Journal of Biosciences and Medicines, 2025, 13(5), 256-272
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Research Progress on Biomarkers for Non-Small Cell Lung Cancer: The Potential and Challenges of MicroRNA

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How to cite this paper: Wang, J.Y., Wu, W.D., Fei, S., Fang, M.X. and Jin, B. (2025) Research Progress on Biomarkers for Non-Small Cell Lung Cancer: The Potential and Challenges of MicroRNA. *Journal of Biosciences and Medicines*, **13**, 256-272.
https://doi.org/10.4236/jbm.2025.135020

Received: April 3, 2025
Accepted: May 23, 2025
Published: May 26, 2025

Abstract

Lung cancer ranks at the top in both incidence and mortality among malignant tumors worldwide. In China, the incidence and mortality of lung cancer are the highest among all malignant tumors. Due to the lack of obvious symptoms in early-stage lung cancer, it is difficult to arouse patients' vigilance, leading to many patients being diagnosed at an advanced stage, thus missing the best opportunity for treatment. MicroRNAs are a class of single-stranded small RNAs in cells that regulate gene expression in eukaryotes and play a crucial role in the occurrence and development of lung cancer. They have become a frontier and a hot topic in the field of lung cancer research. This article aims to comprehensively review the important position of MicroRNAs in lung cancer research and explore their potential application value as biomarkers in common lung cancers.

Keywords

MicroRNA, Non-Small Cell Lung Cancer (NSCLC), Biomarkers

1. Introduction

Primary bronchogenic carcinoma, commonly referred to as lung cancer, is a common malignant tumor. This lesion typically originates from the mucosal epithelium of the trachea and bronchi or the alveolar epithelium, and sometimes from glandular tissues. Histopathologically, lung cancer is primarily divided into two major categories: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) [1]. NSCLC is the most common type of lung cancer in clinical practice. Globally, more than one million people die from lung cancer each year, with an overall 5-year survival rate of only approximately 20% for patients with advanced

lung cancer [2], making it the leading cause of death among all malignancies. Among these deaths, approximately 80% are due to NSCLC [3]. For patients diagnosed with early-stage NSCLC, the 5-year survival rate is only about 15%, and the recurrence rate of this disease is very high [4]. In this review, we will focus on NSCLC, including lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC). Currently, tumor marker detection in serum is a commonly used auxiliary examination method for cancer screening, early diagnosis, and monitoring the efficacy and prognosis of cancer treatment [5]. Therefore, re-evaluating the mechanisms of NSCLC development at the molecular level and discovering more sensitive and representative biomarkers have become urgent needs in the field of lung cancer research.

MicroRNAs (miRNAs) are a class of single-stranded RNAs with a coding length of approximately 20 - 24 nucleotides (nt) that are widely present in eukaryotes and are typically located in intronic regions [6]. Studies have shown that miRNAs exhibit significant differences in expression levels across various tissues and developmental stages, demonstrating distinct spatial and temporal expression patterns [7]. In recent years, a large number of studies have indicated that miRNAs may play a crucial role in regulating gene expression and disease development. By binding to mRNA, miRNAs can influence the expression of oncogenes and tumor suppressor genes, as well as the activity of signaling pathways, thereby affecting key biological processes of tumor growth and invasion [8]-[11]. This article will review the latest research findings on the role of miRNAs in the early diagnosis and development of non-small cell lung cancer (NSCLC) and provide a comprehensive overview of the functions of miRNAs and their mechanisms in the pathogenesis of NSCLC.

2. Synthesis and Function of MicroRNA

In nature, eukaryotic cells share a common set of genetic information, which is stored in the nuclear DNA. Among these, coding RNAs include messenger RNA (mRNA) and heterogeneous nuclear RNA (hnRNA). mRNA acts as a bridge between DNA and proteins, accurately conveying genetic information to the cytoplasm to direct protein synthesis and maintain vital biological processes [11]. All cells can utilize the same genetic code to perform distinct functions and form diverse cell types. Underlying this diversity is the precise regulation of gene expression [12]. In eukaryotic organisms, gene expression is regulated by multiple factors, including non-coding RNAs. A portion of the genetic information may be silenced, preventing the transcription of the corresponding genetic segments. This phenomenon is known as gene silencing [13].

