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Short Communication

Exosomal miRNA-146a is downregulated in clear cell renal cell carcinoma patients with severe immune-related adverse events

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ABSTRACT

Here we report the results of the pilot project of exosomal miRNA expression levels in clear cell renal cell carcinoma (ccRCC) patients with different clinical response to ICIs (nivolumab) and treatment related toxicity. Immune-related adverse events (irAEs) are a major cause of immune checkpoint inhibitors cancellation and therapy failure. Modern studies demonstrate evidence that exosomes are of great importance in the formation of tumor resistance to ICIs drugs and therapy. We performed exosomal miRNA-146a expression analysis using qPCR on 86 ccRCC patients and revealed a statistically significant ($p = 0.01$) decreased expression level in ccRCC patients with CTCAE grade 3–4 (M±SEM 1.71 ± 0.13) compared to CTCAE grade 0–2 group (M±SEM 2.30 ± 0.24). The expression levels of miRNA-126, miRNA-218 and miRNA-410 did not show statistically significant differences in the comparison groups ($p > 0.05$). Association analysis of rs2910164 in the miRNA-146a gene demonstrated that *CC* genotype and *C* allele carriers had higher risk of developing severe irAEs ($p = 0.03$, OR = 6.12; $p = 0.01$, OR = 2.42, respectively) compare with *GG* and *GC* carriers. That is the first attempt to identify biomarkers of ICIs treatment efficacy for ccRCC in the Volga-Ural region based on exosomal miRNAs analysis.

1. Introduction

Renal cancer (RC) is a heterogeneous group of malignant tumors, the vast majority of which are renal cell carcinomas of various morphological types. The most common is clear cell carcinoma renal cell carcinoma (ccRCC), representing up to 85% of all kidney tumors [1].

Radical nephrectomy is considered to be the main method of renal cell carcinoma treatment; at the same time, RCC is highly resistant to chemotherapy and has a poor response to hormonal treatment, while the effectiveness of cytokine therapy (interleukin 2, interferon alfa) is quiet modest [2]. Immune checkpoint inhibitors have significantly improved overall survival, but the effectiveness of this group of drugs varies greatly, up to complete resistance in some patients. In addition, the use of ICI is often accompanied by a wide range of serious adverse events and is costly to the health care system, making it critical to identify biomarkers that can more accurately predict treatment outcome [3].

One of the modern methods that can overcome this problem is the determination of circulating nucleic acids - DNA and RNA - that have entered the systemic circulation. The sources of extracellular nucleic acids in the systemic circulation can be the processes of necrosis, apoptosis [4], as well as active secretion of nucleic acids into the extracellular environment [5]. Exosomes are microvesicles 30–100 nm in size, produced by cells into the environment and containing a whole range of biologically active molecules, including various types of RNA, DNA, proteins and lipids [6]. Thus, the content of exosomes may reflect the events occurring in the original cells [7]. In addition, modern studies demonstrate evidence that exosomes are of great importance in the formation of tumor resistance to drugs and radiotherapy [8–10]. Such features make exosomes potential biomarkers for minimally invasive, so-called liquid biopsy, and the use of exosome content analysis has clear prospects for early diagnosis of malignant tumors and evaluation of the effectiveness of the therapy used. Of particular interest in connection with the immunotherapy of oncopathology are microRNAs (miRNAs) that could directly and indirectly control the expression of immune checkpoint receptors. MiRNAs that are part of exosomes can be absorbed by neighboring and distant cells and, as a result, have a modulating

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effect on recipient cells [11]. It was previously shown that miRNAs in extracellular vesicles are involved in communication between macrophages and resident cells, which can cause damage to resident [12] cells. Previously, it was shown that *PD-L1* expression can be regulated by a number of miRNAs, such as miRNA-34a, miRNA-200 family, miRNA-197, miRNA-513, miRNA-570, and miRNA-138-5p [13].

Here we report the preliminary results of the pilot project of exosomal miRNA expression levels in clear cell renal cell carcinoma (ccRCC) patients with different clinical response to ICIs (nivolumab) and treatment related toxicity.

2. Materials and methods

2.1. Study setting and population

The study includes 86 patients with clear cell renal cell carcinoma treated with nivolumab, from them 51 has effective response on therapy and 35 has low response on it. The criterion for inclusion of patients in the study was a histologically confirmed diagnosis of clear cell renal cell carcinoma. All the patients were treated with second-line nivolumab. The exclusion criteria for patients were receiving radio- and chemotherapy prior to sampling, renal carcinomas of other histological types, the presence of other malignant neoplasms in the family history, urinary tract infections, and urolithiasis. Adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 [14].

