Review Article

Exosomal microRNAs in lung cancer: a narrative review

Zhe Zhang, Fengwu Lin, Wenqi Wu, Jingyuan Jiang, Chen Zhang, Dongliang Qin, Zhenan Xu

Department of Thoracic Surgery, China-Japan Union Hospital of Jilin University, Changchun, China

Contributions: (I) Conception and design: Z Zhang; (II) Administrative support: Z Xu; (III) Provision of study materials or patients: W Wu; (IV) Collection and assembly of data: J Jiang; (V) Data analysis and interpretation: C Zhang, D Qian; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Zhenan Xu, MD. Department of Thoracic Surgery, China-Japan Union Hospital of Jilin University, Xiantai Street 126, Changchun 130033, China. Email: xuzhenan17@jlu.edu.cn.

Background and Objective: Exosomes are nanoscale extracellular vesicles secreted by cells, which can release bioactive macromolecules, such as microRNA (miRNA) to receptor cells. Exosomes can efficiently penetrate various biological barriers which mediate intercellular communication. MiRNA are a class of non-coding RNA that primarily regulate messenger RNA (mRNA) at the post-transcriptional level. MiRNA is abundant in exosomes, which plays an important role by being transported and released through exosomes secreted by lung cancer cells. This review aims to elucidate the roles of exosome-derived miRNAs in lung cancer.

Methods: We focused on the roles of exosome-derived miRNAs in cancer occurrence and development, including angiogenesis, cell proliferation, invasion, metastasis, immune escape, drug resistance, and their clinical value as new diagnostic and prognostic markers for lung cancer.

Key Content and Findings: Exosomal miRNA can not only affect angiogenesis of lung cancer, induce epithelial-mesenchymal transformation, and promote reprogramming of tumor microenvironment, but also affect immune regulation and drug resistance transmission and participate in regulating lung cancer cell proliferation. Therefore, understanding the regulatory roles of exosomal miRNAs in tumor invasion and metastasis can provide new ideas for the treatment of lung cancer.

Conclusions: Exosomal miRNA can provide some unique ideas on how to improve the efficiency of diagnosis and treatment of lung cancer in the future. Targeting tumor-specific exosomal miRNA represents a new strategy for clinical treatment of lung cancer, which can provide potential non-invasive biomarkers in the early diagnosis of lung cancer. Investigation of the involvement of exosomal miRNAs in the occurrence and progression of tumors can yield new opportunities for the clinical diagnosis and treatment of lung cancer.

Keywords: Exosomes; lung cancer; review

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Introduction

Lung cancer is one of the most common malignant tumors worldwide. It is a major cause of cancer-related death, with a mortality rate of approximately 18.4% (1). Most patients have progressed to late stages by the time of diagnosis and missed the opportunity for surgical treatment. The 5-year survival rate is quite low, with that of clinical stages IIIA, IIIB, IIIC, and IV patients having been reported at 16%, 9%, 6%, and 3%, respectively (2). Therefore, early screening and diagnosis are a way to reduce mortality (3). Research has shown that combining genomics and genetics screening can improve the survival rate for lung cancer patients (4-6). Blood is the easiest source to obtain to acquire information about lung cancer (7), including circulating DNA and RNA (8), circulating tumor cells (9),

Table 1 The search strategy summary

Items	Specification
Date of search	01 Dec 2023–01 Jan 2024
Databases and other sources searched	PubMed/MEDLINE
Search terms used	"Lung cancer" AND "miRNA" OR "exosomes"
Timeframe	1979–2024
Inclusion and exclusion criteria	Inclusion criteria: without predefined restriction as to the study type
	Exclusion criteria: restricted to articles published in English
Selection process	Z.Z. and F.L. independently screened data sources. Data analysis was conducted by J.J. and Z.X.

serum metabolites (10), and lipids (11). Although numerous molecular biological markers have been proposed, the detection sensitivity and specificity need to be improved. Therefore, there is an urgent need to identify accurate, reliable, and highly specific molecular biological biomarkers for early diagnosis of lung cancer. In this study, we focused on the roles of exosome-derived microRNAs (miRNA) in cancer occurrence and development, including angiogenesis, cell proliferation, invasion, metastasis, immune escape, and drug resistance, and their clinical value as new diagnostic and prognostic markers for lung cancer. We present this article in accordance with the Narrative Review reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2319/rc).

Methods

A literature search was conducted in PubMed and MEDLINE databases with the keywords "lung cancer" AND "miRNAs" OR "exosomes". We only considered research articles written in English, but without predefined restriction regarding the study type. Data sources were independently screened by two authors. Data analysis was conducted by two authors. The search strategy is summarized in *Table 1*.

Lung cancer and miRNAs

MiRNA is an endogenous non-coding small molecule RNA (18–24 nucleotides in length), which is responsible for the regulation of target genes. MiRNAs are related to the occurrence and development of tumors and cell signal molecule transduction (12). They can affect a variety of cell functional processes, such as cell proliferation, apoptosis, differentiation, and metabolism (13). MiRNAs are not easily degraded by RNA enzymes and resistant to boiling (14). MiRNAs in the blood are considered more stable than other types of RNA. Currently, the circulating miRNAs are serving as potential molecular biomarkers for the diagnosis of lung cancer. Studies have shown that serum or plasma miRNAs are differentially expressed between lung cancer patients and healthy individuals, and circulating miRNAs in lung cancer can pass through the mitogen-activated protein kinase (MAPK) signaling pathway, fibroblast growth factor receptor (FGFR) signaling pathway, glucose transport cell apoptosis and antigen processing and presentation to play their related biological functions (15). Many miRNAs such as miR-17 and miR-19, miR-17, miR-20a, miR-18a, miR-92a-1, miR-19a, and miR-19b-1 participate in cancer-related processes (16). Overexpression of miR-17 and miR-19 in lung cancer can regulate the expression of the *HIF1A*, *PTEN*, *BCL2L11*, *CDKNA*, and *TSP1* genes, and promote tumor growth through hypoxia, proliferation, inhibition of cell apoptosis, and stimulation of cell migration (17). The overexpression of miR-21 in lung cancer cells is related to cell proliferation, invasion, metastasis, and angiogenesis (18). The downregulation of miR-21 induces apoptosis by inhibiting the PI3K/Akt/NF-κB signaling pathway and increasing caspase activity, which can inhibit the invasion and metastasis of lung cancer cells. Circulating miRNA, as a prospective molecular biomarker, has high diagnostic efficacy, sensitivity, and specificity for lung cancer diagnosis. However, literature reports indicate that molecular biological markers have low repeatability or reproducibility in their diagnostic efficacy for lung cancer, which may be influenced by factors such as race, regional differences, genetic characteristics, and different research and analysis methods of lung cancer patients. Therefore, the application of cancer-related functional miRNAs as molecular biological markers for lung cancer diagnosis

