MicroRNA-154 Expression is Associated With The Prognosis in Non-Small Cell Lung Cancer.

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Abstract

Background: MicroRNAs are noncoding RNAs that regulate cellular processes during the progression of tumors. Among various microRNAs, *MicroRNA-154* (*miR-154*) has been reported to be involved in many critical processes of human malignancies. This study aimed to evaluate the significance and prognostic value of *miR-154* in human non-small cell lung cancer (NSCLC).

Methods: A total of 144 NSCLC tissues samples and matched non-tumor adjacent tissues specimens were obtained from NSCLC patients and the quantitative real-time PCR (qRT-PCR) was performed to investigate expression levels of *miR-154*. The correlation between *miR-154* expression and survival outcomes of NSCLC patients was performed by Kaplan-Meier analysis, univariate and multivariate analysis.

Results: *MiR-154* expression was significantly decreased in NSCLC tissues compared with that in matched non-tumor adjacent tissues ($P<0.001$). In addition, low expression of *miR-154* was demonstrated to be associated with tumors size, TNM stages and distant metastasis of NSCLC patients. Survival analysis revealed that patients with low expression of *miR-154* showed significantly lower survival rate for OS, DFS and RFS, respectively (all, log rank test, $P<0.001$) and *miR-154* could be an independent prognostic indicator for NSCLC patients.

Conclusion: The results suggest that *miR-154* has the clinical significance in the progression of NSCLC and could be a potential prognostic biomarker for NSCLC patients.

Background

As a malignant cancer, non-small cell lung cancer (NSCLC) accounts for 85% of primary lung cancer which is the leading cause of cancer-related deaths worldwide [1, 2]. Actually, lung carcinogenesis is a complicated biological process due to mutual dysregulation of different tumor-related genes. Although the treatment including surgery, radiotherapy, and platinum-based combination chemotherapy for NSCLC [3] have improved a lot in recent years, the prognosis of NSCLC remains poor and the five-year survival rate is less than 15% [4, 5]. Therefore, it is still urgent to explore precise and special markers for improving the the survival of NSCLC patients.

MicroRNAs (miRNAs, miR) are a class of small (approximately 18–25 nucleotides), single stranded, conserved and noncoding RNAs, which regulate gene expression by binding to the 3'-untranslated region of specific target messenger RNAs, thereby result in mRNA degradation or translation inhibition [6–8]. It has been widely accepted that miRNAs play an important role in various pathological processes, such as cell proliferation, differentiation, metabolism and apoptosis, indicating their function as suppressor genes or oncogenes [9, 10]. Currently, increasing numbers of researches have provided that miRNAs are involved in different human malignancies including pancreas cancer, prostate cancer, colorectal cancer and lung cancer [11, 12]. For example, *miR-186*, *miR-205* and *miR-21* were all found to promote lung cancer carcinogenesis [13–15]. *MiR-154* is also one of the cancer-related miRNAs. Recent studies have reported

that *miR-154* is down-regulated and functions as a candidate tumor suppressor in various cancers, such as hepatocellular carcinoma, colorectal cancer and prostate cancer [16–18]. However, the expression level of *miR-154* and whether *miR-154* has the clinical significance in NSCLC has not been reported.

Therefore, the aim of the study was to measure the expression level of *miR-154* in NSCLC tissues and investigate the correlation of *miR-154* level with clinicopathological features as well as the prognostic value of *miR-154* in NSCLC patients.

Materials And Methods

Patients and samples

A total of 144 NSCLC tissue samples and matched non-tumor adjacent tissues specimens were obtained from patients who had pathologically confirmed as NSCLC in Cangzhou Central Hospital. None of the patients had undergone adjuvant treatments including radiotherapy, chemotherapy or immunotherapy before surgical resection. According to the criteria of American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system for lung cancer, 35, 20, 33 and 46 specimens exhibited stage I, II, III and IV cancer, respectively. After resection, all tissues were immediately snap-frozen in liquid nitrogen, and then stored at – 80 °C until RNA extraction. The follow-up was performed after surgery from 2 to 86 months (median: 61.5 months) and clinicopathologic characteristics of patients were summarized in Table 1. The protocol of this study was approved by the Ethical Committee of Cangzhou Central Hospital, and all patients signed the informed consent.

