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REVIEW

The potential clinical applications and prospects of microRNAs in lung cancer

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Abstract: Lung cancer is the major cause of cancer deaths worldwide due to its late diagnosis and poor outcome. Understanding genomic medicine may widen our vision into the oncogenesis of lung cancer and may open the door to improvements in the clinical management of lung cancer. It is well known that almost half of all genes are regulated by microRNAs (miRNAs). This review focuses on the role of miRNAs in lung cancer and also touches on the value of miRNA-based novel therapies for lung cancers.

Keywords: microRNA, lung cancer, biomarker, chemotherapy, radiotherapy

Introduction

Lung cancer is the most common invasive cancer and cause of cancer death worldwide, and in all cases, non-small-cell lung cancer (NSCLC) accounts for approximately 80%.[1–3] Although novel therapies have been developed, the 5-year survival rate for NSCLC patients remains at a low 15%.[4] Therapy in NSCLC has reached a plateau. The unfavorable outcome is due to our relatively limited understanding of tumor gene expression profiles and pathogenesis. Thus, understanding genomic medicine may therefore aid investigations into the oncogenesis of lung cancer. It may also yield prospects in accurate new biomarkers, molecular diagnosis, and risk stratification of lung cancer.

In the recent years, the changes in expression levels of microRNAs (miRNAs) have been detected and described. miRNA plays a significant role in a wide variety of pathways by regulating gene expression at the posttranscriptional level. It is well known that almost half of all genes are regulated by miRNAs as they are located in cancer-associated genomic regions or fragile genomic sites.[5] For example, miR-128b directly regulates epidermal growth factor receptor. Emerging evidence suggests that miRNAs may control lung cancer development and play a critical role in its oncogenesis and pathogenesis.[6–14] Since miRNAs play a substantial role and detection samples can easily be obtained, they have become a promising means of comprehending the oncogenesis and pathogenesis of lung cancer. miRNAs may contribute to drug efficacy and serve as outcome predictors in lung cancer.

In this review, we briefly describe the roles of miRNAs in lung carcinogenesis, diagnosis, prognosis, and their potential roles in lung cancer therapy.

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Features of miRNAs

miRNAs are endogenous noncoding and small (20–22 nucleotides) RNAs that have pivotal functions in biological processes.[15,16] miRNAs can regulate gene expression

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at the posttranscriptional level; therefore, they control fundamental cellular activities such as cell growth, differentiation, proliferation, and apoptosis. miRNAs have the potential to regulate at least 20%–30% of all human transcripts,[17] thereby involving them in almost all basic signaling pathways. Furthermore, miRNAs can control the expression of important tumor-related genes in tumorigenesis, including oncogenes and tumor-suppressor genes.[18] Thus, dysregulated miRNAs contribute to a variety of pathological events.

miRNAs as tumor inhibitors or oncogenes in lung cancer

Several studies have showed an important role of miRNAs in the regulation of carcinogenesis in different organs and the cell cycle, leading to the study of miRNAs as regulators of oncogenes and tumor inhibitor genes. Overexpression of let-7a, miR-126, and miR-107 suppresses lung cancer cell growth.[19] It has been reported that the inhibition of let-7 with an anti-let-7 molecule results in a 100% increase in the number of A549 cells.[20] Kumar et al[20] not only showed the ectopic expression of let-7g induced both cell cycle arrest and cell death in lung cancer cells, but also demonstrated that let-7g expression substantially reduced lung tumor burden in an autochthonous model of NSCLC. It has been concluded that cell growth is inhibited by the overexpression of let-7 miRNA, functioning as a tumor suppressor, suggesting the miRNA let-7 family functions as a tumor inhibitor.[8,21,22]

Aside from the let-7 family, miR-29a has been confirmed to reduce invasiveness and proliferation of human carcinoma cell lines.[23–25] miR-29b significantly reduced migration and invasion, and miR-218 is a strong candidate tumor suppressing miRNA, potentially involved in lung cancer.[26] The miR-451 was found to be significantly associated with tumor differentiation, pathological stage, and lymph node metastasis.[27] Furthermore, it was observed that low miR-451 expression levels were also associated with shorter overall survival of NSCLC patients, and miRNA-451 could function as a tumor inhibitor in human NSCLC by targeting ras-related protein 14 (RAB14).[27] Further, miRNAs such as miR-98, miR-101, miR-93, miR-182, miR-197, miR-212, and miR-451 have tumor-suppressive functions in lung cancer.[28–32]