In this regulatory network, miRNAs play a crucial role. Within the cell nucleus, DNA, under the action of RNA polymerase, generates both coding and non-coding RNAs. Primary miRNA (pri-microRNA) has a characteristic hairpin structure. After processing, pri-microRNA is cleaved into smaller double-stranded RNA, which enters the cytoplasm as precursor miRNA (pre-microRNA). Under the ac-

tion of AGO2 protein and Dicer enzyme, pre-microRNA unwinds its double strand, with one strand being released and the other retained as the guide strand, which is the mature miRNA. The mature miRNAs then bind to AGO2 and other proteins to form the RNA-induced silencing complex (microRNA-RISC) [14]. The RNA-induced silencing complex (RISC), as the core functional unit of miRNA-mediated gene expression regulation, has been shown in recent studies to specifically recognize and silence the 3'-UTR region of target mRNAs under the guidance of small RNA "seed sequences", thereby regulating gene expression and achieving gene silencing (**Figure 1**) [15]. The single-stranded mature miRNAs within the microRNA-RISC can base-pair complementarily with the 3'-untranslated region (3' UTR) of the target gene mRNA. Once a successful pairing occurs, the microRNA-RISC begins to exert its function. Current research generally suggests that miRNAs can destabilize target gene mRNA by cleaving the transcription products of target genes or preventing ribosomal subunit binding to inhibit the translation of transcription products, thereby silencing specific gene expression and shutting down the expression of the corresponding genes [16]-[18]. It is estimated that miRNAs may regulate one-third of human genes and are involved in the regulation of cells from development to death. When the regulatory mechanisms of miRNAs are disrupted, severe physiological consequences may ensue, including the development and progression of cancer. In tumor cells, certain miRNAs may be upregulated. Upregulated miRNAs are often overexpressed in various tumors and promote tumorigenesis and metastasis by suppressing target genes. In contrast, other miRNAs may be downregulated. Downregulated miRNAs can inhibit tumor cell proliferation, invasion, and migration, and their reduced expression is associated with increased tumor aggressiveness [19] [20].

In recent cancer treatment research, miRNAs have garnered widespread attention due to their crucial role in gene regulation. The ability of miRNAs to regulate the expression of multiple genes through complementary pairing with mRNA endows them with an important role in the occurrence and development of cancer. They can modulate oncogenes or tumor suppressor genes, thereby influencing tumor formation. Additionally, the role of miRNAs in the tumor microenvironment is increasingly recognized. By affecting the cell cycle, promoting tumor invasion, immune evasion, and angiogenesis, miRNAs participate in tumor progression. With the development of high-throughput sequencing and miRNA analysis technologies, the role of miRNAs in cancer identification, classification, diagnosis, and prognosis has gradually been unveiled. For example [21], miR-34a can inhibit the growth of non-small cell lung cancer (NSCLC) and the characteristics of cancer stem cells by targeting CD44. Similarly, the miR-200 family inhibits the characteristics of pancreatic cancer stem cells by targeting ZEB1 and E-cadherin. The expression patterns of miRNAs as cancer biomarkers in body fluids can be used for early cancer diagnosis and prognostic assessment [22]. Moreover, studying the expression patterns of miRNAs in lung cancer is vital for understanding the mechanisms of tumor cell occurrence and development. Inducing the silencing of pro-

invasive and metastatic miRNAs or promoting the high expression of anti-invasive and metastatic miRNAs may achieve the clinical goal of inhibiting tumor proliferation, invasion, and migration. This holds significant importance for the development of new therapeutic strategies.

