Research Paper

Allium mongolicum Regel Flavonoids Alleviate Hypoxia/Reoxygenation-Induced Cardiomyocyte Injury by Downregulating lncRNA TALNEC2

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Zhang *et al.*: Mechanism of *Allium mongolicum* Regel Flavonoids on Cardiomyocyte Injury

To explore the effect and possible mechanism of *Allium mongolicum* Regel flavonoids on cardiomyocyte injury induced by hypoxia/reoxygenation. H9C2 cardiomyocytes were induced by hypoxia/reoxygenation and treated with different doses of *Allium mongolicum* Regel flavonoids. H9C2 cells were transfected with si-negative control/si-TALNEC2 and treated with hypoxia/reoxygenation. Besides, cells transfected with plasmid cloning deoxyribonucleic acid/plasmid cloning deoxyribonucleic acid-TALNEC2 were treated with *Allium mongolicum* Regel flavonoids and induced with hypoxia/reoxygenation. Malondialdehyde, glutathione peroxidase and superoxide dismutase levels were tested to evaluate oxidative stress. Apoptosis rate was analyzed by flow cytometry. TALNEC2 expression was examined using quantitative reverse transcription-polymerase chain reaction, and cleaved caspase-3 and cleaved caspase-9 protein levels were tested by Western blot. *Allium mongolicum* Regel flavonoids could reduce malondialdehyde level, apoptosis rate, cleaved caspase-3 level, cleaved caspase-9 level, and TALNEC2 expression, while enhanced glutathione peroxidase and superoxide dismutase levels in hypoxia/reoxygenation-induced H9C2 cells in a dose-dependent manner. After transfection of si-TALNEC2, malondialdehyde level, apoptosis rate, cleaved caspase-3 level, and cleaved caspase-9 level were reduced, while superoxide dismutase and glutathione peroxidase levels were enhanced. Transfection of plasmid cloning deoxyribonucleic acid-TALNEC2 could abolish the effect of *Allium mongolicum* Regel flavonoids on cardiomyocyte injury. *Allium mongolicum* Regel flavonoids could inhibit hypoxia/reoxygenation-induced cardiomyocyte apoptosis and oxidative stress *via* reducing TALNEC2 expression.

Key words: *Allium mongolicum* Regel flavonoids, hypoxia/reoxygenation, TALNEC2, cardiovascular disease, malondialdehyde

The mortality of cardiovascular disease is increasing year by year in China[1,2]. Although percutaneous coronary intervention and other treatments have achieved good results, reperfusion therapy can aggravate myocardial tissue damage and cause arrhythmia and other side effects[3,4]. Oxidative stress and apoptosis can cause myocardial Ischemia-Reperfusion (I/R) injury[5,6]. Active ingredients of Traditional Chinese Medicine (TCM) have anti-apoptosis and anti-oxidative stress effects, and can be used to alleviate myocardial I/R injury[7,8]. Therefore, it is of great significance to find effective TCM active ingredients and reveal their potential molecular mechanisms for improving myocardial I/R injury.

Allium mongolicum Regel, belongs to *Allium* genus of Liliaceae, contains many active ingredients and have certain medicinal value[9]. Studies have shown that *Allium mongolicum* Regel Flavonoids (AMRF) can promote the contraction of intestinal smooth muscle and improve constipation in mice[10]. Importantly, AMRF has been confirmed to have anti-oxidant, anti-apoptosis and anti-inflammatory properties[11-13]. However, whether AMRF can improve myocardial I/R injury by suppressing cardiomyocyte apoptosis and oxidative stress is still unknown.

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Long noncoding RNA (lncRNA) has been confirmed to be involved in human diseases development[14,15]. Previous study suggested that lncRNA TALNEC2 knockdown alleviated cerebral I/R injury *via* inhibiting neuronal apoptosis and inflammation[16,17]. Moreover, TALNEC2 was overexpressed in myocardial ischemic patients, and its overexpression could promote Hypoxia-induced Cardiomyocytes (H9C2) injury[18]. Here, we found that AMRF exerted an inhibitory effect on TALNEC2 expression. However, whether AMRF can improve myocardial I/R injury through regulating TALNEC2 expression is unclear.

