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Original Article

Influence of miR-9 on inflammatory factors and VEGF expression in acute kidney injury

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Abstract: Objective: To explore the effects of down-regulating miR-9 on the levels of inflammatory factors and vascular endothelial growth factor (VEGF) in acute kidney injury (AKI). Methods: A total of 60 Sprague Dawley rats were assigned equally into three groups: sham group, AKI group, and miR-9 inhibitor group. AKI was established by 50% glycerol injection intramuscularly. MiR-9 inhibitor was given intravenous as a tail injection immediately after glycerol injection and administered daily. Histological changes, renal function, VEGF expression, inflammatory factor levels, and oxidative stress status were compared among three groups. Results: Compared to sham group, there was widespread destruction with renal tubular swelling, renal tubular epithelial cell edema, glomerular hypertrophy and sever interstitial inflammatory infiltration in the AKI group. In contrast to sham group, the levels of cystatin C (CysC), serum creatinine (Scr), blood urea nitrogen (BUN), miR-9 expression, tumor necrosis factor-alpha (TNF-α), interleukin 6 (IL-6), c-reactive protein (CRP) and malondialdehyde (MDA) were significantly increased, and the levels of VEGF and Superoxide dismutase (SOD) were markedly decreased in the AKI group, and there were remarkable statistical differences (all P<0.001). Compared with the AKI group, the severity of renal lesions and renal tubular injury was significantly relieved in the miR-9 inhibitor group. In addition, the miR-9 inhibitor group showed significantly lower levels of CysC, Scr, BUN, miR-9 expression, TNF-α, IL-6, CRP and MDA and higher levels of VEGF and SOD in contrast to the AKI group, and there were significant statistical differences among the groups (all P<0.001). Conclusions: miR-9 is up-regulated in AKI and inhibition of miR-9 has potential renal protective effects for AKI, possibly due to up-regulated VEGF expression and anti-inflammatory factors.

Keywords: miR-9, acute kidney injury, VEGF, inflammation, renal protection

Introduction

Acute kidney injury (AKI) is a common critical disease characterized by a rapid decline of renal function, which seriously threatens the physical and psychological health of patients [1]. The main causes of AKI include rhabdomyolysis, hemorrhagic shock, and severe dehydration and so on. It is reported that rhabdomyolysis-induced AKI represents about 10%-40% of all diagnosed AKI cases [2]. In clinical practice, AKI is predominantly diagnosed by elevated levels of Cystatin C, blood urea nitrogen and serum creatinine and decreased urine outflow [3]. According to the epidemiological investigation, the mortality of AKI remains very high at about 50% [4]. So far, there are no effective methods to prevent and treat AKI.

Experimental AKI induced by glycerol injection is the most commonly used animal model of rhabdomyolysis-induced AKI [5]. It is reported that numerous genes and multiple signaling pathways are involved in endothelial dysfunction and inflammatory responses are up-regulated or activated [6]. In the injured kidney, numerous inflammatory factors such as Tumor necrosis factor-alpha (TNF-α), interleukin 6 (IL-6) and C-reactive protein (CRP), are up-regulated and produced in renal tissues [7]. In addition, some studies demonstrated that oxidative stress is also a main cause for the pathogenesis of AKI [8]. Superoxide dismutase (SOD) and malondialdehyde (MDA) are the representative biomarker for oxidative stress. VEGF also contributes to the development of AKI and it has been confirmed that VEGF expression can promote the survival of kidney epithelial cells [9]. At present, there is still little known about the detailed mechanism responsible for rhabdomyolysis-induced AKI.

Recently, microRNAs have become one of the hot biomolecules studied in many cellular phys-

iological functions. It is reported that an imbalance in microRNA synthesis may lead pathological states [10]. During the development of AKI, some microRNAs appear to act protectively and others may act pathogenically [11, 12]. However, the role of miR-9 in the development of AKI has not been reported. Previous studies showed that miR-9 was up-regulated in some tumors such as gastric cancer [13] and liver cancer [14], while it was down-regulated in other tumors such as nasopharynx cancer [15] and colon cancer [16]. It was also reported that miR-9 expression is involved in inflammatory responses in body [17]. In this study, we investigate the effect of miR-9 inhibition on rhabdomyolysis-induced AKI and the potential mechanisms involved. The results of this research would provide the experimental foundation for new ideas in treatment of AKI.

