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Original Article

Serum miR-377 Can Be Used as a Diagnostic Marker for Acute Coronary Syndrome and Can Regulate Proinflammatory Factors and Endothelial Injury Markers

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The diagnostic value of microRNA-377 (miR-377) in patients with acute coronary syndrome (ACS) and explored miR-377's potential mechanisms. We performed an qRT-PCR to assess serum miR-377 levels in ACS patients and coronary artery ligation rat models. The diagnostic value of miR-377 was evaluated by determining the ROC curve. An ELISA assay was conducted to detect the model rat endothelial damage markers von Willebrand factor (vWF) and heart-type fatty acid binding protein (H-FABP), and proinflammatory cytokines TNF-α, IL-6, and IL-1β. The serum miR-377 level was elevated in the ACS patients and significantly increased in the ACS rats. MiR-377 has a high diagnostic value in ACS patients, with a 0.844 ROC, 76.47% specificity, and 87.10% sensitivity. MiR-377 was positively correlated with the expressions of vWF, H-FABP, cTnI, TNF-α, IL-6, and IL-1β. In ACS rats, reducing the expression of miR-377 significantly inhibited the increases in vWF, H-FABP, TNF-α, IL-6, and IL-1β. An elevated miR-377 level can be used as a diagnostic marker in patients with ACS. A reduction of miR-377 may alleviate ACS by improving myocardial damage such as endothelial injury and the inflammatory response.

Key words: microRNA-377, acute coronary syndrome, diagnosis, endothelial injury, inflammatory

The morbidity and mortality related to the common heart disease coronary artery disease (CAD) have risen rapidly and now present a major chronic noninfectious disease that seriously endangers public health [1]. As a manifestation of CAD, acute coronary syndrome (ACS) is a major cause of death and disability due to its high morbidity, mortality, and recurrence rate [2]. At present, electrocardiography (ECG) and the cardiac troponin test are routine tests for the diagnosis of ACS, but when ECG is used in emergency departments, approximately half of the patients have no clear symptoms or ECG characteristics [3]. In addition, the myocardial troponin I or T may not continue to increase at the beginning of a myocardial infarction and can be detected only 6-12 h after coronary artery occlusion; high-sensitivity troponin can be detected 3 h after a myocardial infarction [4-6]. At the same time, as ACS is an acute heart attack, it activates systemic inflammation as a defense response to this ischemic tissue damage [7]. Impaired endothelial integrity is considered to be the basis of ACS [8], and a great deal of research has focused on inflammatory factors and markers of endothelial injury that could be used to assess the risk of ACS.

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MicroRNAs (miRNAs) are endogenous, noncoding, small RNA molecules that can degrade target gene mRNA or inhibit target mRNA translation. It has been demonstrated that miRNAs can regulate endothelial dysfunction, inflammation, autophagy, and platelet activation [9-11]. A recent investigation revealed that miRNAs can serve as biomarkers for the diagnosis, treatment and prognosis of cardiovascular diseases (CVDs), including heart failure, atherosclerosis, and ACS [12], like miR-21 and miR-664a-3p [13, 14].

MiR-377 is located on human chromosome 14q32.31, and the dysregulation of its expression has been studied in some CVDs [15, 16]. In apolipoprotein E knockout mice, miR-377 inhibited atherosclerosis by regulating DNA triglyceride metabolism via DNA methyltransferase 1 (DNMT1) [17]. Decreasing miR-377 expression can promote angiogenesis and inhibit brain inflammation to reduce ischemic brain damage [18]. In addition, miR-377 can promote adipose tissue inflammation and reduce insulin sensitivity in obese patients by inhibiting SIRT1 to a certain extent [19]. Although miR-377 has been reported to be involved in vascular endothelial dysfunction, inflammatory responses, and CVD, its role in ACS is unknown.

We conducted the present study to evaluate the expression pattern of miR-377 in patients with ACS, explore the diagnostic value of miR-377, and investigate the correlation between miR-377 and the inflammatory response and endothelial injury in ACS.