still requires a large amount of data support and further exploration and research (19).

Characteristics of exosomes

The exosome is a double vesicle structure with a diameter of 30–200 nm, which is secreted by various cells (20). The cell membrane is invaginated to form multiple endocytosomes, which are fused to form an early endosome. The late endosome is formed after the early endosome encloses the intracellular substances. Exosome is fused with the cell membrane fusion, and then released to the extracellular space (21). Exosome can exist in saliva, urine, blood, milk, and other body fluids, contain the same marker protein molecules, such as CD81, CD9, CD63, TSG101, and Alix, and carry a variety of biological signal molecules, such as lipids, nucleic acids, proteins, miRNAs, messenger RNA (mRNA), and long non-coding RNA (lncRNA) (22). They can participate in information exchange and migration between cells, angiogenesis, and regulate immune function, mediating the occurrence and development of tumors. The exosome in plasma can improve the stability of circulating miRNA, indicating the biological characteristics of the source cells, reflecting the patient's disease status. It can also be detected by collecting peripheral blood, making it convenient for application and providing information for early diagnosis and treatment of tumors (23). Tumor-derived exosomes can be released into the blood and reach the distal organs, thus changing the phenotype of many different cell types, with the functions of immune regulation, tumor growth, tumor treatment resistance, and reconstruction of tumor microenvironment (24,25). Therefore, exosomes are widely used in clinical practice as potential biomarkers for tumor diagnosis (26). Exosome-derived miRNAs are easy to obtain. Nik Mohamed Kamal *et al.* (27) found that exosomes in serum and saliva are enriched in miRNAs. The miRNAs detected in other body fluids (such as urine, cerebrospinal fluid, and breast milk) are mainly exosome-derived miRNAs (28). By combining with exosomes, miRNAs can make their chemical properties more stable. Therefore, exosome-derived miRNAs can escape the digestion of ribonuclease and have good biological stability in human circulation. MiRNAs are taken up by target cells and regulate their activities and biologic function (29). The number and type of miRNAs in exosomes are not random. The expression of miRNAs in exosomes is significantly different from that in donor cells. Although the sorting mechanism of miRNA in exosomes is not clear, a large number of studies have shown that there are three possible mechanisms for miRNA sorting into exosomes: (I) overexpression of neutral sphingomyelin 2 can increase the number of miRNAs in exosomes, and the release of exosome miRNA does not depend on the endosomal sorting complex required for transport in the transport system (30); (II) heterogeneous nuclear ribonucleoprotein A2/B1 (hnRNPA2/B1) is a widely expressed RNA-binding protein in the body. Short sequence motifs overexpressed by miRNA, such as EXOmotifs, can be specifically recognized and bound by hnRNPA2B1. The formed hnRNPA2B1-miRNA complex is then sorted and entered into the exosomes, and miRNA expression in the exosomes can be regulated by directed mutation of a gene sequence or changing the gene expression level of heteronuclear protein A2B1 (31); (III) RNA-induced silencing complex (RISC) contains biomolecules such as miRNA, mRNA that can be inhibited by miRNA, GW182 protein, and AGO2. Research (32) found that the absence of AGO2 reduces the type or abundance of miRNAs that prefer to enter the exosomes; GW182, as a key component of RISC, has also been found to be co localized with multivesicular body, indicating that both may participate as key factors in the secretion regulation of miRNA exosomes.

The function and mechanism of exosomes miRNA in lung cancer

Lung cancer is asymptomatic in the early stages. Most patients are diagnosed with advanced lung cancer when symptoms manifest, with a 5-year survival rate of only 16–18%. Early-stage lung cancer is limited to the local area and can be clinically cured through surgical resection. Late-stage lung cancer involves metastasis to the chest or other parts of the body, and treatment mainly relies on radiotherapy and chemotherapy. Chemotherapy drugs and high-energy radiation not only kill tumor cells, but also damage normal tissues. Therefore, there is an urgent need to develop new treatment methods for lung cancer. Exosome miRNAs participate in tumor metastasis, tumor immune regulation, tumor angiogenesis, and regulation of tumor resistance by controlling the expression of signaling pathway genes, affecting the occurrence and development of lung cancer, and providing new methods for clinical treatment of lung cancer (*Table 2*). In addition, exosome miRNAs can also serve as potential tumor markers, which have significant implications for the early diagnosis of lung cancer (*Figure 1*).

