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# Exosomal MiRNA as a Source of Biomarkers for Clinical Use in Lung Cancer

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## Abstract

Lung cancer is one of the most-deadly known neoplastic illnesses. Despite of new advances in cancer treatment, its prognosis remains very poor. What's worse, early diagnosis of this cancer is still very difficult. In recent years, body fluid biomarkers, including exosomal molecules became more popular and appealing in cancer diagnosis prognosis and treatment. Among these, miRNAs that occur in exosomes are considered to be one of the most promising biomarkers for lung cancer. In lung malignancies, there are about 12 potentially useful miRNA molecules. The most useful miRNA biomarkers include miR-181a/b, miR-29a, miR-150, miR-134, miR-185 and MiR-22. MiRNAs that are included in exosomes are usually associated with tumor progression, invasion and metastasis. Unfortunately, the role of many miRNAs in lung cancer remains poorly understood. In this review, we highlight the potential of miRNAs that are found in exosomes as promising biomarkers for clinical use in lung cancer patients.

**Keywords:** Biomarkers; Diagnostics; Exosomes; Lung; miRNA; NSCLC; Prognosis

**Abbreviations:** AC: Adenocarcinoma; BBC3: BCL2-Binding Component 3; CD107a: Cell Domain 107a; CEACAM6: Carcinoembryonic Antigen-Related Cell Adhesion Molecule 6; CDC42: Cell Division Control Protein 42; CDK4: Cyclin-Dependent Kinase 4; EMT: Epithelial to Mesenchymal Transition; GPC3: Glycan 3; GPM6A: Glycoprotein M6A; GSTP1: Glutathione S-transferase Pi 1; JAK2: Janus Kinase 2; LASP1: LIM and SH3 Protein 1; LCC: Large Cell Carcinoma; LDCT: Low-dose Computed Tomography; MAPK: Mitogen-Activated Protein Kinase; mTOR: Mammalian Target of Rapamycin; NLRP3: NLR Family Pyrin Domain Containing 3; NSCLC: Non-Small Cell Lung Cancer; SCLC: Small Cell Lung Cancer; SOCS3: Suppressor of Cytokine Signaling 3; SOX13: SRY-Box Transcription Factor 13; SPRED1: Sprouty Related EVH1 Domain Containing 1; STAT3: Signal Transducer and Activator of Transcription 3; STC1: Stanniocalcin 1; TAMs: Tumor Associated Macrophages; TLR8: Toll-like Receptor 8; TNM: Tumor Node Metastases; TRIM17: Tripartite Motif Containing 17; TRIM44: Tripartite Motif Containing 44; UBN2: Ubinuclein 2; WRNIP1: WRN Helicase Interacting Protein 1; VEGF: Vascular-Endothelial Growth Factor

## Introduction

Lung cancer is an aggressive type of cancer with high mortality rate. It is mainly because of its high malignancy level and very aggressive course. Despite of understanding risk factors, immunologic control and advances in cancer treatment options, it still remains one of the leading causes of cancer-related deaths worldwide [1]. In the last several decades, lung cancer has been the most frequently diagnosed cancer. For example, in 2018, there was about 2.1 million lung cancer diagnoses, accounting for 12% of the global cancer burden [2]. Although tobacco smoking is the major risk factor, connected with 90% lung cancer diagnoses, there are also some non-tobacco factors. They include chronic lung disease, lung infections, occupational and environmental exposures and lifestyle issues [1,2]. In general, lung cancer can be classified into two subtypes: non-small-cell lung cancer (NSCLC; about 80% of all) and small-cell lung cancer (SCLC; about 20% of all). In histological classification, NSCLC can be divided into ade-

nocarcinoma (AC), large-cell carcinoma (LCC), squamous-cell carcinoma and some other types [3,4].

