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The molecular risk patterns in the pathogenesis of lung cancer

Abstract: Lung cancer is leading cause of mortality from cancer diseases in Kazakhstan. Like most cancer, lung cancer has a multifactorial nature of origin. In its pathogenesis, an important role is played by both genetic/epigenetic changes in the cell. The change in the epigenetic landscape can be associated primarily with the change in the profile of the microRNA.

microRNAs are small non-coding RNAs that are involved in the regulation of target genes at the post-transcriptional level. MicroRNA controls many biological processes, including proliferation, growth and cells' survival. To date, a large amount of evidence has been accumulated about the involvement of microRNA in the carcinogenesis of various malignant neoplasias, including lung cancer.

Thus, microRNAs on the one hand can be markers of the oncological process, on the other hand markers of the impact of adverse environmental factors. In this connection, a comparative analysis of circulating miRs was conducted in a group of patients diagnosed with lung cancer and a control group without lung pathology.

Keywords: lung cancer, microRNA, miR-19b-3p, miR-205-3p, miR-155-5p, miR-125b-3p, let-7a-2.

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Among variety of cancer diseases attention the lung cancer (LC) because of high level of incidence, difficulties in diagnosis, and the diversity of clinical and morphological manifestations, early metastasis and poor effectiveness of treatment.

As in most countries of the world, lung cancer in the Republic of Kazakhstan occupies a dominant position and makes up 11.4% of the total number of malignant tumors [1].

To date, early diagnosis of lung cancer is not effective because of the absence of symptoms of the disease at an early stage of development. Early signs of lung cancer are nonspecific and similar to general clinical symptoms of other pulmonary diseases. Therefore, the diagnosis of lung cancer at the early stages is quite difficult. In this regard, new diagnostic methods are needed that be able to detect lung cancer at the earliest stages of development.

MicroRNAs are tissue-specific molecules and play an important role in the development of tissues and organs. Recent studies have shown that, in various diseases, including cancer, the level of microRNAs expression changes. This suggests that free circulating microRNAs isolated from body fluids can be used as biomarkers for the diagnosis of lung cancer. [2].

Analysis of the literature data showed that the change in the profile of miR-19b-3p, miR-205-3p, miR-155-5p, miR-125b-3p and let-7a-2 was observed in many types of cancer [3]. Impaired expression of miR-19b-3p, miR-155-5p promotes inhibition of apoptosis, uncontrolled cell proliferation and, as a consequence, cancerogenesis. In turn miR-205-3p and let-7a-2 are positioned as tumor suppressors. In this connection, these microRNAs were chosen as candidates for detecting molecular changes that occur in the pathogenesis of lung cancer [3, 4].

Materials and methods: The material for the study was microRNA isolated from the blood of lung cancer patients ant healthy people. A total of 87 subjects was examined, including: i) 37 patients with lung cancer (LC); and ii) 50 healthy controls. The group of lung cancer patients consisted of 31 males and 6 females with a mean age of 57.42 ± 2.34 years. Healthy control was represented by 39 males and 11 females with a mean age of 60.7 ± 1.96 years.

RNA extraction from the blood. A 10 ml sample of blood was collected from each subject in tubes containing EDTA. The blood was centrifuged at 3000 x g for 10 min at room temperature and supernatant was stored at -80 $^{\circ}$ C. A total RNA of 200 μl of plasma was isolated using a MiRCURY ^{TM} Biofluids isolating isolate kit (No. 300112, Exiqon A / S, Vedbaek, Denmark), in accordance

with the manufacturer's protocol. The amount and purity of extracted RNA was evaluated using a spectrophotometer (Nanodrop ^{TM} ND 1000) according to the manufacturer's protocols, and the 230/260 (< 0.50) and 260/280 (> 1.85).

MicroRNA analysis by qPCR. The expression levels of *microRNA* was determined by evaluating the level of fluorescence emitted by SYBR§Green tracer (cat no. 203403; Exiqon A/S, Denmark). All reactions were carried out in triplicate, and the 2- $\Delta\,\Delta$ Cq method (Δ Cq=CTmiR-CTU6). All statistical analyses were performed using GraphPad Prism 6 software (GraphPad Software, Inc., La Jolla, CA, USA) [5].

Results: In our study, a panel of miRNAs, including miR-19b-3p, miR-205-3p, miR-155-5p, miR-125b-3p and let-7a-2 in the peripheral blood plasma of patients with lung cancer was identified. Analysis of the expression of miR-19b-3p, miR-205-3p, miR-155-5p, miR-125b-3p and let-7a-2 was performed using the $\Delta\,\Delta$ Ct method, for the reliability of the obtained results Δ Ct was calculated for each sample, deviation. For the statistical processing of the results obtained, Student's test was used.