Table 2 The role of exosome-derived miRNAs in lung cancer

Function	MiRNA	Target
Neovascularization	miR-126	SPRED1
	miR-23a	PHD1, PHD2, ZO-1
	miR-21	VEGF
	miR-210	JAK2/STAT3
Proliferation and distant metastasis	miR-494	Cadherin-17
	miR-542-3p	Cadherin-17
	miR-193a-3p	STAT3/EMT
	miR-210-3p	STAT3/EMT
	miR-5100	STAT3/EMT
	miR-96	GPC3
	miR-660-5p	UBN2
	miR-499a-5p	EMT
	miR-208a	STAT3
	miR-222-3p	BBC3
	miR-103a	Mzb1
	miR-192	TRIM44
Immunoregulation	miR-21	TLR8/NF-κB
	miR-29	TLR8/NF-κB
	miR-23a	CD107a
	miR-210	NF-κB
Drug resistance	miR-222-3p	SOCS3
	miR-100-5p	mTOR
	miR-146a	Atg12
	miR-21	NLRP3
	miR-133b	GSTP1
	miR-1246	TRIM17

MiRNA, microRNA.

The role of exosome-derived miRNAs in the angiogenesis of lung cancer

Angiogenesis refers to the development of new blood vessels from existing capillaries or veins behind capillaries. Under normal physiological conditions, angiogenesis is a rigorous and precise regulatory process. The generation of new blood vessels is crucial for the growth of tumors, and establishing a new blood vessel network in tumors is crucial for promoting the invasion and metastasis of solid tumors (33). Liu *et al.* (34) found that exosome-derived miR-21 can promote angiogenesis in normal lung tissue and promote malignant epithelial cell transformation. Compared with non-smokers, the expression of exosome-derived miR-21 in the serum of smokers is significantly increased. Further experiments found that cigarette extract-induced transformation of bronchial epithelial cells can transfer miR-21 to normal bronchial epithelial cells through exosomes, and promote the activation of STAT3, leading to an increase in vascular endothelial growth factor (VEGF) levels, promoting angiogenesis of human umbilical vein endothelial cells (HUVECs) and malignant transformation of bronchial epithelial cells. Hypoxia can change the type and content of exosomes miRNAs secreted by lung cancer cells, which affect the generation of the lung cancer vascular system by regulating intercellular signal transduction, and mediate the hypoxia evolution of lung cancer cells' microenvironment, which affect the oxygen supply and nutrition supply of tumor cells. Compared with parental cells under normal oxygen conditions, lung cancer cells under hypoxic conditions can produce more specific types of exosomes, such as a significant increase in miR-23a in lung cancer cells, which transfer miR-23a to endothelial cells through exosomes, directly target the expression of proline hydroxylase 1 and proline hydroxylase 2 in endothelial cells, and promote lung cancer angiogenesis and increase the blood supply the lung cancer cells (35). In addition, miR-23a in the exosomes can also reduce the expression of the tight junction protein 1, thereby increasing vascular permeability and metastasis of lung cancer cells (35). Therefore, early screening of lung cancer can be achieved by detecting changes in specific types of exosome-derived miRNAs in the peripheral blood circulation (36). Under hypoxic conditions, overexpression of exosome-derived miR-619-5p in lung cancer cells can induce angiogenesis by targeting the inhibition of calcineurin regulatory factor 1 and 4, which helps lung cancer cells to obtain a greater blood supply and opportunities for distant migration and invasion (37). Exosome-derived miR-497 can effectively inhibit tumor growth and the expression of *VEGF-A* and other related genes in liver cancer-derived growth factor, cyclin E1, and non-small cell lung cancer (NSCLC) A549 cells, thereby inhibiting the formation of endothelial cell tubular structures and the migration of lung cancer cells (38). PTEN is a phosphatase that plays a central role in the negative regulation of protein kinase B and extracellular signal-regulated kinase pathways, which plays a crucial role