Unfortunately, this type of cancer (like many others) shows no typical symptoms at its early stage. Because of this, most patients are diagnosed with lymph node, local invasion and even distant metastasis. The standard therapeutic options for lung cancer patients include thorax surgery, radiotherapy and chemotherapy. Nevertheless, the 5-year survival rate (SR) is still not satisfying and oscillates between 10-20% [3]. New strategies like targeted drug therapy and immunotherapy turned out to be more effective for patients. However, new cures and therapies doesn't help in diagnosis of cancer at it early stage. Although early diagnosis of lung cancer is still difficult, last research focused on exosomes and their cargo bring some new hopes for its effectiveness. Lung cancer cells release lots of exosomes that carry molecules that are crucial in cancer's development and progression. Among others,

they carry microRNA (miRNA) particles. miRNAs are very small, single-stranded RNA particles, consisting of 21-23 nucleotides. They play important role in regulation of many cellular mechanisms, such as cell signaling and gene expression. These molecules can be used as biomarkers to help diagnose this and many other deadly malignancies at early stage and choose a proper treatment.

### Exosomal miRNA

Exosomes are extracellular vesicles that participate in cell signaling, with diameters ranging from 30 to 150 nm. They are widely present in body fluids. Exosomes that are released from cells migrate to neighboring and distant cells. Each exosome contain cargo, such as miRNA which is specific for the parental cell and the conditions in which they produce them. Exosomal miRNAs modulate various processes, like interfering tumor microenvironment and its immunity, promoting tumor growth, invasion, angiogenesis, metastatic abilities and drug resistance. From this reason, circulating miRNAs in exosomes had the potential to serve as prognostic and predictive biomarkers [5,6]. Recent studies revealed that cancer cells release more exosomes than the normal ones of the same organ type [7,8]. Therefore, they play a key role in the course of many malignancies, including lung cancer. What is more, recent findings show there are at least 12 miRNAs that have promising predictive potential in lung cancer chemotherapy responses, which helps in choosing a more effective therapy [9].

#### MiR-181a and miR-181b

These miRNAs are encoded by genes located on chromosomes 1 and 9. They are expressed in tumor tissue and plasma of lung cancer patients. MiR-181a and miR-181b participate in regulating crucial roles in cellular development, invasion, angiogenesis and metastasis. In lung cancer, expression of this miRNA is decreased, which indicates that depletion of these transcripts may favor lung tumorigenesis, cancer progression and activate drug resistance mechanisms [10]. MiR-181a/b are connected not only to patient's unfavorable prognosis, but also to TNM (tumor node metastases) staging [10,11,12]. These molecules have also significant influence on tumor's immune evasion, especially in NSCLC. The most common immune evasion mechanism is associated with programmed death (PD-1/PD-L1) pathway. Increased PD-L1 expression in NSCLC cells is dependent on miR-181a [13]. In addition, other studies suggest, that miR-181a can reduce radiosensitivity of NSCLC cells, making them resistant for radiotherapy, which makes treatment even more difficult [14]. In general, miR-181a and miR-181b promotes lung cancer development, so they are associated with poor prognosis and survival. Then, miR-181a/b can serve as a prognostic marker in lung cancer treatment.

#### MiR-29a

MiR-29a molecules are often contained in lung cancer exosomes and they are taken up by nearby tumor-associated macrophages (TAMs) [15]. This miRNA plays significant role in many lung malignancies. It acts as a tumor suppressor, that inhibits NSCLC cells growth and tumor progression by binding carcinoem-

bryonic antigen-related cell adhesion molecule 6 (CEACAM6) [16]. According to clinical studies, miR-29a level is significantly lower in NSCLC patients than in the healthy ones [17,18]. MiR-29a also targets cell division control protein 42 (CDC42) and LIM and SH3 protein 1 (LASP1) and regulates invasion, migration and cell proliferation in lung AC [16]. Moreover, recent studies revealed that miR-29a can be used as biomarker for radiotherapy. This molecule was identified in NSCLC patients as a circulating biomarker that correlated with delivered radiation dose. After irradiation, the level of miR-29a increases in intracellular space, but decreases in exosomes. Hence, it is shown that miR-29a is regulated by ionizing radiation and can be used as a relevant marker in clinical practice [19]. What's more, this biomarker turned out to be promising in various types of lung cancer, not only in NSCLC.

