CLINICAL-DIAGNOSTIC STUDIES

SERUM miR-181a AND miR-25 IN PATIENTS WITH MALIGNANT AND BENIGN BREAST DISEASES

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Breast tumor diseases include a wide range of pathologies that require different approaches to their treatment. MicroRNA (miR) levels, reflecting regulation of the gene expression involved in tumorigenesis, can be diagnostic and prognostic markers of breast diseases. The levels of circulating miR-181a and miR-25 were measured in patients with benign breast diseases (BBD), patients with invasive carcinoma of a nonspecific type (ICNT) and also in conditionally healthy women. Expression of both miRs was higher in patients of both groups as compared to controls; at the same time, the content of serum miR-181a and miR-25 was higher in BBD patients than in ICNT patients. The detected changes may be of interest in the context of precancerous changes in BBD. It seems possible to use them in the future as markers of the pathological process as a part of a large diagnostic panel.

Key words: miR-181a; miR-25; breast cancer; benign breast diseases

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INTRODUCTION

Breast cancer (BC) is the most common cancer in women and the leading cause of cancer mortality. The most common histological subtype of breast cancer is invasive breast carcinoma of a nonspecific type (ICNT). This diagnosis covers a wide range of subtypes of malignant epithelial neoplasms, differed in morphology, clinical picture and prognosis, and requiring different, often personalized treatment [1, 2].

The etiology and pathogenesis of ICNT may be associated with dysregulation of microRNAs (miRs) [3], which suppress their target genes at the post-transcriptional level; many of them are involved in cell proliferation, differentiation, migration, and apoptosis [3, 4]. It is expected that miR expression profiling will allow their use as biomarkers for diagnostics, monitoring of response to treatment, and disease prognosis [5]. miR-181a is one of the common exosomal miRs in human blood [6]. Acting on different target genes, it can have both pro-oncogenic [3, 4, 7] and anti-oncogenic effects [4, 8–10] in breast tissue. Despite the fact that data on the level of miR-181a in serum depending on disease status are contradictory [11, 12], changes in its serum level can potentially serve as a diagnostic marker [4]. miR-25 is mainly known as a pro-oncogene [13]. There is evidence that miR-25 promotes tumor proliferation [14], participates in autophagy processes [15], and in TNF-α-dependent cell death [16]. Increased levels of miR-25 are associated with better survival in BC patients [17]; certain evidence also exists that miR-25 may be responsible for inhibition of tumor growth due to its participation in the regulation of the Wnt signaling pathway [18].

Despite the prevalence of benign breast diseases (BBD), the major attention is paid to the diagnostics and treatment of BC [19]. However, BBD may increase the risk of developing BC [20]. For example, complex cyst and complex solid-cystic formation in the mammary gland have a wide variety of pathological types and can be malignant in 23-31% of cases [21]. Adenosis is often associated with fibrocystic alterations, whereas sclerosing and apocrine adenosis correlate with a 1.5–2.0-fold increase in the risk of BC [2]. The relationship between fibrocystic changes and BC is complex and controversial, and the development of methods for diagnostics and treatment of this breast pathology is of great importance. Considering all of the above, analysis of the levels of circulating miR-181a and miR-25 in different types of breast diseases can provide insight into their possible use as diagnostic markers.

The aim of the study was to determine the levels of miR-181a and miR-25 in the serum of patients with BBD, patients with ICNT with and without lymphogenous metastasis and in conditionally healthy individuals, as well as to study the extent of differences in breast pathology and their evaluation as potential biomarkers.

MATERIALS AND METHODS

The Object of the Study

The study was conducted using peripheral blood serum samples from 68 women, including 11 women (average age of 46 years, from 25 years to 60 years), which formed a control group of conditionally healthy individuals (without breast pathology and exacerbation of infectious and inflammatory diseases) (Novosibirsk City Station for Blood Transfusion). Other samples were collected from patients of the regional Kemerovo Clinical Oncologic Dispensary. These included 16 BBD patients (average age of 49 years, from 35 years to 67 years) and 41 ICNT patients (average age of 64 years, from 33 years to 80 years). Neoadjuvant therapy was not performed in ICNT patients. Clinical and morphological characteristics of tumors are shown in Table 1.