Materials and Methods

Patients and sample collection. This study was approved by the Medical Ethics Committee of the Affiliated Hospital of Gansu Medical College. Each participant in the study signed an informed consent form, and the samples were anonymized according to ethical and legal standards. The research methods met the standards set out in the Helsinki Declaration.

From June 2018 to July 2020, 85 patients were diagnosed with ACS at our hospital, and 85 healthy volunteers were used as the control subjects of this study. We excluded ACS patients who had a blood disorder, inflammatory disease, diabetes, infectious disease, myocardial infarction, kidney disease, or severe left ventricular systolic dysfunction. The healthy controls had no coronary artery stenosis.

A venous blood sample was collected from each ACS subjects' upper limb within 3-5 hours after symptom onset and before arteriography. The serum was collected by centrifugation and stored at −80°C for further analysis. Table 1 summarized the age, sex, smoking history, total cholesterol, triglycerides, low-density lipoprotein, high-density lipoprotein, and other basic clinicopathological information of both the ACS and control groups.

RNA extraction and quantitative real-time polymerase chain reaction (qRT-PCR). Total RNA was isolated from the serum samples with the use of TRIzol reagent (Invitrogen, Carlsbad, CA, USA). The extracted RNA was reverse transcribed into complementary (c)DNA using the PrimeScript RT kit (TaKaRa, Shiga, Japan) according to the manufacturer's instructions. Quantitative real-time polymerase chain reactions (qRT-PCRs) were performed using an SYBR Green I Master Mix kit (Invitrogen) in a 7300 real-time PCR system (Applied Biosystems, Foster City, CA). The relative expression of miR-377 was calculated with the $2^{-\Delta\Delta Ct}$ method, and U6 was used as an endogenous control. The primer sequences were as follows: miR-377 forward, 5'-GGGCACACAAAGGC AACTTTTGT-3', reverse, 5'-CTCGCTTCGGC AGCACA-3'; U6 forward, 5'-AACGCTTCACGAA TTTGCGT-3', reverse, 5'-CTCGCTTCGGCAGCA CA-3'. The conditions for qRT-PCR were incubation at 95°C for 10 min, followed by 35 cycles of 95°C for 10 sec and 60°C for 30 sec.

ACS animal model construction and treatment. The animal experiments in this study were approved by the ethics committee of the Affiliated Hospital of Gansu Medical College and conducted following the Guidelines for the Care and Use of Laboratory Animals. Coronary artery ligation, a common rat model of acute coronary syndrome, was performed as described [20]. Male Sprague-Dawley (SD) rats aged 8 weeks and weighing 230 ± 10 g were used to construct a rat model of coronary artery ligation [20]. We first randomly divided the rats into a sham group and an ACS model group. Rats in both models were anesthetized by an intraperitoneal injection of 1% sodium pentobarbital (45 mg/kg). The skin and subcutaneous tissue were then incised at the third and fourth ribs on the left side of a sternum incision, and the subcutaneous tissue and muscle were bluntly separated. After the third rib was cut near the edge of the sternum and the left atrial appendage and the pulmonary cone were separated, the

left coronary artery and aorta were identified. With the left coronary vein as the reference, the anterior and posterior portions of the left coronary artery were punctured with a 6-0 ophthalmic noninvasive suture needle, and a small bundle of myocardial ligation and ligation sites was observed.

The chest was closed gradually, and the changes in the ECG were checked to determine whether the ACS model was successfully constructed. The same-size needle was used for the sham operation group but without knotting at the left coronary artery between the left atrial appendage and the left coronary artery cone. After the operation, each rat was injected intraperitoneally with penicillin (200,000 U) to prevent infection. The above experiments were performed under strict sterile conditions. After the completion of modeling, the rats were monitored by electrocardiography, and the ACS rats were observed to show ST-segment elevation or high-T wave.