Conversely, several miRNAs function as oncogenes to promote tumor progression by inhibiting tumor suppressor genes. Oncogene overexpression is correlated with increased cell proliferation.[33] The polycistronic cluster miR-17-92 is involved in embryonic lung development, consisting of six miRNAs (miR-17, miR-18a, miR-19a, miR-19b-1, miR-20a, miR-92a-1).[34] miR-125a-5p upregulates several downstream genes involved in epidermal growth factor receptor signaling and is associated with lung cancer invasion and metastasis.[35] In addition, it has been shown that miR-31 functions as an oncogenic miRNA by repressing specific tumor suppressors.[36] The engineered knockdown of miR-31 substantially repressed lung cancer cell growth and tumorigenicity in a dose-dependent manner.[36]

The literature suggests that miRNAs might regulate their expression by influencing their epigenetic regulation within the tumor and act directly by targeting oncogenes or tumor suppressor genes. Recently, a novel mechanism has shown that miRNAs also affect lung carcinogenesis by triggering a toll-like receptor-mediated oncogenic inflammatory response. However, miRNAs are involved in lung cancer carcinogenesis through various mechanisms.

miRNAs as biomarkers for chemoresistance or chemosensitivity in NSCLC

Mechanisms of drug resistance are often associated with changes in relevant proteins, such as PDCD4, PTEN, multidrug resistance 1, and P-glycoprotein. Several studies have discussed that aberrant miRNA expression can be related to chemotherapy resistance by resulting in altered function of the target mRNA, which affects the expression of the target proteins and fundamentally silences the target gene.[37]

Current investigations of miRNAs related to chemoresistance have been reported in the literature. They support the hypothesis that the overexpression or underexpression of any miRNA is directly linked to a patient's response to chemotherapeutic agents. miR-92a-2* and miR-574-5p were significantly associated with chemoresistance in small cell lung cancer (SCLC), with higher tumor miR-92a-2* levels related to chemoresistance and decreased survival in patients. Thus, miR-92a-2* may be applied in the screening of patients with SCLC at risk for de novo chemoresistance and predict chemoresistance for SCLC. These miRNA biomarkers may contribute to treatment stratification.[38]

Recently, Xie et al[39] showed that cell-free miRNAs in the supernatant of effusions may predict chemosensitivity to docetaxel. A number of miRNAs have been shown to be differentially expressed in docetaxel-resistant NSCLC, as demonstrated by specifically increased levels of miR-192, miR-98, and miR-424 and decreased levels of miR-200b, miR-194, and miR-212.[40] miR-497 was downregulated in the multidrug-resistant human lung cancer cell line A549/cisplatin; an overexpression of miR-497 sensitized A549/cisplatin cells to anticancer drugs.[41] It was also found

that miR-200c overexpression restored the sensitivity of NCI-H1299 cells to cetuximab and cisplatin.[42]

Chemoresistance is implicated in epithelial-mesenchymal transition (EMT) or stem cell trait of cancer cells, which can be regulated by miRNAs. One study found that the miR-181a–Twist1 pathway played a key role in the development of cisplatin chemoresistance with EMT, which increased the metastatic potential of tongue squamous cell carcinoma.[43] Functional analyses indicated that miR-181a reversed chemoresistance, inhibited EMT, and decreased metastatic potential in tongue squamous cell carcinoma cells. Cisplatin-induced chemoresistance underwent EMT and was accompanied by enhanced metastatic potential, miR-181a downregulation, and Twist1 upregulation.[43] Emerging evidence also proved that the miR-200 family are downregulated in cancer and play an important role in the suppression of EMT, tumor progression, and chemoresistance by targeting and repressing the expression of several key messenger RNAs.[44]

Various studies clearly demonstrate the role of miRNAs in chemosensitivity and chemoresistance, suggesting the manipulation of miRNAs may be beneficial in modulating cancer chemosensitivity and chemoresistance. miRNAs serve as the most accurate predictive biomarkers in providing the most precise prognosis for treatment response and outcomes, establishing personalized medicine currently available in the market.[67] It is anticipated that the therapeutic development of miRNA mimics or antagomirs may improve prognosis for NSCLC and reveal novel therapies. Therefore, miRNAs should be used firstly, as biomarkers to predict drug resistance or sensitivity in order to establish the appropriate personalized treatment and secondly, as possible drug targets to reverse resistance.