The relative level of expression of miR-19b-3p in lung cancer patients was significantly higher than healthy participants in the study.

The data are shown in Table 1.

Table 1-Relative expression level of miR-19b-3p in lung cancer patients compared to control

	miR19b-3p	U6	ΔCt	ΔΔCt	Relative expression level
Control	28,876±0,381	31, 6±0,219	2,728±0,467	0,00±0,467	1 (0,72-1,38)
LC	26,482±0,43	31,998±0,21	5,516±0,516	3,415±0,516	6,91 (4,83-9,9)

miR19b-3p expression level in the group of "lung cancer" was 6.9 times increased ($P < 0.0001$) as compared to those detected in cancer-free "control" (Fig.1). The results are consistent with data from other researchers who found that miR19b-3p expression was significantly higher in the lung adenocarcinoma cell lines (A549) compared to the human lung epithelial cell line. This study also demonstrated that a high level of miR19b-3p expression can promote the spread and migration of lung cancer cells [6]. In addition, the levels of miR-19-3p, miR-21-5p and miR-221-3p were significantly higher in exosomes extracted from the peripheral plasma of patients with lung adenocarcinoma [7].

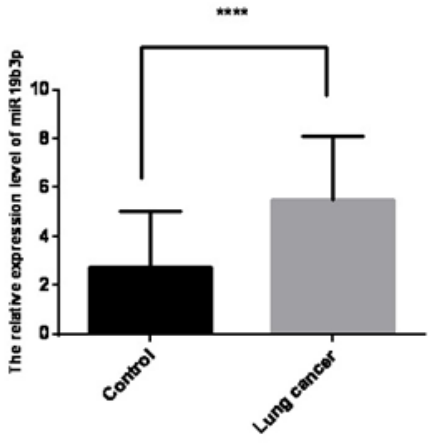

Figure 1 - Relative expression level miR-19-3p in lung cancer patients compared to control

The significant difference between the level of expression in both groups of patients with lung cancer and healthy people shows that miR-19b-3p is a oncolomir associated with the development of lung cancer. Therefore, this microRNA plays a key role in carcinogenesis and can be considered as one of the tumor markers for the diagnosis of lung cancer [5].

A similar pattern is observed for miR-205-3p, miR-155-5p and miR-125b-3p, their level of expression has shown a statistically significant association with the risk of developing lung cancer.

Interesting results were also obtained during the comparative analysis of the expression level of free-circulating miR-205-3p, according to which it can be assumed that miR-205-3p is oncomir and participates in carcinogenesis in lung (Table 2). The obtained data in a number of other studies with different types of cancer, including lung cancer, show contradictory results [5].

Table 2 - Relative expression level of miR-205-3p in lung cancer patients compared to control

	miR-205-3p	U6	ΔCt	ΔΔCt	Relative expression level
Control	34,135±0,44	32,159±0,56	1,98±0,784	0,00±0,784	1(0,581-1,722)
LC	31,13±0,42	32,217±0,41	0,053±0,652	1,93±0,652	3,81(2,43-5,99)

It was found that the level of miR-205-3p expression in patients of the group "Lung cancer" was in 3.81 times higher compared to the control group of healthy individuals ($p < 0.001$) (Table 2).

There were no statistically significant differences in the comparative analysis of miR-205-3p expression depending on the status of smoking, the stage of the disease, the age of the patients and the histological type of lung cancer. Also, there was no association of changes in the level of miR-205-3p with age, gender and nationality.

The role of miR-205-3p in mechanisms of carcinogenesis is ambiguous. Many articles have been published where this microRNA performs the oncopperpressor function. For example, miR-205 acts as a tumor suppressor in colorectal cancer. A decrease in the level of miR-205-3p was observed in patients with prostate cancer and breast cancer. A number of studies have shown that overexpression of miR-205-3p inhibits the migration of tumor cells and the formation of metastases in the lung cancer model [8] and proliferation of adenocarcinoma cells (A549) [9]. However, our results are consistent with the data of Zhang [10], Lebanony [11], Patnaik [12] in the study of which there was an increase in the level of miR-205-3p in squamous cell carcinoma, NSCLC and lung adenocarcinoma.

The miR-155-5p profile change was evaluated using the $\Delta\,\Delta\,$Ct method (see Materials and Methods), to obtain statistically reliable results, the criterion $\Delta\,$Ct and the standard deviation were calculated for each sample. The results of the expression level for all three groups are given in Table 3.