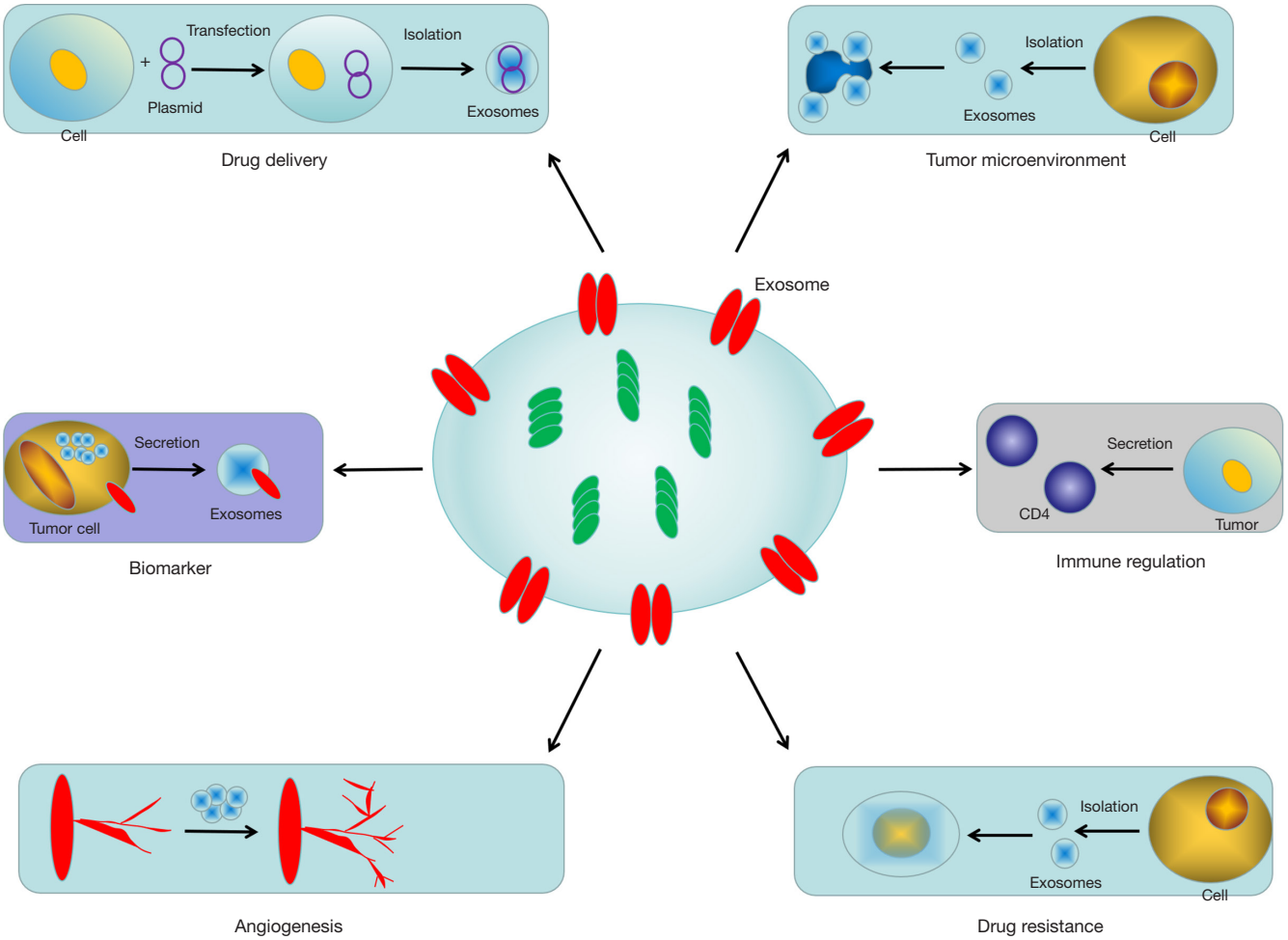

Figure 1 The function of exosomes.

in angiogenesis by inhibiting endothelial cell proliferation. The level of exosome miR-23a secreted by lung cancer cells induced by radiation significantly increases. Overexpression of exosome-derived miR-23a can promote the proliferation and migration of HUVECs by inhibiting the secretion of PTEN, accelerate angiogenesis of lung cancer cells in the radiation environment, and enhance radiation resistance (39). Other studies have found that miR-142-3p derived from lung adenocarcinoma metastasizes to endothelial cells through exosome and inhibits human transforming growth factor-β (TGF-β) receptor I, which promotes angiogenesis, thereby promoting the migration and invasion of lung cancer cells (40). Exosomes miR-103a can downregulate the expression of PTEN, directly affecting the polarization of macrophages, leading to the release of tumor-promoting factors such as interleukin-10, chemokine ligand 2, and VEGF-A. Macrophages that uptake exosomes miR-103a express high levels of VEGF and angiopoietin-1, which promotes the migration, invasion, and angiogenesis of lung cancer. Another study showed that miR-9 from tumor exocrine cells significantly reduced the expression of SOCS5 and promoted endothelial cell migration and neovascularization by activating the JAK-STAT pathway (41). Therefore, regulating the angiogenesis of exosome-derived miRNAs is expected to become a potential target for the treatment of lung cancer.

The role of exosome-derived miRNAs in lung cancer epithelial-mesenchymal transition (EMT)

EMT refers to the biological process in which epithelial cells are transformed into cells with mesenchymal phenotype

through a specific procedure, which is mainly manifested by the loss of typical epithelial cell characteristics and the development of mesenchymal cell-related characteristics, such as decreased expression of cell adhesion molecules, decreased level of keratin in cytoskeleton, increased level of vimentin, and mesenchymal characteristics in cell morphology (42). Tumor cells affect the translation of mRNA in epithelial cells through secreting body-derived miRNA, induce EMT process, and enable epithelial cells to obtain higher capability of migration, invasion, anti-apoptosis, and degradation of extracellular matrix (43). Cancer-associated fibroblasts (CAFs) are an indispensable component of the tumor matrix, which can interact with cells by secreting cytokines and exosome (44). CAF-derived exosomes can enhance the proliferation, migration, and invasion of lung cancer cells, enhance the expression of neurocadherin and vimentin, and inhibit the expression of epithelial cadherin. Further research found that exosome miR-210 derived from CAFs can activate the PTEN/PI3K/Akt pathway, thereby promoting the invasion and metastasis of NSCLC (45). In addition, the exosomal miR-210-3p derived from lung cancer stem cells can target fibroblast growth factor receptor-like 1 and inhibit its function. It can up regulate the expression of neurocadherin, vimentin, matrix metalloproteinase-9, and matrix metalloproteinase-1, and down regulate the expression of epithelial cadherin, to promote the EMT process of lung cancer cells (46). Li *et al.* (47) identified miR-181a as a novel regulator of EMT in lung adenocarcinoma A549 cell line through microarray analysis, and verified its role in targeting PTEN promoter and regulating PTEN expression through functional analysis. Rahman *et al.* (48) used exosomes derived from highly metastatic lung cancer cells and human advanced lung cancer serum to treat human bronchial epithelial cells. The results showed that the expression of epithelial cadherin and zonula occludens-1 in treated bronchial epithelial cells and neurocadherin and vimentin were significantly increased. Furthermore, it has been confirmed that exosomes derived from highly metastatic lung cancer cells and human advanced lung cancer serum can induce EMT in bronchial epithelial cells and enhance their tumorigenicity. As a subpopulation of cells with multiple differentiation potentials, bone marrow mesenchymal stem cells are part of the microenvironment of cancer and can promote the progression of cancer (49). Lung cancer cells treated with exosomes derived from bone marrow mesenchymal stem cells under hypoxia exhibited cell morphology transformation into spindle shaped mesenchymal like cells, and the levels of vimentin and neurocadherin in cells increased significantly. Further research found that exosome-mediated miR-193a-3p, miR-210-3p, and miR-5100 induce epithelial cell EMT through STAT3, promoting lung cancer metastasis (50). He *et al.* (51) found that the expression of miR-499a-5p was upregulated in highly metastatic lung cancer cell lines and their exosomes. Overexpressed exosome-derived miR-499a-5p can promote an increase in epithelial cadherin levels in endothelial cells through the mammalian rapamycin target protein pathway, whereas the levels of annexin and vimentin were decreased, which promoted the proliferation, migration, and EMT of lung adenocarcinoma cells. In addition, under hypoxic conditions, lung cancer-derived exosomal miR-23a can be directly internalized and absorbed by lung endothelial cells, which can not only promote tumor angiogenesis, but also inhibit the expression of ZO-1, promote endothelial cell EMT (35), increase vascular permeability, and make lung cancer cells easier to pass through the gap of vascular endothelium. MiR-23a in exosome regulates the expression of E-cadherin in lung cancer cells and maintains the EMT process through the TGF-β pathway (52). Rana *et al.* (53) found that the secretion miR-494 and miR-542-3p derived from pulmonary interstitial cells can down regulate the expression of cadherin-17, increasing the expression of MMP2 and MMP3, and promoting the distant metastasis of lung cancer cells. Other studies (54,55) have confirmed that the exosomal miRNA can activate TGF-β, ErbB, Wnt, mTOR, P13K-Akt, FoXO, Ras, MAPK, and other signaling pathways and promote the formation of EMT and the metastasis of lung cancer cells.