miR Analysis

miR was isolated from 300 μl of blood serum using the NucleoSpin miRNA Plasma Kit (Macherey-Nagel, Germany) and following the manufacturer's instructions. The miRNA concentration was measured spectrophotometrically. Reverse transcription was performed using miRNA-specific stem-loop adapter primers and reverse transcriptase M-MuLV-RH (Biolabmix, Russia). The reaction was carried out according to the manufacturer's instructions; 25 activity units (AU) of RNase inhibitor, 8 pmol of stem loop primers, and 1 ng of isolated RNA were added. The mixture was incubated at 18°C for 30 min, then at 42°C for 30 min and at 85°C for 5 min. The sequences of the adapter primers are given in Table 2.

miR levels were assessed using Droplet digital PCR (Bio-rad, USA) and TaqMan probes on a QX200 AutoDG Droplet Digital PCR System. To generate droplets in a final volume of 20 μl of the reaction mixture, a twofold ddPCR supermix for probes (Bio-Rad), 7 μl of cDNA sample, and 3 μl of primers were used. Droplets were generated using an automatic droplet generator QX200 (Bio-Rad) and disposable cartridges (Bio-Rad). Thermal cycling conditions were as follows: 95°C for 10 min, 39 cycles of 95°C for 30 s, 55°C for 1 min, and

Table 1. Clinical and morphological characteristics of tumors

Parameter	Value
ICNT, n=41	
Tumor size, cm	1.8 (0.5–5.5)
Lymph node involvement, N	0 (29; 71%) 1 (8; 20%) 2 (1; 2%) 3 (3; 7%)
Subtype	Luminal A (9; 23%) Luminal B, HER2 negative (26; 63%) Luminal B, HER2 positive (3; 7%) Non-luminal B, HER2 positive (1; 2%) Triple negative (2; 5%)
Tumor differentiation grade, G	1 (2; 5%) 2 (39; 95%)
Tumor stage	I (26; 63%) II (15; 37%)
Estrogen receptors	present (38; 93%) absent (3; 7%)
Progesterone receptor	present (38; 93%) absent (3; 7%)
Human epidermal growth factor receptor 2 (HER2)	present (3; 7%) absent (38; 93%)
Ki-67 level	33.9 (5–86)
BBD, n=16	
Diagnoses of patients with BBD	Fibroadenoma (2; 12,5%) Fibrocystic disease (2; 12,5%) Fibroadenomatosis (10; 62,5%) Sclerosing adenosis (2; 12,5%)

The prevalence of categorical clinical and morphological parameters is given in the format (N; P), where N is the number of patients with a given categorical parameter value, P is the percentage of the number of patients with a given categorical parameter value relative to the entire sample.

Table 2. Oligonucleotide sequences for RT-PCR

miR	Type	Oligonucleotide sequence (5′→3′)
miR-181a-5p	Adaptor	GTCGTATCCAGTGCAGGGTCCGAGGTATTCGCACTGGATACGACACTCACCG
	Forward	GCCGCAACATTCAACGCTGT
	Probe	(FAM)-TTCGCACTGGATACGACACTCACCG-(BHQ1)
miR-25-3p	Adaptor	GTCGTATCCAGTGCAGGGTCCGAGGTATTCGCACTGGATACGACTCAGACCG
	Forwards	GCCGCCATTGCACTTGTCT
	Probe	(FAM)-TTCGCACTGGATACGACTCAGACCG-(BHQ1)
RNU6-1	Adaptor	GTCGTATCCAGTGCAGGGTCCGAGGTATTCGCACTGGATACGACGGCCATGC
	Forwards	GCCGCATACAGAGAAGATTA
	Probe	(FAM)-TTCGCACTGGATACGACGGCCATGC-(BHQ1)
Reverse primer (common)		AGTGCAGGGTCCGAGGTA