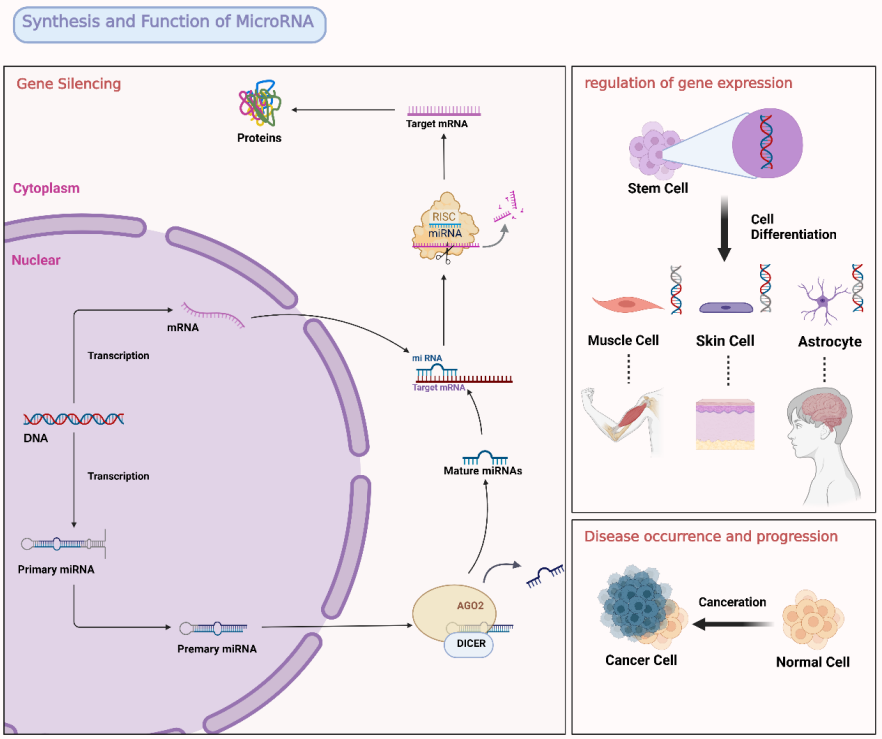

Figure 1. The synthesis and functions of miRNA (The left side of the figure describes the gene silencing mechanism of miRNA; the upper right side shows the role of miRNA in the regulation of gene expression; the lower right side explains the function of miRNA in disease occurrence and progression.)

3. Advances in the Study of MicroRNA as a Biomarker in Lung Cancer

At the beginning of the 21st century, Reinhart B. J. *et al.* [23] first discovered the single-stranded microRNAs lin-4 and let-7 in Caenorhabditis elegans. These were the earliest miRNAs identified in biological cells. They induce translational repression of proteins by base-pairing complementarily with the 3' untranslated region of target gene mRNA, thereby inhibiting protein synthesis and regulating the developmental process of C. elegans through the modulation of a set of key mRNA translations. Subsequently, researchers identified hundreds of miRNAs in a variety of biological species, including mammals. A series of studies has confirmed that miRNAs are involved in the regulation of numerous gene expressions from development to death in living organisms. By regulating gene expression, miRNAs affect cellular biological behaviors, including cell proliferation [23], apoptosis [24], and also influence the proliferation and differentiation of adipocytes [25]. With the deepening of research, the important role

of miRNAs in the occurrence and development of diseases has gradually been revealed.

In 2003, Brennecke J. *et al.* [24] discovered the first oncogenic miRNA—bantam miRNA. Subsequently, in 2005, George A. Calin *et al.* [26] first identified a significant correlation between miRNAs and cancer. Their study found that the 13q14.3 region, which is frequently deleted in chronic lymphocytic leukemia (CLL), contains two tumor suppressor miRNAs, miR-15 and miR-16. The miR-15 and miR-16 genes exert tumor-suppressive effects by directly targeting BCL2, thus being used to treat tumors with Bcl2 expression deficiency. The publication of this study not only established the important position of miRNAs in tumor development and treatment research but also sparked a surge of interest in the study of miRNAs in the field of oncology.

3.1. Advances in the Study of MicroRNA as a Biomarker in the Early Diagnosis of Lung Cancer

MicroRNAs (miRNAs) hold potential prospects as biomarkers for the early diagnosis of lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC). It has been confirmed that miRNAs exhibit significant tumor-associated, tissue-specific, and stable expression profiles in tissues and cells [17] [27]. Therefore, peripheral blood miRNAs may serve as an ideal tumor biomarker. In recent years, several miRNAs have been identified to display significant specificity in early lung cancer through different mechanisms. For example [28], miRNAs such as miR-34a, miR-221, miR-222, and the miR-17-92 cluster play important roles in tumor development by influencing specific mRNA targets in lung cancer. These miRNAs have potential applications as biomarkers in the early diagnosis of cancer.

