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ORIGINAL RESEARCH

MiR-940 Serves as a Diagnostic Biomarker in Patients with Sepsis and Regulates Sepsis-Induced Inflammation and Myocardial Dysfunction

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Introduction: Sepsis is a heterogeneous syndrome with a life-long threat caused by infection. This study aimed to investigate the clinical function of miR-940 and its influence on cardiomyocyte models.

Methods: The relative expression of miR-940 was assessed by qRT-PCR and the roles in the clinical diagnosis of miR-940 were revealed by the ROC curve. The relationship between miR-940 and clinical parameters was validated by Pearson analysis. The sepsis rat models were established by treatment with cecal ligation and perforation (CLP) and clinical items including left ventricular systolic pressure (LVSP), left ventricular and end-diastolic pressure (LVEDP), maximum rate of increase/decrease in left ventricular blood pressure ($\pm$ dp/dt_{max}) as well as troponin (cTnl), creatine kinase isoenzyme (CK-MB), TNF-α, IL-1β, and IL-6 were detected.

Results: The finding of qRT-PCR accentuated that the relative expression of miR-940 was significantly decreased in sepsis patients and CLP-stimulated models. The ROC curve proposed that miR-940 could be a satisfactory diagnostic biomarker for sepsis patients. Pearson analysis reinforced the expression of miR-940 was negatively associated with the PCT, WBC, CRP, Scr, SOFA score, and APACHE II score. The outcome of CLP-steered rat verified that overexpression of miR-940 inhibited the detrimental effects of CLP on myocardial dysfunction and inflammation reactions.

Conclusion: The downregulation of miR-940 was reported and it might be an underlying diagnostic marker in sepsis patients. Overexpression of miR-940 protected myocardial function from damage and inflammation induced by CLP.

Keywords: miR-940, sepsis, inflammation, myocardial disorder

Introduction

Sepsis is a dysregulated host response to infection, leading to multi-organ failure and death.[1] As one of the common complications of patients in intensive care wards, sepsis contributes to a high fatality rate of infection.[2,3] When sepsis occurs, an excessive inflammatory reaction first occurs in the patient's body, which leads to multiple organ failure and endothelial dysfunction, which in turn leads to the death of the patient.[4] When the patients have passed the initial excessive inflammatory response, and then entered the permanent immunosuppressive stage, they cannot resist the primary infection or secondary infection, which caused the death of the patient at this stage.[5] Even in the early sepsis, the patients also face high possibility of mortality induced by the diminishing of CD14/HLA-DR levels.[6] The

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management and therapy of sepsis are complex challenges, which require early identification and management of infection.[7] New targeted therapy strategies need a deeper understanding and research on the pathogenesis of sepsis.[8]

In recent years, the role of miRNA in the occurrence and development of sepsis has been extensively studied. MiR-940 is one of the popular miRNAs among previous publications. The expression of miR-940 was declined in several tumors, such as breast cancer and hepatocellular carcinoma.[9,10] In rat models of cerebral infarction, the expression of miR-940 was obviously decreased in the serum samples and brain tissues.[11] Considering a previous study, miR-940 is lowly expressed in the cartilage samples from patients with osteoarthritis and it is certified as a factor inhibiting inflammation.[12] Besides, in congestive heart failure, the expression of miR-940 is closely associated with inflammatory responses.[13] However, the clinical value and molecular mechanism of miR-940 in sepsis are still unclear.

Consequently, to further understand the potential function of miR-940 in sepsis, this study assessed the expression levels of miR-940 in sepsis patients and rat models. The predictive value of miR-940 was evaluated for discriminating against sepsis patients. The correlation between miR-940 and clinical parameters concerning inflammation and organ dysfunction was examined. In addition, the function of miR-940 on myocardial function and inflammation in rat models was validated in the present experiments.

