a role in cancer immune escape [22].

Another method by which cancer cells circumvent the immune system is through the interaction between the programmed death-ligand 1 (PD-L1), which is present

in both cancer cells and TME cell populations, and the programmed cell death protein 1 (PD-1) receptor, which appears on activated T cells [23]. Exosomal PD-L1 has been identified as a significant factor contributing to tolerance in cancer, with other mechanisms [24]. The presence of exosomal PD-L1 significantly prevented the activation and growth of T cells in in vitro [25, 26]. It also reduced the levels of TH1 cytokines and granzyme B [27]. Additionally, it hindered the ability of T cells to destroy other cells and repressed the activation of extracellular signal-regulated kinase (ERK) and nuclear translocation of nuclear factor kappa B (NF-κB). Furthermore, exosomes have the ability to transport the PD-L1 protein to cancer and TME cells, causing a conversion from PD-L1-negative to PD-L1-positive. This indicates that exosomes can enhance immunosuppression in the TME by horizontally transferring the PD-L1 protein to cells [28]. Patients with advanced NSCLC who have progressed disease features, such as larger tumor size, positive lymph node status, and metastasis, show higher levels of PD-L1 in serum-derived exosomes. This indicates that exosomal PD-L1 can be utilized as a means to monitor the progression of NSCLC [29]. Furthermore, there was a strong correlation between the high levels of PD-L1 found in exosomes obtained from the plasma of patients with NSCLC and the presence of PD-L1 in tumor tissues [30].

Exosomes contain various types of RNAs, including more than a dozen distinct kinds. The majority of these RNAs are classified as non-coding RNAs (ncRNAs), meaning they do not typically encode proteins. However, they can still have an impact on messenger RNAs (mRNAs) by either stabilizing them to protect against degradation or degrading them [31]. These RNAs are of particular interest as they are involved in suppressing immune system constituents and inducing tumor progression. In this regard, Tumor-derived exosomes containing circular ubiquitin-specific protease-7 (circUSP7) suppressed the release of interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), granzyme B, and perforin by CD8+T lymphocytes, hindering their normal function. The presence of CircUSP7 leads to the development of resistance against anti-PD1 immunotherapy, offering a potential treatment approach for patients with non-small cell lung cancer (NSCLC) [32].

The differentiation of M0 macrophages and myeloid-derived suppressor cells into M2 macrophages can be triggered by NSCLC exosomes. M2 macrophages facilitate tumor growth and development through inhibiting immune response. Exosomal circular RNA hsa_circ_0000896 (circFARSA) was highly increased in NSCLC tissues, promoting NSCLC cell metastasis through polarization of macrophages to the M2 phenotype [33]. In another study, miR-770 expression was significantly upregulated in NSCLC cells after transfection with miR-770 agomirs. miR-770 is significantly downregulated in NSCLC-derived exosomes. This miRNA inhibits the process of M2 macrophage polarization and downregulated in NSCLC cells, hence preventing the invasion of NSCLC cells through targeting MAP3K1 [34]. NSCLC cells also induce M2 type polarization while suppressing M1 type by targeting the miR-627-3p/Smads signaling pathway and delivering exosomes to THP-1 cells. These modifications increased EGFR-TKI resistance in the NSCLC H1975 cell line [35]. miRNAs in TDEs can also induce inflammation and tumor invasion by binding to Toll-like receptors (TLRs). For example, miR-21/29a in lung cancer derived exosomes could bind to murine TLR7 and human TLR8, activating NF-κB and releasing pro-metastatic cytokines TNF-α and IL-6 [36].

Hypoxia is an important characteristic of TME caused by an unequal distribution of oxygen supply and consumption by tumor cells. Tumors that experience low oxygen levels, known as hypoxic tumors, display more aggressive characteristics and are linked to unfavorable patient prognosis across a diverse range of cancer types [37]. The cellular reaction to low oxygen levels, known as hypoxia, is primarily controlled by a group of transcription factors called hypoxia-inducible factors (HIFs). This response leads to widespread alterations in gene expression, affecting several genes involved in the advancement of tumors, formation of new blood vessels, tumor invasion, and metastasis [38]. It is thought that the hypoxic condition of tumor cells is reflected in the content of TDEs. Hodge et al. suggested that TDEs decrease cytotoxic factors of NK cells and CTLs by carrying soluble molecules such as prostaglandin E2/cyclooxygenases (PGE-2/COX) [39]. Also, Exosomes derived from hypoxic lung tumor cells transfer TGF-β1 and miR-23a to NK cells and suppress NK cell function by suppressing NKG2D and CD107a, respectively [40].

Myeloid-derived suppressor cells (MDSCs) are a diverse group of cells consisting of immature myeloid cells that are produced in the bone marrow. These cells have the capability to inhibit both the innate and adaptive immune responses [41]. An excessive proliferation of MDSCs has been documented in distinct types of malignancies, including multiple myeloma, bladder carcinoma, renal cell carcinoma, and breast cancer [42–46]. Similarly, MDSCs have been reported to be significantly higher in individuals with lung cancer and were found to have a negative correlation with the duration of survival. MDSCs in circulation were identified as a potential indicator of a negative response to treatment in patients diagnosed with NSCLC [47, 48]. Furthermore, the primary target of lung cancer derived exosomes is MDSCs. MDSCs increase the expression of inhibitory molecules such as ARG-1 and TGF-β by internalizing exosomes derived from lung cancer and soluble factors

like miR-126-3p, miR-27b, miR-320, in conjunction with miR-342-3p [49]. Zhang et al. revealed that miR-21a concentrated in lung carcinoma cell-derived exosomes might enhance MDSCs development through targeting PDCD4, therefore promoting tumor progression [50].