LUAD is the most common type of lung cancer, accounting for approximately 40% of all lung cancer cases, with a relatively higher incidence in female non-smokers. In 2022, Gao, S. *et al.* [29] identified diagnostic biomarkers for early LUAD through high-throughput sequencing analysis of plasma extracellular vesicle miRNAs. The study recognized a diagnostic signature comprising four plasma extracellular vesicle (EV)-derived miRNAs, including hsa-miR-106b-3p, hsa-miR-125a-5p, hsa-miR-3615, and hsa-miR-450b-5p. This signature demonstrated high accuracy in cohorts of LUAD patients and controls, with area under the curve (AUC) values of 0.917 and 0.902, respectively. It was also able to identify patients with adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA), with AUC values of 0.846 and 0.92, respectively. This study provides a potential non-invasive diagnostic method for the detection of early LUAD. Subsequently, Wang, W. *et al.* [30] selected serum samples from 61 lung cancer patients and used real-time quantitative polymerase chain reaction (RT-qPCR) technology to detect the expression levels of miR-21 among different pathological types and the control group. The study found that the expression level of miR-21 in the serum of lung cancer patients was significantly higher than that

in the normal population, and the level of miR-21 in the serum of LUAD patients was significantly higher than that in small cell lung cancer (SCLC) and LUSC patients. This conclusion suggests that serum miR-21 detection may be useful as an auxiliary diagnostic tool for lung cancer, especially for the differentiation and pathological typing of LUAD. However, the study was based on a small sample cohort and lacked large-scale prospective validation, which may affect the reliability of the conclusions. Recently, Wu, J. *et al.* [31] integrated bioinformatics analysis with qRT-PCR experiments and found that the combined detection of hsa-miR-103b, hsa-miR-29c-5p, and hsa-miR-877-5p achieved an AUC value as high as 0.873. This result indicates that miRNAs in plasma exosomes have the potential to serve as non-invasive diagnostic biomarkers for early LUAD.

Table 1. Advances in the Study of microRNA in the early diagnosis of LUAD and LUSC.

Cancer classification	Sources of literature	Year	Involved molecules	Mechanistic design
LUSC	Plasma extracellular vesicle microRNA profiling and the identification of a diagnostic signature for stage I lung adenocarcinoma	2021	hsa-miR-106b-3p, hsa-miR-125a-5p, hsa-miR-3615, hsa-miR-450b-5p	The Tumor Microenviron-ment
	Identification of Target Genes of miR-21 in Lung Cancer Patients and Their Expression and Diagnostic Value in Serum	2022	miR-21	The Tumor Microenviron-ment
	Integration of bioinformatics analysis and experimental validation identifies plasma exosomal miR-103b/877-5p/29c-5p as diagnostic biomarkers for early lung adenocarcinoma	2022	hsa-miR-103, hsa-miR-29c-5p, hsa-miR-877-5p	The Tumor Micro-environ-ment
LUAD	Clinical significance of miRNA-1 and its potential target gene network in lung squamous cell carcinoma	2019	miR-1	Migration and Invasion
	Downregulation of miRNA-126-3p is associated with progression of and poor prognosis for lung squamous cell carcinoma	2022	miRNA-126-3p	Migration and Invasion
	miRNA patterns in male LUSC patients—the 3-way mirror: Tissue, plasma and exosomes	2024	miR-21-5p, miR-155-5p, miR-181a-5p	The Tumor Microenviron-ment

LUSC is a highly malignant tumor and one of the most common types of lung cancer. Recent studies have shown that miRNAs can serve as early diagnostic biomarkers for LUSC. In 2019, Li, X. *et al.* [32] conducted a meta-analysis of 12 studies and pathway enrichment analysis of potential target genes using multiple databases, and for the first time discovered that the expression of miR-1 was significantly downregulated in LUSC, which may serve as a new non-invasive biomarker for the diagnosis of LUSC. Subsequently, Chen, S. W. *et al.* [33] found that the expression level of miRNA-126-3p in LUSC tissues was significantly lower than that in normal tissues, and its expression was associated with

the clinical pathological features of LUSC, especially the T stage of the tumor. This finding provides a new direction for the early diagnosis and differentiation of tumor stages in LUSC. The latest research reported by Bica, C. *et al.* [34] evaluated the levels of three miRNAs, including miR-21-5p, miR-155-5p, and miR-181a-5p, in male LUSC patients, benign tumor tissues (TT), and adjacent normal tissues (NT), as well as their expression levels in plasma and plasma-derived EVs. They found that miR-21-5p, miR-155-5p, and miR-181a-5p could serve as novel miRNA biomarkers for the diagnosis of LUSC in male patients and could be considered for further research as biomarkers for the early detection of LUSC in male patients. These studies provide new information on relevant exosomal miRNAs for the early diagnosis of non-small cell lung cancer (NSCLC) and offer new molecular markers for potential non-invasive diagnosis (**Table 1**).