Table 1
The relationship between *miR-154* expression and the clinicopathological characteristics in NSCLC patients

Variables	N	<i>miR-154</i> expression		P value
		High	Low	
Age				0.070
≥ 55	76	31	45	
< 55	68	38	30	
Gender				0.053
male	89	37	52	
female	55	32	23	
Tumor size				0.001**
≥ 3 cm	73	25	48	
< 3 cm	71	44	27	
TNM				0.003**
I,II	79	29	50	
III,IV	65	40	25	
Lymph node metastasis				0.216
Absent	43	24	19	
Present	101	45	56	
Differentiation				0.076
Well/ moderately	58	33	25	
Poorly	86	36	50	
Distant metastasis				0.005**
Present	80	30	50	
Absent	64	39	25	
Smoking				0.064
Yes	70	28	42	
No	74	41	33	

Total RNA was isolated from the frozen tissues using TRIzol reagent (Invitrogen) according to the manufacturer's protocol, and then the first cDNA was synthesized using a Reverse Transcription Kit (Takara). QRT-PCR was performed with the Applied Biosystems 7900 Fast Real-Time PCR system (Applied Biosystems, Foster City, CA, USA) to quantify *miR-154*. U6 was taken as the endogenous control and the sequences of primers were as follows: *miR-154*, forward 5'-CGCGAATTTCGCATCTAGGACCTCCATCAC-3' and reverse 5'-ACGGGATCCGAACCATCCCTTCACTTACC-3'; U6 forward 5'-CTCGCTTCGGCAGCACA-3' and reverse 5'-AACGCTTCACGAATTTGCGT-3'. The relative expression levels of *miR-154* were calculated by $2^{-\Delta\Delta Ct}$ method and all experiments were presented in triplicate.

Statistical analysis

All statistical analyses were conducted using SPSS version 18.0 software (SPSS, Chicago, IL) and GraphPad Prism 5.0 (Graphpad Software Inc.). All quantified variables were presented as mean $\pm$ SD. The Student's t test was used to evaluate the difference between two groups while the differences among three or more groups was evaluated by Chi-square test. Moreover, Kaplan-Meier method with log-rank test was performed to compare survival curves. The analysis of prognostic analysis was carried out using univariate and multivariate Cox proportional hazards model. The difference was significant when a *P* value < 0.05 .

Results

The down-regulated expression of *miR-154* in NSCLC

We measured the expression levels of *miR-154* in 144 samples of NSCLC tissues and matched adjacent specimens by qRT-PCR. As shown in Fig. 1A, *miR-154* expression level in NSCLC tissues was significantly lower than those in the corresponding adjacent normal tissues (0.290 ± 0.152 vs 0.725 ± 0.280 , $P < 0.001$).

Association between *miR-154* expression and clinical features

To analyze whether *miR-154* was associated with the development and progression of NSCLC, we divided the samples into high and low *miR-154* expression groups according to the mean value of *miR-154* levels, and then investigated its relationship with the clinicopathological features. As summarized in Table 1, the significant associations between *miR-154* expression and tumor size ($P = 0.001$), TNM ($P = 0.003$) and distant metastasis ($P = 0.005$) were identified. Concretely, low level of *miR-154* expression was significantly correlated with larger tumor size (≥ 3 cm), TNM stages in III, IV, and present distant metastasis (all, $P < 0.001$, Fig. 1B). All these results demonstrated that *miR-154* was related to NSCLC progression and it might act as a tumor suppressor. However, no significant relationship had been found between *miR-154* expression and other clinical factors including age, gender, lymph node metastasis, differentiation or the or history of smoking.

The correlation between *miR-154* level and survival of NSCLC patients

To further evaluate the correlation between *miR-154* expression and clinical outcomes, we determined the prognostic value of *miR-154* expression on overall survival (OS), disease-free survival (DFS) and recurrence-free survival (RFS) in NSCLC patients. As determined by Kaplan-Meier method with log rank test, the patients with low expression of *miR-154* presented a shorter OS ($P < 0.001$; Fig. 2A), shorter DFS ($P < 0.001$; Fig. 2B) and shorter RFS ($P < 0.001$; Fig. 2C) respectively than those with high *miR-154* expression, indicating reduced expression of *miR-154* predicted a poor prognosis in patients with NSCLC.