Materials and methods

Reagents and instruments

Mirvana™ miRNA Isolation Kit was obtained from American Thermo Fisher Scientific Inc. TaqMan MicroRNA reverse transcription kit was purchased from American Life technologies Corporation. Rabbit-anti-rat VEGF antibody and GAPDH antibody were purchased from Santa Cruz. Detection Kits of Cystatin C, urea nitrogen and creatinine were obtained from Swiss Roche Group. ELISA Kits of Tumor necrosis factor-alpha (TNF-α), interleukin 6 (IL-6) and C-reactive protein (CRP) were purchased from American R&D Systems. Detection Kits of superoxide dismutase (SOD) and malondialdehyde (MDA) were obtained from American Sigma Company. Hitachi 7600 type automatic biochemical analyzer was purchased from Japanese Hitachi Limited Corporation. Light microscope was purchased from Japanese Olympus Corp.

AKI animal model

The animal experiments were approved by the ethics committee of Zhuji People's Hospital and all the experiments were conducted in accordance with the guidelines established by Zhuji People's Hospital for animal experimentation. A total of 60 adult male Sprague-dawley (SD) rats that weighed 200-250 g were kept in an environment with controlled temperature (20°C-22°C) and a 12-hour light-dark cycle and provided with tap water and standard chow ad libitum. After fasting and water deprivation for 24 h, these rats underwent a 50% glycerol-induced rhabdomyolysis model of AKI. According to the methods described previously [18], rats underwent anesthesia using 10% chloral hydrate solution and then they were injected with 50% glycerol (6 ml/kg) to both hind legs intramuscularly. The sham group was injected with normal saline as a control. To detect the effect of miR-9 inhibitor on AKI, miR-9 inhibitor was given intravenous injection via the tail vein immediately after glycerol injection that was administered daily. These rats were selected as the miR-9 inhibitor group. There were 20 rats in each group.

Specimen collection

After glycerol injection, the rats were placed in cages for 48 h. Then, the animals were anesthetized using intraperitoneal injection of 10% chloral hydrate solution for blood and kidney specimens. Blood samples were collected from the inferior vena and serum was obtained by 4000 r/min centrifugation for 5 min. These serum samples were stored at -80°C. The kidneys were harvested after bilateral kidneys lavage via abdominal aorta injection of phosphate buffer saline solution. Then, the kidneys were immediately stored in liquid nitrogen for protein analysis and histological examination.

qPCR detection

Total miRNAs from kidney tissues were extracted according to the instructions of a mirvana™ miRNA Isolation Kit. The above miRNAs were reversely transcribed into complementary cDNA via TaqMan MicroRNA reverse transcription kit, and quantitative real-time polymerase chain reaction was conducted using TaqMan probes. miR-9 upstream primer: 5'-ATAAAGCTAGATAACCGAAAGT-3', miR-9 downstream primer: 5'-TTGGGGTGCTCGTGCAGATCGAA-3'. Internal reference U6 upstream primer: 5'-CTCGCTTCGGCAGCACA-3', Internal reference U6 downstream primer: 5'-AACGCTTCACGAATTTGCGT-3', After mixture of the reaction system, the reaction requirements were performed as follows: pre denaturation 10 min in 95°C, denaturation 30 s in 95°C, annealing 1 min at 60°C, extension 2 min at 68°C, a total of 40 cycles. ABI 7300 System software was applied to analyze the gene amplification conditions and the corresponding Ct value was calculated. The copy number of PCR templates was corrected through U6 as a control. At last, the relative expression amount of gene was obtained by 2-ΔΔCt method.