3.2. Advances in the Study of MicroRNA as a Biomarker in the Development and Progression of Lung Cancer

MicroRNAs (miRNAs) play a significant role in the development and progression of tumors. Studies have confirmed that miRNAs can act as tumor suppressors or oncogenes, exerting crucial effects on tumorigenesis and tumor development by influencing the proliferation of tumor cells.

In recent years, numerous studies have revealed that miRNAs promote the development of LUAD. In 2019, Chen, P. *et al.* [35] first explored the co-regulatory roles of miRNA-126-3p and miRNA-126-5p in LUAD. The study used RT-qPCR technology to detect the expression levels of miRNA-126-3p and miRNA-126-5p in 101 LUAD and 101 normal lung tissue samples. Eight key common target genes were identified through chip data validation and target prediction tools. The research found that the low expression of miRNA-126-3p and miRNA-126-5p is associated with vascular invasion, lymph node metastasis (LNM), and advanced tumor/node/metastasis (TNM) staging in LUAD. However, the study was limited to bioinformatics prediction and expression analysis, lacking further functional experiments to verify their targeting regulatory mechanisms. Subsequently, Wang, J. *et al.* [36] found that the expression level of miR-15b in LUAD tissues is higher than that in normal lung tissues and that it can target and regulate BCL2. They further verified the proliferative activity and migratory capacity of SPC-A1 cells using the CCK-8 assay and Transwell experiments. Additionally, they confirmed through dual-luciferase reporter assays that miR-15b promotes the epithelial-mesenchymal transition (EMT) process in LUAD tumor cells by specifically inhibiting the expression of BCL2. In 2022, Wang, C. *et al.* [37] discovered that miR-3646 directly downregulates SORBS1 via the JNK signaling pathway, thereby promoting LUAD cell proliferation and adhesion and reducing apoptosis. Additionally, miRNAs can act as tumor suppressors by forming different regulatory axes through downregulation of target genes, thereby inhibiting the biological behavior of tumors. In 2020, Liu, T. *et al.* [38] discov-

ered the targeting effect of miR-124 on AKT2. Luciferase reporter assays and Western blotting were employed to verify that the overexpression of miR-124 negatively regulates AKT2, thereby inhibiting the progression of LUAD. Bu, L. *et al.* [39] discovered that miR-195-5p exerts tumor-suppressive functions in LUAD cells by targeting TrxR2. Moreover, Yuan, C. *et al.* [40] found that miR-195-5p inhibits cancer cell growth, invasion, and migration by targeting HOXA10, arrests the cell cycle, promotes apoptosis, and sensitizes LUAD cells to X-ray irradiation, thus exerting potent antitumor effects. Song, Y. *et al.* [41] discovered through bioinformatics analysis combined with functional enrichment analysis that hsa-miR-30a-3p may inhibit the occurrence and development of lung cancer via the Wnt and AKT signaling pathways. However, this study also lacked in vitro cell function experiments to further verify the regulatory mechanisms.

Table 2. Advances in the study of MicroRNA in the development and progression of LUAD and LUSC.

Cancer classification	Sources of literature	Year	Involved molecules	Involved signaling pathways	Mechanistic design	Cancer mechanisms
LUSC	Expression levels and co-targets of miRNA-126-3p and miRNA-126-5p in lung adenocarcinoma tissues: An exploration with RT-qPCR, microarray and bioinformatic analyses	2019	miRNA-126-3p, miRNA-126-5p		protooncogene	Metabolic reprogramming
	miR-15b enhances the proliferation and migration of lung adenocarcinoma by targeting BCL2	2020	miR-15b	miR-15b Targeted Regulation of BCL2	protooncogene	Sustained proliferative signaling
	MicroRNA miR-3646 promotes malignancy of lung adenocarcinoma cells by suppressing sorbin and SH3 domain-containing protein 1 via the c-Jun NH2-terminal kinase signaling pathway	2022	miR-3646	Downregulation of SORBS1 via the JNK Signaling Pathway	protooncogene	Sustained proliferative signaling
	AKT2 drives cancer progression and is negatively modulated by miR-124 in human lung adenocarcinoma	2020	miR-124	Overexpression of miR-124 can negatively regulate AKT2.	Tumor Suppressor Gene	Evading growth suppression
	miR-195-5p exerts tumor-suppressive functions in human lung cancer cells through targeting TrxR2	2021	miR-195-5p	miR-195-5p Targeted Regulation of TrxR2	Tumor Suppressor Gene	Resisting cell death
	Effects of MicroRNA-195-5p on Biological Behaviors and Radiosensitivity of Lung Adenocarcinoma Cells via targeting HOXA10	2021	miR-195-5p	miR-195-5p Targeted Regulation of HOXA10	Tumor Suppressor Gene	Evading growth suppression
	Microarray data analysis to identify miRNA biomarkers and construct the lncRNA-miRNA-mRNA network in lung adenocarcinoma	2022	Hsa-miR-30a-3p	The Wnt and AKT Signaling Pathways	Tumor Suppressor Gene	Epigenetic regulation