Table 3 - Relative expression level of miR-155-5p in lung cancer patients compared to control

	miR-155-5p	U6	ΔCt	ΔΔCt	Relative expression level
Control	34,65±0,57	32±0,51	2,65±0,8	0,00±0,8	1(0,57-1,74)
LC	33,51±0,41	32,02±0,47	1,498±0,7	(-1,152)±0,7	2,2 (1,37-3,61)

Based on the data given in Table 3, in the group of patients with lung cancer, the level of miR-155-5p was 2 times higher than in the control group of healthy individuals ($p < 0.010$) (Fig.2). In connection with the obtained results, it can be assumed that miR-155-5p is involved in the pathogenesis of lung cancer as oncomir, which does not contradict the data of other studies. In the literature, among well-known oncologists, this microRNA is described as the most significant, because of its involvement in a variety of oncogenic processes.

As shown in Table 4, the relative expression level of miR-125b-5p in lung cancer patients was in 4 times higher than in healthy people ($p < 0.001$). Thus, it can be concluded that this microRNA is a biomarker of a malignant process in the lung tissue.

Table 4 - Relative expression level miR-125b-5p in lung cancer patients compared to control

	miR-125b-5p	U6	ΔCt	ΔΔCt	Relative expression level
Control	34,14±0,4	32,1598±0,6	1,98±0,8	0,00±0,8	1(0,581-1,72)
LC	32,05±0,4	32,1796±0,5	(-0,134)±0,7	(-2,11)±0,7	4,32(2,7-4,8)

Based on the results obtained, we can assume that miR-125b-5p is oncomir and is involved in carcinogenesis of lung cancer. Literature data from several other studies with different types of cancer, including lung, show conflicting results. miR-125b-5p functions as an oncogene in glioblastoma cells and inhibits apoptosis of cells through P53 and p38MAPA-independent pathways [13]. Nishida N et al. confirmed the connection of miR-125b with the pathogenesis of colorectal cancer and poor

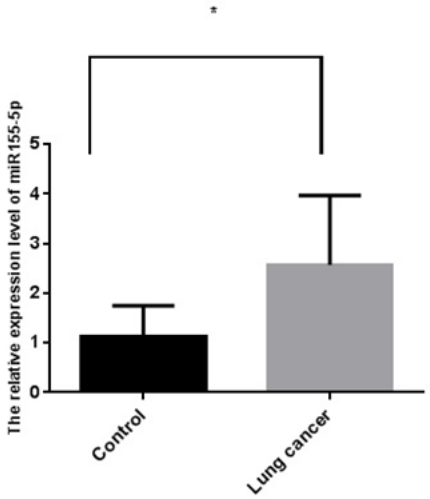

Figure 2 - Relative expression level miR-155-5p in lung cancer patients compared to control

patient survival. An increase in the level of miR-125b is indicated in myeloid, B-cell lymphoblastic and T-cell lymphoblastic leukemia [14, 15].

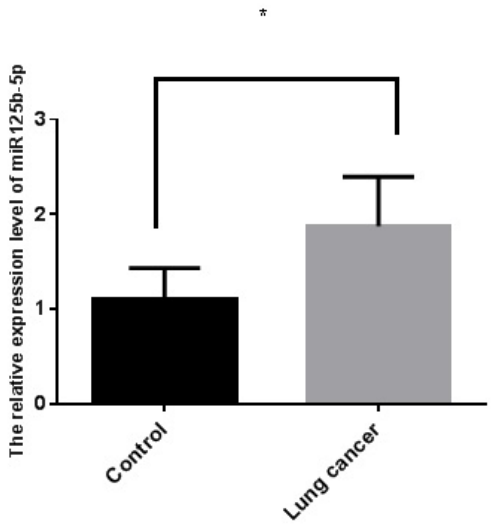

Figure 3 - Relative expression level miR-125b-5p in lung cancer patients compared to control

Our results agree with the data of Wang X et al. Of Southeast University (China) and Li Q. et al. From the University of Tongji who showed the oncogenic activity of miR-125b in the lung adenocarcinoma cell line (95D) and in human NSCLC cells [16, 17]. In this connection, it can be assumed that miR-125b-5p plays a significant role in malignant cell transformation in lung cancer as an oncomir.

A study of the expression level of free-circulating microRNAs depending on the histological type of the lung tumor showed that lung adenocarcinoma is characterized by a decrease in let-7a-2 expression level by almost three times compared to the control. For all other types of microRNA, the association was not identified.

According to the obtained results, the let-7a- 2 was down regulated in both groups of lung cancer patients compared to control (Fig. 4, Table 5).

Table 5- Relative expression level let-7a-2 in lung cancer patients compared to control

	let-7a-2	U6	ΔCt	ΔΔCt	Relative expression level
Control	34,68±0,2	31, 8±0,5	2,88±0,55	0,00±0,55	1 (0,68-1,5)
LC	35,5±0,5	32,5±0,5	3±0,8	0,11±0,516	0,9 (0,7-1,4)

Analysis of the let-7a-2 expression level in various histological types of lung cancer showed that in patients with adenocarcinoma the level of let-7a-2 was almost three times lower compared to the control (Table 6).