Tumor proliferation

Cancer cell proliferation is aberrant, which is one of the characteristics that distinguishes tumor cells from normal cells. Enhanced cell cycle progression, suppression of apoptosis, and glycolysis are thought to be significant factors in tumor growth [51]. Proliferation refers to variations in the expression or activity of cell cycle-related proteins, which are critical for lung cancer growth [52].

TDEs improve tumor growth by autocrine or paracrine signaling, including reprogramming the bone marrow environment and tumor stroma, promoting neovascularization, cell differentiation, migration, and leading to metastatic tumor. Over all, TDEs seem to participate in tumorigenesis [53]. According to Janowska-Wieczorek et al., platelet exosomes transfer glycoprotein IIbIIIa (CD41) to lung cancer cells, promoting cyclinD2 expression and phosphorylation of MAPKp4244, which promotes lung cancer cell proliferation [54]. Lung TDEs containing EGFR can activate tolerogenic dendritic cells (DCs) and tumor antigen-specific Tregs, inhibiting anti-tumor function and promoting tumor growth [16]. NSCLC derived exosomes also triggered NSCLC cell proliferation and suppressed apoptosis via transferring alpha- smooth muscle actin (ASMA) [55].

Cancer cells that are exposed to exosomal miRNAs experience physiological alterations that can either enhance or inhibit their ability to proliferate and migrate. Exosomes containing miR-96 from H1299 cells, a human lung adenocarcinoma cell, block LIM-domain only protein 7 (LMO7) and enhance tumor cell proliferation [56]. miR-34c exhibits a substantial decrease in expression levels in several cancer types including lung cancer. This miRNA reduces proliferation, promotes apoptosis, and prevents tumor cell invasion by targeting Pituitary adenylate cyclase-activating polypeptide type 1/mitogen-activated protein kinase (PAC1)/(MAPK) pathway [57]. In addition to this, the proliferation and migration of lung cancer cells were suppressed by miR-302b transferred by exosomes, acting through the TGFβRII/ERK pathways. This indicates that miR-302b could be an appealing target for the treatment of lung cancer [58].

Circular RNAs (circRNAs) in TDEs have a significant regulatory function in the development of tumors. For instance, it was revealed that overexpression of circRNA_102481 promotes EGFR tyrosine kinase inhibitors (EGFR-TKIs)-resistant NSCLC cell proliferation and reduces cell apoptosis through microRNA-30a-5p/ROR1 axis in this cancer [59]. EGFR-TKIs have been effective in treating NSCLC with EGFR sensitive mutation. However, nearly all patients who initially respond well to this therapy will experience a recurrence within 8_ 10 months and develop drug resistance. Also, circRNA special AT-rich sequence-binding protein 2 (CircSATB2) may modulate Fascin Actin-Bundling Protein 1 (FSCN1) expression by binding to miR-326, which promotes NSCLC cell proliferation, migration, and invasion [60].

Cancer cells engage in interactions with neighboring cells known as Cancer-associated fibroblasts (CAFs), which constitute a significant portion of the TME, and recruit these fibroblasts into this area. CAFs transport vital nutrients to cancer cells through exosomes, thereby inhibiting oxygen-dependent energy synthesis in cancer cells. During nutritional stress or deprivation, CAFs induce tumor growth in the TME by releasing exosomes containing lipids, amino acids, and three carboxylic acid (TCA)-cycle intermediates [61].

In conclusion, these researches have shown that lung cancer derived exosomes have a significant effect on the growth and advancement of NSCLC. These exosomes contain various substances and offer a new potential for NSCLC treatment.

Tumor angiogenesis and metastasis

Angiogenesis is the generation of new blood vessels from pre-existing ones [62]. The angiogenesis, intravasation, and metastasis in lung cancer are caused by the communication between these components and tumor cells [63]. By providing cancer with oxygen, nutrients, and other metabolites, tumor neovascularization also promotes the growth of tumors and is further supported by the proliferation of endothelial cells in blood vessels. A proper blood supply to the tumor enhances the influx of tumor cells into circulation, initiating the metastatic process. Indeed, from the onset of carcinogenesis, to the carcinoma in situ and developed stages of cancer, angiogenesis and inflammation are crucial processes that contribute to cancer development [64].

Increasing angiogenesis occurs via a discrepancy between pro- and anti-angiogenic factors, driven by hypoxia-induced tissue excessive production of vascular endothelial growth factor (VEGF) which leads to tumor progression [65]. Hypoxia and VEGF activity have been shown to increase the expression of ANGPT-2 in tumor-associated vessels in a few human cancers [66]. The angiopoietin (ANGPT)-TIE system is essential for the angiogenic change in cancers and, along with VEGF-A, enhances angiogenesis and the development of new vessels [67].

Exosomes contain different cargoes that promote angiogenesis and participate in cancer invasion [68]. The miRNAs that originate from exosomes in lung cancer cells participate in the stimulation of hypoxia [69].

Exosomal miR-497 inhibits VEGF-A expression and hinders tumor growth. So, it could be employed as a treatment target for lung cancer [70]. In addition, signal transducer and activator of transcription (STAT)3-regulated exosomal miR-21 can enhance angiogenesis and malignant transformation in human bronchial epithelial cells [71].

