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RESEARCH ARTICLE

Methylation of a group of microRNA genes as a marker for the diagnosis and prognosis of non-small cell lung cancer

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Abstract

Objectives. Lung cancer, representing a difficult-to-diagnose heterogeneous malignant neoplasm, is characterized by an asymptomatic course up to late stages, a high incidence of adverse outcomes, and a high probability of metastasis. Its most common form is non-small cell lung cancer (NSCLC). Recent studies have demonstrated a significant role of non-coding RNAs—in particular, microRNAs—in the development of NSCLC. MicroRNAs, which function as post-transcriptional regulators of the expression of protein-coding genes, including those associated with oncogenesis, are involved in the processes of cell proliferation, differentiation, and apoptosis. One of the approaches for regulating the expression of microRNAs themselves is to change the methylation of the CpG island adjacent to the microRNA gene or overlapping it. It has been shown that microRNA genes are several times more likely to undergo methylation than protein-coding genes. The aim of the present work is to study changes in the level of methylation of a number of microRNA genes and compile a potential panel of markers for the diagnosis and prognosis of NSCLC.

Methods. Samples of NSCLC tumors were collected and clinically characterized at the Blokhin National Medical Research Center of Oncology, Ministry of Health of the Russian Federation, Moscow, Russia. High-molecular-weight DNA was isolated from tissues using a standard method. The level of methylation was analyzed using bisulfite conversion of DNA and quantitative methyl-specific polymerase chain reaction with real-time detection. The significance of differences between the studied groups was assessed by the nonparametric Mann–Whitney U test for independent samples. Differences were considered significant at $p < 0.05$.

Results. The analysis of methylation levels of microRNA genes revealed a significant ($p < 0.05$) increase in the methylation level of eight microRNA genes: MIR124-1/2/3, MIR125B-1, MIR129-2, MIR137, MIR375, MIR1258, and MIR339 ($p < 0.01$, false discovery rate ≤ 0.25). On the basis of receiver operating characteristic analysis, a panel of markers is proposed for the diagnosis of NSCLC according to the nature of methylation of the studied microRNA genes in the tumor and in the normal tissue.

Conclusions. Our results, which contribute to the understanding of molecular mechanisms involved in NSCLC development, can be used in the development of new diagnostic and prognostic approaches in clinical oncology.

Keywords

microRNA, methylation, panel of markers, non-small cell lung cancer

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НАУЧНАЯ СТАТЬЯ

Метилирование группы генов микроРНК как маркер диагностики и прогноза немелкоклеточного рака легкого

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Аннотация

Цели. Рак легкого представляет собой гетерогенное злокачественное новообразование с низким диагностическим потенциалом, характеризующееся бессимптомным течением вплоть до поздних стадий, высокой частотой неблагоприятных исходов и высокой вероятностью метастазирования. Его самой распространенной формой является немелкоклеточный рак легкого (НМРЛ). Последние исследования показывают значительную роль некодирующих РНК, в частности, микроРНК, в развитии НМРЛ. МикроРНК выполняют функцию пост-транскрипционных регуляторов экспрессии белок-кодирующих генов, в том числе, связанных с онкогенезом, и вовлечены в процессы пролиферации, дифференцировки и апоптоза клеток. Одним из путей регуляции экспрессии самих микроРНК является изменение метилирования CpG-островка, прилежащего к гену микроРНК или перекрывающего его. Показано, что гены микроРНК в несколько раз чаще подвергаются метилированию, чем белок-кодирующие гены. Целью настоящего исследования являлось изучение изменения уровня метилирования ряда генов микроРНК и составление потенциальной панели маркеров для диагностики и прогноза НМРЛ.

Методы. Образцы опухолей НМРЛ собраны и клинически охарактеризованы в НИИ клинической онкологии Национального медицинского исследовательского центра онкологии им. Н.Н. Блохина. Высокомолекулярную ДНК выделяли из ткани стандартным методом. Анализ уровня метилирования проводили с применением бисульфитной конверсии ДНК и количественной метилспецифичной полимеразной цепной реакцией с детекцией в реальном времени. Для оценки значимости различий между исследуемыми группами применяли непараметрический критерий Манна–Уитни для независимых выборок. Различия считали достоверными при $p < 0.05$.

Результаты. В результате анализа уровней метилирования генов микроРНК нами было показано значимое ($p < 0.05$) увеличение уровня метилирования восьми генов микроРНК: MIR124-1/2/3, MIR125B-1, MIR129-2, MIR137, MIR375, MIR1258, MIR339 ($p < 0.01$, FDR ≤ 0.25). Был проведен ROC-анализ, позволивший предложить панель маркеров для диагностики НМРЛ по характеру метилирования исследованных генов микроРНК в опухоли и норме.

