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

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Introduction

Immune checkpoint inhibitor (ICI) therapy has shown a significant benefit in the treatment of clear cell renal cell carcinoma (ccRCC). However, immune-related adverse events (irAEs) occur frequently and can lead to ICI treatment termination.

A better understanding of the pathogenesis of irAEs could help to identify robust biomarkers predicting ICI toxicity. Recent studies have constantly demonstrated that microRNAs (miRNAs) could become suitable biomarkers for ICIs treatment response.

Objectives

We aimed to evaluate exosomal miRNA expression levels in ccRCC patients with different clinical response to ICIs (nivolumab) and treatment related toxicity.

Methodology

The study includes 86 ccRCC patients treated with nivolumab: 51 patients 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.

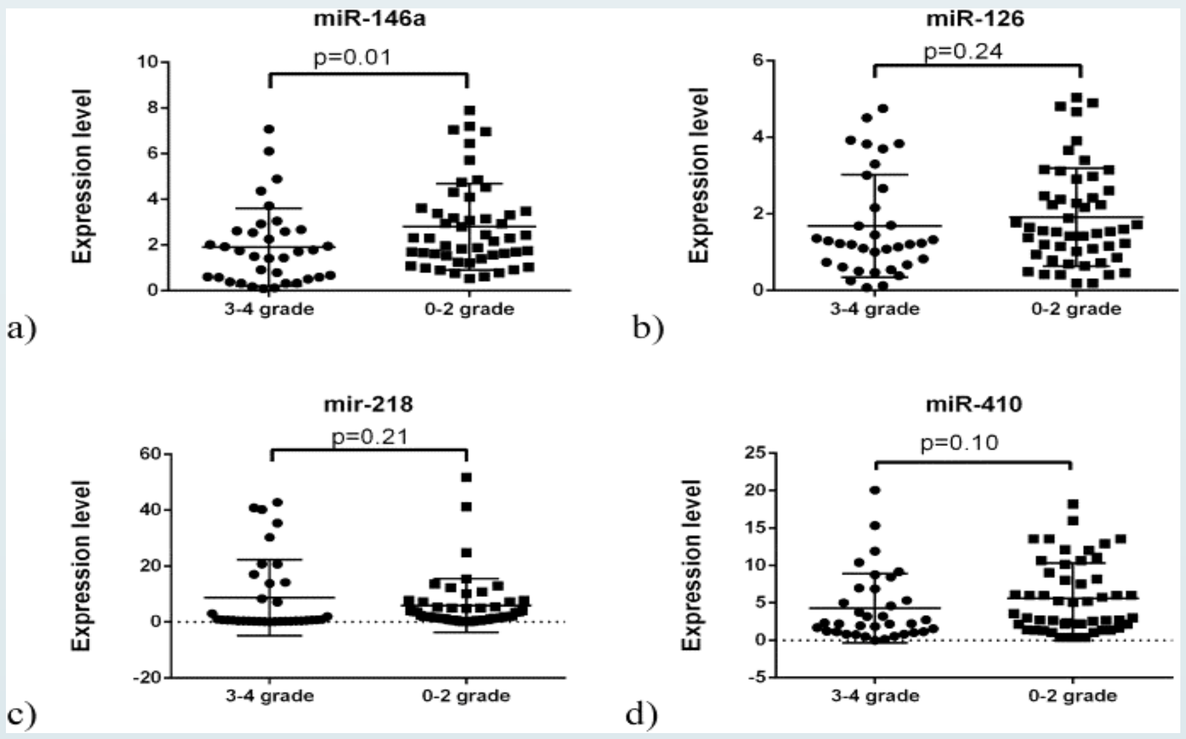

Fig. 1. Expression levels of exosomal miRNAs in clear cell renal cell carcinoma patients with different grades of immune-related adverse events after second-line nivolumab therapy. 0

Results

Exosomal miRNA expression analysis

We performed exosomal miRNA-146a expression analysis using qPCR on 86 ccRCC patients and revealed a statistically significant ($p = 0.01$) decreased expression level of miRNA-146 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 difference in the comparison groups ($p > 0.05$).

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

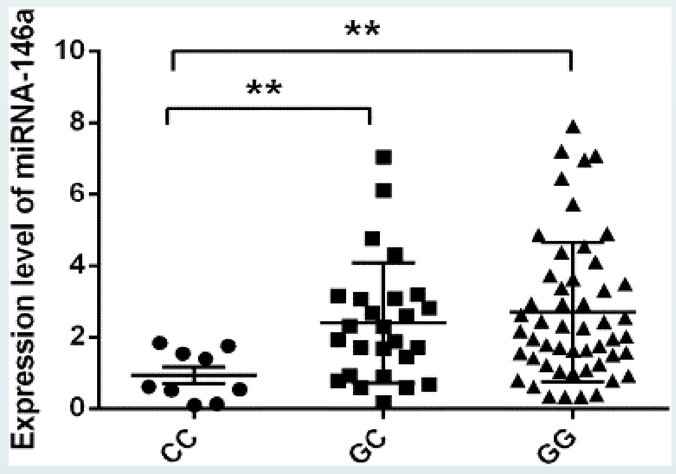

Fig. 2. Expression level of miRNA-146a in each rs2910164 genotype group of ccRCC patients. ** - p-value<0.01.

Conclusion

We analyzed the expression level of miRNA-146a and an effect of SNP rs2910164 in the miRNA-146a on irAE severity in ccRCC patients treated with ICIs and found that the SNP rs2910164*CC genotype led to reduced miR-146a expression, and it is associated with an increased risk of developing severe irAEs. According to the results expression levels of miRNA-146a and rs2910164 may be biomarkers to predict severe irAE development in ICI-treated patients.