Angiogenesis is also promoted by the activation of TGF-β signaling through the exosome derived from NSCLC cells with LRG1. Leucine-rich glycoprotein alpha2 (LRG1) is elevated in NSCLC tissues, which facilitates invasion of NSCLC cells [72]. Also, the targeting of prolyl hydroxylase 1 and 2 (PHD1 and 2) by miR-23a in exosomes results in suppression of expression in endothelial cells. The accumulation of HIF-1α in endothelial cells enhances angiogenesis. Furthermore, the tight junction protein ZO-1, which is associated with cell migration and vascular permeation, can be blocked by the exosomal miR-23a [73].

Metastasis is a major cause of death in lung cancer patients, resulting from various mechanisms and phases. Tumor-derived exosomes facilitate metastasis by serving as vehicles for the transmission of information, exerting both direct and indirect effects [74]. Exosomes have the ability to enhance the development of the microenvironment in the lungs, which leads to an increase in the ability of tumor cells to invade surrounding tissues [75]. The release of exosomes by tumor cells is promoted by factors such as oncogene instability, hypoxia, acidosis, and inflammatory immune response. This leads to the formation of a tumor microenvironment, which facilitates the rapid development and invasive capabilities of tumor cells [38, 76]. Tumor-derived exosomes are linked to invadopodia, which are responsible for initiating invasion by breaking down the extracellular matrix [77]. Exosomal contents have the ability to enhance the spread of cancer to other parts of the body and transmit the ability to form new tumors to other cells [74]. Epithelial-mesenchymal transition (EMT) is the transformation of epithelial cells into stromal cells, a crucial step in the metastasis of tumor cells [78]. This process involves various changes, such as alterations in the cytoskeleton and the suppression of the expression of the adherens junction molecule E-cadherin [79]. NSCLC metastasis.

commonly happens in the brain, adrenal glands, bones, and liver [63]. Metastasis begins with the formation of a pre metastatic niche, which occurs after tumor cells are changed. Exosomes regulate the establishment of pre-metastatic niches during metastasis [80]. Studies found elevated levels of exosomal Tim-3 and exosomal Galectin-9 in plasma of NSCLC patients, which is associated with multiple malignant criteria, such as larger tumor dimension, lymph node metastasis and distant metastases [81]. Exosomal TGF-β and IL-10 can also improve migration in vitro during hypoxia [76].

Exosomal RNAs have a direct link to the development of NSCLC. Huang et al. showed the downregulated expression of miR-34c-3p especially in exosomes of NSCLC patients in comparison with normal expression, which could promote NSCLC migration and invasion via upregulating α2β1 integrin [82]. Zang et al. found elevated levels of lncRNA UFC1 expression in tumor tissues, serum, and serum exosomes in NSCLC patients. Elevated levels of UFC1 have been related to tumor invasion [4, 83].

The effects of immune cell-derived exosomes on NSCLC

TDEs can influence the immune response through increasing the polarization of macrophages towards M2 and the proliferation of MDSC. They can induce the apoptosis of CTLs and differentiation of Treg cells [94]. On the other hand, immune cell-derived exosomes (IDEs) mimic the functional features of their source immune cells. APC-derived exosomes activate CD4+and CD8+T lymphocytes by expressing an antigen-MHC complex on their surface [95]. MHC class I and II, as well as co-stimulatory molecules, are expressed on APC-derived exosomes, CD56 on NK-derived exosomes, and the TCR/CD3 complex on T cell-derived exosomes [96].

Immune cells also release exosomes that possess immunomodulatory capabilities. For instance, it has been demonstrated that Treg cells release exosomes that express CD73 and prohibit the growth of CD4+T cells [97]. Furthermore, exosomes derived from T lymphocytes have the ability to attach to DC, triggering apoptosis of DC and thereby suppressing T cell responses [98]. Exosomes derived from both innate and adaptive immune system cells might communicate directly with tumor cells and trigger different immune reactions (Fig. 2). Therefore, exosome-targeted therapies have the potential to enhance the anti-tumor response via altering cell interactions.

Dendritic cells derived exosomes (dex)

Some anti-tumor functions of the exosome have become clear recently. Numerous studies have shown that dendritic cell (DC) and tumor -derived exosomes got have high numbers of major histocompatibility complex class I (MHC I) molecules and markers of tumor including heat shock protein (HSP), that led to antigen presentation and activation of T cells in conjunction with promotion of CD8+T cell-dependent anti-cancer responses was illustrated [99]. Subsequently, use of exosomes as carriers to promote anti- cancer immune responses and deliver anti-cancer drugs in immune therapy is critical in respects to cancer progression [100].