Выводы. Полученные нами результаты способствуют пониманию молекулярных механизмов развития НМРЛ и могут быть использованы при разработке новых диагностических и прогностических подходов в клинической онкологии.

Ключевые слова

микроРНК, метилирование, панель маркеров, немелкоклеточный рак легкого

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INTRODUCTION

Representing the most common type of lung cancer (up to 85% of cases), non-small cell lung cancer (NSCLC) is difficult to diagnose due to its heterogeneity (lung adenocarcinoma, squamous cell lung cancer, large cell lung cancer, etc.) and low detection rate in the early stages. NSCLC has a high metastatic potential. It is noted that up to 40% of detected NSCLC cases were identified as metastatic tumors. For this reason, in the diagnosis and prognosis of this type of cancer, a molecular approach is important [1].

At the moment, there is no unified system of molecular diagnostics and prognosis for determining the development of the early-stage oncological process and assessing its metastatic potential. As for any multifactorial disease, there are both genetic and epigenetic development triggers for each type of cancer [2]. One of the most significant epigenetic regulatory mechanisms, which dynamically and specifically influence processes in the cell, including gene expression, is the DNA methylation mechanism, which provokes tumor development when in an aberrant state. Aberrant methylation involves two differently directed processes: hypermethylation of tumor suppressor genes and demethylation of oncogenes. Aberrant methylation is associated with the regulation of many genes, including microRNA genes, which themselves constitute a regulatory element of the gene expression system [3].

MicroRNAs belong to the group of short non-coding RNAs, which perform a regulatory function in the body at the post-transcriptional level. MicroRNAs are involved in many cellular processes, including proliferation, differentiation, and apoptosis, whose disruption can lead to tumorigenesis [4]. Methylation/demethylation has been shown to play a much larger role in the regulation of microRNA genes than protein-coding genes. Hypermethylation leads to the switching off of the microRNA gene, while demethylation, conversely, causes its activation. Methylation and expression profiles of microRNA genes turned out to be highly specific for tumors of different locations and histological profiles [5]. NSCLC is characterized by a specific level of microRNA gene expression, which is associated with the clinical and pathological properties of a tumor. However, the methylation status of miRNA genes, which influences expression, is rarely studied. Detection of hypermethylation of a number of microRNA genes that exhibit tumor suppressor properties in NSCLC is a priority research area due to the possibility of creating a system of diagnostic and prognostic markers based on hypermethylated microRNA genes [6].

The aim of the present work is to create a potential marker system for the diagnosis and prognosis of NSCLC based on changes in the methylation level of a number of microRNA genes in a tumor.

EXPERIMENTAL

Collection of material. The level of methylation of microRNA genes was analyzed using 70 paired samples of tumor and adjacent normal lung tissue from NSCLC patients treated at the Blokhin National Medical Research Center of Oncology, Ministry of Health of the Russian Federation, Moscow, Russia. Samples were collected during elective surgery. All tumors were classified according to the TNM classification of the International Union Against Cancer and histologically verified based on the World Health Organization classification criteria [7]. The diagnosis was carried out on the basis of histological findings. Table presents clinical data of patients.

The study included samples of NSCLC tissue from patients who had not received radiation therapy, chemotherapy, or hormone therapy before surgery. The work was carried out in compliance with the principles of voluntariness and confidentiality in accordance with the Declaration of Helsinki of the World Medical Association [8].

DNA extraction. High-molecular-weight DNA was isolated from tissue by a standard method using phenol–chloroform extraction [9]. The DNA concentration was determined by optical density using a NanoDrop ND-1000 spectrophotometer (*Thermo Fisher Scientific*, USA).

Determination of the level of methylation. The methylation of microRNA genes was analyzed using quantitative methyl-specific polymerase chain reaction with real-time detection (qMS-RT-PCR) following bisulfite conversion of DNA according to the published procedure [10]. The completeness of DNA conversion was determined using the ACTB (ACTin Beta) control locus using oligonucleotides specific to the unconverted template. Amplification was carried out using a qPCRmix-HS SYBR reagent kit according to

Table. Clinicopathological characteristics of the studied samples

Clinicopathological parameter		Total number, $N = 70$	%
Histologic type	Squamous cell lung cancer	39	55.7
	Lung adenocarcinoma	31	44.3
Tumor stage	I	14	20.0
	II	28	40.0
	III	20	28.6
	IV	8	11.4
Degree of differentiation	G1	6	8.6
	G2	35	50.0
	G3	29	41.4
Tumor size	T1	11	15.7
	T2	35	50.0
	T3	13	18.6
	T4	11	15.7
Lymphatic metastasis	N0	29	41.4
	N1	41	58.6
Distant metastasis	M0	62	88.6
	M1	8	11.4

the *Evrogen* (Russia) protocol in the Bio-Rad CFX96 Real-Time PCR Detection System (*Bio-Rad*, USA). Oligonucleotide sequences and PCR conditions for microRNA genes were as presented in previous work [11]. Commercial human genomic DNA #G1471 (*Promega*, USA) was used as a control for unmethylated alleles. Commercial human genomic DNA #SD1131 (*Thermo Fisher Scientific*, USA) was used as a control for 100% methylation.

