MiRNAs Related with the Cell Cycle as Targets and Therapies in Lung Cancer Treatment

Jason Burns*
Editorial office, European Journal of Clinical Oncology, UK

Corresponding Author*

Jason Burns
Editorial office,
European Journal of Clinical Oncology, UK
E-mail: oncology@scholarlymed.com

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Abstract

Lung cancer is the leading cause of cancer deaths worldwide. The main obstacles to this cancer's clinical success are limited therapy alternatives and resistance to existing medications. Several studies over the last decade have demonstrated the significance of microRNA (miRNA) driven cell cycle regulation in lung cancer growth. As a result, these tiny nucleotide compounds could be useful in lung cancer therapy. We highlighted current advances in lung cancer therapy employing cell cycle associated miRNAs in this review. By emphasizing the roles of particular cell cycle core regulators associated with miRNAs in lung cancer, we explained how these miRNAs might be investigated in early detection and therapy efforts to avoid lung cancer. More medical efforts can ensure a potential breakthrough in miRNA-based lung cancer therapy with the information provided in our review.

Keywords: miRNA • NSCLC • Cell cycle • Biomarker • Cancer therapy

Introduction

According to GLOBOCAN (Global Cancer Incidence, Mortality, and Prevalence), 2020, lung cancer is the second most common malignancy and the leading cause of cancer-related mortality, accounting for around 2.2 million (11.4%) new cases and 1.8 million (18%) deaths worldwide. Pathologically, lung cancer can be divided into two types: Small Cell Lung Cancer (SCLC) and Non-Small Cell Lung Cancer (NSCLC). While SCLC is more likely to spread, NSCLC accounts for 85% of modern lung cancer cases, making it one of the most common cancers at the time. This cancer has become a major concern due to the fact that the majority of patients are diagnosed at advanced stages, when the possibility of potentially curative surgical treatment is limited. Five-year survival rates have been proven to be greatly improved when it is identified at an early stage; regrettably, the diagnostic rate at this stage is just 16%, and the 5-year survival rate for metastatic tumors in advanced stages appears to be only 4%. Although Low-Dose Computed Tomography (LDCT) screening is being used to detect cancer at an early stage in high-risk patients, its usage is limited because to high false positive rates, exposure to potentially harmful radiation, and the inability to discriminate benign nodules from malignancies. These difficulties highlight the critical importance of validated biomarkers with high sensitivity and specificity for early lung cancer detection [1-5]. One of the most noticeable features of lung cancer is abnormal cell growth. Cell-cycle progression and inhibition associated proteins both contribute to the precise regulation of the cell cycle. Furthermore, abnormal or dysfunctional miRNAs have been implicated in the cell cycle regulation of lung cancer. miRNAs and these cell cycle associated regulators interact in such a way that miRNAs control cell cycle regulator expression as either oncogenic or tumor suppressor miRNAs. Furthermore, miRNAs can efficiently repress target genes while simultaneously regulating a large variety of genes of interest, which helps to treat cancer as a diverse illness. As a result of the identification and validation of miRNAs' effective function in cell cycle progression, fresh therapy approaches for all types of cancer progression have emerged.

The most common traditional methods utilized in lung cancer treatment include surgery, chemotherapy, and radiotherapy. However, due to the involvement of different regulatory variables and genes in the development of resistance to the processes, these approaches fail to provide effective treatment for advanced cancer patients. As a result, there is an urgent need to develop a more advanced and effective therapy technique that can kill tumor cells without invading or destroying normal cells. Furthermore, new research suggests that abnormal miRNA function in lung malignancies may be involved in resistance to both radiation and chemotherapy. As a result, we attempted to focus on the miRNAs implicated in lung cancer cell cycle regulation in order to highlight them as genomic therapeutics. Based on their reaction to these two classic lung cancer medicines, this could be an emerging sector as an individual therapeutic system or used in combination with radiation or chemical drugs.

In this review, we discuss the significance of miRNAs in cell cycle control as well as their association with lung cancer progression. Furthermore, we attempted to study the most promising papers published to investigate the clinical capabilities of miRNAs, either as biomarkers or treatments. We also highlighted miRNAs' response to chemotherapy and radiotherapy in order to propose a combinatorial therapeutic approach for lung cancer treatment.

Following the identification of the predictive value of let-7 miRNA in lung cancer, the diagnostic utility of the miRNAs in lung cancer was also investigated. One of the key arguments for using miRNAs as biomarkers and prognostic tools against lung cancer has been cited as the stability of miRNAs in blood samples and tissue sections. MiRNA delivery systems are still being investigated and developed, despite the likelihood of non-specific side effects from miRNAs due to their complicated molecular structure. MiR-34a was the first miRNA to enter clinical trials (NCT01829971) for patients with NSCLC or other solid and metastatic malignancies in 2013.

Combinatorial therapies in the form of miRNA-targeted drugs, combinations of other miRNAs, and combinations of miRNA-siRNAs have been proposed over the years to boost the efficacy of miR-34a. To avoid miRNA off-target effects, synthetic miRNA mimics are utilized, which have the same effect as tumor suppressor miRNAs found in sick tissues. Most notably, Marina Biotech Inc. created MRX34, a miR34a mimic encapsulated in lipid vesicle that entered clinical trials in 2014. Specific anti-sense oligonucleotides against the miRNAs that are up-regulated in various cancers—now termed as anti-miRNAs—have been developed. The term antagomiR was coined in 2004 to describe the suppression of the let-7 miRNA [6,7].