Moreover, as respect to the influence of *miR-154* levels and clinicopathological characteristics on patient survival, we performed univariate Cox regression analysis. As shown in Table 2, the tumor size, TNM, lymph node metastasis, distant metastasis and *miR-154* expression (all, $P < 0.001$) were all associated with the OS, DFS and RFS, respectively. Further multivariate analysis indicated that, for NSCLS patients, down-regulated *miR-154* level was an independent factor for OS (HR = 2.890, 95% CI, 1.432–5.830; $P = 0.003$), DFS (HR = 2.659, 95% CI, 1.347–5.250; $P = 0.005$) and RFS (HR = 11.657, 95% CI, 4.526–30.027; $P = 0.001$). Furthermore, tumor size were independent factors associated with OS (HR = 2.890, 95% CI, 1.432–5.830; $P = 0.003$) and RFS (HR = 1.963, 95% CI, 1.216–4.266; $P = 0.016$), and the TNM could also be an independent factor for OS (HR = 2.659, 95% CI, 1.347–5.250; $P = 0.005$) and DFS (HR = 3.265, 95% CI, 1.895–6.889; $P = 0.001$) (Table 3).

Table 2
Univariate survival analysis of OS, DFS and RFS in patients with NSCLC

Variables	OS		DFS		RFS	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.010(0.515–1.981)	0.976	1.121 (0.612–2.013)	0.785	1.321 (0.845–2.414)	0.856
Gender	1.280 (0.672–2.438)	0.452	1.162 (0.712–2.315)	0.352	1.032 (0.456–1.963)	0.096
Tumor size	1.565 (0.821–2.983)	0.014	1.632 (0.789–3.025)	0.018	1.526 (0.812–2.856)	0.002
TNM	2.413 (1.236–4.713)	0.010	3.212 (1.463–5.426)	0.025	2.856 (1.326–4.632)	0.011
Lymph node metastasis	2.086 (1.078–4.038)	0.029	2.417 (1.123–4.291)	< 0.001	2.621 (1.325–4.521)	0.006
Differentiation	2.900 (1.432–5.876)	0.003	1.890 (1.263–4.215)	0.008	2.236 (1.365–5.026)	< 0.001
Distant metastasis	1.145 (0.603–2.173)	0.019	1.256 (0.732–2.653)	< 0.001	1.026 (0.589–2.036)	0.035
Smoking	1.783 (0.920–3.457)	0.087	1.235 (0.856–3.647)	0.052	1.426 (0.889–3.212)	0.126
<i>miR-154</i> level	8.108 (3.398–19.345)	< 0.001	9.632 (3.536–20.168)	< 0.001	9.256 (3.126–19.563)	< 0.001

Table 3
Multivariate survival analysis of OS, DFS and RFS in patients with NSCLC

Variables	OS		DFS		RFS	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Tumor size	2.890 (1.432–5.830)	0.003	-	-	1.963 (1.216–4.266)	0.016
TNM	2.659 (1.347–5.250)	0.005	3.265 (1.895–6.889)	0.001	-	-
<i>miR-154</i> level	11.657 (4.526–30.027)	< 0.001	9.123 (3.217–28.132)	< 0.001	12.163 (4.521–31.263)	< 0.001

Discussion

As the most common malignant disease in the world, lung cancer is the leading cause of mortality in China [19]. According to the past researches, several prognostic factors and biomarkers for NSCLC have been identified [20–23], which have improved the outcome of the NSCLC patients. However, the 5-year survival rate for the NSCLC is still unsatisfactory. Therefore, it is still urgent to identify novel and reliable prognostic markers to improve the prognosis of NSCLC patients.

Previous researches reveal that, till now, approximately 1,900 human miRNAs have been identified [7], which have great importance in the regulation of gene expression by regulating cellular functions such as proliferation, apoptosis and differentiation [24, 25]. Additionally, the roles of miRNAs in the progression and tumorigenesis of lung cancer have been gradually recognized. *miR-10b* in lung cancer is closely associated with lymph node metastasis [26]. Moreover the abnormal expression of several miRNAs are found to be involved in lung cancer [27–29]. For example, Foss et al. reported that the expression of *miR-1254* and *miR-574-5p* was significantly increased in the early-stage of NSCLC samples and they may serve as valuable biomarkers for NSCLC early detection [27]. Jia et al. have demonstrated that the *miR-146a* expression was significantly decreased in NSCLC patients [28]. In addition, the study of Nasser et al. found that *miR-1* was down-regulated in human primary lung cancer tissues and cell lines and it has potential therapeutic application against lung cancers [29].