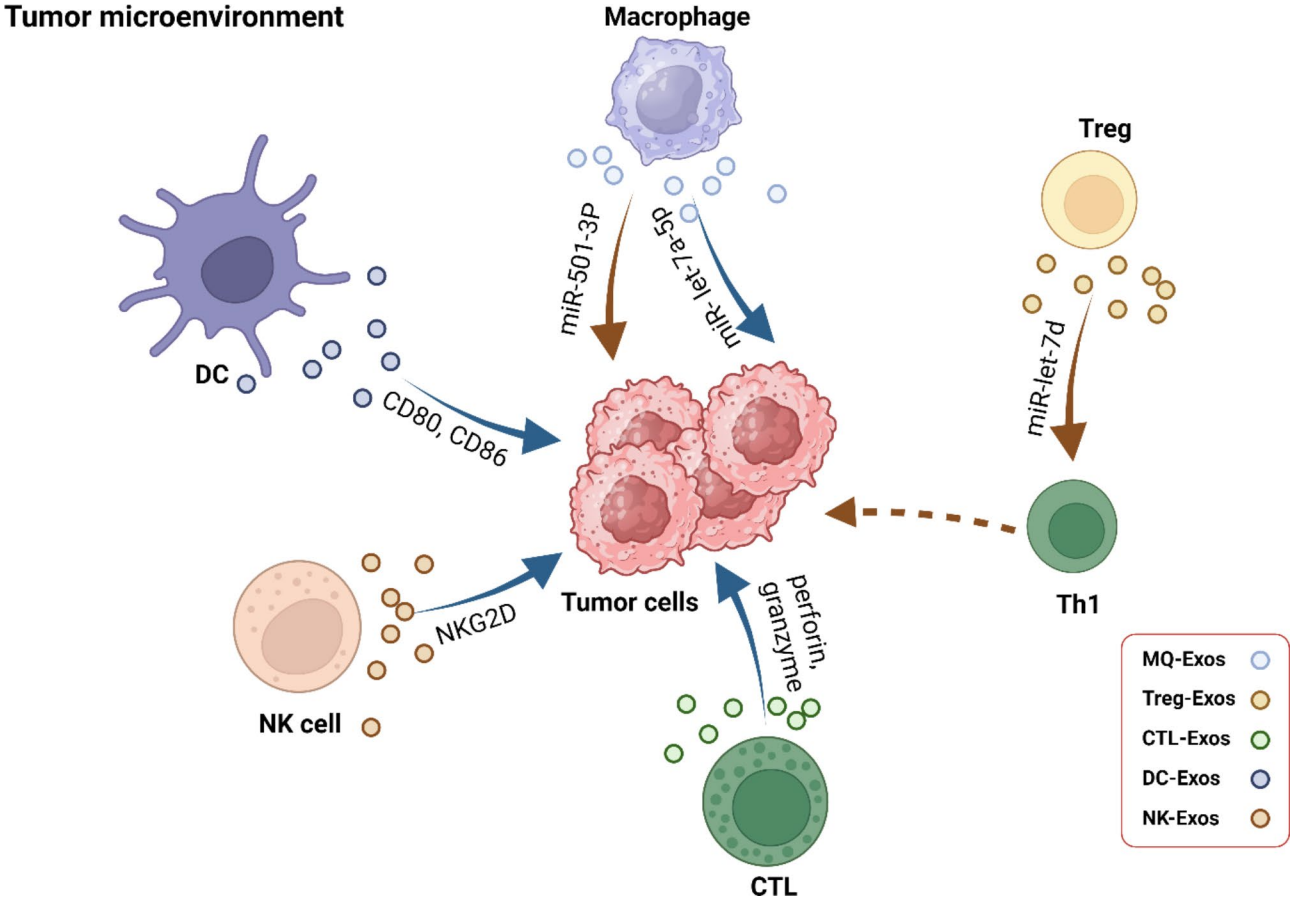

Fig. 2 Role of immune cell-derived exosomes in the stimulation of the immune response against the tumor. This figure demonstrates the potential of exosomes as tools in immunotherapy for NSCLC. Dendritic cell-derived exosomes (Dex) and NK cell-derived exosomes (NK-Exos) activate cytotoxic responses. Additionally, highlights the role of exosomal miRNAs in modulating the immune microenvironment and enhancing therapeutic outcomes

Dex as small extracellular vesicles which are 50_150 nm diameter extracted by high-speed ultracentrifugation with a molecular composition that offers them with powerful immune stimulatory characteristics. Dex keeps up the primary functions of DCs in their capacity to present tumor associated antigens (TAA) and to actuate TAA specific immune reactions. The outer membrane of Dex got has a high amount of antigen presentation including MHC class I, class II, CD1, also adhesions (ICAM), costimulatory (CD80, CD86), in conjunction with docking (integrin) molecules [19, 101]. Clearly, the communication of Dex by tumor cells has the potential to transform tumor cells into more immunogenic targets, creating new possibilities for treatment approaches aimed at enhancing immune targeting of malignancies.

NK cell derived exosomes (NK-Exos)

NK cells can eliminate aberrant cells and promote an adaptive immune reaction by secreting pro-inflammatory cytokines and chemokines [102]. NK cells have been used to treat a variety of conditions, including hematologic malignancies (acute myeloid leukemia, acute lymphoblastic leukemia, multiple myelomas), solid tumors (neuroblastoma, lung cancer, hepatocellular carcinoma), and nonmalignant disorders like thrombocytopenic purpura and psoriasis [103]. However, the cytokine profile of the TME has a significant role in the infiltration of NK cells into tumors, including lung cancer, which can impede their activities [104].

NK-Exos, like parental cells, carry the NK marker CD56 as well as receptors such as NKG2D, which bind to ligands expressed only in malignant cells, and include cytolytic molecules like FasL, perforin, and granzymes [105]. NK cells can limit tumor growth through cytolytic activity, cytokine generation, and promoting Th1 responses [106]. The decreased activity of NK cells in peripheral blood may raise the risk of cancer [107].

It is noteworthy that NK exosomes are swiftly taken in by tumor cells and can have cytotoxic impacts even at low concentrations, suggesting that they could be employed in cancer treatments. NK exosomes were highly effective against tumor cells, whereas non-tumor cells were less susceptible to their lysis [104]. Exosomes released by human NK cells contain NK-related components,

including CD56, NKG2D, NCRs, Granzyme A-B, Granulosyn, and Perforin. The latter can cause a cytotoxic impact on tumor cells, leading to the suppression of tumor growth [108–110]. The elimination of tumor cells by NK exosomes is believed to occur through various pathways, which include the involvement of Granzymes/Perforin and Fas receptor [111, 112]. In addition, NK exosomes contain LFA-1 and DNAM1, two other substances known to be involved in NK-mediated cancer cell mortality. Pace et al. found that DNAM1 expression was reduced in tumor infiltrating NK cells of lung cancer [104]. The inhibition of DNAM1 expression, on the other hand, is linked to the malfunctioning of natural killer (NK) cells, and the blocking of DNAM1 with an anti-DNAM1 antibody leads to the elimination of tumor cell degradation in vitro [113].