Statistical processing of the results was carried out using the IBM SPSS Statistics 22 software[1]. The significance of differences between the studied groups was assessed by the nonparametric Mann–Whitney U test for independent samples. Differences were considered significant at $p < 0.05$. Data were expressed as median (Me), lower (Q1), and upper (Q3) quartiles. Correlation analysis was performed by Spearman's rank correlation method, and its significance level was calculated [12]. To compile a panel with certain sensitivity and specificity coefficients, receiver operating characteristic (ROC) analysis was performed. Differences were considered significant and reliable at $p \leq 0.05$. False discovery rate ≤ 0.25.

RESULTS AND DISCUSSION

Using a representative statistical sample of NSCLC samples (70 tumor/normal pairs), changes in the methylation level of ten microRNA genes were studied: MIR124-1, MIR124-2, MIR124-3, MIR125B-1,

[1] https://soware.ru/products/ibm-spss-statistics. Accessed March 6, 2024.

MIR127, MIR129-2, MIR137, MIR375, MIR1258, and MIR339. According to the obtained results, a statistically significant ($p < 0.01$) increase in the level of their methylation (Fig. 1) in the tumor in comparison with the adjacent histologically unchanged normal tissue was found for the genes of eight out of ten microRNAs (MIR124-1/2/3, MIR127, MIR129-2, MIR137, MIR1258, and MIR339). We have previously presented convincing data for other types of cancer about the role of hypermethylation of these eight microRNAs [11, 13]. Note that, for NSCLC, a high level of methylation for the microRNA gene MIR339 was identified for the first time.

In the present work, we noted a correlation between the methylation levels of the studied microRNA genes and the clinicopathological characteristics of tumors. For example, methylation of the MIR125B-1, MIR1258, and MIR339 genes was observed in all NSCLC tumor samples ($p < 0.05$), regardless of histological type, stage and degree of differentiation, and the presence or absence of metastases. We also noted an association between hypermethylation of the MIR124-3, MIR125B-1, MIR137, and MIR1258 genes with the presence of metastases to lymph nodes and distant metastases ($p < 0.05$). Using the ROC analysis results, we developed two potential test systems for assessing the development and progression of NSCLC, which have the potential for use in the diagnosis and prognosis of this disease (Fig. 2).

The potential diagnostic panel consists of three markers: MIR125B-1, MIR1258, and MIR339 (sensitivity Se = 92.7, specificity Sp = 85.8, area under the curve AUC = 0.967, $p < 10^{-5}$) (Fig. 2a). The potential prognostic panel consists of four markers: MIR124-3,

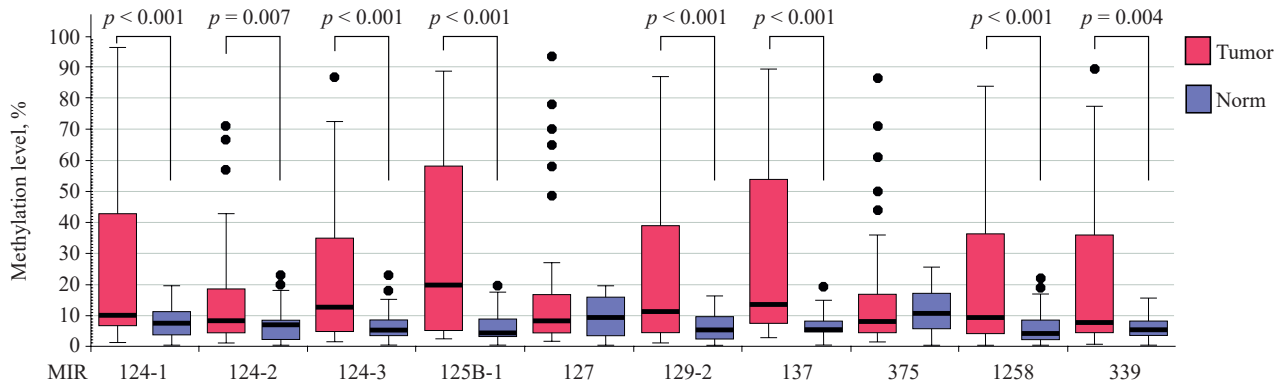

Fig. 1. Changes in the methylation level of ten microRNA genes in 70 paired tumor samples and histologically unchanged lung tissue in NSCLC