The following year, the first in vivo mammalian study with antagomiRs was undertaken on mammals to silence numerous miRNAs via intravenous injection. Locked nucleic acid (LNA) injection is another technique of silencing oncomiRs. The first report of LNA-anti-miRNA successfully making its mark was found in a 2008 study in which the African Green Monkey demonstrated long-lasting and non-

toxic resistance to miR-122 after being infected with the appropriate LNA-anti-miRNA. Miravirsen, a chemical medication, was the first miRNA-inhibiting medicine to enter clinical trials in 2010. Katrien et al. explored the role of miR-155 in chemotherapy resistance and tested anti-miR-155 therapy to reestablish chemosensitivity in 2017. They discovered that combining anti-miR-155-DOPC with chemotherapy was non-toxic and reversed drug-induced apoptosis. The highly controlled phases of the cell cycle, which involve the activation or inactivation of positive and negative regulators, coordinate the sequential process of cell division. The genetic information of one cell generation is passed to the next during the duplication process via genome replication in S-phase and segregation in M-phase. During this cyclic process, two preliminary gaps are observed: M is separated from S by the G1 phase, and S is separated from M by the G2 phase. As a result, cell cycle checkpoints are primarily responsible for monitoring the timing, order, integrity, and fidelity of cell cycle events.

When the damage is repaired, the cell cycle resumes; otherwise, the cell is destroyed by apoptosis. The balance between cell proliferation and cell apoptosis is based on numerous protein families known as essential regulators of the cell cycle, which perform particular roles in each phase and ultimately control the complicated mechanism of cell division. The cyclins-CDKs holoenzymes and the E2F transcription factors operate as positive regulators in the cell cycle, whereas the retinoblastoma protein pRB and the CDK-inhibitor families act as negative regulators. Cyclins are proteins that regulate the transition between phases by forming a complex with Cyclin-Dependent Kinases (CDKs). Furthermore, CDK catalytic activity is influenced by interactions with cyclins and Cdk inhibitors. The close coordination of this trio, however, maintains an orderly pattern of cell cycle development.

Several studies have shown that miRNAs play a role in cell-cycle machinery by interacting with numerous cell cycle regulators by pairing to the 3' untranslated region of target transcripts. These non-coding miRNAs help to halt the cell cycle by modulating positive critical regulators. For example, miR-892b was discovered to target Cyclin D1 and Cyclin D2, two critical mediators of the G1 phase. MiR-17-5p, a member of the miR-17-92 cluster, plays an important function during the G1/S cell cycle transition by targeting both the inhibitor and activator of cell growth. Given the stability and consistency of miRNAs in serum and plasma as opposed to mRNAs, it may be concluded that miRNAs are properly justified in being chosen as non-invasive biomarkers for following disease progression and, eventually, cancer categorization. Indeed, as we know, numerous miRNAs are dysregulated in a variety of malignancies and correspond to a diverse set of target genes participating in the oncogenic process. As a result, using miRNAs for diagnostic and monitoring purposes may appear to be a formidable option. Even as a therapy option, miRNA (or anti-miRNA) therapies have gained popularity and attention in the recent decade or so. However, due to the complexity with which miRNAs function, non-specific side effects are unavoidable. Certain obstacles have inevitably accompanied the process of lung cancer therapy employing miRNAs. For one thing, miRNA and anti-miRNA treatments used in lung cancer instances are insufficient. So far, only a few projects, such as Targo-miRs (*MesomiR 1*) and *MRX34*, have been able to enter clinical trials in patients with *NSCLC*. Nonetheless, *MRX34* had to be stopped in phase-I due to several unfavorable immunological reactions in *NSCLC* patients, whereas Targo-miRs made it past phase-I. There has yet to be produced a trial of miRNAs influencing the Tumor Microenvironment (TME) of lung cancer. There is also a lack of reproducibility among studies dedicated to the diagnosis of lung cancer by miRNAs, which can be attributed to limited case numbers in large scale projects, variety in procedures used within, and discrepancies in serum miRNA levels across persons studied. MiRNA distribution mechanisms are as important as miRNAs themselves, and so can be a source of increasing difficulty. Clinical use of viral vectors for miRNA delivery, for example, has been discouraged.

Conclusion

Based on our findings, multiple miRNAs have the potential to be sensitive to current lung cancer therapies. These miRNAs could be studied further in conjunction with radiotherapy or chemotherapy to develop a more effective therapeutic approach for lung cancer. Lung cancer is one of the most serious cancers in the world, accounting for a large proportion of cancer-related fatalities worldwide. The primary barriers to success in lung cancer treatment are a lack of early detection technologies and widespread drug resistance. Many approaches have been presented over time in quest of a unique remedy to such a troublesome development, including consideration of miRNA-based therapies. As a result, we have gathered diverse information on miRNA participation in lung tumors from various sources. We have reduced our large pipeline for miRNA research into a selective but effective set of candidates and zoomed in on each of the prospects for determining their respective biological roles in lung cancer, eligibility as biomarkers in prognosis or diagnosis of lung cancer, usability as therapeutic plans, and response mechanisms against radio or chemotherapy for a detailed but precise u With the rise of systems biology, a better understanding of the miRNA-mediated gene regulatory network might aid in the development of safer miRNA treatments for the clinic.

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