Exosomes generated from natural killer (NK) cells offer a highly effective option for the treatment of some types of malignancies. They inherently produce IFN-γ, FasL, and several cytotoxic proteins that can trigger apoptosis via different mechanisms of cell death. The intrinsic capacity of exosomes to move across cells can induce more activity within the tumor microenvironment or facilitate communication with neighboring cells, so triggering their deadly effects [112]. Tae Kang et al. employed NK-graphene oxide (GO) microfluidic chips to separate NK-Exos from the blood of NSCLC patients. This innovative strategy for isolating NK-Exos reveals their great cytotoxic efficacy against circulating tumor cells [114]. Also, Exosomes generated from NK-92 cells treated with IL-15 and IL-21 showed increased cytolytic activity against cervical and lung cancer [115].

T cell derived exosomes

T lymphocytes are immune cells that support the immune response against pathogens, self, allergies, and cancer [116]. Exosomes from T cells can stimulate and suppress immune cells, as well as license APCs [117]. T cell-derived EVs transmit miRNA from T cells to APCs and facilitate their activation [118]. Activated T cell-derived EVs are transported to DNA-primed DCs via antigen-driven interactions [98]. Also, T cell-derived exosomal CD40L can maintain signalings that enhances B cell proliferation and differentiation [119].

CTL-derived EVs (CTL-Exos) also contain effector molecules such as perforin and granzyme [120]. CTL-Exos exosomes can prevent tumor development, but these exosomes can have adverse impacts on tumor growth and progression [121]. For instance, exhausted CD8+T cells release large amounts of EVs, which may be taken up by normal CD8+T cells. This inhibits their proliferation (Ki67), activity (CD69), and production of cytokines such as IFN-γ and IL-2 [122].

CAR-T cell-derived exosomes have been shown in preclinical trials to suppress solid tumors such as TNBC and lung cancer while remaining safe [121].

Treg-derived exosomes (Treg-Exos)

Tregs suppress effector T cells through releasing exosome transferring miRNAs. Treg-derived EVs have both mature and premature miRNAs, with pro-apoptotic or anti-proliferative effects. Okoye et al. found that the microRNA Let-7d was selectively packed into Treg EVs and transported to Th1 cells, inhibiting Th1 cell proliferation and IFN-γ release [123]. Furthermore, Regulatory Treg-derived EVs include CD25, cytotoxic T-lymphocyte associated protein 4 (CTLA-4), and CD73. CD73-positive Treg EVs may transform extracellular denosine-5-monophosphate to adenosine. When adenosine binds to receptors on active effector T cells, it inhibits cytokine synthesis and T cell responses [124]. So, Regulatory Treg-derived EVs may be a promising target for cancer immunotherapy [120].

Macrophage-derived exosomes (MQ-Exos)

Macrophage-targeted treatment methods are mostly divided into three parts: [1] Reduction of macrophages in the TME; [2] Reduces macrophage recruitment; and [3] Repolarizes M2 macrophages to M1 macrophages in the TME [125]. M1 macrophages phagocytose tumor cells, while M2 macrophages enhance tumor development and metastasis [126]. M1 macrophages reduce angiogenesis in NSCLC patients and contribute positively to their survival time [127, 128]. However, M2 macrophages have been shown to enhance NSCLC metastasis by activating Epithelial-mesenchymal transition (EMT) and lung cancer cell invasion [128, 129].

MQ-Exos perform many activities based on the phenotypes of their originating cells. Endogenous and external stimuli affect the production of MQ-Exos [130]. Solid tumors often have a hypoxic microenvironment, which can lead to increased release of macrophage-derived EVs [131]. In addition, M2-Exos can invigorate the growth of NSCLC in hypoxic microenvironments [132].

Furthermore, M2-like macrophage-derived exosomes transmit ITG αVβ3 to NSCLC cells, activating focal adhesion kinase (FAK) signaling in recipient cells and promoting migration and invasion [133]. Kim et al. discovered that irradiation of apoptotic lung cancer cells triggers macrophages to transfer exosomal PTEN proteins to recipient cells and preventing EMT [134]. Also, M2-Exos enhance gefitinib resistance in NSCLC, and the process may involve reactivation of the AKT, ERK1/2, and STAT3 signaling pathways [135].

M2-Exos contain a variety of miRNAs which have a significant role in tumorigenesis. miR-155 and miR-196a-5p are essential functional molecules in M2-Exos

which stimulate EMT in NSCLC cells by targeting RASSF4 [136]. Lei et al. found that M2-Exos transferring miR-501-3p to lung cancer cells may stimulate cell proliferation by down-regulating WDR82 expression, leading to further tumor growth [137]. Also, Exosomal miR-let-7a-5p from macrophages suppresses lung cancer cell proliferation, migration, and invasion by downregulation of BCL2L1 expression [138].