The role of exosome-derived miRNAs in immune regulation of lung cancer

The immune escape of tumor cells can affect the effectiveness of tumor immunotherapy, and the signal transduction of natural immune cells mediated by exosomes plays an important role in receptor molecule recognition and signal initiation (56). In the process of anti-tumor immunity, dendritic cells responsible for processing antigens present antigens to killer T cells through exosomes to trigger anti-tumor responses (57). Some miRNAs transfer from tumor cells to target immune cells through exosomes, affect the functioning of immune effector cell, assist tumor cells in immune escape, and enhance tumor

invasion and metastasis (58). Besse *et al.* (59) found that exosomes derived from dendritic cells can play the role of natural killer (NK) cell, directly activate NK cell, and also enhance the killing activity of NK cell in patients with advanced NSCLC. The miR-231 secreted by breast cancer cells can escape the immune monitoring of the body with the help of exosome encapsulation. Exosome-derived miR-231 enters lung cancer cells and inhibits the proliferation and migration of A549 lung cancer cells by blocking the PTEN/PI3K/Akt signaling pathway (60). Fan *et al.* (61) found that compared to normal weight lung adenocarcinoma patients, obese lung adenocarcinoma patients had a more significant immunotherapy effect. Further research found that exosomal miR-27a-3p derived from adipocytes can inhibit the proliferation of inducible costimulatory molecule (ICOS) T cells and interferon-γ secretion by downregulating the secretion of exosomal miR-27a-3p from adipocytes in obese lung adenocarcinoma patients. Targeting ICOS-related genes and promoting the proliferation of ICOS+T cells interferon-γ secretion will affect the tumor immune microenvironment and inhibit the invasion and metastasis of lung cancer. Fabbri *et al.* (62) found that lung cancer cell-derived exosomal miR-21 and miR-29 can serve as paracrine agonists of the toll-like receptor (TLR) family, binding to human TLR8 (mouse TLR7) receptors and activating TLR-mediated NF-κB pathway, generating a tumor inflammatory environment and promoting the growth and metastasis of lung cancer. CD107a is an inhibitory receptor for NK cells (63). Research reported that tumor cells secreted exosome through the transformation of TGF-β1, which reduced the expression of NKG2D on NK cells, thereby reducing the activity of NK cells (64). Berchem *et al.* (65) found that under hypoxic conditions, high levels of miR-210 and miR-23a in the exosomes secreted by tumor cells could participate in NK cell cytotoxicity damage both *in vivo* and *in vitro* through two mechanisms: on the one hand, exosome-derived miR-210 can mediate the TGF-β transferring to NK cells to reduce the expression of NKG2D on the surface of NK cells, thereby inhibiting the function of NK cells. On the other hand, miR-23a-derived from exosomes can directly target the 107a subtype of the white blood cell differentiation antigen family in NK cells and reduce its expression, thereby reducing its anti-tumor immune response. Xiao *et al.* (66) found in their study on the involvement of exosome in the regulation of cisplatin (DDP) sensitivity in A549 cell lines that DDP treatment can significantly enhance the secretion ability of exosome in A549 cells and stimulate the enrichment of miR-21 in A549 cells. Co-culturing the miR-21 rich exosome produced by DDP-treated A549 cells with wild-type (WT) cells could significantly enhance the resistance of WT cells to DDP. Meanwhile, the detection of miR-21 levels in WT cells that develop drug resistance revealed a significant increase in its expression level, indicating that upregulation of miR-21 expression in exosomes reduces the sensitivity of lung cancer cells to DDP. Therefore, studying the mechanism of exosome-derived miRNAs in immune regulation of lung cancer can provide new ideas for inhibiting lung cancer progression and developing immunotherapies targeting lung cancer.

The role of exosome-derived miRNA in the tumor microenvironment of lung cancer

Tumor microenvironment refers to the internal environment of tumor cells. It also includes fibroblasts, immune cells, inflammatory cells, and glial cells. Tumor microenvironment is regarded as the main influencing factor of tumor resistance to radiotherapy and chemotherapy, which plays a key role in the initiation, growth, migration, and invasion of tumor cells (67). Exosome-derived miRNA is considered an important information medium of tumor microenvironment. Tumor cells release specific exosomes, modify the microenvironment before tumor metastasis by interacting with other cells in the microenvironment, regulate the expression of receptor cells through local or remote communication, reprogram the tumor microenvironment, and make it more conducive to tumor invasion and metastasis (68). Exosomes miR-3473b derived from Lewis lung cancer cells is engulfed by lung fibroblasts which promotes lung fibroblast NF-κB activation and intrapulmonary colonization of lung cancer cells (69). Increasing energy acquisition is an important goal for tumor cells to transform the microenvironment. Tumor cells can down regulate the level of pyruvate kinase in glycolysis by secreting miR-122, inhibit the glucose uptake of non-tumor cells in the microenvironment, and promote tumor cells to obtain more energy intake through reprogramming of energy metabolism (70). MiR-182 can upregulate hypoxia-inducible factor-1α, which controls glucose metabolism in NSCLC cells (71). Zhai *et al.* (72) found that miR-33b could downregulate the expression of lactate dehydrogenase (LDH)A by targeting the 3'-untranslated region (3'-UTR)