Sampling of venous blood samples from patients after a 4-weeks period with nivolumab treatment was carried out by employees of the Republican Clinical Oncological Dispensary, Departments of Oncology and Urology of the Clinic of Bashkir State Medical University. Informed consent was obtained from each patient for the collection of biological material and molecular genetic studies.

2.2. Exosome and RNA isolation, reverse transcription-quantitative PCR

Exosomes were isolated from blood plasma obtained by double centrifugation at 4° Celsius (10 min at 1900 g and 15 min at 3000 g). The resulting plasma and tissue samples are stored at −70° Celsius until the exosome and miRNA isolation step.

Total RNA was isolated from 1 ml of filtered blood plasma using the exoRNeasy Midi Kit (Qiagen, Germany) according to the manufacturer's protocol. Based on the total RNA of the samples, cDNA was obtained using reverse transcriptase and miRCURY LNA RT Kit (Qiagen, Germany). Quantitative real-time PCR was performed using the miRCURY LNA SYBR Green PCR Kit (Qiagen, Germany) and the LightCycler96 real-time PCR product detection system (Roche). For the detection of control and target miRNAs, commercial kits of primers and probes miRCURY LNA miRNA PCR Assay (Qiagen, Germany) were used. At the stage of validation, miRNA-16 was used as reference genes (endogenous control). Exogenous controls for isolation and reverse transcription and amplification included artificially synthesized molecules UniSp2, UniSp4, UniSp5, UniSp6, resembling in structure, but not similar in sequence to miRNA, as well as synthetic cel-miRNA-39 (RNA Spike-In Kit, For RT (Qiagen, Germany)).

2.3. Genotyping of rs2910164

It has been shown that the functional polymorphism rs2910164 located within the mature miRNA-146a causes a decrease in its expression and, as a result, silencing of target genes [15]. The association of the rs2910164 polymorphism in miRNA-146a with the development of malignant tumors has been well documented in many studies of various cancer types, such as lung cancer, hepatocellular carcinoma, gastric cancer, nasopharyngeal cancer, and others. However, the results of these studies are controversial [16]. In addition, an association between response to chemotherapy and carriage of a particular rs2910164 genotype has been demonstrated in lung cancer [17], esophageal squamous cell carcinoma [18]. Thus, we suggested possible association of rs2910164 with developing severe irAEs in ccRCC patients treated with nivolumab.

Genotyping of rs2910164 in miRNA-146a was performed as describe recently in Ref. [19]. Genomic DNA was extracted from 7 mL peripheral blood sample collected from each subject by phenol-chloroform extraction. Genotyping was performed using a TaqMan PCR allelic discrimination method with a LightCycler96 (Roche) instrument according to the manufacturer's instructions. For all genotypes, the assay success rate was >99%, and the repeated samples' results were 100% concordant.

2.4. Statistical analysis

To quantify gene expression, the 2-ΔΔCt method was used, based on the fact that the difference in the value of the "threshold cycle" (ΔCt) between the gene under study and the control gene is proportional to the level of relative expression of the gene under study. When comparing groups on a quantitative basis, the equality of the variances of the distributions of signs was checked using the Mann-Whitney *U* test. ANOVA and Kruskal–Wallis tests were used for the comparisons of genes expression levels between rs2910164 genotypes for the normally distributed and for the nonparametric data, respectively. Calculations were made using GraphPad Prism 6.07 software (California, USA).

The chi-square test ($\chi 2$) was used to evaluate the Hardy-Weinberg equilibrium (HWE) in allele and genotype frequencies. Differences between comparison groups were assessed using the chi-square test ($\chi 2$). The assessment of the risk of developing severe irAEs, taking into account the carriage of a certain genotype or allele of the polymorphism, was carried out using the odds ratio (OR) with their 95% confidence intervals (CI). Two-tailed $p < 0.05$ was considered to be statistically significant.

3. Results

3.1. Patient characteristics

A total of 86 patients were included in this study. The median age was 60 years (range = 38–81 years). The cohort comprised 66 (76.74%) male and 20 (23.26%) female. All patients have clear cell histological type of renal cell carcinoma and received nivolumab as second-line therapy. The median number of treatment cycles of nivolumab was 16 (range = 5–26 cycles). Table 1 summarizes the patients' clinical features.