Materials and Methods

Patients and Sample Collection

We collected 90 sepsis patients totally from Yidu Central Hospital of Weifang. A total of 92 healthy individuals was enrolled from the physical examination center of the same hospital. An international consensus was applied to identify sepsis patients.[1] Patients with a malignant tumor, positive human immunodeficiency virus, severe chronic dysfunction, and immunodeficiency were limited to participate in this study. The sepsis patients were all from ICU and healthy subjects were taken for regular health check-ups. Within the 24 hours of submission, the blood samples were collected from patients, and the SOFA score and APACHE II score were evaluated. This study was performed in accordance with the ethical standards as laid down in the Declaration of 1964 Helsinki and its later amendments. The medical ethics committee of Yidu Central Hospital of Weifang provided approval to our design [No.2018036]. All individuals signed the informed consent.

Animal Grouping and Model Construction

Sprague-Dawley (SD) rats were obtained from Animal Center (Shanghai, China) and housed in an atmosphere with 50% air humidity and cycles of 12-h light and 12-h dark at 23°C. MiR-940 agomir and its negative control (NC) were purchased from GenePharma (Shanghai, China). Forty SD rats were randomly divided into sham group, cecal ligation and perforation (CLP) group, CLP + miR-940 NC group, and CLP + miR-940 agomir group. 1 mL of normal saline was injected intravenously into the tails of rats in the sham group and CLP group. 10 μg miR-940 NC and 10 μg miR-940 agomir were separately injected into the tails of rats in the CLP + miR-940 NC group and CLP + miR-940 agomir group. All rats except the sham group were undergone cecal ligation operation in accordance with the previous standardized procedure.[14] The experiment was approved by the Animal Care and Use Committee of Yidu Central Hospital of Weifang (IACUC-2018055) and conducted based on the Laboratory animal-Guideline for ethical review of animal welfare (GB/T 35892-2018, issued by the General Administration of Quality Supervision, Inspection and Quarantine of the People's Republic of China).

Clinical Function Measurement and Blood Cytokines Assessments

After 24 hours of CLP treatment, the items concerning cardiac function were detected, eg, left ventricular systolic pressure (LVSP), left ventricular and end-diastolic pressure (LVEDP), and maximum rate of increase/decrease in left ventricular blood pressure (± dp/dt_{max}). 5 mL blood specimens were collected to access inflammation cytokines, troponin (cTnl), creatine kinase isoenzyme (CK-MB), TNF-α, IL-1β, and IL-6.

RNA Extraction and Quantitative Real-Time PCR (qRT-PCR)

Rats were sacrificed by cervical dislocation at the end of the experiment and heart tissues were isolated and stored at −80°C. We used TRIzol LS reagent to extract total RNA from individuals and rats following the recommended suggestions (HaiGene Biotech, Harbin, China). Qubit

RNA HS assay kit from HaiTech (Shanghai, China) was purchased to detect the concentration of RNA samples. The first line of cDNA was obtained using a microRNA reverse transcription kit (BioTNT, Shanghai, China). The relative expression of miR-940 was detected on a 7900 fluorescence quantitative PCR instrument using SuperReal PreMix Plus (TIANGEN, Beijing, China) in line with the manufacturer's specifications.

Statistical Analysis

The comparison between the control group and sepsis group was calculated with the chi-square test and Student's *t*-test. The diagnostic significance of miR-940 on sepsis was unveiled by the area under the curve (ROC) of the receiver operating characteristic (ROC) curve. The correlations between miR-940 and clinical characteristics were indicated by Pearson correlation analysis. The influence of miR-940 on rat models was analyzed using one-way ANOVA. All experiments were conducted at least three times and the data were expressed as mean ± SD or number.

Results

Clinicopathological Parameters of All Objects

Some clinical characteristics were summarized and analyzed to interpret the difference between sepsis patients and healthy objects. As shown in Table 1, the age, BMI, and gender had no significant difference from that in healthy individuals ($P > 0.05$). Compared to the control group, the levels of procalcitonin (PCT), white blood cell (WBC), C-reactive protein (CRP), and serum creatinine (Scr) were increased due to the sepsis ($P < 0.001$). Besides, the albumin was remarkably reduced in the sepsis group in comparison with healthy controls ($P < 0.001$).