#### MiR-150

MiR-150 is located on chromosome 19 in loci 19q13. This miRNA may work either as tumor suppressor or oncogene, depending on tumor type. In lung cancer, such as NSCLC, dysregulation of this miRNA leads to aberrant cell proliferation. MiR-150 is associated with pro-metastatic properties of NSCLC, but its critical role in lung malignancies metastasis remains uncertain [20]. However, recent studies suggest that miR-150 is abnormally high in NSCLC patients and it negatively correlates with proapoptotic protein p53 expression. Because it specifically targets p53, increased expression of this miRNA results in significant decrease of p53 level [21]. Nevertheless, other research showed that miR-150 can suppress tumor growth in NSCLC by inhibiting Wnt signaling pathway [22,23]. Low miR-150 expression is connected to patient's shorter progression-free period and overall survival time, what makes it a promising biomarker for predicting NSCLC progression [23].

#### MiR-134

This miRNA is found to be associated with cell proliferation in many cancer types. In lung cancer, it is one of the crucial miRNAs that have influence on cancer cells growth. MiR-134 is responsible for regulating cell migration, proliferation, apoptosis and repression of epithelial to mesenchymal transition (EMT) in NSCLC [24]. Last reports suggest that high level of MiR-134 inhibits lung cancer cells proliferation by downregulating epidermal growth factor receptor (EGFR). MiR-134 targets EGFR in NSCLC and upregulation of this miRNA suppresses EGFR-correlated signaling pathway [25]. It was also observed that MiR-134 promotes p21 protein expression and inhibits cyclin-dependent kinase 4 (CDK4), cyclin D1 and cyclin D2 expression. It indicates, that MiR-134 can repress cancer cells proliferation in NSCLC [25,26]. Therefore, high expression of MiR-134 is associated with favorable prognosis in lung cancer patients, while its low level worsen their survival. Expression of this miRNA have prognostic value, what makes it another relevant biomarker for lung cancer.

#### MiR-185

This miRNA is one of the most promising exosomal biomarker for early diagnosis and prognosis prediction of NSCLC. Recent

studies demonstrated that, miR-185 expression level is significantly lower in NSCLC tissues than in normal ones, which shows good perspective to be an indicator for early detection of this cancer. What's important, miR-185 serum level turns out to be associated with worse clinical parameters and unfavorable survival prognosis. Moreover, serum miR-185 level is an independent prognostic marker in NSCLC [27]. MiR-185 can also promote lung cancer treatment. Another research showed, that overexpression of this molecule suppress carcinogenesis of NSCLC and enhances its chemosensitivity via regulation of SOX13 [27,28]. These findings revealed that miR-185 might be helpful in both diagnosis, prognosis and treatment of lung cancer, such as NSCLC.

#### MiR-22 (miR-22-3p)

MiR-22 acts as a tumor suppressor in many tumor types and affects many signaling pathways. According to the studies, down-regulation of this miRNA is found in many cancers, including those of the lung [29]. MiR-22 can facilitate lung cancer cell invasion and EMT by elevating Snail protein and therefore it plays significant role in regulating lung cancer invasion [30]. It inhibits invasion

and growth of lung cancer through downregulating ErbB3 expression [24,31]. MiR-22 represses also TGF- $\beta$ -mediated EMT [32]. Moreover, recent research revealed, that this miRNA might serve as relevant biomarker in SCLC radiotherapy. It was shown, that miR-22 enhances radiosensitivity by targeting WRN Helicase Interacting Protein 1 (WRNIP1), which turns out to be a direct target gene for this miRNA. MiR-22 not only increases radiosensitivity, but also promotes SCLC cells apoptosis by upregulating the expression of glycoprotein M6A (GPM6A) and Stanniocalcin-1 (STC1), which are apoptosis-inducing factors [33]. Therefore, miR-22 is one of the most promising miRNA biomarkers, that may help in lung cancer prognosis and treatment planning.

#### Other miRNAs

The amount of promising miRNA biomarkers for lung malignancies gradually increases. There are still many miRNAs, which role in cancer development, progression and metastasis is partially understood or completely unknown. The table below shows other miRNA molecules and their targets, that could potentially be used for lung cancer diagnosis, prognosis and treatment (Table 1).