The incidence of irAEs is presented in Table 2. Eighty-four patients out of 86 patients included in the study showed irAEs of any grade. The most common irAEs involved endocrine-related events, diarrhea/colitis and skin-related events.

Table 1
Baseline patient characteristics.

Age, years	N° of patients	%
Median	60	
Range	38–81	
Gender		
Male	66	76.74
Female	20	23.26
Histology		
Clear cell	86	100.00
Non-clear cell	0	0
IMDC risk classification		
Favorable	0	0
Intermediate	59	68.60
Poor	27	31.40

IMDC: International Metastatic Renal Cell Carcinoma Database Consortium.

Table 2
Observed irAEs according to category and grade.

	Grading, Number of patients	
Category	Grade 0-2	Grade 3-4
	n (%)	n (%)
Skin-related events	10 (19.60)	5 (14.30)
Pneumonitis	3 (5.90)	5 (14.30)
Diarrhea/colitis	9 (17.60)	8 (22.90)
Endocrine-related events	20 (39.20)	6 (17.10)
Pancreatitis	1 (1.90)	5 (14.30)
Hepatitis	6 (11.70)	1 (2.90)
Nephritis	1 (1.90)	0
Myalgia	1 (1.90)	0
Joint pain	1 (1.90)	0
Others	0	5 (14.30)

3.2. Differential expression of miRNA

The analysis revealed a statistically significant ($p = 0.01$) decrease in the expression level of miRNA-146a in patients with CTCAE grade 3–4 (M±SEM 1.71 ± 0.13) compared to CTCAE grade 0–2 group (M±SEM 2.30 ± 0.24) (Fig. 1a). The expression levels of miRNA-126, miRNA-218 and miRNA-410 did not show statistically significant differences in the comparison groups ($p > 0.05$) (Fig. 1b, c, d).

3.3. Genotyping of rs2910164

Association analysis of rs2910164 in miRNA-146a has demonstrated that *CC* genotype and *C* allele carriers had higher risk of developing severe irAEs ($p = 0.03$, OR = 6.12; $p = 0.013$, OR = 2.42, respectively) compared to GG and GC carriers (Table 3).

In addition the level of miRNA-146a expression was evaluated depending on the rs2910164 genotypes. It was shown that expression in the *CC* genotype groups was significantly lower ($p < 0.01$) compared with *GG* and *GC* carriers (Fig. 2).

Table 3
Association analysis of rs2910164 in ccRCC patients with immune-related adverse events after nivolumab treatment.

Variables	CTCAE grade 0-2 (n = 51) n (%)	CTCAE grade 3-4 (n = 35) n (%)	χ^2	OR	95% CI	p-value
GG genotype	34 (67)	17 (49)	2.11	0.47	0.19–1.14	0.47
GC genotype	15 (28.8)	11 (30)	0.00	1.00	–	1.00
CC genotype	2 (4.2)	7 (21)	4.13	6.12	1.19–31.53	0.028
G allele	83 (81.4)	45 (64.3)	5.5	0.41	0.21–0.82	0.013
C allele	19 (18.6)	25 (35.7)		2.42	1.2–4.8	

4. Discussion

It has been previously shown that miRNA-146a has reduced expression levels in tumor tissues of prostate cancer patients, stomach, liver, lungs, etc. [20]. It is known that activation of miRNA-146a expression results in inhibition of cell proliferation, invasion and angiogenesis by targeting *EGFR*, *RAF6*, *CCND1/2*, *Notch1* or *Rac1*, causes cell apoptosis and increased chemosensitivity [21]. In addition, the ability of miRNA-146a to regulate tumor-induced inflammation has been demonstrated [22]. In ovarian cancer exosome miRNA-146a demonstrated the ability to reduce the chemo-resistance via the PI3K/Akt signaling pathway [23]. Another study showed that the expression of miRNA-146a had a significant effect on the survival rates