Table 1 Comparison of the Baseline Data Between the Two Groups

Parameters	Control (n = 92)	Sepsis (n = 90)	*P* value
Age (year)	51.53 ± 10.09	52.43 ± 12.33	0.590
BMI (kg/m^2)	23.38 ± 3.50	22.86 ± 3.42	0.318
Gender (male/female)	47/45	53/37	0.290
PCT (ng/mL)	0.08 ± 0.03	10.05 ± 2.60	<0.001
WBC (×10^9/L)	8.08 ± 1.61	16.57 ± 2.73	<0.001
CRP (mg/L)	7.77 ± 2.42	63.49 ± 18.07	<0.001
Albumin (g/L)	37.09 ± 3.13	29.07 ± 5.79	<0.001
Scr (mg/dL)	0.95 ± 0.22	1.70 ± 0.18	<0.001
SOFA score	–	5.10 ± 1.33	–
APACHE II score	–	13.36 ± 6.32	–

Abbreviations: BMI, body mass index; PCT, procalcitonin; WBC, white blood cell; CRP, C-reactive protein; Scr, serum creatinine; SOFA, sequential organ failure assessment; APACHE, acute physiology and chronic health evaluation.

Decreased Levels of miR-940 and Its Relationship with Examination Items in Sepsis Patients

The change of miR-940 expression in sepsis was provided by qRT-PCR. As demonstrated in Figure 1A, the miR-940 was lowly expressed in the sepsis patients, manifesting miR-940 might be a regulator in the sepsis ($P < 0.001$).

Furthermore, Table 2 elucidated that the amount of miR-940 was inversely proportionate to the levels of PCT ($P < 0.001$, R = −0.640), WBC ($P < 0.001$, R = −0.594), CRP ($P < 0.001$, R = −0.448), Scr ($P = 0.020$, R = −0.244), SOFA score ($P < 0.001$, R = −0.618), and APACHE II score ($P < 0.001$, R = −0.604). Based on these results, we speculated that the miR-940 might be a protective indicator in sepsis by inhibiting inflammatory responses and restoring organ function. Nonetheless, miR-940 had no prominent association with age, BMI, gender, and albumin ($P > 0.05$).

Diagnostic Accuracy of miR-940 for Sepsis Patients

To pinpoint the diagnostic value of miR-940 in clinical management, a ROC curve was applied. The result provided a possibility of miR-940 as a promising biomarker by the evidence that the AUC was 0.908, as well as specificity was 0.826, and sensitivity was 0.889 (Figure 1B).

Influence of miR-940 on Cardiac Dysfunction in Sepsis Rat Models

Considering the alternation of miR-940 levels in sepsis, the experiments concerning the mechanism of miR-940 on rat models induced by CLP were put into practice. As demonstrated in Figure 2A, the expression of miR-940 was significantly decreased in the serum samples of sepsis rat models, and injection of miR-940 agomir reversed the declined levels of miR-940 successfully ($P < 0.01$). Noteworthily, the same tendency was demonstrated in the tissues from experimental rats, namely the miR-940 agomir changed the decreased levels of miR-940 caused by CLP ($P < 0.01$, Figure 2B).

Moreover, some indexes about the cardiac function of rat models were detected to manifest the roles of miR-940 on cardiac dysfunction. As shown, the CLP experiments contributed to the damage of myocardial dysfunction by