**Table 1:** miRNA biomarkers in lung cancer [34].

Function	miRNA	Target Gene/Protein
Proliferation and metastasis	miR-96	GPC <sub>3</sub> (Glypican 3) – regulator of Yap and Wnt/ $\beta$ -catenin signaling pathways [35]
	miR-192	TRIM <sub>44</sub> (Tripartite Motif Containing 44) - negative regulator of PAX6 expression [36]
	miR-103a	Mzb1 (Marginal zone B and B1 cell specific protein) – positively regulates cell proliferation
	miR-208a	STAT <sub>3</sub> (Signal transducer and activator of transcription 3) – mediator of cellular response to interleukins and many other growth factors [37]
	miR-494	Cadherin-17 – works as a proton-dependent peptide transporter that participates in absorption of peptide drugs [38,39]
	miR-542-3p	Cadherin-17
	miR-210-3p	STAT <sub>3</sub> /EMT – oncogenic pathway that can promote tumor growth, its migratory abilities and even drug resistance [40]
	miR-193a-3p	STAT3/EMT
	miR-222-3p	BBC <sub>3</sub> (BCL2 Binding Component 3) – inhibitor of apoptosis, binds to BCL-2 family proteins, activating mitochondrial dysfunction and caspase cascade activation
	miR-660-5p	UBN2 (Ubinuclein 2) – nuclear protein connected with cancer progression, interacts with many transcription factors [41]
	miR-5100	STAT <sub>3</sub> /EMT
	miR-499a-5p	EMT

Angiogenesis	miR-210	JAK <sub>2</sub> /STAT <sub>3</sub> - (Janus kinase 2/ Signal transducer and activator of transcription 3) - signaling pathway that participates in signal transduction from extracellular space to the nucleus [41]
	miR-23a	<i>PHD<sub>1</sub></i> , <i>PHD<sub>2</sub></i> - act as oxygen-sensing enzymes and promote hydroxylation of HIF- $\alpha$ (Hypoxia induced factor) subunits [42]
	miR-126	SPRED1 (Sprouty Related EVH1 Domain Containing 1) - encodes a protein involved in the Ras/MAPK (mitogen-activated protein kinase) signaling pathway [43]
	miR-21	<i>VEGF</i> (Vascular-endothelial growth factor) - participates in angiogenesis
Drug resistance	miR-222-3p	<i>SOCS<sub>3</sub></i> (Suppressor of cytokine signaling 3) - a major regulator of immune response, involved in pro- and anti-inflammation mechanisms [44]
	miR-21	<i>NLRP<sub>3</sub></i> (NLR family pyrin domain containing 3) - regulates cell survival via activity of gasdermin-D and caspase-1 [45]
	miR-100-5p	mTOR (Mammalian target of rapamycin) - component of PI3K/Akt/mTOR signaling pathway, that is critical for cancer cells survival, proliferation and growth [46]
	miR-133b	<i>GSTP<sub>1</sub></i> (Glutathione S-transferase Pi 1) - plays important regulatory role in anti-oxidative damage and detoxification [47], participates in glutathione conjugates formation
	miR-1246	TRIM17 (Tripartite motif containing 17) - one of critical ubiquitin ligases; NSCLC patients with elevated TRIM17 expression have shorter progression-free survival [48]
Immunoregulation	miR-21	TLR8/NF- $\kappa$ B (Toll-like receptor 8/Nuclear factor kappa B) - activator of NF- $\kappa$ B; its ligations to NF- $\kappa$ B leads to activation of this factor and upregulation of BCL-2 protein expression [49]
	miR-210	NF- $\kappa$ B (Nuclear factor kappa B) - component of pathways involved in inflammation processes
	miR-23a	CD107a (Cell domain 107a) - protein that protects cytotoxic lymphocytes from degranulation [50]