Continued

LUAD	Fibroblast-derived exosomal microRNA-369 potentiates migration and invasion of lung squamous cell carcinoma cells via NF1-mediated MAPK signaling pathway	2020	miR-369	Mitogen-Activated Protein Kinase (MAPK) Signaling Pathway	protooncogene	Invasion and metastasis
	MicroRNA-375 restrains the progression of lung squamous cell carcinoma by modulating the ERK pathway via UBE3A-mediated DUSP1 degradation	2021	MicroRNA-375	The miR375/UBE3A/DUSP1/ERK Axis	protooncogene	Invasion and metastasis
	MicroRNA-665 facilitates cell proliferation and represses apoptosis through modulating Wnt5a/β-Catenin and Caspase-3 signaling pathways by targeting TRIM8 in LUSC	2023	MicroRNA-665	The Wnt5a/β-Catenin Signaling Pathway	protooncogene	Sustained proliferative signaling& Resisting cell death
	MiR-497-5p down-regulates CDCA4 to restrains lung squamous cell carcinoma progression	2021	miR-497-5p	miR-497-5p Targeted Regulation of CDCA4	Tumor Suppressor Gene	Immune evasion

In the study of LUSC, it is widely accepted that cancer-associated fibroblasts (CAFs) have tumor-promoting properties and are therefore potential therapeutic targets for cancer. Based on this, Guo, L. *et al.* [42] confirmed through bioinformatics analysis and experimental validation that the overexpression of miR-369 activates the mitogen-activated protein kinase signaling pathway by interacting with NF1. Moreover, the expression level of miR-369 in CAFs-EVs is relatively high. Combined with in vivo tumor formation and metastasis experiments, it was found that miR-369 in CAFs-EVs plays a role in controlling the migration, invasion, and tumorigenesis of LUSC cells. Subsequently, Chen, T. J. *et al.* [43] discovered that miR-665 promotes LUSC cell proliferation and cell cycle progression by regulating the Wnt5a/β-Catenin signaling pathway and inhibits apoptosis by directly targeting TRIM8 and regulating the Caspase-3 signaling pathway. Gan, J. *et al.* [44] conducted gain-of-function and loss-of-function experiments both in vitro and in vivo, identifying the targeting interactions within the miR-375/UBE3A/DUSP1/ERK axis. They validated the mechanisms of interaction through dual-luciferase reporter assays, immunoprecipitation (IP) analysis, immunofluorescence (IF) detection, and ubiquitination assays. They proposed a novel mechanism by which the miR-375/UBE3A/DUSP1/ERK axis promotes tumorigenesis and metastasis in LUSC. Proposed a novel mechanism for LUSC tumorigenesis and metastasis via the miR-375/UBE3A/DUSP1/ERK axis. Additionally, Hu, J. [45] *et al.* found that miR-497-5p inhibits the development of LUSC by targeting CDCA4. In 2022, Shan, X. *et al.* [46] discovered that miR-338-3p inhibits tumor cell proliferation and migration in LUSC by targeting FGFR2 and FRS2 (**Table 2**).