Based on the above, our study investigated whether AMRF affected myocardial I/R injury *via* regulating TALNEC2 using Hypoxia/Reoxygenation (H/R)-induced H9C2 cells.

MATERIALS AND METHODS

Preparation of AMRF:

Allium mongolicum Regel (Sihehui Trading, Inner Mongolia, China) was extracted by 75 % ethanol for 2 h (70°), and then the supernatant was obtained by centrifugation. The supernatant was concentrated under the reduced pressure by a rotary evaporator. Sodium hydroxide reaction method was used to determine the composition of flavonoids in the extract (obtained 12.96 mg/g AMRF). AMRF was diluted by Dimethylsulfoxide (DMSO) to prepare different concentrations.

Cell culture and grouping:

H9C2 cells (Procell, Wuhan, China) were cultured in Dulbecco's Modified Eagle Medium (DMEM) containing 10 % Fetal Bovine Serum (FBS). To construct H/R cell model, H9C2 cells were cultured under hypoxia condition (5 % Carbon dioxide (CO_2), 95 % Nitrogen (N_2) and 0.1 % Oxygen (O2)) for 6 h and then performed reoxygenation (5 % CO_2 and 95 % air) for 12 h[19]. Normal cultured cells were used as control group. H9C2 cells were treated with different concentrations (25, 50, and 100 µg/ml) of AMRF for 24 h and then induced with H/R, which were recorded as H/R+low-AMRF group, H/R+middle-AMRF group and H/R+high-AMRF group, respectively. H9C2 cells were transfected with si-NC/si-TALNEC2 using Lipofectamine 3000 (Invitrogen, Carlsbad, California, United states of America (USA)) and then induced with H/R, which were recorded as H/R+si-NC group and H/R+si-TALNEC2 group. Also, H9C2 cells transfected with plasmid cloning deoxyribonucleic acid (pcDNA)/pcDNA-TALNEC2 were treated with 100 µg/ml AMRF and induced with H/R, which were recorded as H/R+high-AMRF+pcDNA group and H/R+high-AMRF+pcDNA-TALNEC2 group.

Assessing of oxidative stress:

H9C2 cells were collected and lysed by repeated freeze-thaw method. Malondialdehyde (MDA), Glutathione Peroxidase (GSh-Px) and Superoxide Dismutase (SOD) levels were detected by corresponding kits according to kit instructions.

Flow cytometry:

H9C2 cells were digested to collect cell suspensions. After suspended with binding buffer, cells were stained with Annexin V-Fluorescein Isothiocyanate (FITC) and Propidium Iodide (PI) (Beyotime, Shanghai, China), and cell apoptosis rate was detected by FACS Calibur flow cytometry.

Quantitative Reverse Transcription Polymerase Chain Reaction (qRT-PCR):

Total Ribonuclic Acid (RNA) was extracted and complementary DNA (cDNA) was synthesized. qRT-PCR was amplified using SYBR Green (Invitrogen), cDNA and specific primers of TALNEC2. Relative expression was calculated by $2^{-\Delta\Delta Ct}$ method.

Western blot:

Radioimmunoprecipitation Assay (RIPA) buffer was used to extract total protein. Protein was taken for Sodium Dodecyl Sulphate-Polyacrylamide Gel Electrophoresis (SDS-PAGE) reaction and Polyvinylidene Difluoride (PVDF) membrane transferring. Membrane was incubated with anti-cleaved caspase-3 (ab90437; 1:1000), anti-cleaved caspase-9 (1:1000), anti-Glyceraldehyde 3-Phosphate Dehydrogenase (GAPDH) (1:2500, ab9485), and secondary antibody (1:50000, ab205718). Protein bands were visualized by Enhanced Chemiluminescence (ECL) reagent (Beyotime) and quantitatively analyzed by Quantity One® software.

Statistical analysis:

Data were expressed as $\bar{x}\pm s$ and analyzed by Statistical Package for the Social Sciences (SPSS) 21.0 software. Student's t-test and Analysis of Variance (ANOVA) were used for comparisons.

p<0.05 was considered significant difference.