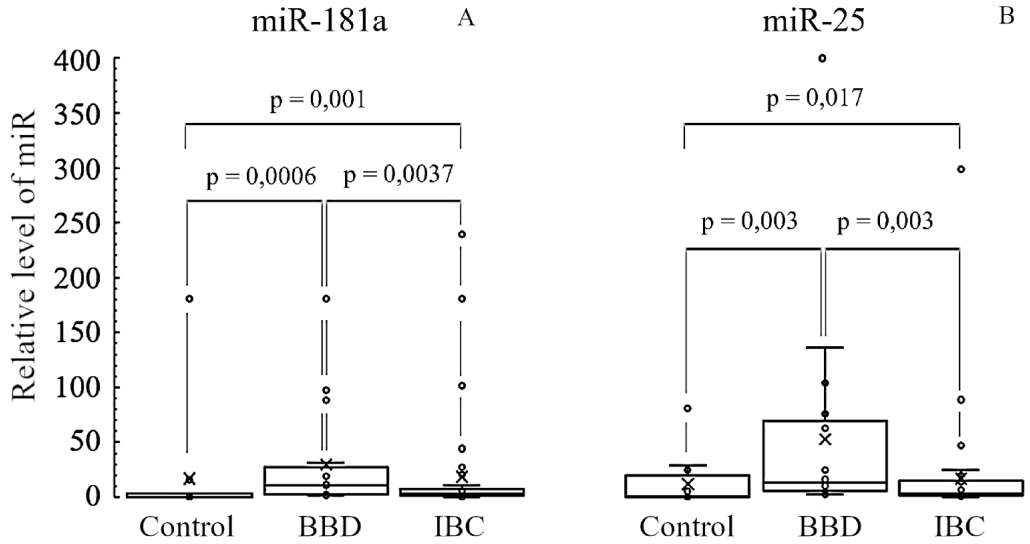

Figure 1. Serum levels of miR-181a (**A**) and miR-25 (**B**) in the control group and in patients with BBD and ICNT. Data are normalized to the level of *RNU6-1*.

the final step at 98°C for 10 min. After completion of the PCR, the droplets were read in a QX200 reader and analyzed using the Quantasoft™ software (Bio-Rad). The software measures the number of positive and negative droplets for each fluorophore in each sample and applies a Poisson algorithm to the fraction of positive droplets to determine the initial concentration of the target molecules in units of "target copies per microliter" ("copies/μl"). Each analysis included a no-template control. Data were normalized to the expression level of U6 small nuclear RNA, which served as an internal standard. The relative level values of miR-181a/RNU6-1 and miR-25/RNU6-1 were used in the statistical analysis. The reaction was carried out twice.

Statistical Analysis

Statistical processing of the results was carried out using the STATISTICA software package, SPSS v. 22.0 for Windows, and MS Excel. The mode of data distribution was determined using the Kolmogorov-Smirnov test with the Lilliefors correction. Independent groups were compared using the Kruskal-Wallis H test, followed by intergroup comparisons using the Mann-Whitney U test. The optimal cutoff value of miR-181a and miR-25 expression was performed using Receiver Operating Characteristic (ROC) analysis.

RESULTS AND DISCUSSION

We have compared the serum levels of miR-181a and miR-25 in patients with BBD, ICNT and also in conditionally healthy individuals, and analyzed ROC curves to assess the quality of the data obtained and determine threshold values of microRNAs that distinguish the presence or absence of pathology.

Evaluation performed using the Kruskal-Wallis test revealed statistically significant differences in miR-181a (p=0.0002) and miR-25 (p=0.0005) levels. Figure 1 shows the significance of differences between groups using the Mann-Whitney U test. Pairwise comparison showed that, the serum levels of miR-181a (Fig. 1A) and miR-25 (Fig. 1B) were higher in patients with BBD and ICNT as compared with the control group; BBD patients had higher levels of these miRs than ICNT patients

Figure 2 shows the differences between subgroups of ICNT patients with or without regional lymph node metastases. The relative level of miR-181a in these groups differed insignificantly, but the relative level of miR-25 was lower in the group of ICNT patients with metastases.

The ROC curve analysis was performed to determine the optimal cutoff values for serum miR-181a and miR-25, which could best indicate the presence of BDD, ICNT, and lymphogenous metastasis. The results are presented in Figure 3 and Table 3. It should be noted that the area under the ROC curve (AUC) of 0.680 for miR-181a in patients with BDD and ICNT (Fig. 3B), as well as AUC = 0.610 for miR-181a in patients with ICNT with and without lymphogenous metastasis (Fig. 3D) indicate the average quality of the model, which does not allow using the obtained data and identifying cut-off points.

The results of ROC analysis made it possible to evaluate the quality of the data obtained and to set threshold values for the levels of miR-181a and miR-25, separating datasets corresponding to the presence and absence of pathology in each studied pair. Additionally, selected threshold values (cut-off points) were tested using the Fisher's exact test. The miR level values equal to or above the cut-off point indicate the presence of BDD in comparison with healthy controls (miR-181a p=0.0006; miR-25 p=0.0020 by the Fisher's exact test), the presence of ICNT in comparison with healthy controls (miR-181a p=0.00003; miR-25 p=0.0025) and the presence of BDD in comparison with ICNT (miR-25 p=0.003). The miR-25 values equal to or below the cut-off point indicate the presence of lymphogenous metastases as compared to their absence in ICNT patients (miR-25 p=0.002 by Fisher's exact test).