An miR-377 inhibitor (5'-ACAAAAGUUGCC UUUGUGUGAU-3') or miRNA negative control (miR-NC, 5'- CAGUACUUUUGUGUAGUACAA-3') was injected near the left coronary artery myocardium of each successful ACS model rat to regulate the expression of miR-377 *in vivo*. The miR-377 inhibitor and miR-NC were purchased from RiboBio (Guangzhou, China). The rats were euthanized by the inhalation of an overdose of anesthetic drugs, confirmed by cervical dislocation. At 5 days post-surgery, a 1.5- to 2-mL fresh blood sample was obtained from the tail vein of each mouse. The serum was collected and stored at −80°C.

Enzyme-linked immunosorbent assay (ELISA). We performed an ELISA to analyze the changes in endothelial injury markers and inflammatory factors in the human and rat serum samples. The rat and human endothelial injury markers included heart-type fatty acid-binding protein (H-FABP, Cusabio Biotech, College Park, MD, USA) and von Willebrand factor (vWF, Abcam, USA), and inflammatory factors included interleukin 6 (IL-6, Abcam, Cambridge, MA, USA), tumor necrosis factor-alpha (TNF-α, Abcam, USA), and interleukin 1beta (IL-1β, Abcam, USA). The ELISA assay were performed in accord with the manufacturers' instructions.

Statistical analyses. All data statistics and analyses were conducted with SPSS 21.0 software and GraphPad Prism 7.0 software, and the data are presented as the mean ± standard deviation (SD). Data were checked for normality via the Kolmogorov–Smirnov (K-S) normality test. Student's *t*-test and a one-way analysis of variance (ANOVA) with Tukey's test were used to compare the differences between groups. The receiver operating characteristic (ROC) curve was plotted to evaluate the diagnostic value of miR-377 in the patients with ACS. We performed a Spearman correlation analysis to determine the correlations between miR-377 and endothelial injury markers or inflammatory factors. Probability (p)-values < 0.05 were considered significant. All assays were repeated at least three times.

Results

Clinical characteristics and demographics. The demographic and clinical characteristics of the subjects are shown in Table 1. There was no significant difference between the ACS patients (22 females / 63 males, mean age 54.31 ± 5.40 years) and the healthy control group (24 females / 61 males, mean age 55.64 ± 5.19 years) in age, sex, body mass index (BMI), smoking, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), or triglyceride ($p > 0.05$).

Serum level of miR-377 in the ACS patients. The expression levels of miR-377 in the serum of the patients with ACS and the healthy controls were evaluated by qRT-PCR. As shown in Fig. 1, the serum

Table 1 Clinical characteristics of the participants included in this study

Characteristics	Healthy controls (n = 80)	ACS patients (n = 80)	*P*-value
Age (years, mean ± SD)	55.64 ± 5.19	54.31 ± 5.40	0.101
Gender (female / male)	24 / 61	22 / 63	0.605
BMI (kg/m^2)	24.30 ± 2.266	25.10 ± 3.22	0.063
Smoking (n)	42	47	0.446
Total cholesterol (mmol/L)	4.66 ± 0.24	4.62 ± 0.44	0.497
HDL (mmol/L)	1.46 ± 0.31	1.38 ± 0.22	0.056
LDL (mmol/L)	2.61 ± 0.37	2.72 ± 0.36	0.053
Triglyceride (mmol/L)	1.35 ± 0.30	1.43 ± 0.32	0.089

LDL, low-density lipoprotein; HDL, High-density lipoprotein.

expression of miR-377 in the ACS group (4.695 ± 0.113) was significantly higher than that in the healthy controls (3.137 ± 0.100, $p < 0.001$). We thus speculate that miR-377 plays a vital role in ACS.