Western blot

The protein lysis RIPA buffer was added after kidney fragments were homogenized, and the total tissue proteins were extracted. The protein concentration was detected by the BCA protein determination method. SDS-PAGE gel electrophoresis was conducted to separate the total extracted proteins. Then, these separated proteins were transferred to a PVDF membrane. Next, the membrane underwent immunoblot analyses with the primary polyclonal antibodies against VEGF. Then the PVDF membrane was incubated with an anti-rabbit secondary antibody. ECL luminescence reagent was used for color development. The signals were detected using Gel imaging system in chemical exposure mode. GAPDH was selected as internal reference.

Hematoxylin-eosin (H&E) staining

Kidney tissues were fixed in 4% neutral formalin for 24 h and then embedded in paraffin. Using a microtome, 3-μm sections were obtained from each paraffin block. They were stained with hematoxylin and eosin reported by previous studies [19]. These samples were immersed in xylene and alcohol, respectively. Then, they were stained with hematoxylin for 3 min and eosin for 1 min. Next, they were immersed in alcohol and xylene again. Finally, a synthetic resin was applied for mounting slides. Slides were observed under a light microscope.

Renal function analysis

The serological levels of Cystatin C (CysC), urea nitrogen, and creatinine were detected in automatic biochemical analyzer using commercially available kits according to the manufacturer's instructions.

Inflammatory factor assay

The renal quantification of tumor necrosis factor-alpha, interleukin 6 and C-reactive protein were examined by ELISA methods based on the manufacturer's protocols.

Oxidative stress status assay

The levels of SOD and MDA in kidney tissues were assessed by commercially available detection Kits according to the manufacturer's instructions.

Statistical analysis

SPSS 21.0 software was used for the statistical analysis. The measurement data was expressed by Mean ± Standard Deviation (SD). Differences among groups were analyzed using One-way analysis of variance (ANOVA) test followed by Bonferronni's post hoc analysis. The enumeration data was presented as percentage. Differences among groups were examined by Chi-square test. $P<0.05$ indicated that the statistical difference was significant.

Results

Comparison of renal function

As seen in **Figure 1**, compared with those in the sham group, the levels of CysC, blood urea nitrogen (BUN), and serum creatinine (Scr) in the AKI group and miR-9 inhibitor group were significantly higher, and there were statistical differences between groups (all $P<0.001$). The levels of CysC, blood urea nitrogen (BUN), and serum creatinine (Scr) in miR-9 inhibitor group were remarkably lower than those in the AKI group, and significant differences were found (all $P<0.001$).

Histological findings among groups

As seen in **Figure 2**, H&E staining results showed that there was a normal kidney tissue structure with the intact renal tubular epithelium and no obvious pathological changes in the renal interstitium and glomerular. In the AKI group, there was widespread destruction with renal tubular dilatation and cavity expansion, epithelial cell edema in the renal tubular lumen, glomerular hypertrophy, and sever interstitial inflammatory infiltration. In the miR-9 inhibitor group, the severity of renal lesions and renal tubular injury was markedly inhibited.

Expression levels of miR-9 in renal tissues.

qPCR results showed that the expression level of miR-9 in the AKI group or miR-9 inhibitor group was significantly higher than that in the sham group, and there were significant differences between groups (all $P<0.001$). The expression level of miR-9 in the miR-9 inhibitor group was obviously lower than that in the AKI group and a marked difference was found between the two groups ($P<0.001$), as shown in **Figure 3**.