In summary, miRNAs can act as tumor suppressors or oncogenes in LUAD and LUSC. By upregulating or downregulating miRNAs, they directly or indirectly af-

fect target genes, thereby regulating the biological behavior of corresponding tumor cells. Among these miRNAs, miR-15b, miR-3646, and miR-665 target BCL2, SORBS1, and activate the Wnt/β-Catenin pathway, respectively, driving cancer cells to exert continuous proliferation signals and promoting tumor proliferation. MiR-369, miR-375, and miR-338-3p regulate the MAPK, ERK, and FGFR2 pathways, respectively, to drive or inhibit cancer cells from exerting invasive and metastatic functions. MiR-665 inhibits the Caspase-3 pathway, while miR-195-5p targets TrxR2 to confer apoptosis resistance in cancer cells. MiR-124 and miR-195-5p restore growth inhibition by regulating AKT2 and HOXA10, respectively. Additionally, miR-126-3p/5p may be involved in angiogenesis-related metabolic reprogramming, miR-497-5p affects the immune microenvironment through CDCA4, and miR-124 and miR-30a-3p are respectively involved in genome stability and epigenetic regulation. The multidimensional regulatory roles of miRNAs in cancer hallmarks provide new molecular targets and biomarkers for the early diagnosis, prognosis assessment, and treatment of LUAD and LUSC. They reveal the important roles of miRNAs in tumor biology and offer new strategies and directions for future therapies.

4. Pan-Cancer Regulation by MicroRNA

MicroRNAs (miRNAs) play important roles not only in non-small cell lung cancer (NSCLC) but also exhibit diverse regulatory functions in other cancers. In NSCLC, miRNA-126-3p inhibits tumor progression by regulating angiogenesis- and metastasis-related pathways. However, in angioimmunoblastic T-cell lymphoma (AITL) [47], upregulated miRNA-126-3p inhibits T-cell migration by targeting RhoA-GTPase, revealing its functional heterogeneity across different cancer types. Similarly, miR-15b promotes tumor proliferation and migration in NSCLC by targeting BCL2. In gastric cancer [48], exosomal miR-15b-3p enhances tumor invasiveness by inhibiting DYNLT1 and activating the Caspase pathway. In breast cancer [49], miR-15b-5p promotes cell proliferation and metastasis by targeting HPSE2, indicating its cancer type-specific effects. Additionally, in NSCLC, miR-3646 promotes tumor malignancy via the JNK signaling pathway. In breast cancer [50], its upregulation may serve as a predictive biomarker for malignancy, suggesting its potential as a pan-cancer diagnostic target. On the other hand, some miRNAs exhibit conserved tumor-suppressive or oncogenic functions across different cancers. For example, miR-124 inhibits tumor proliferation and metastasis by targeting different genes (such as AKT2, EZH2, and MGAT5) in NSCLC, prostate cancer [51], and breast cancer [52]. MiR-375 exerts tumor-suppressive effects by regulating the UBE3A/DUSP1/ERK axis in NSCLC and by targeting HOXA5 in breast cancer [53]. These findings highlight that the regulatory networks of miRNAs in cancers are both specific and conserved. Moreover, miR-665 promotes tumor progression via the Wnt/β-Catenin pathway in NSCLC, but exerts opposite tumor-suppressive effects by inhibiting NR4A3 or CRIM1 in breast cancer [54] and gastric cancer [55], further highlighting the context-dependent nature of miRNA

functions. From a clinical perspective, comparative studies of miRNAs across cancers not only help reveal core mechanisms of tumorigenesis but also provide new ideas for developing pan-cancer or cancer-specific diagnostic biomarkers and therapeutic targets. For example, miR-497-5p inhibits tumor growth by targeting different genes in both NSCLC and colorectal cancer [56], suggesting its potential as a pan-cancer therapeutic target. Future research should further integrate data from multiple cancers to explore the common mechanisms of miRNAs in the tumor microenvironment, immune regulation, and treatment resistance, and combine personalized medical strategies to promote their application in early diagnosis and precision treatment of lung cancer.

5. MiRNA Biomarkers vs. Traditional Biomarkers

Compared with traditional protein tumor biomarkers such as CEA, miRNA biomarkers have significant advantages. Exosomal miRNAs, for example miR-106b-3p + miR-450b-5p, have higher sensitivity, with a detection rate for early-stage lung cancer (AUC 0.92) that is significantly better than that of CEA (AUC 0.65-0.70). This is due to the early release characteristics of miRNAs in the tumor microenvironment. Some miRNAs also have advantages in terms of timeliness. For example, miR-21 can be detected at the precancerous stage, providing an early warning of tumor risk 6 - 12 months ahead of traditional biomarkers. However, miRNA biomarkers still have limitations such as low standardization and poor stability in plasma (half-life of 2 - 4 hours). Therefore, the complementary use of both types of biomarkers will be more beneficial for clinical practice.