The diagnostic value of miR-377 in ACS. Since miR-377 was significantly upregulated in the ACS patients, we further analyzed the diagnostic value of miR-377 in ACS by determining the ROC curves for the ACS and healthy controls. As shown in Fig. 2, the area under the curve (AUC) for miR-377 was 0.884, the critical value was 0.635, the sensitivity was 87.10%, and the specificity was 76.47%. The ROC curve showed that miR-377 had a good diagnostic value for ACS.

Correlations of the miR-377 level with endothelial injury and inflammation in the ACS patients. Since endothelial injury and the inflammatory response are considered key events in the progression of ACS, we further examined the expression of endothelial injury and inflammatory markers. As shown in Table 2, the levels of the endothelial injury markers vWF and H-FABP in the ACS patients were significantly increased compared to those in the healthy controls ($p < 0.001$). In addition, a highly characteristic protein of myocardial injury, cardiac troponin I (cTnI), is a key factor involved in the diagnosis of ACS, and it was significantly elevated in the present ACS patients ($p < 0.001$). The levels of the proinflammatory factors IL-6, IL-1β, and TNF-α in the ACS patients were also significantly higher than those in the healthy controls ($p < 0.001$).

We also analyzed the correlation between miR-377 expression and the levels of the endothelial injury markers and proinflammatory factors. As shown in Table 3, the expression of serum miR-377 was significantly positively correlated with the levels of vWF (r = 0.727, $p < 0.001$), H-FABP (r = 0.707, $p < 0.001$), cTnI (r = 0.740, $p < 0.001$), IL-1β (r = 0.619, $p < 0.001$), IL-6 (r = 0.602, $p < 0.001$), and TNF-α (r = 0.665, $p < 0.001$). Together these results indicate that an abnormal expression of miR-377 may be related to endothelial injury and the inflammatory response.

Effects of miR-377 on endothelial injury and inflammation in the rats with ACS. We further examined the role of miR-377 in endothelial injury and inflammation in ACS by constructing a rat ACS model. As shown in Fig. 3A, the level of miR-377 was significantly increased in the rats with ACS compared to the sham-operated group ($p < 0.001$). After the use of the miR-377 inhibitor, the serum miR-377 level in the ACS rats was significantly decreased ($p < 0.001$). Our assessment of changes in the endothelial injury markers and inflammatory factors in rat serum revealed that when the miR-377 expression was inhibited, the expressions of vWF, H-FABP, IL-1β, IL-6, and TNF-α caused by the ACS model surgery were significantly reduced ($p < 0.05$, Fig. 3B-F).

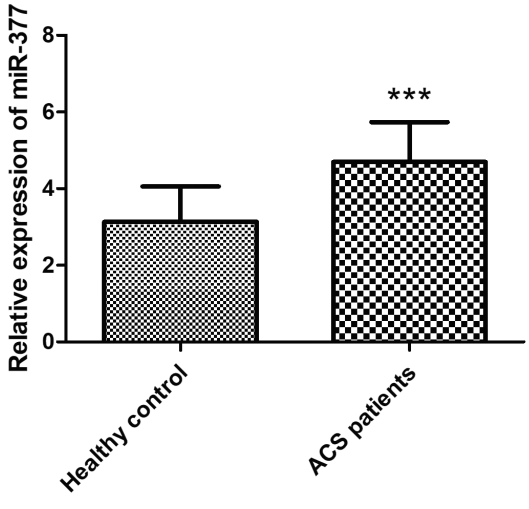

Fig. 1 A qRT-PCR was used to analyze the expression of miR-377 in the ACS patients and healthy controls. Compared with the healthy controls, the serum miR-377 was significantly increased in the patients with ACS. ***$p < 0.001$.