The observed dynamics of changes in miR-181a and miR-25 may reflect the complexity of changes associated with the development of benign or malignant tumors. Both miRs have multiple (including divergent) effects on tumor initiation, development, and progression.

It can be assumed that in BDD, miR-181a plays the role of an antioncogene, targeting one of its known molecular targets, for example, proteins associated with autophagy [10] or PHLDA1 [4], which can be a mediator of apoptosis, proliferation, differentiation, and cell migration [22], or to an unknown molecular target. It can be assumed that in ICNT, possible pro-oncogenic activities of miR-181a may require a less pronounced increase in the miR-181a level. These results are partly consistent with the work by Guo and Zhang [23]; these authors found that miR-181a levels were significantly lower in patients with early-stage breast cancer (ductal carcinoma *in situ*, TNM I and II) as compared to healthy controls. We did not observe differences in miR-181 levels in patients with or without metastases in regional lymph nodes. This may indicate processes in cells acting in different directions at the level of miR-181 or technical difficulties in diagnosing invasion and metastasis at this stage of the disease.

In the future, it seems necessary to study the level of molecules — candidates for molecular targets of the studied miRs in patients with BDD and ICNT to verify our suggestions. The search for an unknown molecular target may be particularly relevant for miR-25. This miR is considered as predominantly pro-tumorigenic; however, although we observed an increase in serum miR-25 in ICNT patients as compared with healthy controls, the highest miR-25 level was observed in BBD patients. There is no information in the literature about the level of miR-25 in BDD patients. It can be assumed that the increased level of serum miR-25 found in these patients reflects the pathological processes of tissue proliferation in BBD. As for patients with malignant pathologies, on the one hand, increased expression of miR-25 can serve as a negative

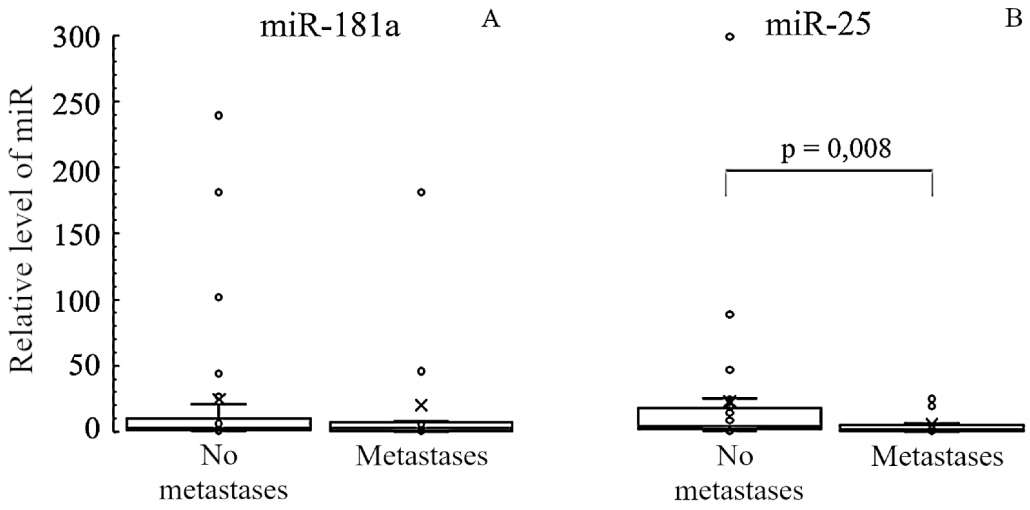

Figure 2. Serum levels of miR-181a (**A**) and miR-25 (**B**) in ICNT patients with or without metastases in regional lymph nodes. Data are normalized to the level of *RNU6-1*.