## Discussion

The emerging role of exosomal miRNAs as potential biomarkers in lung cancer represents a promising advancement in oncological diagnostics and therapy. Despite significant strides in understanding lung cancer pathology, early detection and precise prognostic assessments remain critical challenges. The unique attributes of miRNAs, particularly their stability in biological fluids and regulatory roles in tumor progression, make them invaluable for clinical applications. One of the most compelling advantages of exosomal miRNAs is their potential for non-invasive or minimally invasive diagnostics. Traditional lung cancer screening relies heavily on imaging techniques such as low-dose computed tomography (LDCT), which, despite being effective, is costly and

exposes patients to radiation. On the other hand, exosomal miRNAs, being present in easily accessible biofluids such as blood and saliva, offer a less invasive yet highly specific diagnostic tool. Research indicates that several miRNAs, including miR-181a, miR-181b, miR-150, and miR-134, hold significant prognostic value by reflecting tumor burden, metastatic potential, and resistance to therapy [10,15,20,24].

Furthermore, the functional versatility of exosomal miRNAs extends beyond diagnostics to therapeutic monitoring. For example, miR-29a has been demonstrated to predict radiotherapy response, with its levels fluctuating in response to ionizing radiation, thus serving as a potential biomarker for treatment efficacy [19]. Similarly, miR-22 has been identified as a critical modulator

of radiosensitivity in small-cell lung cancer (SCLC), enhancing tumor cell apoptosis and suppressing resistance mechanisms [33-41]. These findings underscore the clinical relevance of exosomal miRNAs not only in prognosis but also in optimizing personalized treatment strategies. Despite these promising developments, several limitations and challenges need to be addressed before exosomal miRNAs can be fully integrated into routine clinical practice. First, the standardization of miRNA detection methods remains a crucial hurdle. Current techniques, including quantitative reverse transcription polymerase chain reaction (qRT-PCR), next-generation sequencing (NGS), and microarrays, exhibit variability in sensitivity and specificity. Ensuring reproducibility and accuracy in miRNA quantification is essential for their reliable use as biomarkers [5,7,8].

Additionally, while several miRNAs have been identified as potential biomarkers, their precise roles in lung cancer pathogenesis are not yet fully understood. Many studies report conflicting findings regarding miRNA expression levels and their functional consequences in tumor progression. For instance, while miR-150 has been associated with pro-metastatic properties in non-small-cell lung cancer (NSCLC), other studies suggest that it can act as a tumor suppressor by inhibiting the Wnt signaling pathway [21-23]. This dichotomy highlights the necessity for further investigation into the context-dependent functions of miRNAs in different lung cancer subtypes. Another challenge lies in the specificity of miRNA biomarkers. Although many miRNAs are associated with lung cancer, they are also implicated in other malignancies and pathological conditions [42-48]. For example, miR-185 and miR-134 have been reported in multiple cancer types, raising concerns about their specificity for lung cancer diagnosis [25,27]. Developing panels of multiple miRNAs, rather than relying on single markers, could improve diagnostic accuracy and differentiate lung cancer from other diseases [49,50].

Moreover, the clinical translation of exosomal miRNA research necessitates large-scale, multicenter validation studies. Most studies conducted thus far have been limited in sample size and geographic scope, which may impact the generalizability of findings. Expanding research to diverse populations will enhance the robustness of miRNA-based biomarkers and facilitate their eventual approval for clinical use. In conclusion, exosomal miRNAs hold immense promise as novel biomarkers for lung cancer diagnosis, prognosis, and treatment monitoring. Their stability in biological fluids, regulatory roles in tumor progression, and potential for non-invasive detection make them attractive candidates for clinical application. However, significant challenges, including standardization of detection techniques, understanding miRNA functions, and ensuring specificity, must be addressed. Future research should focus on validating promising miRNA candidates through large-scale clinical trials and refining detection methodologies to enhance their clinical utility. With continued advancements in this field, exosomal miRNA-based diagnostics and therapeutics could revolutionize lung cancer management,

ultimately improving patient outcomes and survival rates.

## Conclusion

Exosomal miRNAs have a great potential in lung cancer diagnostics, prognosis, monitoring and treatment. Many of them are perfect candidates for biomarkers in clinical use. They may significantly help improving early diagnosis of lung cancer and effective treatment of this fatal disease.

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