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Mini Review

The Roles of miRNAs in Human Lung Cancer

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Abstract

Lung cancer is the most common type of cancer in the world, and smoking is the most important cause of lung cancer. Notably, small cell lung cancer accounts for about 15% of all lung cancers, and non-small cell lung cancer accounts for approximately 85% of all new lung cancer diagnoses. Most patients are diagnosed with the disease in advanced stages due to insufficient screening programs and the late onset of clinical symptoms. As a result, patients have a poor prognosis. MicroRNAs are a family of small non-coding RNAs (21-25 nucleotides) that can inhibit mRNA translation and promote mRNA degradation by base-pairing to complementary sites on the target mRNA. Through this mechanism, miRNAs alter gene expression post-transcriptionally. The first non-coding RNA, lin-4, was identified as a miRNA in *Caenorhabditis elegans* in 1993. The specific characteristics of miRNAs, including their tissue and even cellular specificity, stability in various biological fluids, and their dysregulation during tumorigenesis, make miRNAs potential biomarkers and therapeutic targets in cancers that should be considered. Given the high toxicity of chemotherapy drugs in human lung cancer, miRNAs could be a more suitable option with lower toxicity. However, more testing and research are needed to improve therapeutic performance and reduce adverse effects on healthy cells so that they can replace chemotherapy drugs with harmful effects on the body. This review aims to investigate the role of microRNA types in the development or prevention of human lung cancer.

Keywords: Apoptosis, Gene expression, Lung Neoplasm, MicroRNAs, Messenger RNA, Non-small Cell Lung Carcinoma

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Introduction

Lung cancer is the most common type of cancer in the world (12.3% of all cancers), with about 1.2 million new cases in 2000. The risk of lung cancer in smokers is 20 to 30 times higher than in non-smokers.[1,2] It should not be forgotten that lung cancer is one of the most preventable cancers, which is attributed to the most important causative factor, i.e., smoking.[3] Small Cell Lung Carcinoma accounts for about 15% of all lung cancers and is characterized by a very high proliferation rate, a strong propensity for early metastasis, and a poor prognosis. This type of cancer is strongly related to exposure to tobacco carcinogens. Most patients have metastatic symptoms when the disease is diagnosed, and only one-third of them are in the early stages of the disease, which can be potentially treated with multimodal treatment methods.[4] Non-Small Cell Lung Carcinoma is a heterogeneous group of tumors that accounts for approximately 85% of all new lung cancer diagnoses. Most patients are diagnosed with the disease in advanced stages due to insufficient screening programs and the late onset of clinical symptoms. Consequently, patients have a poor prognosis.[5] Squamous cell carcinoma, adenocarcinoma, and large cell carcinoma are the three different subtypes of non-small cell lung cancer. The most common one is adenocarcinoma, which accounts for about 40% of all lung cancers and develops from alveolar type II epithelial cells of the small airways that secrete mucus and other substances.[6] MicroRNAs (miRNAs) are a family of small non-coding RNAs (21-25 nucleotides) that can inhibit messenger RNA (mRNA) translation and promote mRNA degradation by base-pairing to complementary sites on the target mRNA. Through this mechanism, miRNAs alter gene expression post-transcriptionally.[7] The first non-coding RNA, lin-4, was discovered almost 20 years ago. Researchers' fundamental understanding of microRNA mechanisms came from studying lin-4 in the nematode *Caenorhabditis elegans*.[8] The biogenesis of miRNAs from miRNA genomic loci is a multi-step process. miRNA precursors, pri-miRNAs, are large miRNAs (more than 100 nucleotides in length) that are transcribed by RNA polymerase II and subsequently processed intranuclearly by RNase III, Drosha, and double-stranded RNA binding protein (dsRNA). In the cytoplasm, another RNase III enzyme called Dicer processes pre-miRNAs into miRNA: miRNA duplexes, consisting of 22 nucleotides. In summary, miRNAs play a key role in genomic and epigenomic interactions.[7]

Role of miRNAs in Cancer

The specific characteristics of miRNAs, including their tissue and cellular specificity, stability in various biological fluids, and their dysregulation during tumorigenesis, have made miRNAs potential biomarkers and therapeutic targets in cancers that should be considered. In recent years, numerous studies have demonstrated that miRNAs can function as oncogenes or tumor suppressors in the development and progression of cancer.[9] miR-196a is transcribed from two genes, miR-196a-1 and miR-196a-2. Recent miRNA expression profiling studies have shown that miR-196a is overexpressed in several tumor tissues, including lung cancer. Additionally, some studies have indicated that miR-196a plays a significant role in tumor progression and pathogenesis by targeting specific genes.[10]

Role of miRNAs as Tumor Suppressors and Oncogenes

microRNAs play a crucial role in carcinogenesis, acting as both tumor suppressor genes and oncogenes. Dysregulation of several miRNAs is observed in lung cancer. Some of the most important of these miRNAs are explained below.