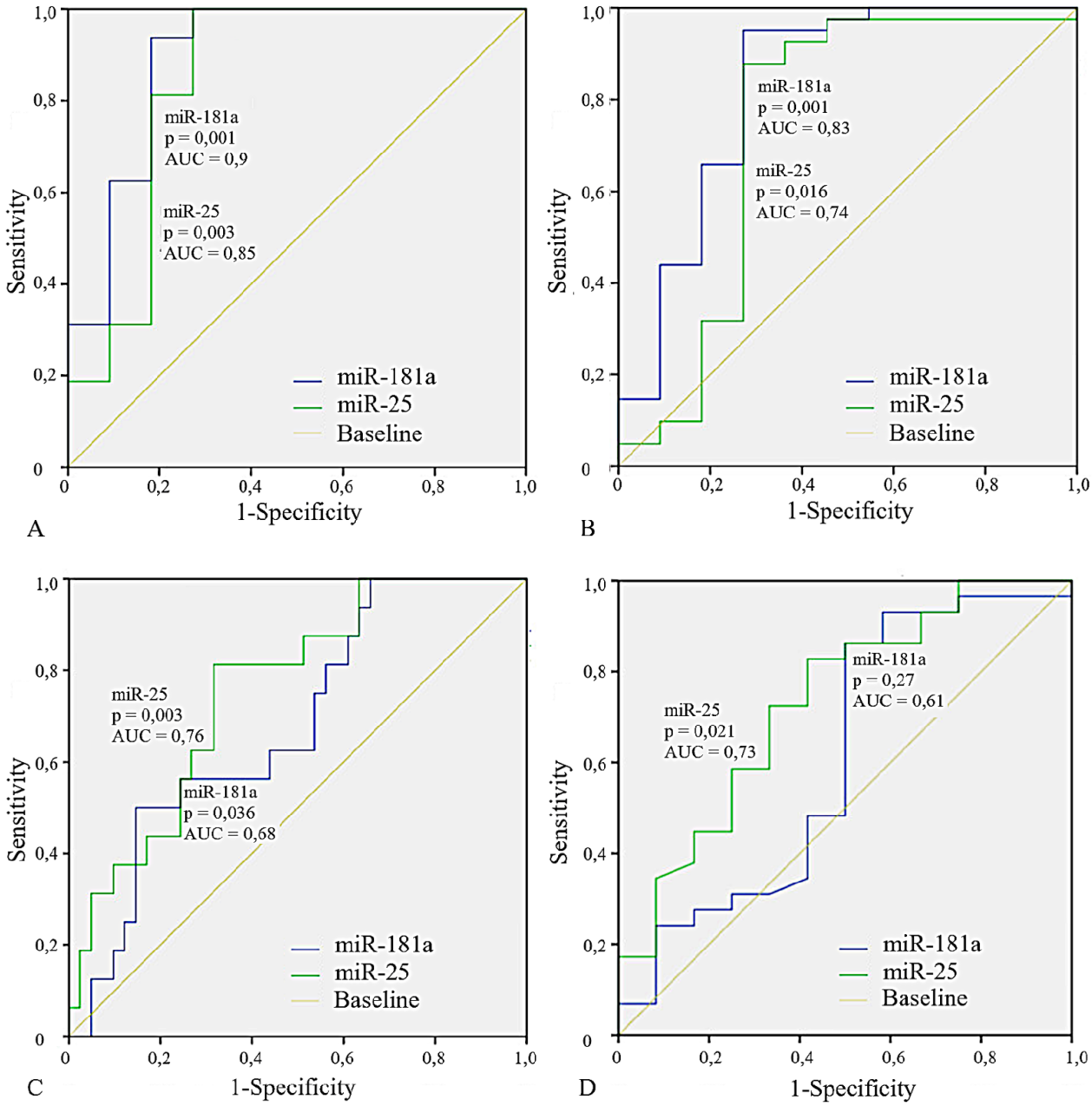

Figure 3. ROC curves obtained from ROC analysis of the serum levels of miR-181a and miR-25 in BBD patients and conditionally healthy controls (**A**), in ICNT patients and conditionally healthy controls (**B**), in patients with BBD and ICNT (**C**) and in patients with ICNT with and without lymphogenous metastases (**D**).

Table 3. Results of analysis of ROC curves for the expression of miR-181a and miR-25 in patients with breast diseases

Studied groups	miR	AUC	*p*	Sensitivity	Specificity	Optimal cut-off point
BBD and healthy control	miR-181a	0.90 (90%)	*p*=0.001	94%	82%	1.89
	miR-25	0.85 (85%)	*p*=0.003	81%	82%	5.51
ICNT and healthy control	miR-181a	0.83 (83%)	*p*=0.001	95%	73%	0.53
	miR-25	0.74 (74%)	*p*=0.016	88%	73%	0.91
BDD and ICNT	miR-25	0.76 (76%)	*p*=0.003	75%	69%	5.65
ICNT with and without lymphogenic metastases	miR-25	0.73 (73%)	*p*=0.021	83%	58%	2.10