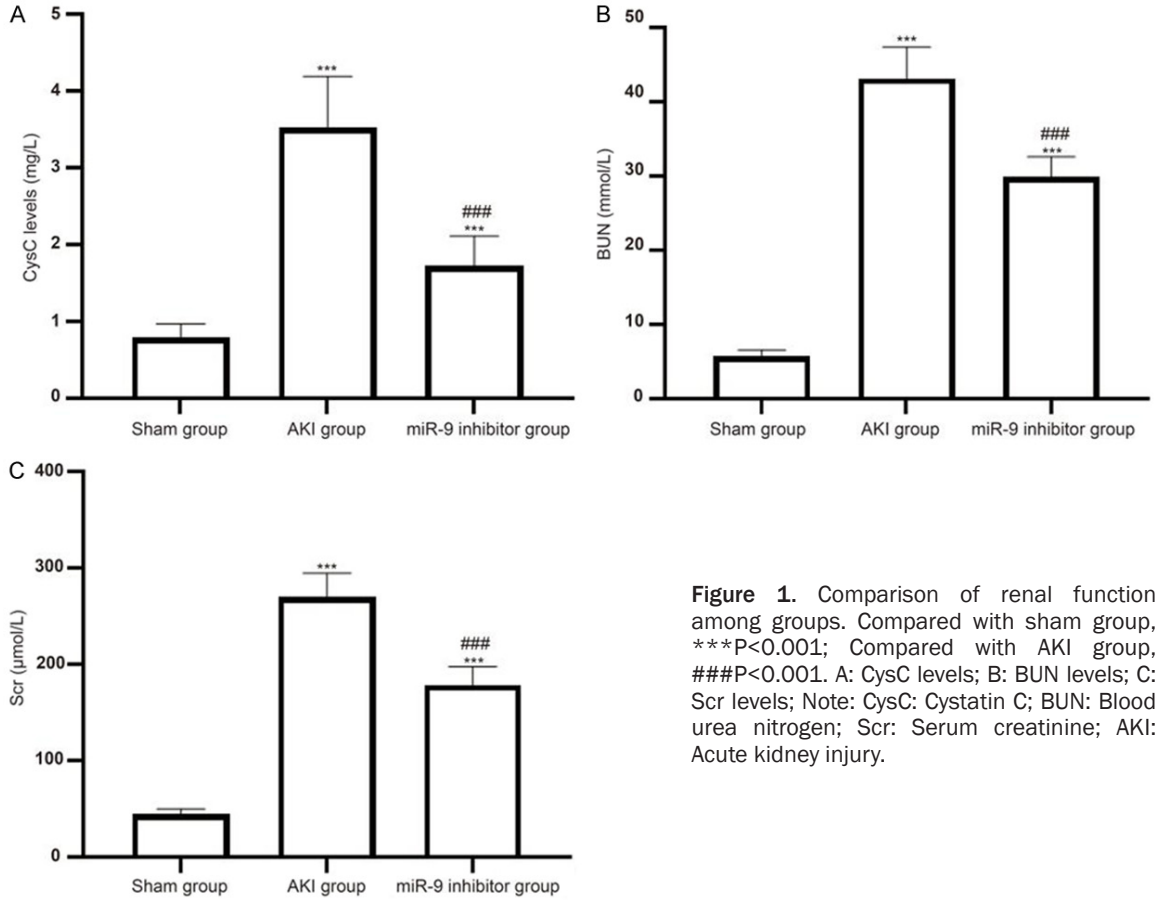

Figure 1. Comparison of renal function among groups. Compared with sham group, ***P<0.001; Compared with AKI group, ###P<0.001. A: CysC levels; B: BUN levels; C: Scr levels; Note: CysC: Cystatin C; BUN: Blood urea nitrogen; Scr: Serum creatinine; AKI: Acute kidney injury.