Exosome based immunotherapy in NSCLC

Immunotherapy as a new treatment has demonstrated promising results in lung cancer treatment and improved patient prognosis [139]. In general, cancer immunotherapy is a kind of treatment that aims to control and eliminate tumors via modulating the immune system to reactivate the antitumor immune response and evade the pathways that lead to cancer scape [140]. Major therapeutic approaches of immunotherapy are nonspecific immune stimulation, immune checkpoint blockade, adoptive cell transfer, and vaccination strategies [100]. In recent years, immunotherapy has become an area of research due to its immune system strengthening properties, involvement in various types of cancer, and ongoing response.

Exosome-based therapy has the potential to be a novel strategy for cancer immunotherapy since exosomes can be employed as carriers to induce anti-cancer immune responses as well as an instrument for delivering anti-cancer medicines [141]. Furthermore, exosomes have numerous advantages in terms of biocompatibility, immunogenicity, stability, pharmacokinetics, bio distribution, and cellular uptake mechanism, making them promising therapies for cancer [142]. Over all, finding exosomes, as one of the methods of liquid biopsies, is extremely valuable for guiding diagnosis and treatment [143].

Exosome-based vaccine

Cancer vaccines are expected to play a therapeutic function in combination therapy for individuals with advanced or metastatic tumors [144]. Melief et al. found that an effective cancer vaccine design needs to allow for the emergence of vigorous effector CD4+and CD8+T-cell responses [145]. In 1998, Zitvogel et al. discovered that DEXs carry functional MHC class I and II molecules. They demonstrated that tumor peptide-pulsed DCs produced DEXs expressing tumor antigens, resulting in in vivo CTL activation and inhibition of tumor development [146]. Wolfers at el. revealed that TDEs also serve as a source of T-cell cross-priming by antigen transfer to DCs, which produce CTL anti-tumor responses both in vitro and in vivo [147].

The potential use of Dex in immunotherapeutic approaches for its long term stability after freezing, a wide range of MHC- peptide complexes that deliver to surrounding antigen presenting cells and the capacity to activate NK cells via membrane bound IL-15/IL-15Ra and NKG2D ligand [148] exposure was demonstrated. Consequently, over the last decade, Dex has been created as a clinical cell-free cancer vaccine [149, 150]. Initial Phase I clinical trials, among patients with NSCLC (stage IIIb or IV) who were HLA-A2 positive and expressed MAGE-A3 or A4 antigen completed the therapy demonstrated the effectiveness of Dex as a vaccine against non-small cell lung cancer (NSCLC) prepared from MoDC loaded with MHC-I and MHC-II melanoma-associated antigen (MAGE) peptide epitopes. The Dex vaccine was approved for use in NSCLC patients and was shown to be safe and well tolerated. Some patients showed promoted immune efficacy and long-term disease stability [151, 152]. Unlike Dex derived from immature MoDCs, Dex derived from mature DCs has more potential in stimulating T cell proliferation. Consequently, IFN- was used to activate human MoDCs in culture, leading to the development of a second generation Dex (IFN-γ-Dex) with improved immunostimulatory capabilities [153]. It was found that IFN- γ matured DEXs that were loaded with MHC class I and II tumor peptide were found to enhance the NK cell activity of patients with non-small cell lung cancer (NSCLC) [154, 155].

Exosomal PD-L1 targeting

PD-L1 expressed on TDEs has a critical role in tumor invasion and immune escape [81]. TGF-β and IFN-γ are examples of cytokines that have been discovered to stimulate the production of PD-L1 in exosomes [156, 157]. Exosomal PD-L1 has a crucial function in facilitating an immunosuppressive microenvironment, which is a significant element in the progression of cancer and evasion of the immune system, specifically in lung cancer. The development of the tumor immunomodulating microenvironment by exosomal PD-L1 is an intricate process that includes several types of immune cells and signaling molecules.

Multiple studies have shown that exosome release can be impeded by utilizing antibodies, pharmacological inhibitors, or genetic alteration. This, in turn, improves the efficacy of treatment for metastatic cancer [158–160]. For example, Anti-PD-L1 antibodies counteract the immunosuppressive impact induced by exosomes released by Lewis lung carcinoma tumor cells. These exosomes trigger the expression of PD-L1 on dendritic cells, thereby impeding the proliferation of CD4+T cells [161]. Overall, blocking the production and release of exosomal PD-L1 has emerged as a novel and significant approach for the development of anti-cancer drugs.

Targeted drug delivery

The initial achievement of targeted delivery of drugs to the target cells by exosomes has been accomplished. Scientists have recently created a drug delivery system named nanosomes by combining gold nanoparticles (GNPs) with the anticancer medication doxorubicin (Dox) and then attaching them to the exosome pH-sensitive hydrazone. Significantly, the examination of cell viability demonstrated that nanosomes exhibited selective cytotoxicity towards cancer cells [162]. Given the extensive surface area of the lungs, it is imperative that the drug delivery mechanism for lung tumors enables the gradual and regulated release of the medication. Exosomes are gaining significant interest as medication delivery methods for the medical management of lung cancer. During their work, Munagala, R. et al. utilized encapsulated Berry-derived chemicals, including aglycones and anthocyanins, which have therapeutic properties, in exosomes. These compounds were employed in the treatment of lung tumors in nude mice. The researchers observed a notable result with improved therapeutic efficacy, suggesting that exosomes have a vital function in the treatment of lung cancer as a carrier for delivering drugs [163]. Kim and his colleagues presented a study on a method to deliver drugs for lung cancer therapy called AA-PEG-exoPTX. This system utilizes exosomes and successfully ceased the spread of cancer cells by specifically targeting the overexpression of the sigma receptor in tumor cells [164]. In summary, it is evident that exosomes have a vital function in the management of lung cancer.

DEXs loaded with HLA-restricted melanoma-associated antigen (MAGE) peptides that were delivered to individuals with HLA A2+NSCLC [151].