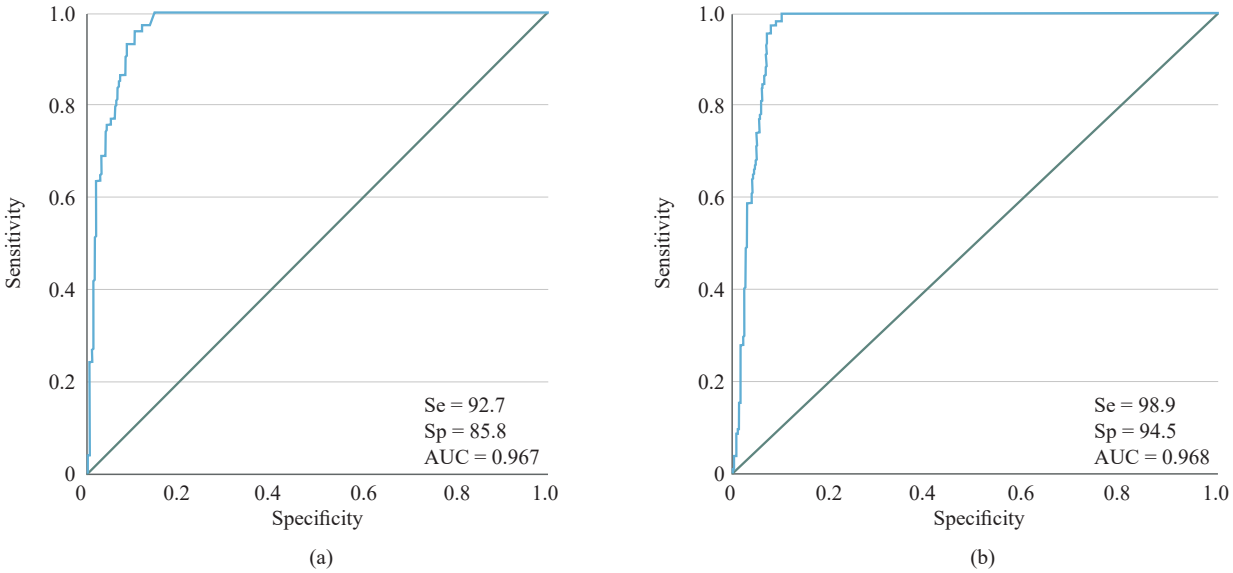

Fig. 2. ROC analysis of potential panels of markers based on assessing the methylation level of microRNA genes for the diagnosis and prognosis of NSCLC: (a) panel 1 (diagnostic): MIR125B-1, MIR1258, MIR339; (b) panel 2 (prognostic): MIR124-3, MIR125B-1, MIR1258, MIR137. Se—sensitivity; Sp—specificity; AUC—area under the curve

MIR125B-1, MIR137, and MIR1258 (Se = 98.9, Sp = 94.5, AUC = 0.968, $p = 1 \cdot 10^{-6}$) (Fig. 2b). The detection of hypermethylation of all microRNA genes included in the diagnostic panel suggests that the patient has NSCLC. If methylation of all genes included in the prognostic panel is detected, the patient has a high probability of developing metastatic NSCLC. Due to the high sensitivity (which exceeds 90%) and specificity of the prognostic panel of markers, their use as screening test systems with further confirmation by validated methods is justified. The detection of four hypermethylated miRNA genes of this panel may signal the need for additional monitoring of the patient for early detection and prevention of the development of metastases.

At the present stage of development of medicine, instrumental, biochemical, and histological studies of biopsy and/or resection material remain the main diagnostic methods. However, these methods are often insufficient for making a confident diagnosis. In this connection, the use of validated test systems based on molecular genetic studies could significantly change approaches to diagnosis through early detection of cell malignancy and prognosis by assessing certain tumor markers of different localizations, including NSCLC [14, 15]. The use of microRNAs as test systems for the diagnosis and prognosis of NSCLC and other types of cancer is particularly promising due to their tissue specificity, which links them to the specific course of the cancer [14].

CONCLUSIONS

As well as contributing to an enhanced understanding of the important role played by microRNA gene methylation in the regulation of the occurrence and progression of NSCLC, the results of the study also suggest new potential biomarkers for diagnosis and prognosis, offering the possibility to develop new therapeutic targets for drug development.

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Authors' contributions

M.S. Gubenko, I.V. Pronina, P.V Postnikov—responsible for experimental data.

A.M. Burdennyy—concept and structure of the article.

Yu.A. Efimova, F.V. Radus, E.S. Mochalova—statistical data processing.

V.I. Loginov—bioinformatic analysis, preparation of illustrative material.

T.P. Kazubskaya—collection of clinical samples.

All co-authors have approved the final version of the article, checked the integrity of all sections of the article.

The authors declare no conflicts of interest.

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