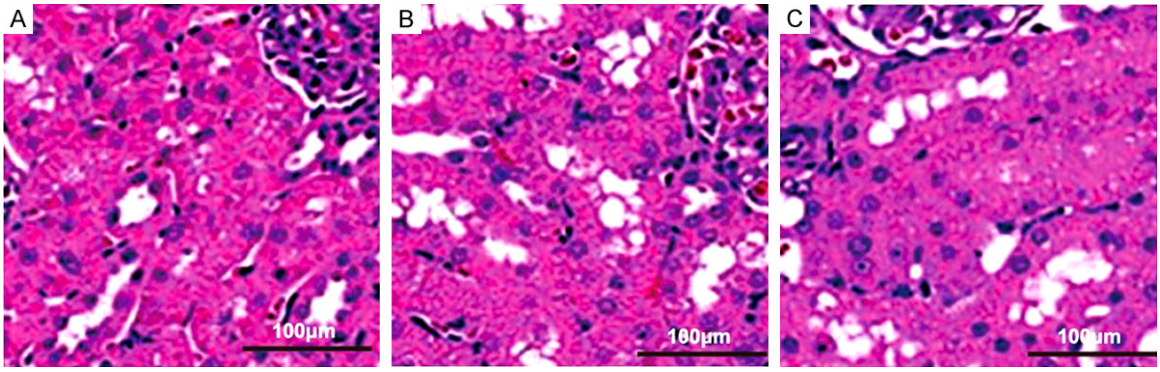

Figure 2. Comparison of histological changes among groups by H&E staining. A: Sham group; B: AKI group; C: miR-9 inhibitor group. Note: H&E: Hematoxylin-eosin; AKI: Acute kidney injury.

Comparison of inflammatory factors among groups

ELISA results showed that TNF-α, IL-6 and CRP levels in the miR-9 inhibitor group were significantly decreased compared to those in the AKI group, and were markedly increased compared to those in the sham group (all P<0.001). In addition, there was a significant increase in the expression levels of TNF-α, IL-6 and CRP from the AKI group compared to those in the sham group (P<0.001), as shown in **Table 1**.

VEGF protein expression in renal tissues

Western blot results showed that VEGF protein expression in the AKI group or miR-9 inhibitor group was significantly lower compared to those in the sham group, and there were statistical differences between groups (all P<0.001).

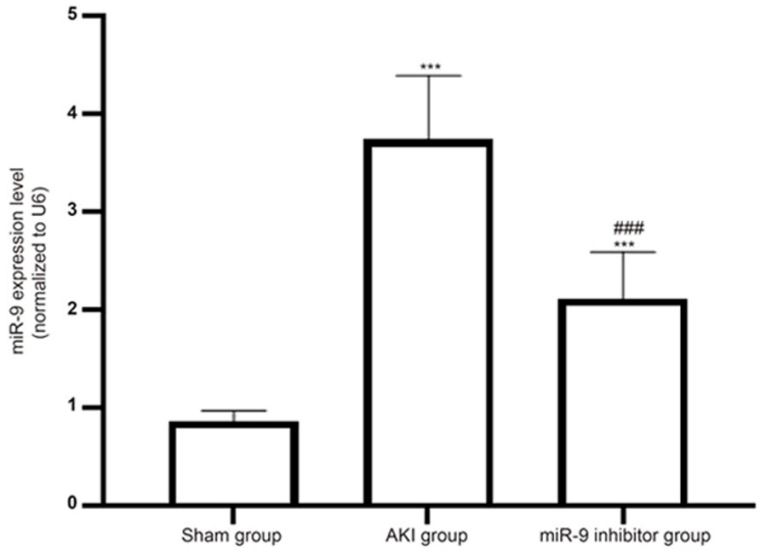

Figure 3. Comparison of miR-9 expression among groups. Compared with sham group, ***P<0.001; Compared with AKI group, ###P<0.001. Note: AKI: Acute kidney injury.

Besides, VEGF protein expression in the miR-9 inhibitor group was markedly higher than that in the AKI group, and a significant difference was found (P<0.001), as shown in **Figure 4**.

Comparison of SOD and MDA levels in renal tissue among groups

As shown in **Table 2**, the rat tissues showed a remarkable decrease in SOD levels compared to that in the sham group, whereas an obvious increase was found in MDA levels. Moreover, the imbalance between oxidant and antioxidant activity was restored in the miR-9 inhibitor group, as evidenced by increased SOD levels and reduced MDA levels compared to the AKI group. A significantly statistical differences were found among groups (all P<0.001).