Area under the curve (AUC) values: 0.9-1 – excellent model quality; 0.8-0.9 – very good quality of the model; 0.7-0.8 – good quality model; 0.6-0.7 – average quality of the model; 0.5-0.6 – unsatisfactory quality of the model.

prognostic factor, for example, in squamous cell carcinoma of the esophagus [24]. On the other hand, downregulation of miR-25 was observed in cisplatin-resistant cervical cancer cells with higher invasion and migration capacity. In contrast, overexpression of miR-25 in these cells suppressed tumor growth, Sema4C and Snail mRNA levels, and increased E-cadherin expression in mice as compared to the control group animals [25]. Considering that in our work, the level of miR-25 was reduced in patients with ICNT and metastases to lymph nodes as compared to ICNT patients without metastases, we can assume a mechanism similar to that observed in cervical cancer tissues and described by Song and Li [25].

In some cases, elevated levels of miR-181a and miR-25 may reflect a precancerous process. For example, miR-181a and miR-25 were identified in a 6-miR expression signature that predicts the status of BRCA1/2 mutations, for which standard testing can produce false negative results [26]. Our results support the viewpoint that increased miR-181a and miR-25 may be a signal for more careful detection of possible BRCA1/2 mutations.

CONCLUSIONS

Although molecular biomarkers play an important role in the early detection of diseases and treatment of patients, sensitive and specific markers for detecting cancer at early stages, as well as for identifying the risk of malignancy in benign tumors, are still absent.

In this context circulating miRs may be of great importance as potential biomarkers. We have found an increased serum level of miR-181a and miR-25 in patients with breast diseases, and the highest level of the studied miRs was observed in BBD patients. No clinically significant molecular/genetic abnormalities are known in BBD patients [2]. In this regard, the results obtained in this study may be used for the development of a diagnostic panel of precancerous changes based on miRs. In patients with ICNT, the serum levels of miR-181a and miR-25 may reflect both favorable and unfavorable processes in the tumor due to the multiple effects of the studied miRs. They can influence expression of several genes and simultaneously influence several targets, pathways and processes, including number of multidirectional effects on tumor progression. These targets may be modulated by other miRs, and autoregulatory loops are likely to exist.

The expression profile of single miRs does not have a stable diagnostic potential for BC [27]. The use of miR-181a and miR-25 as markers seems possible only within the framework of a large diagnostic panel, which may include miR-181a and miR-25, as well as their target genes. Such panel has yet to be developed.

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COMPLIANCE WITH ETHICAL STANDARDS

The study was conducted in accordance with the World Medical Association Declaration of Helsinki 1964 as amended in 2013 at the 64th WMAJ General Assembly (Fortaleza, Brazil, October 2013). All patients gave their voluntary informed consent to participate in the study. The study protocol was approved by the Ethics Committee at the Research Institute of Molecular Biology and Biophysics, Federal Research Center for Fundamental and Translational Medicine (Protocol No. 17 of June 2023).

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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МикроРНК miR-181a И miR-25 В СЫВОРОТКЕ КРОВИ ПАЦИЕНТОВ СО ЗЛОКАЧЕСТВЕННЫМИ И ДОБРОКАЧЕСТВЕННЫМИ ЗАБОЛЕВАНИЯМИ МОЛОЧНОЙ ЖЕЛЕЗЫ

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Опухолевые заболевания молочной железы включают широкий спектр патологий, требующих разных подходов к лечению. Уровни микроРНК (miR), отражающие регуляцию экспрессии генов, вовлечённых в онкогенез, могут быть диагностическими и прогностическими маркерами заболеваний молочной железы. Измеряли уровень циркулирующих miR-181a и miR-25 у пациентов с доброкачественными заболеваниями молочной железы (ДЗМЖ), а также инвазивной карциномой неспецифического типа (ИКНТ) и у условно-здоровых лиц. Экспрессия обеих miR была выше у пациентов обеих групп по сравнению с контролем; при этом содержание miR-181a и miR-25 в сыворотке крови пациентов с ДЗМЖ было выше, чем у пациентов с ИКНТ. Обнаруженные изменения могут представлять интерес в контексте предраковых изменений при ДЗМЖ. Представляется возможным их использование в будущем в качестве маркеров патологического процесса в рамках большой диагностической панели.

Полный текст статьи на русском языке доступен на сайте журнала (http://pbmc.ibmc.msk.ru).

Ключевые слова: miR-181a; miR-25; рак молочной железы; доброкачественные заболевания молочной железы

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