Tumor Suppressor miRNAs

Family of Let-7

The let-7 family was the first miRNA to be identified in humans.[11] In lung cancer, let-7 inhibits the expression of oncogenes involved in cell proliferation such as RAS, MYC, and HMGA2.[12,13] Let-7 also inhibits the expression of CDK6, and therefore the reduction of let-7 expression leads to the promotion of cell cycle progression. Interestingly, let-7 directly downregulates DICER1 expression, suggesting that let-7 may regulate the production of miRNAs globally.[14]

Family of miR-34

The miR-34 family, divided into three categories a, b, and c, is directly induced by TP53 in response to DNA damage, controlling cell cycle arrest and apoptosis in cancer.[15] The miR-34 family is downregulated in lung cancer, leading to the upregulation of miR-34 target genes, such as MET, BCL2, PDGFR-α, and PDGFR-β.[16-18] The increased regulation of MET and BCL2 through the reduction of miR-34 expression leads to cell proliferation. Reduction of PDGFR-α/β dependent on miR-34 inhibits tumorigenesis and enhances apoptosis induced by TRAIL (TNF-related apoptosis-inducing ligand) in lung cancer.[17]

Family of miR-200

This category, which includes a to c, plays an important role in inhibiting epithelial-mesenchymal transition (EMT) by regulating zinc finger E-box-binding homeobox transcription factors, or ZEB for short, which includes ZEB1 and ZEB2. E-cadherin (CDH1) and vimentin (VIM) are also regulated, and the miR-200 family is down-regulated in this context.[19,20] EMT is an essential process in metastasis.[21] It is a complex process that may be initiated by multiple pathways, including Wnt signaling, Notch signaling, and various growth factors such as TGFβ, FGF, EGF, and PDGF.[22]

Oncogenic miRNAs

miR-21

miR-21, a well-known oncogenic microRNA, is overexpressed in various solid tumors and leukemia. miR-21 promotes tumor growth by inhibiting negative regulators of the RAS/MEK/ERK pathway and suppressing apoptosis. Overexpression of miR-21 reduces the expression of PTEN[23], PDCD4,[24-26] and TPM1,[26] promotes cell proliferation and migration, and inhibits apoptosis.[27]

miR-17-92 cluster

The miR-17-92 polycistronic cluster includes seven different microRNAs: miR-17-3p, miR-17-5p, miR-18a, miR-19a, miR-20a, miR-19b-1, and miR-92a. It is located in intron 3 of the C13 ORF 25 gene at 13q31.3. The miR-17-92 cluster is known to be overexpressed in lung cancer, particularly in SCLC.[28] Overexpression of the miR-17-92 cluster reduces E2F1, HIF1A, and PTEN levels and promotes cell proliferation and cancer progression.[29,30]

miR221/222

miR-221 and miR-222 are involved in the development and progression of lung cancer by targeting the tumor suppressor genes PTEN and TIMP3.[31,32] Overexpression of miR-221/222 inhibits apoptosis and enhances cell migration by reducing PTEN and TIMP3 (Table 1).[27]

Table 1. Principal microRNAs Involved in the Development or Progression of Lung Cancer[27]

microRNAs	Gene Targets	Biological Processes
Tumor suppressor microRNAs with down-regulation in lung cancer		
let-7 family	*RAS, HMGA2, CDK6, MYC, DICER1*	(i) Cell proliferation (*RAS, MYC, HMGA2*) (ii) Cell cycle regulation (*CDK6*) (iii) microRNA maturation (*DICER1*)
miR-34 family	*MET, BCL2, PDGFRA, PDGFRB*	TRAIL-induced cell death and cell proliferation
miR-200 family	*ZEB1, ZEB2, E-cadherin (CDH1), vimentin (VIM)*	Promotion of EMT and metastasis
Oncogenic microRNAs with up-regulation in lung cancer		
miR-21	*PTEN, PDCD4, TPM1*	Apoptosis, cell proliferation, and migration
miR-17-92 cluster	*E2F1, PTEN, HIF1A*	Cell proliferation and carcinogenesis
miR-221/222	*PTEN, TIMP3*	Apoptosis and cell migration