MiR-154 is located on human chromosome 14q32, which is frequently lost in human cancers [30, 31]. According to recent studies, *miR-154* has been reported to be down-regulated in various types of cancer tissues, and closely associated with the outcome of prognosis for several tumors. For instance, Pang et al. showed that *miR-154* functioned as a tumor suppressor in hepatocellular carcinoma by targeting ZEB2 and it may serve as a potential target for HCC [16]. Yang et al. indicated that low expression of *miR-154* was associated with tumor progression of colorectal cancer and it may be an independent prognostic marker for CRC patient [17]. Moreover, Zhu et al. reported that *miR-154* expression significantly decreased in primary prostate cancer samples and played a prominent role in prostate cancer proliferation by suppressing CCND2 [18]. However, the clinical significance of *miR-154* in lung cancer are poor characterized.

In the present study, we explored the expression of *miR-154* and its clinical value in predicting survival outcome in patients with NSCLC. The results confirmed that the *miR-154* expression was significantly down-regulated in NSCLC tissues compared to the adjacent normal specimens. Subsequently, the association between *miR-154* expression levels and clinicopathological characteristics in NSCLC revealed that down-regulation of *miR-154* was closely correlated with tumor size, TNM stage and distant metastasis. In contrast, there was no correlation between *miR-154* expression and age, gender, lymph node metastasis, differentiation or smoking history. All these results suggest that *miR-154* plays an important role in the progression of NSCLC. Moreover, survival analysis revealed that patients with low *miR-154* expression have worse survival outcome. This result is consistent with report examining the prognostic role of *miR-154* [17]. According to multivariate analyses, *miR-154* was an independent prognostic factor for OS, DFS and RFS.

This present study had several limitations. First, the sample size was relatively small. Secondly, the underlying mechanisms of *miR-154* in NSCLC have not been well characterized. Therefore, identification of *miR-154* function and its downstream genes in lung cancer would be an important goal in future studies.

Conclusions

In conclusion, in the present study, we explored that the expression of *miR-154* was down-regulated in NSCLC, and the patients with low *miR-154* expression had shorter survival time in the OS, DFS and RFS analysis than those with high *miR-154* expression. All these findings demonstrated that *miR-154* could be regarded as an independent prognostic factor for patients with NSCLC.

Abbreviations

MicroRNA-154 (miR-154)

non-small cell lung cancer (NSCLC)

quantitative real-time PCR (qRT-PCR)

MicroRNAs (miRNAs, miR)

American Joint Committee on Cancer (AJCC)

tumor-node-metastasis (TNM)

overall survival (OS)

disease-free survival (DFS)

recurrence-free survival (RFS)

Declarations

Ethics approval and consent to participate

This study was supported by the Ethics Committee of Cangzhou Central Hospital and also has been carried out in accordance with the World Medical Association Declaration of Helsinki.

The subjects had been informed the objective. Certainly, written consents were signed by every subject in this study.

Consent for publication

We obtaining permission from participants to publish their data.

Availability of data and materials Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Competing interests The authors declare that they have no competing interests.

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Authors' contributions Y.Z. design of the work; Y.Z. the acquisition, analysis, Y.Z. interpretation of data; X.K. the creation of new software used in the work; H.W. have drafted the work or substantively revised it. All authors read and approved the final manuscript.

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Figures

Figure 1

Analysis of miR-154 expression in NSCLC tissues. (A) Relative expression of miR-154 in NSCLC tissues was significantly decreased compared with that in corresponding non-tumor tissues ($P<0.001$). (B) miR-154 expression was significantly lower in patients with advanced tumor size (size ≥ 3), high TNM stage (stage ≥ 3 , ≥ 3) and present distant metastasis.

Figure 2

Survival analysis. The patients with low miR-154 expression had shorter overall survival (OS, $P<0.001$; A) disease-free survival (DFS, $P<0.001$; B) and recurrence-free survival (RFS, $P<0.001$; C) than patients with high miR-154 expression.