Discussion

AKI is one of the most severe complications of rhabdomyolysis. It was reported that about 10%-60% of patients with rhabdomyolysis may develop AKI [20]. In the process of rhabdomyolysis-induced AKI, myoglobin-associated renal toxicity plays an important role through increasing inflammation, oxidative stress and endothelial dysfunction [21]. Understanding the molecular mechanism of these processes will help to devise therapeutic strategies for AKI. The most commonly used animal model for investigating rhabdomyolysis-associated AKI is obtained in the rat by intramuscular injection of 50% glycerol. It was reported that these animal models produce a myoglobinuric state similar to clinical rhabdomyolysis [18]. In this study, Rats in the AKI group showed remarkably increased CysC, BUN and Scr levels and renal histological changes. These results indicated that the animal model of rhabdomyolysis- associated AKI was successfully established, with similar symptoms to those observed clinically [22]. Thus, this animal model was applied for exploring the molecular mechanism of AKI.

MiRNAs are highly conserved endogenous non coding small molecule RNAs. miRNAs are involved in pathogenesis of various diseases by post-transcriptional inhibition of target gene expression. In recent years, more and more miRNAs have been confirmed to participate in the development of renal disease [23, 24]. Previous studies reported that miR-9 played a key role in the development, invasion and metastasis of tumors and tissue fibrosis [25, 26]. However, the role of miR-9 in AKI still remains unclear. To investigate the role of miR-9 in AKI, miR-9 inhibitor was given intravenously via tail vein injection. The results of this study showed that miR-9 expression was significantly increased in renal tissues from the AKI group. Compared with the AKI group, rats that were given miR-9 inhibitor in the miR-9 inhibitor group showed significantly lower miR-9 expression and CysC, BUN, and Scr levels and exhibited overall better cellular microstructure. Therefore, miR-9 played a critical role in development of AKI.

Inflammatory factors and oxidative stress are involved in the development of rhabdomyolysis-associated AKI. IL-6 and TNF-α are expressed in inflammation and injury sites, and subsequently can initiate the release of other pro-inflammatory factors [27]. Previous studies reported that IL-6 and TNF-α levels were remarkably increased in rat models of AKI and

Table 1. Comparison of TNF-α, IL-6 and CRP levels among groups

Group	TNF-α (pg/mL)	IL-6 (pg/mL)	CRP (ng/mL)
Sham group	5.97±0.84	16.82±2.35	14.10±3.28
AKI group	37.75±6.18***	55.08±7.34***	47.18±6.72***
miR-9 inhibitor group	23.61±4.57***,###	37.25±5.61***,###	25.26±5.19***,###
F value	254.400	242.000	205.100
P value	<0.001	<0.001	<0.001

Note: Compared with sham group, ***P<0.001; Compared with AKI group, ###P<0.001. AKI: Acute kidney injury; TNF-α: Tumor necrosis factor-alpha; IL-6: Interleukin 6; CRP: C-reactive protein.