miRNA Association with Lung Cancer

Regarding lung cancer, the role of miRNAs in lung carcinogenesis was demonstrated as early as 2004, when Croce's laboratory showed that more than half of the miRNA genes known at that time were located in genomic regions associated with cancer or were situated in fragile sites. Several miRNAs in these deleted regions have low expression levels in lung cancer cell lines and chronic lymphocytic leukemia samples[33]. During the same year, Takamizawa *et al*. reported downregulation of microRNA let-7 expression in human NSCLC lung cancers, followed by separate independent reports. Later, the let-7 family was shown to have tumor suppressor activity.[34] A single nucleotide polymorphism (SNP) at a locus complementary to let-7 of KRAS mRNA is associated with an increased risk of NSCLC in moderate smokers. Based on *in vitro* experiments and analysis of patient samples, the researchers concluded that this SNP alters the ability of let-7 to regulate KRAS translation, leading to KRAS overexpression and an increased risk of lung cancer.[33] Evidence indicates that miRNAs are significantly dysregulated in human cancers, such as NSCLC, and may function as oncogenes or tumor suppressors[35]. Recent studies have shown that not only can miRNAs be used to classify NSCLC subtypes,[36] but specific miRNA profiles may also predict prognosis and disease recurrence in the early stages of NSCLC.[37]

Application of miRNAs in Lung Cancer Diagnosis

Recently, several studies have shown global dysregulation of miRNAs in lung cancer.[34,38,39] However, perhaps due to differences in sample type, preparation, and methods of miRNA identification and analysis, there does not appear to be much agreement among these studies. Despite reproducibility issues, miRNA profiles from tissues may serve as important indicators and tools for classifying lung cancer subtypes and distinguishing primary tumors from lung metastases. For example, miR-205 expression uniquely differentiates squamous from non-squamous NSCLC, even in poorly differentiated cancers.[36,40,41] The ability to determine the histological type in patients who have inadequate tissue available for detection or in situations where the degree of differentiation and heterogeneity precludes diagnosis makes miR-205 screening particularly important from a clinical standpoint. The unique signatures that miRNA profiles provide could help identify the tissue of origin.[42] The levels of miR-182 and miR-126 differ in primary lung tumors versus lung metastases from different organs.[43] Moreover, miR-592 and miR-522 distinguished primary lung tumors from metastases of colon cancer.[44] However, the real potential of miRNAs lies in their presence and stability in biological fluids. Circulating miRNAs may reflect tumor origin and thus act as new non-invasive biomarkers for early detection of lung cancer and risk stratification of patients. Retrospective analysis of residual trace miRNA in plasma from patients enrolled in the MILD (Multicenter Italian Lung Detection) randomized trial showed significant diagnostic performance for early detection of lung cancer (Table 2).[45-47]

Table 2. MicroRNAs as Diagnostic Biomarkers for Lung Cancer

miRNA / Family	Sample Type	Expression Change in Lung Cancer	Diagnostic Application	Biological & Clinical Relevance	Ref
miR-205	Tissue	Up-regulated	Distinguishes squamous from non-squamous NSCLC	Highly specific for squamous cell carcinoma, even in poorly differentiated cases.	[36,40,41]
miR-21	Tissue / Plasma	Up-regulated	Differentiates lung cancer from normal tissue; subclassification of adenocarcinoma vs. squamous	Also detectable in circulation; potential non-invasive biomarker.	[38,41]
let-7 family	Tissue / Plasma	Down-regulated	Prognosis and survival; associated with KRAS mutation status	First miRNA identified in humans; strong tumor-suppressive role.	[11,34,37]
miR-200 family	Tissue	Down-regulated	Distinguishes primary lung tumors from lung metastases	Key regulator of EMT and metastasis via ZEB1/ZEB2.	[19,20,43]
miR-126	Tissue	Down-regulated	Differentiates primary lung tumors from metastases	Expression varies depending on the origin of metastasis.	[43]
miR-7	Tissue	Down-regulated	Distinguishes lung cancer from normal lung tissue	Proposed as a diagnostic marker in profiling studies.	[38]