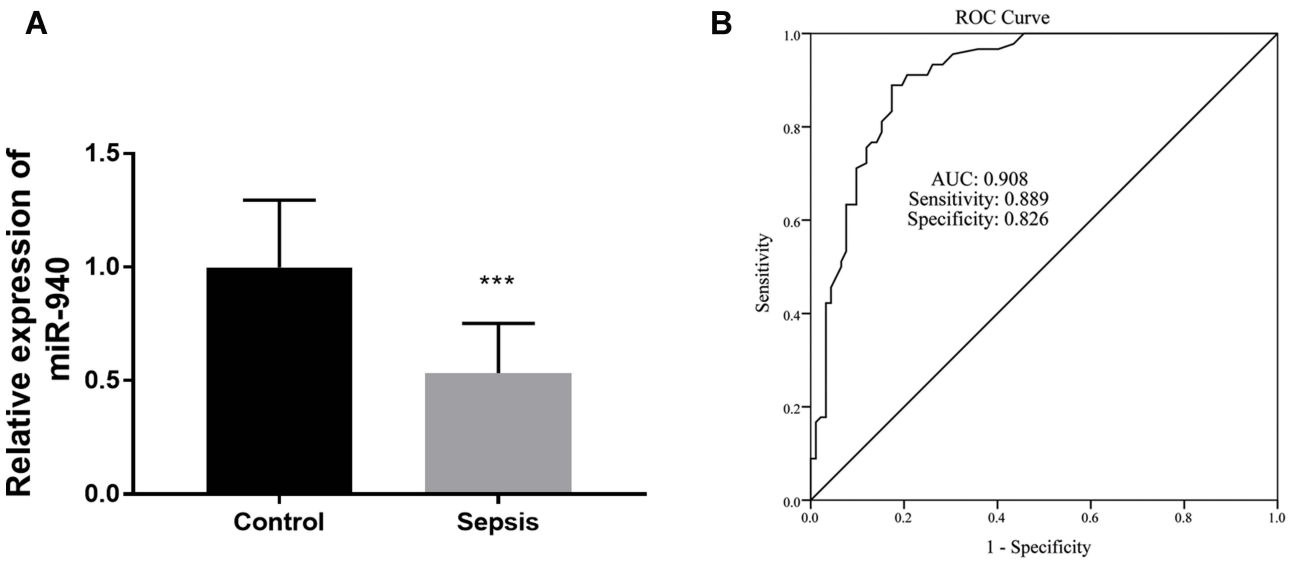

Figure 1 (**A**) The relative levels of miR-940 in sepsis patients. (**B**) The diagnostic significance of miR-940 for sepsis patients in clinical. ***$P < 0.001$.

decreasing LVSP, $+dp/dt_{max}$, and elevating LVEP, cTnl, CK-MB, and $\pm dp/dt_{max}$ ($P < 0.001$, Figure 3A–E). However, the increased miR-940 ameliorated the injured myocardial function in the aspects of LVSP, LVEP, cTnl, CK-MB, and $\pm dp/dt_{max}$ ($P < 0.05$, Figure 3A–E).

Influence of miR-940 on Inflammation of Sepsis Rat Models

The inflammatory reactions on sepsis and the alternation of miR-940 were investigated by detecting the concentration of TNF-α, IL-1β, and IL-6 in experimental rats. The results are shown in Figure 4A–C, which proposed the inflammatory responses aggravated due to the CLP treatment, whereas, the overexpression of miR-940 mitigated the inflammatory progression by restricting the amount of pro-inflammatory cytokines ($P < 0.01$).

Table 2 Correlation Between the Levels of miR-940 and Clinical Characteristics

Parameters	The Expression of miR-940	
	P value	Correlation Coefficient (*r*)
Age	0.670	0.045
BMI	0.691	−0.042
Gender	0.215	0.131
PCT	<0.001	−0.640
WBC	<0.001	−0.594
CRP	<0.001	−0.448
Albumin	0.084	0.182
Scr	0.020	−0.244
SOFA score	<0.001	−0.618
APACHE II score	<0.001	−0.604

Abbreviations: BMI, body mass index; PCT, procalcitonin; WBC, white blood cell; CRP, C-reactive protein; Scr, serum creatinine; SOFA, sequential organ failure assessment; APACHE, acute physiology and chronic health evaluation.

Discussion

Sepsis is defined as the life-threatening organ dysfunction caused by the host reaction imbalance caused by infection, which is the main cause of death caused by infection.[15,16] The inflammatory reaction caused by sepsis is mediated by cytokines, among which cytokines confirmed to be related to pathogenesis are divided into pro-inflammatory and anti-inflammatory.[17] As a severe common complication both in adults and children, myocardial damage accompanied by sepsis is characterized by increased factors of myocardial injury and increased mortality.[18,19] In spite of a great deal of achievement that has been done for decades, there is no specific treatment for sepsis so far.[20] Thus, the investigation for the instinct mechanism of sepsis is crucial for target therapy and management of sepsis.