DEXs generated from mature DCs pulsed with IFN-γ for individuals with NSCLC found no toxicity. Also, DEX vaccines promoted NK cell activities, but did not elicit a cancer-specific T-cell immune response [153]. In another study, vaccination of mice with the ES-exo/GM-CSF suppressed the development of metastatic lung cancers. ES-exo/GM-CSF also decreased the frequency of tumor-infiltrating immunosuppressive immune cells, such as Tregs, MDSCs, and tumor-associated macrophages, while increasing effector cytokine release from CD8+T cells [165].

Chemosensitivity

The problem of chemotherapy resistance must also be confronted when treating lung cancer. While certain exosomes have been found to enhance resistance to chemotherapy, others play a crucial role in inhibiting chemotherapy in lung tumors. For example, the overexpression of miR-1 enhanced the sensitivity of NSCLC cells to cisplatin by suppressing autophagy related 3 (ATG3)-mediated autophagy. This mechanism ultimately leads to an increased effectiveness of anti-tumor medicines used in the treatment of NSCLC [166]. Another study has shown that miR-539 enhances the effectiveness of cisplatin chemotherapy in NSCLC by specifically targeting Doublecortin Like Kinase 1(DCLK1) [167]. In addition, Xiaoyuan Wang et al. performed a study demonstrating that the miR-181b/Notch2 axis suppressed chemoresistance by controlling cancer stem cell-like characteristics in NSCLC. This finding suggests a potential alternative treatment target for overcoming drug resistance in NSCLC [168].

Exosome modified

According to recent studies, exosomes may be effective carriers for anti-cancer detection and treatment [169] (Table 2). Yang et al. established an integrated microfluidic system capable of detecting lung cancer-specific exosomes from urine of patients with great sensitivity and specificity [170].

Table 2 Research on exosome roles in lung cancer treatment

Source of Exosome	Exosome Modification	Brief Result	Ref.
Milk exosomes	Loaded Celastrol	The enhanced efficacy and reduced dose related toxicity.	[177]
Raw bovine milk exosomes	Loaded Anthos	The enhanced therapeutic response and no signs of systemic toxicity.	[178]
Engineered exosomes	Loaded miR-449a	Inhibitory effects on proliferation of A549 cells and promotion of their apoptosis.	[179]
Engineered exosomes	Loaded miR-563	Engineered exosomes suppress the growth of A549 cells in vitro by reducing tumor cell proliferation, migration, and invasion while increasing apoptosis rates.	[180]
MDA-MB-231 exosomes	Loaded miR-126	Inhibitory effects on proliferation and migration of A549 cells.	[181]
CAR-T-cell derived exosomes	Loaded Paclitaxel	The enhanced the targeted antitumor effects of paclitaxel.	[182]
LUAD cell derived exosomes	Transferred LOC85009	Inhibitory effects on Docetaxel resistance in LUAD.	[183]
Serum and cell derived exosomes	Transferred circKIF20B	Suppression of Gefitinib resistance and cell proliferation in NSCLC.	[184]
Cell exosomes	LAMTOR1	Suppression of the exosomes of PD-L1 and promotion the infiltration of $CD8^+$cells in NSCLC.	[185]
Bone marrow mesenchymal stem cell (BMSC) derived exosomes	Transferred miR-30b-5p	Promotion of apoptosis in NSCLC cells.	[186]

Exosomes as drug delivery systems (DDSs) have emerged a promising medication delivery method for chemotherapy drugs. For example, Docetaxel-loaded exosomes (EXO-DTX) demonstrated anticancer efficacy in vitro, inhibiting proliferation, promoting apoptosis, disrupting the cell cycle, and preventing A549 tumor cell migration. Besides, EXO-DTX could disrupt metabolism and have a therapeutic impact through controlling ROS levels in cells. Also, in vivo experiments show that EXO-DTX is a more effective tumor-targeting agent than free DTX due to its sustained-release formulation and higher pharmacological potency [171]. Lipid content of exosomes enhances drug stability and extends its half-life in the bloodstream and facilitates their fusion with target cells.

Autogenous exosomes also lower immune system activation levels. Exosomes have been used to carry gene medicines such as non-coding RNAs for tumor therapy. Exosomes loaded with miR-499a may lower lung cancer cell proliferation, migration, and invasion. Moreover, it was found that miR-499a may suppress the expression of Bcl-2, an apoptosis inhibitor, leading to cell apoptosis [172]. Also, it was found that miR-563 loaded engineered exosomes could suppress the growth of lung cancer in both in vivo and in vitro studies. Thus, they may offer a new therapeutic target for lung cancer therapy [173]. Engineered MSC-derived exo-mediated miR-631 delivery has been found to regulate the transcription factor 2/phosphatidylinositol 3-kinase/Akt signaling pathway in NSCLC cell and animal models, controlling malignant behavior [174]. Also, engineered MSC-exos transfer miR-204 to NSCLC cells. Increased levels of miR-204 suppress KLF7 expression and AKT/HIF-1α pathway activity, reducing NSCLC migration and invasion [175].

Engineered exosomes are spatially suited based on the molecules on their surface, resulting in higher concentrations in tumors compared to healthy organs including the liver, spleen, and kidney. Despite numerous studies on specific exosome techniques, there is still a need for specific ligands that can guide exosomes to tumor locations while minimizing absorption by normal organs [176].