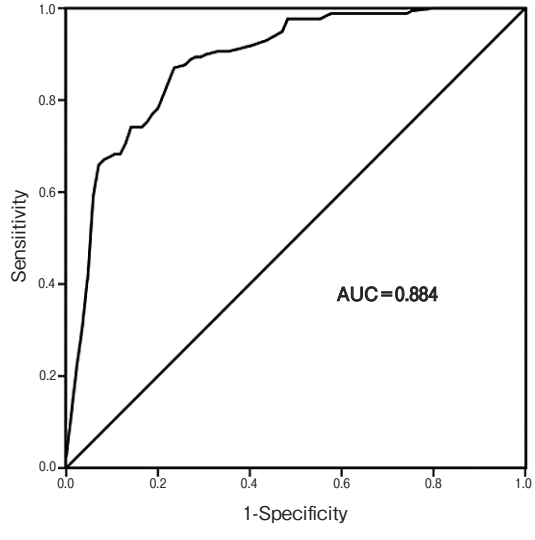

Fig. 2 ROC curve based on the miR-377 expression. Serum miR-377 had high diagnostic accuracy in the ACS patients, with an area under the curve (AUC) of 0.884.

Table 2 Serum concentration of endothelial injury markers and pro-inflammatory cytokines

Parameters	Healthy controls	ACS patients	*P*-value
vWF (ng/mL)	4.32 ± 2.04	7.19 ± 1.30	<0.001
H-FABP (ng/mL)	3.63 ± 0.59	20.94 ± 3.00	<0.001
cTnI (ng/mL)	0.10 ± 0.07	1.65 ± 0.92	<0.001
IL-6 (ng/L)	9.13 ± 1.84	21.64 ± 2.61	<0.001
TNF-α (ng/L)	9.01 ± 1.73	28.59 ± 2.91	<0.001
IL-1β (ng/L)	7.38 ± 3.80	30.60 ± 2.90	<0.001

vWF, von Willebrand factor; H-FABP, heart-type fatty acid-binding protein; cTnI, cardiac troponin I; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1 beta.

Table 3 Correlation of serum miR-377 with markers of endothelial injury and pro-inflammatory factors in ACS patients

Parameters	95% CI	r	*P*-value
vWF (ng/mL)	0.608–0.814	0.727	<0.001
H-FABP (ng/mL)	0.571–0.801	0.707	<0.001
cTnI (ng/mL)	0.625–0.823	0.740	<0.001
IL-6 (ng/L)	0.445–0.723	0.602	<0.001
TNF-α (ng/L)	0.526–0.770	0.665	<0.001
IL-1β (ng/L)	0.468–0.735	0.619	<0.001

vWF, von Willebrand factor; H-FABP, heart-type fatty acid-binding protein; cTnI, cardiac troponin I; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1 beta.