of LDHA in NSCLC cells, thereby reducing glucose uptake by tumor cells and inhibiting tumor cell growth. Syndecan-1 is a transmembrane proteoglycan that is expressed in lung epithelial cells and can regulate cell proliferation, migration, adhesion, and survival. Parimon *et al.* (73) found that lung cancer cells lacking syndecan-1 can enhance the signal transduction of tumor forming pathway, promote the formation of tumor microenvironment, and then promote the migration and invasion of tumor cells by changing the type and number of exocrine miRNAs released by cancer cells. Therefore, the clinical prognosis of lung cancer patients with missing syndecan-1 expression is generally poor. Other studies have shown that miR-21 can transfer from lung adenocarcinoma cells to osteoclast progenitor cells by means of exosomes, and target the programmed cell death protein 4 gene to promote osteoclast maturation and bone matrix dissolution, such as excessive bone matrix dissolution, subsequent to which, stored growth factors (such as human TGF-β receptors) are released into the microenvironment, further promoting the invasion of lung cancer cells and bone metastasis (74). Therefore, exosome miRNA can not only regulate the microenvironment of lung cancer cells, but also remotely induce the formation of ecological niche before metastasis, affecting the invasion and metastasis of lung cancer (75).

The role of exosome-derived miRNAs in lung cancer drug resistance

Drug resistance is one of the most common causes of lung cancer recurrence. Although some progress has been made in drug therapy, the resistance of tumor cells remains a challenge in cancer treatment. In recent years, the discovery of exosome-derived miRNAs has provided new ideas for exploring the mechanism of drug resistance in tumor cells. Relevant study showed that exosome-derived miRNAs can transmit the drug resistance phenotype of drug-resistant cells to sensitive cells, induce tumor cells to form drug resistance, and promote tumor invasion and metastasis (76). DDP is the most commonly used chemotherapy drug for cancer treatment. However, tumor cells gradually develop resistance to DDP as treatment progresses. Research found that there is a significant difference in the levels of 6 circulating exosome miRNAs (miR-425-3p, miR-1273h, miR-4755-5p, miR-9-5p, miR-146a-5p, and miR-215-5p) between DDP-resistant and DDP-sensitive patients in the serum of NSCLC patients. Further research found that late-stage NSCLC patients with low levels of exosome miR-146a-5p have a higher recurrence rate. At the same time, during the DDP-induced resistance process, the expression of miR-146a-5p in NSCLC cell lines or exosome gradually decreases, indicating that overexpression of miR-146a-5p can reverse the resistance of lung cancer to DDP (77,78). Exosome-derived miR-425-3p upregulates autophagy by targeting Akt1, and the increase in autophagy in tumor cells promotes the development of DDP resistance in NSCLC cells, leading to a reduced drug treatment response (79). Other studies found that DDP can upregulates the expression of exosome-derived miR-425-3p in NSCLC cells, and the overexpressed exosome-derived miR-425-3p promotes autophagy activation in receptor cells by targeting Akt, ultimately leading to chemical resistance. MiR-146a can specifically bind cyclin mRNA and promote its degradation; at the same time, it can induce tumor cell G0/G1 phase stagnation, inhibit cell movement, promote cell apoptosis, and increase the sensitivity of lung cancer cells to DDP (80,81). Therefore, serum exosome miR-146a-5p and miR-425-3p can serve as new biomarkers for predicting the efficacy of DDP in NSCLC patients and real-time monitoring of drug resistance. The increased expression of exosome-derived miR-96 in lung cancer patients, especially highly invasive lung cancer, can promote lung cancer progression by targeting LMO7 and increase tumor cell resistance to DDP. Therefore, exosome-derived miR-96 has been recognized as a serum biomarker for lung cancer by relevant studies and can be used as one of the clinical screening indicators for early lung cancer (82). In addition, exosome-derived miR-100-5p can reverse the expression of mammalian rapamycin target proteins through binding to the 3'-UTR of the *mTOR* gene, and enhance the sensitivity of lung cancer cells to DDP, which improve the chemotherapy effect of DDP by increasing secretion of miR-100-5p (83). In addition, exosome-derived miR-222-3p from lung cancer cells resistant to gemcitabine can be transferred to sensitive cells through the endocytosis pathway dependent on podocyte proteins and lipid rafts. By directly targeting the promoter of cytokine signaling inhibitory factor 3, it enhances the migration, invasion, and anti-apoptotic ability of sensitive lung cancer cells, and also spreads gemcitabine resistance to sensitive cells (84). Exosome-derived miR-522-3p released by lung cancer cells carrying epidermal growth factor receptor T790M mutation can propagate gefitinib resistance in sensitive cells by activating the PI3K/Akt signaling pathway (85). Gupta

Table 3 Clinical use of exosome as biomarkers

Classification	MiRNA
Prognosis	Let-7a-5p
	miR-451a
	miR-23a
	miR-32
	miR-425-3p
	miR-21
	miR-146a-5p
	miR-155
Diagnosis	miR-17
	miR-1-3p
	miR-144-5p
	miR-150-5p
	miR-19-3p
	miR-23a-3p
	miR-361-5p
	miR-200b-5p
	miR-629
	miR-205-5p
	miR-200b
	miR-100
	miR-151a-5p
	miR-361-5p
	miR-15b-5p
	miR-21-5p
	miR-486-5p
	miR-320b
	miR-30a-3p
	miR-23a
	miR-155
	miR-126
	miR-205
Recurrence	miR-4257
	miR-21
Therapy	miR-221-3p
	miR-146a-5p
	miR-150
	miR-29a

MiRNA, microRNA.

et al. (86) found that activating miR-145 represents a potential strategy to significantly reduce drug resistance in NSCLC through targeting MALAT1 and BMI1.