Recently, with the deepening of clinical research on sepsis, more and more new biomarkers provide new ideas for early diagnosis of this comorbidity.[21] Existing studies have found that miRNA has many biological functions in cell animal models, and participates in the occurrence and development of many immune disorders.[22] In an investigation of C57BL/6 mice induced by CLP, the raised miR-539-5p reduced the pulmonary injury and inflammation triggered by CLP.[23] In another publication written by Chen et al, downregulation of miR-126-3p was found in

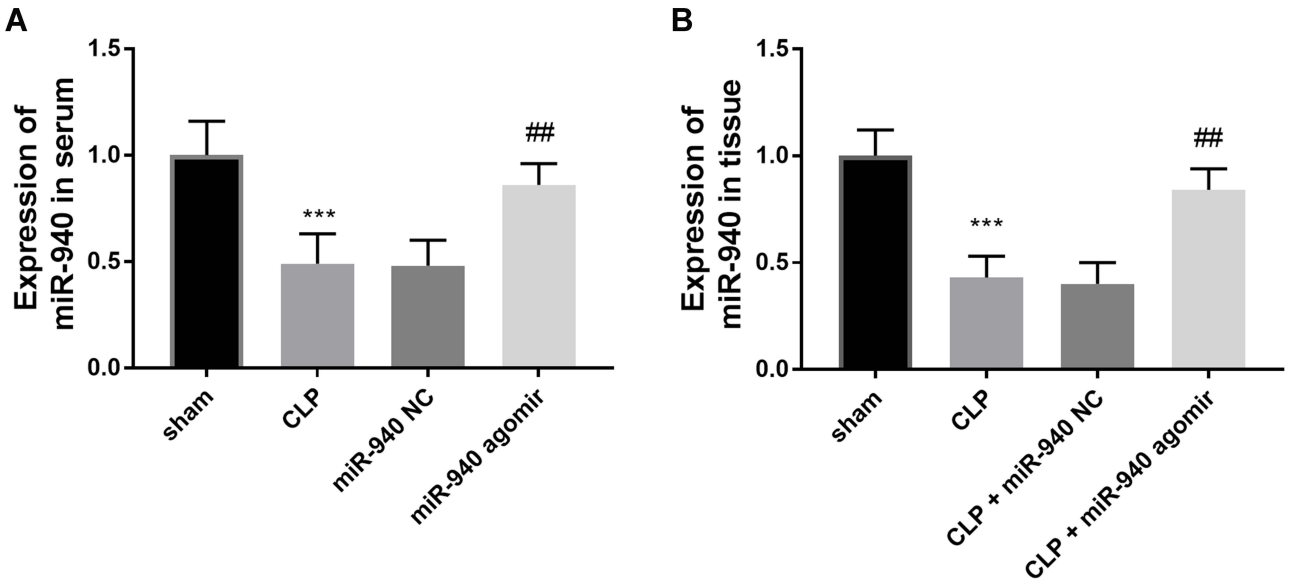

Figure 2 (**A** and **B**) Injection of miR-940 agomir reversed the declined expression of miR-940 in serum and tissues from CLP-damaged rats. ***$P < 0.001$, compared with the sham group; ##$P < 0.01$, compared with the CLP group.