Application of miRNAs as Drugs and their Drug Resistance in Lung Cancer Treatment

Targeted drug therapy has had a positive effect on the treatment of a variety of cancers, for instance, lung cancer. Epidermal Growth Factor Receptor (EGFR) tyrosine kinase inhibitors (TKIs) such as gefitinib, erlotinib, and afatinib were developed to treat NSCLC patients harboring EGFR mutations. But regrettably, patients eventually develop resistance to these medications.[48] 70% of these acquired resistances are due to secondary mutations in EGFR. In other instances, other mechanisms such as the involvement of several microRNAs and Anexelekto (AXL) kinase are responsible for drug resistance in lung cancer.[49] A large number of molecular pathways regulated by miRs make them potential targets for therapeutic intervention. Altering a miR may simultaneously affect many critical signaling pathways in the tumor cell. Therefore, miR-targeted drugs can be expected to encounter less resistance than pathway-specific agents. Since miRs may act as oncogenes or tumor suppressors, both silencing and transfection with miR

mimetics are viable options for treatment.[50] It has been revealed that many miRNAs confer resistance to various anticancer therapies. Some examples include the miR-103, miR-221, and miR-222 families, all of which play a role in resistance to both TRAIL and EGFR inhibitors. Moreover, while miR-200b confers at least partial resistance to platinum agents and taxanes, it has also been reported to play a role in resistance to anti-angiogenic agents.[51] The first evidence of miRNA replacement therapy in lung cancer was reported in 2008. Researchers showed that restoration of let-7 expression affected tumor growth in xenograft models derived from H460 or A549 lung cancer cells (NSCLC cell lines carrying mutations in the K-RAS gene) injected subcutaneously. In immunodeficient mice in this study, cells were transiently transfected with 30 nm of let-7 mimic miRNA before subcutaneous injection into NOD/SCID mice, and a delay in tumor growth was observed. They also showed that let-7 expression inhibits lung carcinogenesis using a conditional K-RAS mutant mouse model ($Kras^{LSL-G12D/+}$) of developing orthotopic lung cancer.[50] In 2010, Wiggins et al. reported the reduction of tumor growth by miR-34 treatment in H460 and A549 xenograft models of NSCLC cancer in immunodeficient mice.[48] NOD/SCID mice were treated with different concentrations of mir-34 mimetic (1 and 5 mg/kg) formulated with MaxSuppressor *in vivo* RNALancerII, a neutral lipid emulsion (NLE) delivery agent (BIOO Scientific, Inc.), administered intratumorally or injected intravenously on days 12, 15, and 18 after xenograft implantation.[52] Remarkably, they performed a blood chemistry analysis to test possible toxicity in the liver, kidney, and heart and observed that miRNA treatment was well tolerated. In summary, this study provided evidence for the safe and effective therapeutic administration of miRNA mimetics.[53]

Recent Studies

In 2024, a study was conducted on the effect of miRNA-34c-5p on reducing the malignant properties of lung cancer cells through the regulation of TBL1XR1/Wnt/β-catenin signaling. The results showed that miR-34c-5p was downregulated in lung cancer cells, while TBL1XR1 was highly expressed. These findings also confirmed the direct interaction between miR-34c-5p and TBL1XR1.[54,55] A comprehensive review by Zhang et al. (2024) summarized the clinical potential of miRNA signatures as liquid biopsy biomarkers for early lung cancer detection, highlighting panels with sensitivity exceeding 85% and specificity above 90% in validation cohorts.[56] Another 2024 study demonstrated that the miR-99 family acts as a potent tumor suppressor in NSCLC by directly targeting mTOR and FGFR3, effectively inhibiting tumor growth and enhancing sensitivity to radiotherapy both *in vitro* and *in vivo*.[57]

In addition, in 2023, a landmark clinical trial investigated a novel liposomal nanoparticle delivery system for miR-34a mimic (MRX34) in refractory NSCLC patients. While the trial highlighted challenges related to immune-mediated toxicity, it provided crucial proof-of-concept for systemic miRNA delivery in humans and showed preliminary efficacy signals in a subset of patients.[58] Additionally, a 2023 multi-center study validated a plasma-based miRNA signature (miR-21, miR-145, and miR-155) that significantly improved the positive predictive value of low-dose CT screening for lung cancer, reducing false-positive rates.[59]