Future perspectives

The evolving function of exosomes in the TME of NSCLC illustrates promising opportunities for advancing both diagnostic and therapeutic approaches(Table 3). Future research should focus on the standardization of exosome isolation and characterization techniques in order to better define their biomolecular cargo, enabling their reliable use as biomarkers for early NSCLC detection and disease progression monitoring. Also, deeper investigation into the specific molecular mechanisms by which exosomal RNA and protein cargo influence immune evasion and therapeutic resistance could provide novel therapeutic targets.

Emerging exosome-based therapeutics, such as exosomal vaccinations and targeted drug delivery systems, hold promise for improving treatment outcomes in NSCLC. However, further clinical trials are needed to establish the safety, efficacy, and long-term impact of these approaches. The integration of exosome-modifying strategies with current immunotherapies, particularly immune checkpoint inhibitors like PD-1/PD-L1, could improve anti-tumor responses and overcome resistance mechanisms in advanced NSCLC cases.

In the future, personalized medicine approaches could leverage the specific exosomal profiles of individual patients to tailor treatments, improving response rates and minimizing side effects. Ultimately, the clinical translation of exosome-based research could revolutionize NSCLC management, offering more precise diagnostic

Table 3 Current clinical trials using exosomes in NSCLC

Study title	Condition	Stage	Location	Clinical trial
Molecular Profiling of Exosomes in Tumor-draining Vein of Early-staged Lung Cancer	NSCLC	Recruiting early stage	Limoges, France	NCT04939324
Trial of a Vaccination with Tumor Antigen-loaded Dendritic Cell-derived Exosomes	NSCLC	Phase II	Villejuif, France	NCT01159288
Non-small Cell Lung Cancer with Central Nervous System Metastasis	NSCLC with central nervous system metastases	Recruiting	Taipei, Taiwan	NCT06026735
Olmutinib Trial in T790M (+) NSCLC Patients Detected by Liquid Biopsy Using BALF Extracellular Vesicular DNA	NSCLC	Phase II	Seoul, Korea	NCT03228277
The Study of Exosome EML4-ALK Fusion in NSCLC Clinical Diagnosis and Dynamic Monitoring	Untreated Advanced NSCLC	Recruiting	Beijing, China	NCT04499794
Exosomes Detection for the Prediction of the Efficacy and Adverse Reactions of Anlotinib in Patients with Advanced NSCLC	NSCLC	Not Applicable	Location not provided	NCT05218759
Prediction of Immunotherapeutic Effect of Advanced Non-small Cell Lung Cancer	NSCLC	Not Applicable	Shanghai, Shanghai, China	NCT04427475

tools and more effective, targeted therapies for patients with this challenging disease.

Conclusion

Exosome-based therapy is a promising new approach to treating non-small cell lung cancer (NSCLC). The ability of exosomes to carry therapeutic cargo to target cells, modify the tumor microenvironment, and increase anti-tumor immune responses has the potential to significantly improve patient outcomes. Exosome- based treatments have been shown in preclinical trials to be effective in reducing tumor growth and metastasis, and clinical trials are under ongoing to prepare them for clinical use. However, various obstacles, such as standardization of production protocols and process optimization, must be addressed before exosome-based therapy for NSCLC may reach its full potential. Despite these obstacles, recent advances in exosome research and technology offer optimism for the development of reliable and efficient treatments that will affect the management of NSCLC and other tumors in the near future.

Abbreviations

ANGP	Angiopoietin
ASMA	Alpha- smooth muscle actin
B4GALT3	β-1,4-galactosyltransferases III
CAFs	Cancer-associated fibroblasts
circRNAs	Circular RNAs
circUSP7	Circular ubiquitin-specific protease-7
CTLA-4	Cytotoxic T-lymphocyte associated protein 4
CTLs	Cytotoxic T lymphocytes
DCLK1	Doublecortin Like Kinase 1
DCs	Dendritic cells
DDS	Drug delivery system
ECM	Extracellular matrix
EGFR	Epidermal growth factor receptor
EMT	Epithelial–mesenchymal transition
ERK	Extracellular signal-regulated kinase
FAK	Focal adhesion kinase
FSCN1	Fascin Actin-Bundling Protein 1
HSP	Heat shock protein
IDEs	Immune cell-derived exosomes
IFN-γ	Interferon-γ
IL-10	Interleukin-10
LMO7	LIM-domain only protein 7
LRG1	Leucine-rich glycoprotein alpha2
MDSCs	Myeloid-derived suppressor cells
MAGE	Melanoma-associated antigen
MAPK	Mitogen-activated protein kinase
MHC	Major histocompatibility complex
mRNAs	Messenger RNAs
ncRNAs	Non-coding RNAs
NF-κB	Nuclear factor kappa B
NKs	Natural killer cells
NSCLC	Non-small cell lung cancer
OSER1-AS1	OSER1 antisense RNA 1
PAC1	Pituitary adenylate cyclase-activating polypeptide type 1
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PGE2	Prostaglandin E2
PHD	Prolyl hydroxylase
RCAN1	Regulator of calcineurin 1
SFRP1	Secreted frizzled-related protein 1
SOCS5	Suppressor of cytokine signalling 5
STAT	Signal transducer and activator of transcription
TAA	Tumor associated antigens
TAM	Tumor associated macrophage
TCA	Three carboxylic acid
TDEs	Tumor-derived exosomes
TGF-β1	Tumor growth factor- β1
TKIs	Tyrosine kinase inhibitors
TLRs	Toll-like receptors
TME	Tumor microenvironment
TNF-α	Tumor necrosis factor-α
TRAIL	TNF-related apoptosis inducing ligand
Treg	Regulatory T cell
VEGF	Vascular endothelial growth factor

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