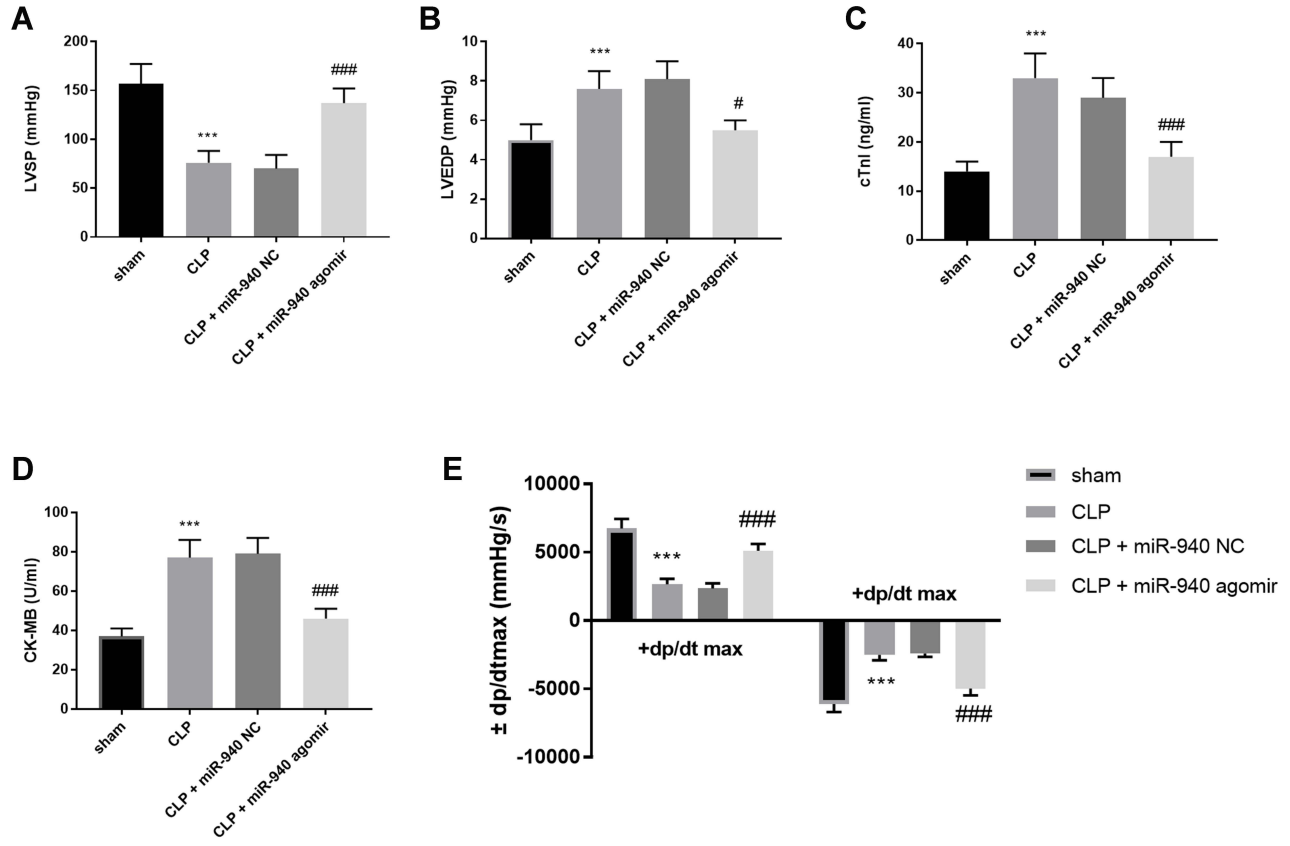

Figure 3 (**A**–**E**) Overexpression of miR-940 ameliorated the myocardial injury stimulated by CLP. ***$P < 0.001$, compared with the sham group; #$P < 0.05$, ###$P < 0.001$, compared with the CLP group.