The role of exosomes miRNA in the diagnosis of lung cancer

The diagnosis of exosomes miRNA in NSCLC may become an effective biomarker for screening, diagnosing, and detecting cancer (*Table 3*). Giallombardo *et al.* (87) detected 8 miRNAs (miR-30b, miR-30c, miR-103, miR-122, miR-195, miR-203, miR-221, and miR-222) associated with NSCLC through polymerase chain reaction (PCR). Munagala *et al.* (88) found that the expression of both miR-21 and miR-155 were significantly increased in recurrent lung cancer, indicating that exosomal miRNAs play an important role in distinguishing between recurrent and primary lung cancer. Jin *et al.* (89) isolated and sequenced tumor-derived exosomes from the plasma of NSCLC patients and healthy individuals to verify their diagnostic accuracy. They found that miR-181-5p, miR-30a-3p, miR-30e-3p, miR-361-5p, miR-10b-5p, miR-15b-5p, and miR-320b can be used for the diagnosis of early NSCLC. Grimolizzi *et al.* (90) found that in the early stage of NSCLC, there was a significant difference in the expression of exosome miR-126 in the serum between patients and healthy control groups. Exosome miR-126 can serve as a circulating marker for the progression of NSCLC, and the area under the curve (AUC) for diagnosing NSCLC is 0.859 (*Table 4*). The expression of miR-181b-5p and miR-21-5p were upregulated in tissues and serum samples of NSCLC patients, whereas the expression of miR-486-5p was downregulated (91). Further quantitative analysis revealed that miR-181b-5p and miR-21-5p were significantly enriched in serum exosome of NSCLC patients, but there was no significant difference in the expression of miR-486-5p between serum and serum-derived exosome (92,93). The expression of miR-126 and miR-let-7a in the bronchoalveolar lavage fluid of lung adenocarcinoma patients obtained through non-invasive methods were significantly higher than those in the healthy control group, which can be used as diagnostic markers for early lung adenocarcinoma (94,95). Chen *et al.* (96) compared tumor-derived exosome miRNAs from early lung adenocarcinoma and squamous cell carcinoma patients and healthy individuals. They found that exosomes miR-30a-3p and miR-30e-3p were specifically downregulated, whereas exosomes miR-181-5p and miR-361-5p were

Table 4 The role of exosomes miRNA in the diagnosis of lung cancer

MiRNA	AUC	Sensitivity	Specificity
miR-451a	0.97	0.95	0.71
miR-185-5p	0.91	0.59	1.00
miR-146a-5p	0.90	0.83	0.90
miR-216b	0.84	0.87	0.75
miR-210-5p	0.74	0.81	0.61
miR-1290	0.94	0.80	0.97
miR-378	0.84	0.78	0.82
miR-7977	0.82	0.81	0.75
miR-5684	0.74	0.81	0.61
miR-10b-5p, miR-320b	0.91	0.83	0.90
miR-181-5p	0.94	0.81	0.92
miR-1290	0.94	–	–
miR-126	0.86	–	–

miRNA, microRNA; AUC, area under the curve.

specifically upregulated. In lung squamous cell carcinoma, the expression of miR-10b-5p and miR-15b-5p in exosome were downregulated, whereas miR-320b in exosome was upregulated. The expression of exosomal miR-let-7e-5p was significantly downregulated in plasma samples of stage I clinical patients with lung adenocarcinoma and squamous cell carcinoma, whereas that of exosomal miR-7b-5p, miR-24-3p, and miR-486-5p was upregulated. However, the exosomal miR-486-5p has shown low expression in some studies (92,93). Further research is needed to confirm the specific reasons. The expressions of serum exosomal miR-378a, miR-379, miR-139-5p, and miR-200b-5p in lung adenocarcinoma patients were higher than those in healthy smokers. At the same time, there was a significant difference in the expression levels of serum exosomal miR-139-5p, miR-30a-3p, miR-378a, miR-502-5p, miR-100, miR-17, and miR-151a-5p between lung adenocarcinoma patients and lung granuloma patients. These studies reveal that exosomal miRNA, as a valuable blood marker for lung cancer, can effectively distinguish between lung cancer and benign lung lesions. In the analysis of serum from lung adenocarcinoma patients who did not receive radiotherapy and chemotherapy, the expression of exosomal miR-7977 was abnormally elevated, significantly correlated with the N stage of lung adenocarcinoma ($P<0.05$), and the AUC value of diagnosed patients was 0.787. In addition, *in vitro* transfection of miR-7977 mimics can inhibit the proliferation, invasion, and promote apoptosis of A549 cells, which has the potential to become a new therapeutic target for lung cancer patients (96). Jin *et al.* (89) found that plasma exosomal miR-10b-5p, miR-15b-5p in lung squamous cell carcinoma patients were down regulated, whereas that of miR-320b was up regulated. The AUC value of combined miR-10b-5p and miR-320b for diagnosis of squamous cell carcinoma was 0.911, sensitivity was 83.33%, and specificity was 90.32%. In lung adenocarcinoma patients, exosomal miR-181-5p and miR-361-5p were upregulated, whereas miR-30a-3p and miR-30e-3p were downregulated. The AUC value of lung adenocarcinoma was 0.936, sensitivity was 80.65%, and specificity was 91.67%. For healthy controls, the expression of serum miR-1290 in lung adenocarcinoma patients was significantly upregulated, but significantly downregulated after surgery. The validation results showed that their AUC value was 0.937. In addition, the level of miR-1290 was positively correlated with tumor-node-metastasis (TNM) staging and lymph node metastasis ($P<0.05$).