RESULTS AND DISCUSSION

MDA level was enhanced, while GSH-Px and SOD levels were suppressed in the H/R group (Table 1). Furthermore, MDA level was reduced, while GSH-Px and SOD levels were increased in the H/R+low-AMRF, H/R+middle-AMRF and H/R+high-AMRF groups (Table 1).

Apoptosis rate, cleaved caspase-3 and cleaved caspase-9 levels were enhanced in the H/R group (fig. 1A), while were reduced in the H/R+low-AMRF, H/R+middle-AMRF and H/R+high-AMRF groups (Table 2 and fig. 1B).

TALNEC2 level was enhanced in the H/R group, while was reduced in the H/R+low-AMRF, H/R+middle-AMRF and H/R+high-AMRF groups (Table 3). MDA level was decreased, while GSH-Px and SOD levels were increased in H/R+si-TALNEC2 group (Table 4). Apoptosis rate, cleaved caspase-3 and cleaved caspase-9 levels were reduced in H/R+si-TALNEC2 group (Table 5 and fig. 2). As shown in fig. 3 and Table 6, MDA level, apoptosis rate, cleaved caspase-3 and cleaved caspase-9 levels were enhanced, while GSH-Px and SOD levels were decreased in the H/R+high-AMRF+pcDNA-TALNEC2 group.

TABLE 1: EFFECTS OF AMRF ON H/R-INDUCED CELL OXIDATIVE STRESS

Group	MDA (nmol/l)	SOD (U/ml)	GSH-Px (U/ml)
Control	5.62±0.49	68.44±5.92	82.78±6.86
H/R	45.46±4.29*	21.22±2.12*	33.24±3.02*
H/R+low-AMRF	31.61±3.13$^{\#}$	34.25±3.37$^{\#}$	45.03±4.08$^{\#}$
H/R+middle-AMRF	19.91±1.77$^{\#\&}$	46.16±4.41$^{\#\&}$	60.02±4.09$^{\#\&}$
H/R+high-AMRF	9.87±0.86$^{\#\&\$}$	57.65±5.52$^{\#\&\$}$	74.42±6.65$^{\#\&\$}$
F	369.497	155.151	139.85
p	0.000	0.000	0.000

Note: *p<0.05 *vs.* H/R; $^{\#}$p<0.05 *vs.* H/R+low-AMRF; $^{\&}$p<0.05 *vs.* H/R+middle-AMRF and $^{\$}$p<0.05 *vs.* H/R+high-AMRF groups

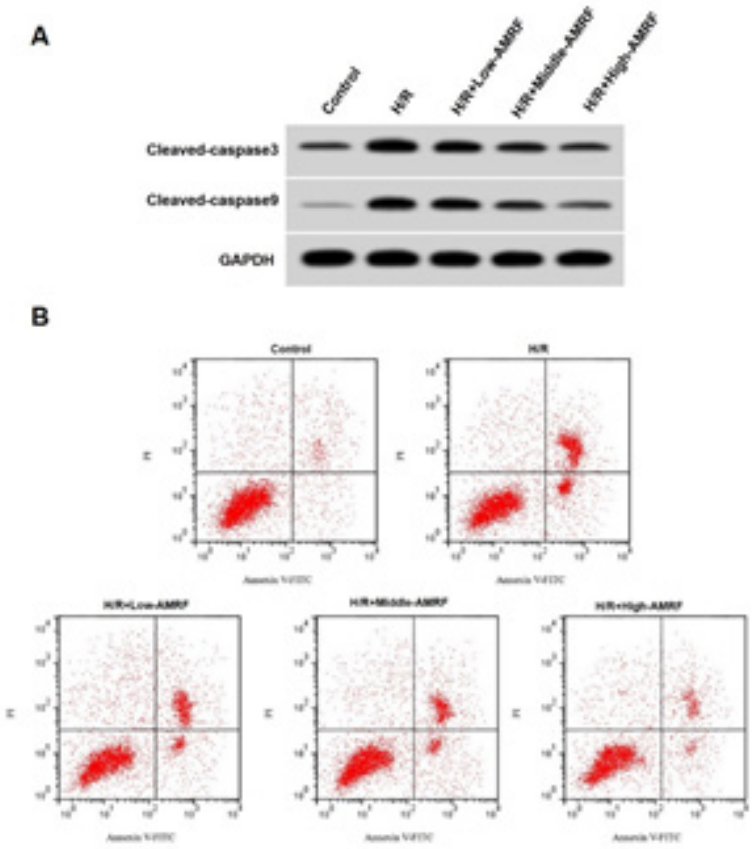

Fig. 1: Effects of AMRF on H/R-induced apoptosis, (A): Western blot and (B): Flow cytometry