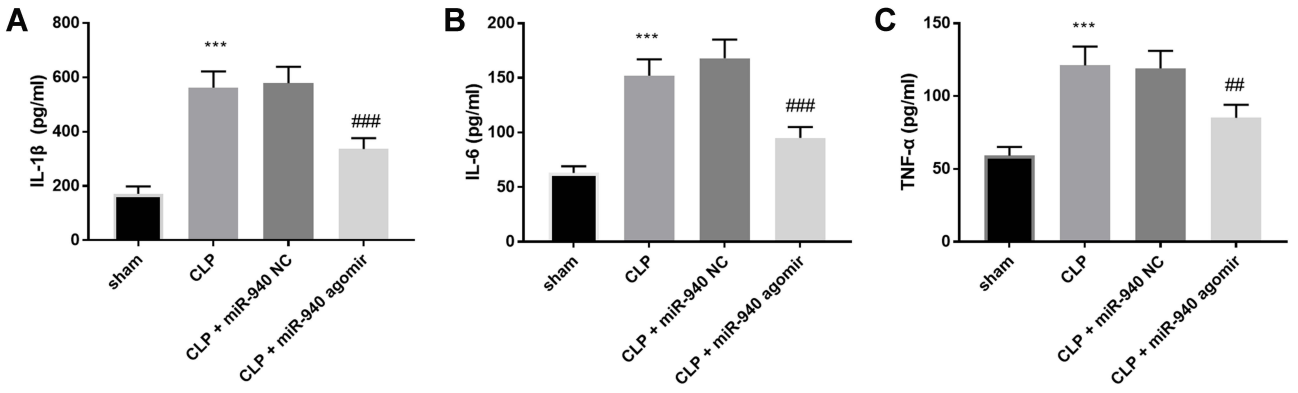

Figure 4 (**A**–**C**) Upregulation of miR-940 led to the amelioration of inflammation caused by CLP. ***$P < 0.001$, compared with the sham group; ###$P < 0.01$, ####$P < 0.001$, compared with the CLP group.

the patients with sepsis and its association with inflammation and organ dysfunction is determined.[24] Decreased miR-181-5p was found in CLP-stimulated rats and overexpression of miR-181-5p lead to a satisfactory survival outcome in these experimental rats.[25] All these uncover that abnormally expressed miRNAs may have clinical effects in sepsis and play expansionary or inhibitive influence by accommodating organ dysfunction and inflammation.

In the present project, we forecasted that miR-940 exerted protective roles in sepsis based on the evidence that the miR-940 was expressed at a lowly level in sepsis patients in comparison with that of healthy subjects. Furthermore, there was a negative connection between the levels of miR-940 and parameters, including PCT, WBC, CRP, Scr, SOFA score, and APACHE II score. These observations implied that the high levels of miR-940 could suppress the severity of sepsis and organ dysfunction. Singh et al substantiated the declined expression of miR-940 in patients with acute viral hepatitis engendered by hepatitis B virus, which propound another instantiation to ascertain our previous findings.[26] Significantly, our observation indicated that the levels of miR-940 showed a probability for distinguishing sepsis patients among healthy individuals. However, the ability of miR-940 on distinguishing sepsis from other critical diseases needed further discussion. Previous publications accentuate that novel biomarkers deliver a solid discriminative competence of among critically ill patients with sepsis which also relates to prognosis.[27,28] Lan et al discover that the diagnostic significance of miR-155-5p and miR-133a-3p with promising sensitivity and specificity, suggesting the potential of specific miRNA as an alternative biomarker in sepsis.[29]

CLP-elicited animal models are the most commonly used models in sepsis to explore the mechanism of sepsis.[30] Our investigation established rat models by CLP and proposed that miR-940 lowly expressed in the serum specimens and brain tissues of experimental models. Interestingly, miR-940 agomir reversed the declined trend of miR-940 both in serum and tissues. In the aspects of myocardial function, we reported the myocardial function was significantly damaged in the CLP-irritated rats by enhancing LVEDP, cTnl, CK-MB, and -dp/dt_{max}, and attenuating LVSP and +dp/dt_{max}, however, upregulation of miR-940 ameliorated this adverse effect. Although our study has confirmed the possible clinical role of miR-940, our study was limited to animal experiments, and its clinical role remained to be further confirmed. The outcome of SD rats predicted a possible influence of miR-940 on sepsis patients due to the missing clinical information regarding the net response of septic animal models.[31] Moreover, the overexpression of miR-940 alleviated the inflammation steered by CLP. In an observation about the mice model of spinal cord injury, an abundance of miR-940 contributed to the reduced amount of inflammatory factors in animal models.[32] Cao et al also substantiated the increased miR-940 restricted the influence of IL-1β in osteoarthritis.[12]

Conclusion

Taken together, the declined miR-940 was found in the sepsis patients and CLP-injured rats. The amount of miR-940 was inversely associated with the severity of sepsis. The level of miR-940 might be an indicator for identifying sepsis patients. Besides, in the CLP-treated rat models, overexpression of miR-940 contributed to the restoration

of myocardial disorders and inflammation actions triggered by CLP.

Disclosure

The authors report no conflicts of interest in this work.

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