Table 6 – Relative expression level of let-7a-2 in patients with adenocarcinoma

	let-7a-2	U6	ΔCt	ΔΔCt	Relative expression level
Control	34,68±0,2	31, 8±0,5	2,88±0,55	0,00±0,55	1 (0,68-1,5)
Adenocarcinoma	36,01±1	31,4±0,33	4,64±1,3	1,76±1,3	0,29

In connection with the above, the miRNA let-7a-2 appears to be very promising biomarker for early diagnosis of lung cancer. Moreover, expression of let-7a-2 is characterized by a dependence on the histological type of lung cancer.

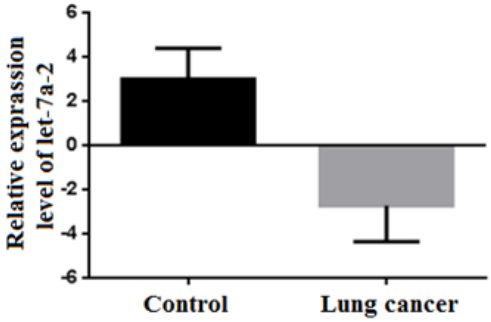

Figure 4 - Relative expression level let-7a-2 in lung cancer patients compared to control

Thus, the observed overexpression of miR-19b-3p, miR-205-3p, miR-155-5p, miR-125b-3p and let-7a-2 in the group of patients with lung cancer compared to the control group allows positioning as a molecular oncomarker for development of a non-invasive method for early diagnosis of lung cancer. One of the priority areas of molecular biology is the search for universal molecular markers - microRNAs associated with the risk of lung cancer and the creation of highly specific and effective method for the early diagnosis based on them.

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Өкпе қатерлі ісігі патогенезіндегі молекулалық паттерндер

Аннотация: Өкпе қатерлі ісігі Қазақстанда онкологиялық аурулар өлімінің басты себебі болып табылады. Басқа қатерлі ісік аурулары сияқты өкпе қатерлі ісігі де шығу тегі жағынан көп факторлы сипатқа ие. Оның патогенезінде клеткадағы генетикалық-эпигенетикалық өзгерістер маңызды роль атқарады. Эпигенетикалық ландшафттың өзгеруі, негізінен, микроРНК профилінің өзгеруіне байланысты болуы мүмкін. МикроРНК посттранскрипциялық деңгейде ген нысандардың реттелуіне қатысатын кодталмайтын РНҚ түрінде болады. МикроРНК клеткалардың пролиферациясы, өсуі және тіршілік етуі сияқты биологиялық процесстерді бақылайды. Бүгінгі таңда көптеген қатерлі ісіктердің, соның ішінде өкпе қатерлі ісігінің канцерогенезіне микроРНҚ-ның қатысуы туралы көптеген деректер жинақталған. Сонымен қатар, микроРНҚ, онкологиялық процестер маркері, қоршаған ортаның қолайсыз факторлары әсерлерінің маркерлері де болуы мүмкін. Осыған байланысты еркін айналатын микроРНК салыстырмалы талдауы өкпе қатерлі ісігі науқастары на және бақылау топтары, яғни өкпе қатерлі ісігі патаологиясы жоқ топтарға жүргізілді.

Түйін сөздер: өкпе қатерлі ісігі, микроРНК, miR-19b-3p, miR-205-3p, miR-155-5p, miR-125b-3p, let-7a-2.

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Молекулярные паттерны риска в патогенезе рака легкого

Аннотация: Рак легких является основной причиной смертности от онкологических заболеваний в Казахстане. Как и большинство видов рака, рак легких имеет многофакторный характер происхождения. В его патогенезе важную роль играют как генетические так и эпигенетические изменения в клетке. Изменение эпигенетического ландшафта может быть связано прежде всего с изменением профиля микроРНК. МикроРНК представляют собой небольшие некодирующие РНК, которые участвуют в регуляции генов-мишеней на посттранскрипционном уровне. МикроРНК контролируют многие биологические процессы, включая пролиферацию, рост и выживаемость клеток. На сегодняшний день накоплено большое количество данных об участии микроРНК в канцерогенезе различных злокачественных новообразований, включая рак легких. Таким образом, микроРНК, с одной стороны, могут быть маркерами онкологического процесса, с другой стороны, маркерами воздействия неблагоприятных факторов окружающей среды. В связи с этим сравнительный анализ циркулирующих miRs проводился в группе пациентов с диагнозом рака легких и контрольной группе без патологии легких.

Ключевые слова: рак легкого, микроРНК, miR-19b-3p, miR-205-3p, miR-155-5p, miR-125b-3p, let-7a-2

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