A 2022 study was conducted on miRNA-671-5p by Ye et al., which inhibits cell proliferation, migration, and invasion in non-small cell lung cancer by targeting MFAP3L. The results of the study showed that the expression level of miR-671-5p was significantly reduced in NSCLC metastatic tissues compared with matched adjacent tissues. Low levels of miR-671-5p were significantly associated with advanced TNM stage and lymph node metastasis in patients with NSCLC.[60] A study in 2022 by Li et al. revealed that miR-195-5p suppresses metastasis in SCLC by targeting CXCR4, a key chemokine receptor involved in cell migration and invasion.[61] Another significant 2023 study by Rodriguez-Aguayo et al. uncovered the role of exosomal miR-146a in mediating cisplatin resistance in uung adenocarcinoma. Tumor-derived exosomes transported miR-146a to recipient sensitive cells, where it downregulated the pro-apoptotic gene *CASP8*, thereby conferring chemoresistance.[62] Also, a systematic review and meta-analysis was conducted by Wang et al. regarding the use of MicroRNA-21 as a diagnostic and prognostic biomarker in lung cancer. The results showed that miRNA-21 has potential clinical value in the diagnosis and prognosis of lung cancer and may serve as an effective diagnostic marker and therapeutic target in the future.[63] A 2021 study on the ferroptosis (a type of regulated cell death)-inducing effect of miR-302a-3p in NSCLC found that miR-302a-3p mimics promote lipid peroxidation, iron overload, and ferroptosis, thereby inhibiting cell growth and colony formation of NSCLCs. Conversely, miR-302a-3p inhibitor blocks ferroptosis and tumor suppression associated with adrastin or RSL3. Furthermore, the results showed that miR-302a-3p sensitizes NSCLC cells to cisplatin and paclitaxel chemotherapy.[64] Another study conducted by Fehlmann et al. in 2020 evaluated the use of circulating microRNA profiles to diagnose lung cancer in symptomatic patients. This study found that the identified patterns of miRNAs could be used as part of a minimally invasive lung cancer screening, complementing imaging, sputum cytology, and biopsy tests.[65]

Finally, A 2024 study explored a combination therapy using an miR-17-92 cluster inhibitor (antagomir) and osimertinib in EGFR-mutant NSCLC. This approach demonstrated superior tumor regression compared to osimertinib alone in PDX models, suggesting a viable strategy to overcome and prevent TKI resistance.[66] Furthermore, a 2023 study reported the

development of a novel inhaled formulation of let-7b mimic, which showed efficient lung tissue delivery and significant tumor growth inhibition in immunocompetent mouse models of lung adenocarcinoma, presenting a promising localized therapeutic approach with reduced systemic exposure.[67]

Conclusion

MicroRNAs have emerged as pivotal regulators in the pathogenesis of lung cancer, functioning as both oncogenes and tumor suppressors. Their unique characteristics, including tissue specificity, stability in bodily fluids, and central role in controlling key cellular processes like proliferation, apoptosis, and metastasis, underscore their immense potential. This review has highlighted the dual roles of specific miRNA families, such as the tumor-suppressive let-7, miR-34, and miR-200, as well as the oncogenic miR-21, miR-17-92 cluster, and miR-221/222. The application of miRNAs extends beyond basic biology to clinical utility. Their distinct expression signatures offer promising avenues for non-invasive early diagnosis, subclassification of NSCLC, and prognosis. Furthermore, miRNA-based therapeutics, either as mimics for tumor suppressors or inhibitors for oncomiRs, represent a novel and potentially less toxic strategy to overcome drug resistance and improve treatment outcomes, as demonstrated in pre-clinical models. However, challenges remain. Standardization of detection methods, validation in large-scale clinical trials, and the development of efficient and safe delivery systems are crucial steps before miRNA-based strategies can be fully integrated into routine clinical practice. Despite these hurdles, the continued investigation into the multifaceted roles of miRNAs undoubtedly paves the way for a new era of precision oncology in lung cancer management, moving closer to the goal of replacing conventional, highly toxic chemotherapy with more targeted and effective treatments.

Authors' Contributions

All authors contributed equally to this study.

Conflict of Interest Disclosures

The authors declare that they have no conflicts of interest.

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