6. Discussion and Prospects

This review summarizes the research status and progress of miRNAs in lung cancer, especially their applications as biomarkers in LUAD and LUSC. Compared with previous reviews focusing on miRNA biogenesis or pan-cancer regulatory mechanisms, this article, for the first time, categorizes NSCLC-related miRNAs based on functional phenotypes such as pro-proliferation, pro-metastasis, or tumor-suppressive roles. For example, miR-3646 and miR-665 are classified as pro-proliferative genes, while miR-124 and miR-497-5p are listed as tumor suppressors. This classification better meets the needs of clinical practice. Additionally, this article systematically compares the diagnostic efficacy of exosomal miRNAs and free miRNAs, confirming that exosomal miRNAs, with higher stability and tissue specificity (AUC values reaching 0.85 - 0.92), hold greater clinical potential. Moreover, based on the latest clinical trials from 2020 to 2024, this article constructs a translational pathway from basic research to clinical application, including multicenter validation of exosomal miRNA panels, development of standardized detection protocols, and exploration of targeted therapies. This addresses the previous research gap of focusing on mechanisms while neglecting translation. These innovations not only refine the theoretical understanding of the miRNA regulatory network but also provide practical guidance for clinical translation.

Although multiple studies have confirmed the potential of miRNAs in the diagnosis and treatment of NSCLC, existing research still has limitations. There are still methodological flaws in the current evidence. For example, the study by Wang Wendong *et al.* [29] only included 61 lung cancer patients and lacked large-scale prospective validation, which may affect the reliability of the conclusions. In addition, there are significant differences in the miRNA detection technologies and sample sources used in different studies, making it difficult to directly compare the data. Publication bias is also common in existing studies, with positive results more likely to be reported while negative data are often ignored, making clinical translation quite challenging. For example, although miR-21 has shown diagnostic value in multiple studies, it also increases in non-cancerous diseases such as chronic inflammation, and its specificity is not sufficient. Despite the above limitations, miRNAs are still an important breakthrough in the research of NSCLC. It is particularly important in the future to establish unified miRNA detection standards, reduce technical bias, and design clinical trials based on miRNAs to verify their feasibility as diagnostic biomarkers or therapeutic targets.

MicroRNAs (miRNAs) have shown great potential as biomarkers in lung cancer research, yet there are still many unknown areas awaiting exploration. Currently, most studies focus on the relationship between the expression levels of specific miRNAs and lung cancer, while the interactions of miRNAs with other biomolecular networks and their mechanisms of action in the tumor microenvironment remain incompletely understood. Moreover, the heterogeneity of miRNAs in lung cancer and their expression differences across various lung cancer subtypes require further investigation. Additionally, although some studies have explored the potential of miRNAs as therapeutic targets, there is currently a lack of specific methods to translate these research findings into clinical therapeutic strategies, and the issue of miRNA resistance in lung cancer treatment also warrants further study. Lastly, most studies have concentrated on the application of miRNAs as single biomarkers, while combining miRNAs with other biomarkers may improve the accuracy of diagnosis and prognostic assessment. Therefore, developing biomarker combination models based on multi-omics data is an important direction for future research.

Future research can focus on the interactions between miRNAs and other biomolecules to reveal their complex regulatory networks in the development and progression of lung cancer; explore the potential applications of miRNAs in lung cancer treatment, including as therapeutic targets and in drug delivery systems; investigate the heterogeneity of miRNAs in lung cancer to identify new biomarkers and provide a basis for personalized treatment; develop biomarker combination models based on multi-omics data to enhance the accuracy of early diagnosis and prognostic assessment of lung cancer; and conduct large-scale clinical trials to validate the clinical value of miRNAs as biomarkers.

Future research needs to delve into molecular mechanisms, biomarker combination models, and clinical applications. Through these studies, we can better un-

derstand the role of miRNAs in lung cancer and provide new strategies for early diagnosis, prognostic assessment, and personalized treatment. This will not only help improve the treatment outcomes and quality of life for lung cancer patients but also advance the development of precision medicine.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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