TABLE 2: EFFECTS OF AMRF ON H/R-INDUCED APOPTOSIS

Group	Apoptosis rate (%)	Cleaved caspase-3	Cleaved caspase-9
Control	5.32±0.45	0.25±0.02	0.12±0.02
H/R	32.74±2.94*	0.79±0.06*	0.58±0.04*
H/R+low-AMRF	23.34±2.34$^{\#}$	0.64±0.05$^{\#}$	0.42±0.03$^{\#}$
H/R+middle-AMRF	16.15±1.42$^{\#\&}$	0.51±0.04$^{\#\&}$	0.31±0.03$^{\#\&}$
H/R+high-AMRF	8.61±0.74$^{\#\&\$}$	0.34±0.03$^{\#\&\$}$	0.18±0.02$^{\#\&\$}$
F	329.932	239.650	367.714
p	0.000	0.000	0.000

Note: *p<0.05 *vs.* H/R; $^{\#}$p<0.05 *vs.* H/R+low-AMRF; $^{\&}$p<0.05 *vs.* H/R+middle-AMRF and $^{\$}$p<0.05 *vs.* H/R+high-AMRF groups

TABLE 3: EFFECTS OF AMRF ON TALNEC2 EXPRESSION

Group	TALNEC2
Control	1.00±0.00
H/R	3.54±0.27*
H/R+low-AMRF	2.66±0.23$^{\#}$
H/R+middle-AMRF	1.98±0.12$^{\#\&}$
H/R+high-AMRF	1.36±0.12$^{\#\&\$}$
F	302.635
p	0.000

Note: *p<0.05 *vs.* H/R; $^{\#}$p<0.05 *vs.* H/R+low-AMRF; $^{\&}$p<0.05 *vs.* H/R+middle-AMRF and $^{\$}$p<0.05 *vs.* H/R+high-AMRF groups

TABLE 4: EFFECTS OF TALNEC2 KNOCKDOWN ON H/R-INDUCED OXIDATIVE STRESS

Group	TALNEC2	MDA (nmol/l)	SOD (U/ml)	GSH-Px (U/ml)
H/R+si-NC	1.00±0.00	48.79±4.41	20.58±2.01	31.54±3.14
H/R+si-TALNEC2	0.32±0.03*	15.54±1.22*	50.31±4.07*	67.07±5.08*
t	68.000	21.800	19.649	17.848
p	0.000	0.000	0.000	0.000

Note: *p<0.05 *vs.* H/R+si-TALNEC2 group

TABLE 5: EFFECTS OF TALNEC2 KNOCKDOWN ON H/R-INDUCED APOPTOSIS

Group	Apoptosis rate (%)	Cleaved caspase-3	Cleaved caspase-9
H/R+si-NC	34.23±3.02	0.77±0.04	0.57±0.05
H/R+si-TALNEC2	12.69±1.26*	0.40±0.04*	0.24±0.02*
t	19.748	19.622	18.384
p	0.000	0.000	0.000

Note: *p<0.05 *vs.* H/R+si-TALNEC2 group

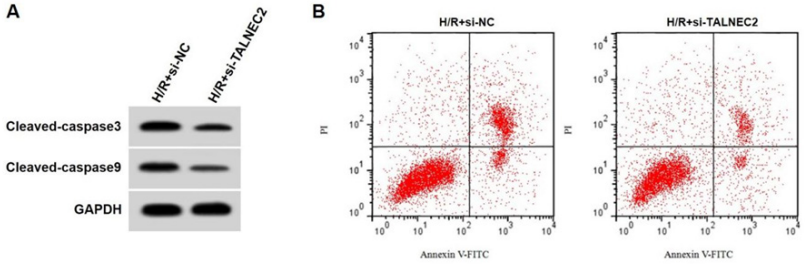

Fig. 2: Effects of TALNEC2 knockdown on H/R-induced apoptosis, (A): Western blot and (B): Flow cytometry