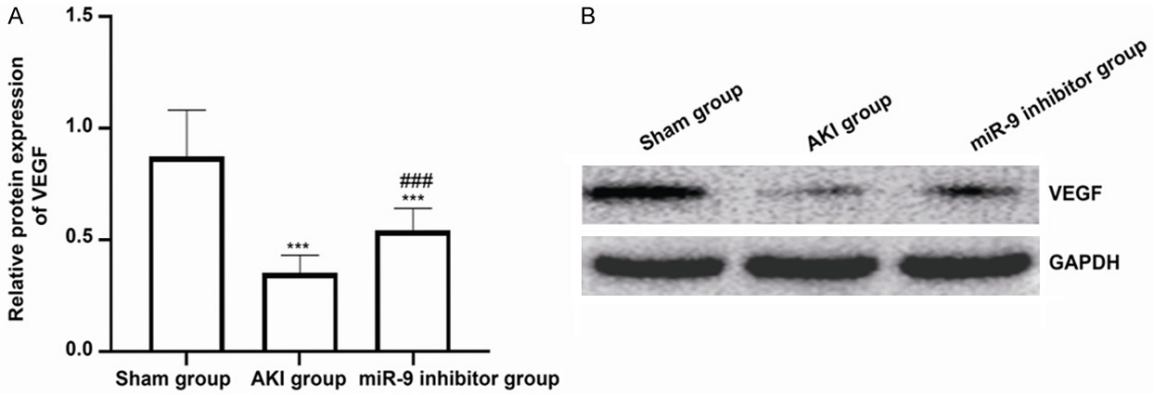

Figure 4. Comparison of VEGF protein expression in renal tissues among groups. A: Quantitative analysis of VEGF protein expression; B: Western blot of VEGF protein. Compared with sham group, ***P<0.001; Compared with AKI group, ###P<0.001. Note: VEGF: Vascular endothelial growth factor; AKI: Acute kidney injury.

Table 2. Comparison of SOD and MDA levels among groups

Group	SOD (U/g)	MDA (nmol/g)
Sham group	78.46±10.13	26.81±7.25
AKI group	32.15±7. 84***	95.78±15.26***
miR-9 inhibitor group	53.92±8.67***,###	59.03±10.64***,###
F value	134.600	179.200
P value	<0.001	<0.001

Note: Compared with sham group, ***P<0.001; Compared with AKI group, ###P<0.001. AKI: Acute kidney injury; SOD: Superoxide dismutase; MDA: Malondialdehyde.

chronic renal failure [28]. CRP is an early inflammation biomarker which is expression in injury and inflammation sites of rhw kidney [29]. In this study, the levels of IL-6, TNF-α and CRP in rhw AKI groups were significantly increased, and these inflammatory factors were markedly decreased following the inhibition of miR-9 expression. It is indicated that pro-inflammatory factors play a prominent role in the progression of AKI and miR-9 inhibitor's renoprotective effect might be partially attributable to suppression of inflammatory factors. These results is similar with Jin et al's report [30]. SOD and MDA are two key biomarkers of oxidative stress in renal tissues. It was reported that accumulated myoglobin in the renal tubules could lead to production of reactive oxygen species, which can further damage the kidney injury [31]. SOD activity can be decreased by rhabdomyolysis in renal tissues and MDA synthesis induced by reactive oxygen species can mediate alterations of DNA and proteins [32]. The results of this study found that inhibition of miR-9 expression can significantly preserve SOD and suppress MDA in renal tissues of rats with rhabdomyolysis-induced AKI. It is suggested that miR-9 inhibition has a protective effect in development of AKI against oxidative stress, which is in accordance with Nampoothiri et al's study [33].

In addition, VEGF has been considered as one of the key signaling pathway molecules regulating endothelial function in progress of AKI. In normal conditions, renal tubular epithelial cells

can produce angiogenic factors such as VEGF, which regulate the normal structure and function of capillaries; and in the conditions of AKI the VEGF expression is significantly decreased in renal tubular epithelial cells [9]. It was also reported that the increased expression of VEGF can significant improve renal injury induced by ischemia reperfusion [34]. In this study, in contrast to the AKI group, VEGF expression in the miR-9 inhibitor group was significantly increased by Western blot assay. It is indicated that the inhibition of miR-9 has a renal protective effect in AKI via regulation of VEGF expression. Other studies reported that miR-9 could inhibit retinal neovascularization and tubule formation in diabetic retinopathy by targeting VEGF [35].

In summary, our research revealed that the increased expression level of miR-9 was found in renal tissues of glycerol-induced AKI and the inhibition of miR-9 had renoprotective effects by reducing the inflammatory response, oxidative stress and VEGF in development in AKI. It is suggested that miR-9 might be a useful therapeutic agent for treatment of AKI. However, in the future it is necessary to make further investigation of miR-9-regulated target genes and related signaling pathways, so as to provide experimental foundation for the targeted treatment of rhabdomyolysis-induced AKI.

Disclosure of conflict of interest

None.

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