miRNAs as biomarkers for radioresistance or radiosensitivity in NSCLC

The resistance of hypoxic cells to radiotherapy is also a major problem in the treatment of cancer. Recently, an additional mode of hypoxia-inducible factor (HIF)-dependent transcriptional regulation has emerged. Grosso et al[45] have recently shown that miR-210 appears to be a component of the radioresistance of hypoxic cancer cells. Given the high stability of most miRNAs, such as in the case of HIF-1 induction of miR-210 which also stabilizes HIF-1 through a positive regulatory loop, this advantage could be used by tumor cells where reoxygenation has occurred and implies that strategies targeting miR-210 could enhance tumor radiosensitization.[45]

miR-34 is another important miRNA involved in p53-mediated apoptosis. The overexpression of p53 activated miR-34a/SIRT1/p53, which in turn was inhibited by ursodeoxycholic acid via decreased p53 transcriptional activity.[46] Another study demonstrated that restoration of miR-34a expression enhanced radiation-induced apoptosis, partly by suppressing the LyGDI signaling pathway. miR-34a could be used as a radiosensitizer since it is transcriptionally induced by the tumor suppressor gene p53 and is often downregulated in NSCLC.[47] In addition, some miRNAs are demonstrated to be epigenetically silenced by DNA methylation, while DNA methylation is associated with chemotherapy and radiotherapy cross-resistance, and finely balanced DNA methylation is needed to ensure proper radiation and drug responsiveness.[48,49]

Let-7a and let-7b were also shown to radiosensitize lung cancer cells and probably so do other members in the let-7 family, except let-7g for which it was confirmed the expression pattern changes after irradiation.[50–52] Let-7g was shown to be radiosensitizing in two studies but radioprotective in another study for lung cancer cells.[50–52] miR-26b was reported to radiosensitize lung cancer cells,[50–52] whereas miR-9, miR-155, miR-126, and miR-7 had the opposite effect.[52–56] In this situation, combining miRNA mimics or inhibitors with traditional therapies may potentiate the efficacy of the treatment, but more research is required to address this question.[50–56]

Clinical implications in NSCLC

miRNA based therapies for lung cancer

With the significant roles that miRNAs play in the prognosis and diagnosis of lung cancer, increasing efforts are dedicated to the development of miRNA-based therapies. There is great interest in the potential application of the restoring functions of tumor suppressive miRNAs and the inhibiting oncogenic miRNAs.[57]

Exogenous delivery of let-7 into mouse models of lung cancers significantly reduced tumor growth or decreased tumor burden.[22,58–59] The results suggested that miRNA replacement therapy could be promising. Liposome-based delivery of miR-7 into mouse xenografts of lung tumors resulted in significant shrinking of the tumors,[60] and an miR-34a based strategy has also been proved effective in mouse lung cancer models.[61,62] Several types of miRNA inhibitors have been developed to achieve therapeutic effects. A new class of miRNA inhibitors can be expressed in cells from transgenes of tandem miRNA binding sites linked to a strong promoter.[63] A locked nucleic acid-anti-miR against miR-122 has been shown to effectively silence miR-122 in primates

without evidence for toxicity. This suggests the feasibility of miRNA inhibitors for utilization in clinical settings.[64] miRNAs are less toxic and capable of "multitargeting", pointing to their potential to enter clinical practice compared to small interfering RNA-based therapies, which are already in clinical trials.[65] The critical issues for the development of this therapy are effective and fast delivery into target sites, potency of the therapy, and elimination of off-target effects. To solve these issues, double stranded miRNA mimics promise a cost-effective source, easier mechanism of function, and less nonspecific effects than mature miRNAs.

In general, miRNAs have theoretical and clinical implications in lung cancer settings since they play an important role in lung tissue and plasma as predictors of lung cancer development and aggressiveness. The results may improve the ability of clinicians to determine the most effective management for individual patients. The strategy, such as the integration of microarray-based genomic information with existing clinicopathological models, may improve survival rates and reduce treatment-related morbidity in patients with NSCLC. For example, Roybal et al[66] concluded that miR-200 suppresses lung tumorigenesis by targeting Flt1, which correlates inversely with the duration of survival. This was based on the finding that forced miR-200 expression suppressed Flt1 levels, and Flt1 knockdown decreased the growth and metastasis of tumor cells.[66,67] Although still in its infancy, further application prospects of miRNAs as biomarkers for chemo/radioresistance or chemo/radiosensitivity in NSCLC is anticipated, and these potential miRNA-based therapies are promising whether administered alone or in combination with conventional therapies.

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Disclosure

The authors report no conflicts of interest in this work.

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