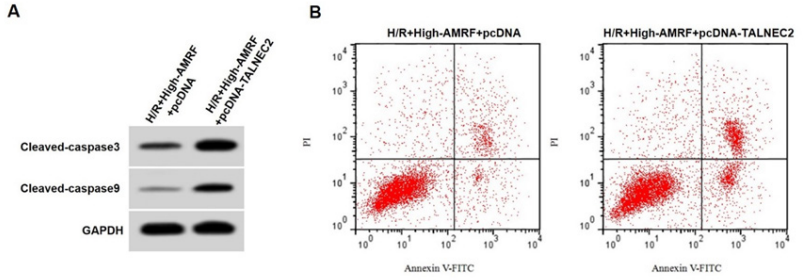

Fig. 3: Effects of TALNEC2 overexpression on cell apoptosis, (A): Western blot and (B): Flow cytometry

TABLE 6: EFFECTS OF TALNEC2 OVEREXPRESSION ON CELL INJURY

Group	TALNEC2	MDA (nmol/l)	SOD (U/ml)	GSH-Px (U/ml)	Apoptosis rate (%)	Cleaved caspase-3	Cleaved caspase-9
H/R+high-AMRF+pcDNA	1.00±0.00	9.51±0.83	59.09±4.71	76.29±6.92	8.26±0.62	0.31±0.03	0.17±0.02
H/R+high-AMRF+pcDNA-TALNEC2	3.26±0.29*	33.24±3.02*	32.75±2.91*	42.99±4.18*	22.04±1.78*	0.68±0.04*	0.47±0.03*
t	23.379	22.730	14.273	13.228	21.932	22.200	24.962
p	0.000	0.000	0.000	0.000	0.000	0.000	0.000

Note: *p<0.05 *vs.* H/R+high-AMRF+pcDNA-TALNEC2 group

Cardiomyocyte ischemia causes oxidative stress, and reperfusion causes cardiomyocyte apoptosis[20,21]. Studies have shown that TCM can inhibit cardiomyocyte apoptosis and oxidative stress by regulating multiple targets[22,23]. lncRNA has been confirmed to be abnormally expressed in myocardial I/R injury[24,25]. However, whether lncRNA can be served as a potential target for TCM to alleviate myocardial I/R injury needs to be further explored.

The polysaccharides and flavonoids of *Allium mongolicum* Regel may slow down the progression of many diseases[11-13]. Similar to the reports of previous studies[26,27], we found that H/R induction elevated MDA level and decreased GSH-Px and SOD levels in cardiomyocytes, suggesting that H/R induction promoted oxidative stress in cardiomyocytes. Further studies revealed that AMRF reduced MDA level, while enhanced GSH-Px and SOD levels in H/R-induced cardiomyocytes, indicating that AMRF could inhibit cardiomyocyte oxidative stress. Besides, H/R induced cardiomyocyte apoptosis, which were consistent with the previously studies[28,29]. Furthermore, H/R-induced apoptosis could be inhibited with the increasing of AMRF concentrations, revealing that AMRF repressed H/R-induced apoptosis in cardiomyocytes.

TALNEC2 was upregulated in cerebral I/R injury mouse models, which promoted neuronal apoptosis to facilitate cell injury[16,17]. Besides, inhibition of TALNEC2 attenuated hypoxia-induced injury in mouse embryonic osteoblasts[30]. Our study revealed that TALNEC2 expression was elevated in H/R-induced cardiomyocytes, and AMRF was able to reduce TALNEC2 expression in a concentration-dependent manner. Furthermore, TALNEC2 knockdown inhibited cardiomyocyte injury, whereas its upregulation attenuated the inhibitory effect of AMRF on cardiomyocyte injury. Here, AMRF mitigated myocardial I/R injury by decreasing TALNEC2 level.

In summary, AMRF inhibited H/R-induced apoptosis and oxidative stress in cardiomyocytes depending on reducing TALNEC2 expression. Our findings confirmed that TALNEC2 might serve as a potential target for AMRF in treating myocardial I/R injury.

Conflict of interests:

The authors declared no conflict of interests.

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