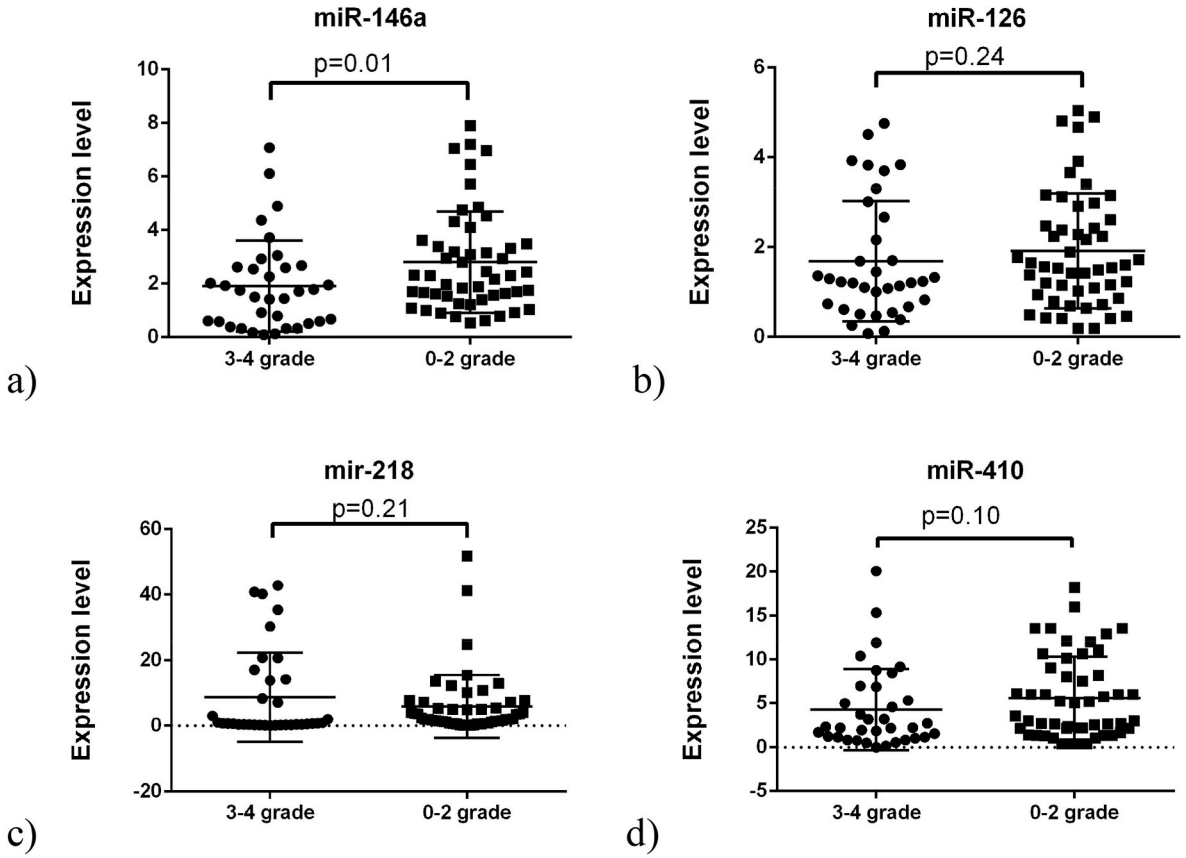

Fig. 1. Expression level of exosomal miRNAs in clear cell renal cell carcinoma patients with different grade of immune-related adverse events after second-line nivolumab therapy.

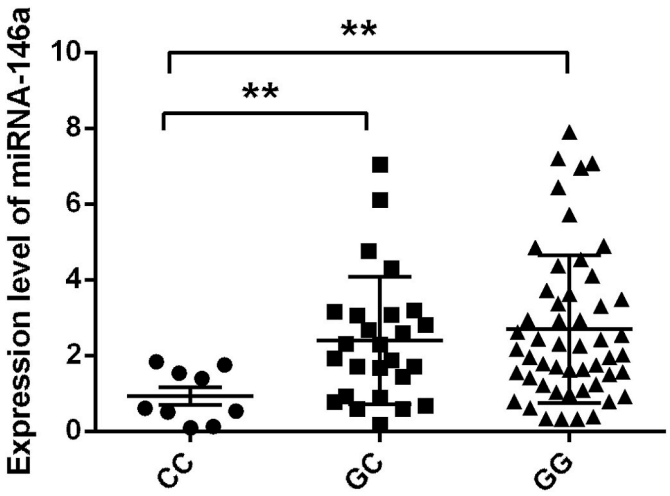

Fig. 2. Expression level of miRNA-146a in each rs2910164 genotype group of ccRCC patients. ** - p-value<0.01.

of patients with advanced gastric cancer. Patients with high expression levels of miRNA-146a had significantly higher survival rates, compared with patients with low expression levels of miRNA-146a. In addition, the expression level of miRNA-146a had a correlation with chemotherapeutic sensitivity and demonstrated the highest level in patients with complete remission compare to disease progression group [24]. Thus, miRNA-146a can function as a tumor suppressor gene.