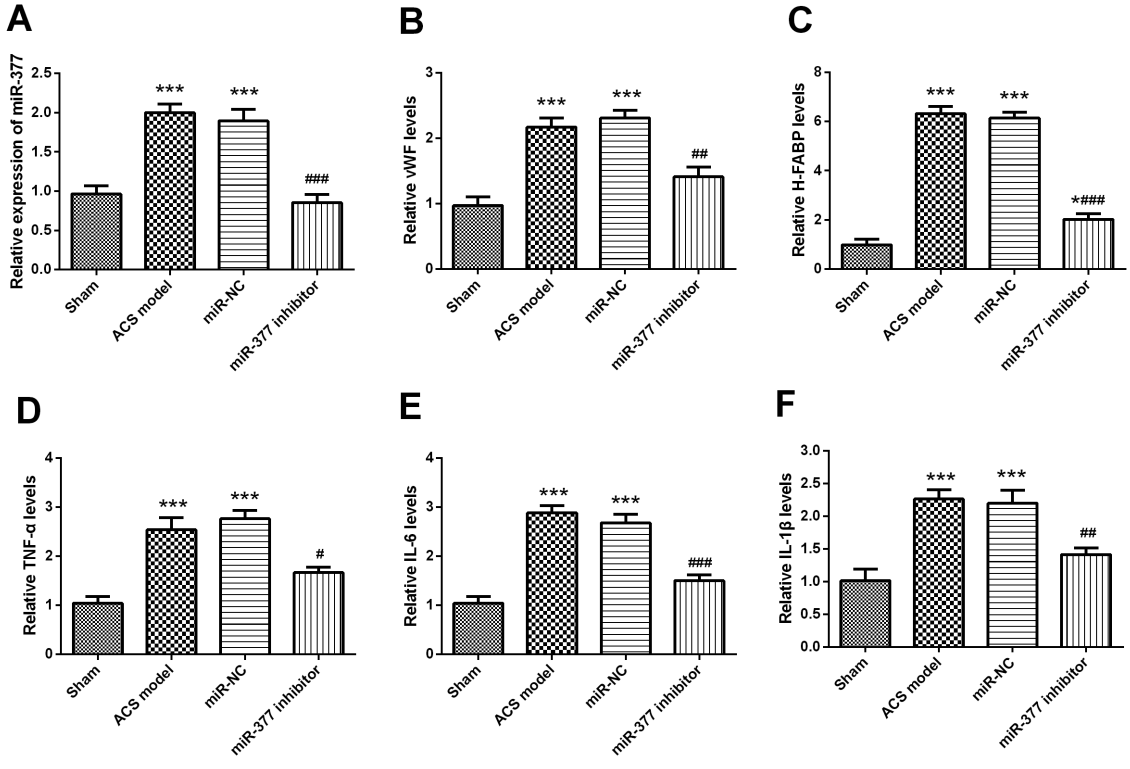

Fig. 3 The effects of the miR-377 level on endothelial injury and inflammation in the ACS rats. **A**: The expression of miR-377 was increased in the serum of the ACS rats, and the inhibition of miR-377 significantly reduced the expression of serum miR-377. **B-F**: The serum levels of vWF (**B**), H-FABP (**C**), TNF-α (**D**), IL-6 (**E**), and IL-1β (**F**) in the ACS rats were significantly increased, and they were significantly inhibited when the expression levels of miR-377 were decreased. $^{*}p<0.05$, $^{***}p<0.001$ vs. the sham group. $^{\#}p<0.05$, $^{\#\#}p<0.01$, $^{\#\#\#}p<0.001$ vs. the ACS model group, one-way ANOVA with Tukey's test.

Discussion

Roles of miRNAs have been confirmed in various human diseases, including CAD. For example, miR-302 is highly expressed in the plasma of patients with acute heart failure and are a potential diagnostic marker for acute heart failure [21]. The evaluation of circulating miR-132 levels improved the prediction of the risk of hospitalization among patients with chronic heart failure [22]. Exosomes mediate the transfer of miR-155 from vascular smooth muscle to endothelial cells; they also induce endothelial injury and promote atherosclerosis [23].

Previous studies have shown that miRNA levels are

related to the development of ACS. Serum miR-499 and miR-210 are associated with unstable angina (UA) and myocardial infarction in ACS and are novel biomarkers for the diagnosis of emergency ACS patients [24]. In an ACS rat model, the overexpression of miR-330 was reported to target mitogen-activated protein kinase 8 (MAPK8) through the Wnt signaling pathway and inhibit the formation of atherosclerotic plaques [20]. In mice with ACS, miR-150 restored endothelial function and alleviated vascular remodeling through the nuclear factor (NF)-κB signaling pathway [25]. These studies demonstrated the potential of miRNAs in the diagnosis and treatment of ACS.

miR-377 has been described as an oncogene or suppressor gene in certain cancers (*e.g.*, esophageal cancer, cervical cancer, and non-small-cell lung cancer) [26-28] and has been reported in diseases other than cancer. For example, miR-377 plays an important role in glomerular podocyte oxidative stress, inflammation, and injury caused by high fructose [29], and miR-377 was reported to regulate angiogenesis induced by ischemic heart mesenchymal stem cells by targeting vascular endothelial growth factor (VEGF) [30]. The expression of miR-377 in patients with heart failure is significantly increased, and the transfection of miR-377 knockout CD34 (+) cells into ischemic myocardium can promote angiogenesis and reduce left ventricular remodeling and cardiac fibrosis [31]. In the present study we determined the expression level of miR-377 in the serum of ACS patients and healthy controls, and the results confirmed that miR-377 was significantly upregulated in the serum of the ACS patients.