The potential of exosomal miRNAs in the treatment of lung cancer

In recent years, exosomal miRNAs were discovered for targeted therapy (97). Xu *et al.* (74) found that the expression of miR-21 in the exosomes was positively correlated with that in A549 cells transfecting with miR-21. High expression of miR-21 promoted the formation of osteoclast. Further studies showed that the exosomal miR-21 negatively regulated the activity of transcription factor AP-1 by directly targeting Pdcd4, inducing the formation of osteoclast and promoting bone metastasis of lung cancer. Therefore, downregulating the expression of miR-21 in tumor-derived exosomes could represent a potential therapeutic target for suppressing lung cancer bone metastasis. Syndecan-1 is a heparan sulfate proteoglycan expressed by endothelial cells, which plays an important role in the occurrence and development of tumors (98). Syndecan-1 can specifically regulate the miRNA profile in lung adenocarcinoma cell-derived exosomes. The increased expression of syndecan-1 can alter the expression level of lung cancer cell-derived exosomal miRNAs, thereby regulating the expression of signaling pathway genes and inhibiting the growth, invasion, and metastasis of lung cancer (73). Research (82) found that the expression level

of lung cancer-derived exosome miR-96 is upregulated with the increase of miR-96 expression in lung cancer cells. MiR-96 regulates lung cancer progression by targeting LMO7, whereas downregulating miR-96 can inhibit cell proliferation, migration, and drug resistance. Therefore, exosomal miRNA, as an important factor in the process of gene transcriptional regulation and post transcriptional regulation, plays an irreplaceable role in the occurrence and development of tumors. Using exosomal miRNAs as a new target for lung cancer treatment and regulating the expression profile of exosome-related miRNAs can effectively inhibit the invasion, migration, and proliferation of various solid malignant tumors, including lung cancer.

The potential of exosomal miRNAs in the proliferation of lung cancer

Lung cancer is a tumor formed by malignant proliferation of lung epithelial cells. The malignant proliferation of tumor cells is related to excessive cell division, cell cycle disruption, and dysregulation of apoptosis. KLF9 is one of the zinc finger proteins involved in gene transcription regulation, widely involved in cell proliferation, differentiation, and the differentiation and development of tissues and organs. Studies have reported a significant increase in miR-660-5p in the plasma exosomes of NSCLC patients, which promotes NSCLC progression by targeting KLF9 (99). In addition, studies revealed that the exosomes of lung cancer cells contained miR-96, which promoted the proliferation of human lung adenocarcinoma H1299 cells by targeting LMO7. Fabbri *et al.* (62) found that miR-29a and miR-21 in A549 exosomes were significantly up-regulated, which could bind to TLRs on the surface of immune cells in the tumor microenvironment and affect the proliferation of lung cancer cells. Grimolizzi *et al.* (90) highlighted that in early and advanced NSCLC patients, miR-126 does not exist in a free form, but is enriched in exosomes. These miR-126 derived from exosomes are believed to have dual regulatory properties. On the one hand, exosome-derived miR-126 from early- and late-stage NSCLC patients can induce malignant transformation of human bronchial epithelial cells; on the other hand, exosome-derived miR-126 from normal endothelial cells can inhibit the growth of and induce the absence of malignant behavior in NSCLC cells (90). Exosome-derived miR-1246 can inhibit tumor cell growth by targeting DR5, while also enhancing tumor cell sensitivity to radiation. The latest study by Tang *et al.* (100) reported that circulating exosomal miR-208a in lung cancer patients can promote lung cancer cell proliferation and inhibit tumor cell apoptosis by targeting the p21 and AKT/mTOR pathways. At the same time, exosomal miR-208a can reduce the sensitivity of lung cancer cells to radiation. Therefore, miR-208a plays a crucial role in the progression of lung cancer.

Limitations to the overview

Due to the immaturity of the relevant research, the clinical application of exosomal miRNAs in lung cancer is still in the initial exploratory stage. Meanwhile, the mechanism of miRNAs sorted into exosome is not fully understood, and further research and exploration are needed. Moreover, due to the heterogeneity of exosome, there may be differences in the number and type of miRNAs derived from the same mother cell, which may lead to false positive or false negative during early diagnosis of lung cancer.

Conclusions

Exosomes were extensively researched in the recent 20 years. Skog *et al.* (101) reported that RNA and proteins enclosed in exosome could be absorbed by tumors and promote their proliferation and migration. Jeppesen *et al.* (102) introduced a new model for active secretion of extracellular DNA through an autophagy- and multivesicular-endosome-dependent but exosome-independent mechanism. Zhang *et al.* (50) reported that exosomes could serve as potential circulating biomarkers and therapeutic targets for a host of human diseases.

As an important regulator of gene expression, exosomal miRNA is involved in the communication between tumor cells in the microenvironment to mediate immune escape, regulate drug resistance, promote tumor cell metastasis and angiogenesis, and affect the occurrence and development of tumors. Targeting tumor-specific exosomal miRNA provides a new strategy for clinical treatment of lung cancer. In addition, exosomal miRNAs, as potential non-invasive biomarkers, have important clinical value in the early diagnosis of lung cancer. The discovery of the involvement of exosomal miRNAs in the occurrence and progression of tumors has brought new opportunities for the clinical diagnosis and treatment of lung cancer. However, due to the immaturity of these studies, the clinical application of exosomal miRNAs in lung cancer is still in the initial exploration stage. Meanwhile, the mechanism of miRNAs sorted into exosome is not fully understood, and further

research and exploration are needed. Moreover, due to the heterogeneity of exosome, there may be differences in the number and type of miRNAs derived from the same mother cell, which may lead to false positive or false negative during early diagnosis of lung cancer. As a potential new target for lung cancer treatment, exosomal miRNA need to be continuously explored for their potential regulatory mechanisms in the occurrence and development of lung cancer.

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Footnote

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