On the other hand it was shown that miRNA-146a may act as oncogenic factor. For example, in bladder cancer miRNA-146a was upregulated and promoted invasion, migration, and proliferation of cells of bladder cancer cell lines [25]. Overexpression of miRNA-146a is also reported in papillary thyroid carcinoma, the highly metastatic human breast cancer cell line MDA-MB-231, and cervical cancer tissues, leading to remarkable downregulation of *IRAK1* and *TRAF6*, inhibiting nuclear factor-κB (NF-κB) activity [26]. IRAK1 is one of the serine/threonine protein kinases, capable of activating the Toll interleukin receptor (TIR) NF-κB. In turn, promoted NF-κB upregulates of pro-inflammatory cytokines such as IL-6, tissue-degrading matrix metalloproteinases, TNF-α, IL-8, and chemokines [27]. Upregulation of miRNA-146a was previously described to play an important role in enhancing immune suppression through increasing the regulatory T cells' population and could modulating drug resistance of tumor cells [28].

Moreover miRNA-146a was identified as a crucial miRNA regulating irAE severity of ICI therapy. MiRNA-146a as it was suggested could regulate IFN-γ and perforin production in T cells thereby ameliorating irAE severity. Interestingly that treatment with the miRNA-146a mimic effectively reduced irAE severity, providing evidence that miRNA-146a replacement therapy might be effective in patients with severe irAEs. In addition the miRNA-146a SNP rs2910164 CC genotype in patients with solid tumors treated with checkpoint inhibitors was identified as perspective prognostic marker for ICI therapy effectiveness estimating [29]. In contrast to this finding it was shown that rs2910164 GC and *GG* genotypes were associated with a poorer survival rate among RCC patients compared to patients with the *CC* genotype [30].

It is known that rs2910164 in miRNA-146a affects the level of expression of this miRNA, which in turn leads to a change in the regulation of its target genes [31]. It was previously shown that the replacement of *G* by *C* is accompanied by a decrease in free energy, which indicates a less stable structure of the C allele compared to the *G* allele [32]. It was also found that the miRNA-146a precursor carrying the *G* rs2910164 allele demonstrates higher levels of mature miRNA production [33].

Recently it was shown that miRNA-146a is upregulated in ccRCC tumor and could accelerate the progression of disease by targeting tumor suppressor *CADM2* [34]. At the same time miRNA-146a was described to be downregulated in metastatic primary ccRCC compared to non-metastatic tumors. It was demonstrated that miRNA-146a have two potential targets *CXCL8* and *UHRF1*, which could promote cancer progression and metastasis [21]. Moreover miRNA-146a-5p may globally affect the expression of genes involved in key metabolic pathways in RCC such as those associated with the pentose-phosphate pathway [35], and simultaneously and oppositely regulate the tumor cell expression of the inflammatory response mediators [36].

5. Conclusion

That is the first attempt to identify biomarkers of ICIs treatment efficacy for ccRCC in the Volga-Ural region based on exosomal miRNAs analysis. At this stage of the work, we can talk about the potential role of miRNA-146a in the regulation of adverse events in patients with clear cell renal cell carcinoma. Besides, it seems possible to use the rs2910164 in miRNA-146a as an additional molecular marker to assess the possible efficacy of ICIs in ccRCC patients from the Volga-Ural region.

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Institutional review board statement

The current study was performed according to the ethical standards of Bioethics Committee developed the Declaration of Helsinki of the World Association "The ethical principles of medical research involving human subjects" and approved by the Research Ethics Committee of the Institute of Biochemistry and Genetics - Subdivision of the Ufa Federal Research Centre of the Russian Academy of Sciences. A signed informed consent was collected from every study participant who agreed to participate in the study.

CRediT authorship contribution statement

E. Ivanova: Formal analysis, Investigation, Writing – original draft. **D. Asadullina:** Investigation. **R. Rakhimov:** Resources, Methodology. **A. Izmailov:** Resources, Methodology, Conceptualization. **Al. Izmailov:** Resources. **G. Gilyazova:** Investigation. **Sh. Galimov:** Conceptualization. **V. Pavlov:** Conceptualization, Writing – review & editing. **E. Khusnutdinova:** Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare no conflicts of interest.

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