ACS is one of the most serious CVDs worldwide. It includes acute myocardial infarction (AMI) and UA, which are the leading causes of morbidity [32]. ACS has a complex phenotype that is affected by environmental and genetic factors. Its pathological process involves endothelial dysfunction, inflammation changes, and interactions between thrombus components [8, 33]. For patients with ACS, the pathological progress of coronary artery disease is very rapid, and the guidelines recommend timely revascularization treatment within 3 h after the onset of symptoms in order to save the ischemic myocardium and reduce final mortality; an early diagnosis and treatment are crucial for ACS [4]. Inflammation and endothelial dysfunction also play important roles in the acute treatment and long-term management of ACS patients [4].

In the present investigation, in light of the high expression of miR-377 in the serum of the ACS patients, we further analyzed the diagnostic ability of miR-377 by conducting an ROC curve analysis. The results demonstrated that the expression of miR-377 had high diagnostic accuracy that could distinguish the ACS patients from the healthy controls. As a highly characteristic protein of myocardial injury, cTnI has been a key factor involved in the diagnosis of ACS, and we observed that cTnI was significantly elevated in our ACS patients and positively correlated with miR-377. All of these findings suggest the potential of miR-377 as a diagnostic biomarker for ACS. Our study also revealed that the expression of miR-377 in serum was significantly positively correlated with the levels of endothelial injury markers and proinflammatory cytokines. We therefore believe that the expression of miR-377 may participate in the progression of ACS by regulating inflammatory factors and endothelial injury.

To further investigate whether the expression level of miR-377 is related to the involvement of inflammatory factors and endothelial injury in the progression of ACS, we constructed a rat model of ACS by coronary ligation. The miR-377 level in the serum of the ACS rats was significantly increased, and this result is consistent with the expression of miR-377 in the ACS patients, indicating that miR-377 has a crucial role in the pathogenesis of ACS. By regulating the expression of miR-377 *in vivo*, we also observed that reducing the expression of miR-377 significantly inhibited the expression of pro-inflammatory factors and endothelial injury markers in the serum of the ACS rats, suggesting that reducing miR-377 can significantly inhibit the inflammatory response of ACS and may alleviate the progression of ACS.

It was reported that miR-377 promotes the inflammation of white adipose tissue and inhibits insulin sensitivity to a certain extent by inhibiting sirtuin-1 (SIRT1) [34]. The long noncoding (lnc)RNA NEAT1 affects the expression of SIRT1, VEGF, and B-cell lymphoma-extra large (BCL-XL) by targeting miR-377 to promote oxygen-glucose deprivation-induced cerebral vascular endothelial cell survival and angiogenesis [35]. In addition, miR-377 inhibits high glucose- and hypoxia-induced retinal endothelial cell angiogenesis and the inflammatory response by targeting SIRT1 [19]. We thus speculate that the effect of miR-377 on the inflammatory response and endothelial injury markers in ACS

may be achieved through a targeted regulation of SIRT1, but the specific mechanism of action of miR-377 in ACS needs further study.

There are some study limitations to address. We did not determine the time-course values of the expression of miR-377 in the rat model. In addition, although miR-377 was reported to reduce the myocardial infarct size in myocardial ischemic heart disease [30] and heart failure [31], we did not evaluate the effect of miR-377 on the infarct size of the ACS rats. We will focus on this in a future investigation of the mechanisms underlying the effects of miR-377.

In summary, the results of this study confirmed that the expression of miR-377 is a potential diagnostic marker for patients with ACS. A decrease in the level of miR-377 may improve the progression of ACS by affecting the endothelial injury and inflammatory response in the process of ACS. Reducing the expression of miR-377 may thus have the potential to improve ACS treatment.

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