SIRT1 suppresses cardiomyocyte apoptosis in diabetic cardiomyopathy: An insight into endoplasmic reticulum stress response mechanism

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1. Introduction

Diabetic cardiomyopathy (DCM) is characterized by ventricular systolic dysfunction and (or) diastolic dysfunction that occur in patients with diabetes independent of coronary artery disease, hypertension, and other cardiovascular diseases [1]. A recent study reported that DCM was relatively common in the diabetic community with a prevalence of 1.1%, but the morbidity and mortality of patients with DCM are high [2]. Although the exact mechanism of DCM pathogenesis is still unclear, cardiac apoptotic cell death has been shown to play an important role in the development of DCM [3,4]. Myocardocyte apoptosis can be caused by different mechanisms, such as palmitate toxicity, free radicals formation, endoplasmic reticulum (ER) stress, membrane destabilization, and inflammation [5]. Recently, ER stress–dependent apoptosis was well-established [6–8]. In addition, Li Z et al. [9] reported that ER stress had been found in the myocardium of streptozotocin (STZ)–induced diabetic rats, and ER stress was associated with apoptosis of myocardocyte in diabetic rats. Therefore, ER stress plays a significant role in diabetes-induced cardiac cell death.

Sirtuin 1 (SIRT1) is a nicotinamide adenine dinucleotide NAD(+)–dependent deacetylase involved in the regulation of metabolism, cell survival, and organismal lifespan [10]. Increasing number of evidence showed beneficial effects of SIRT1 activation in treatment of diabetes and its complications [11–15]. However, the relationship between SIRT1 and diabetes-induced myocardocyte apoptosis is not fully investigated.

In this study, we hypothesize that SIRT1 can decrease diabetes-induced apoptosis in cardiomyocyte via inhibition of ER stress. In
addition, potential mechanisms underlying the SIRT1 attenuation of ER stress in cardiomyocyte apoptosis have been explored in present study.

2. Materials and methods

Unless otherwise stated, all the chemical reagents in this study were purchased from Sigma Chemical Co. (St. Louis, USA). H9C2 embryonic rat heart-derived cells were obtained from the Institute of Biochemistry and Cell Biology (Shanghai Institute for Biological Science, the Chinese Academy of Sciences, Shanghai, China). The details regarding the preparation of AGE proteins are included in the Supplementary materials.

2.1. Animals

All experiments were performed according to the Guidelines of Animal Experiments from the Committee of Medical Ethics at the National Health Department of China and were approved by the Laboratory Center of Shanghai Tenth People’s Hospital. We also adhered to the statement of ethical publishing as it appears in the International of Cardiology. Thirty male Sprague–Dawley (SD) rats that weighed around 200 g were purchased from the Shanghai Slac Laboratory Animal Co. Ltd., and housed in plastic cages with well-ventilated stainless steel grid tops at room temperature in a 12-hour light/dark cycle. Diabetes was induced in the rats by high-fat diet and a low dose of STZ as reported previously [16]. Detailed managements of animals are

Fig. 1. Effect of SIRT1 activator resveratrol on heart/body weight ratio, cardiac dysfunction, and cardiomyocyte apoptosis in STZ-induced diabetic rats. (A) Heart/body weight ratio is lower in resveratrol-treated group. (B) The left ventricular posterior wall is significantly reduced at 32 weeks in diabetic rats treated with resveratrol. (C) Inter-ventricular-septum is higher in diabetic rats without resveratrol treatment at 16 and 32 weeks. (D) Left ventricular ejection fraction is lower in diabetic rats at 16 and 32 weeks, but it was restored in resveratrol-treated rats at 16 and 32 weeks. (E) and (F) deceleration time and E/A ratio are significantly improved in rats treated with resveratrol compared to diabetic untreated rats. (G) Representative TUNEL staining images in the cardiac tissues of rats. (H) Densitometric analysis shows that the rate of cardiomyocyte apoptosis was higher in diabetic rats, and that apoptosis could be inhibited by resveratrol treatment. Black bar: 100 μm. R: resveratrol (RSV). *p < 0.05 indicates significant differences between control and untreated diabetic group. #p < 0.05 indicates significant differences between untreated diabetic group and resveratrol-treated diabetic group.
found in the Supplementary materials. At the end of the study, the rats were anesthetized by using 3% pentobarbital (30 mg/kg, intraperitoneally). Plasma (8–10 mL per animal) was immediately collected from the femoral artery and processed into serum. After being washed in ice-cold saline solution, the hearts of the animals were weighed and carefully isolated for immunohistochemical staining. The remaining cardiac samples were frozen and stored at −80 °C for western blotting and real-time PCR analyses.

2.2. Cardiac structure and function

Transthoracic echocardiography was performed by using an animal specific instrument (Visual Sonics Vevo770, Visual Sonics Inc.). Animals were anesthetized with 1.5% isoflurane-O2 before and after the treatment. Both M-mode and two-dimensional (2D) echocardiograms were obtained using a 12 MHz ultra-band sector transducer (Doppler). Images were obtained from the left and right parasternal window in a supine decubitus position. The following parameters were measured and calculated from M-mode tracing and Doppler echocardiographic imaging: ejection fraction, deceleration time, and the ratio of the early (E) to late (A) ventricular filling velocities. Wall thickness of four segments [anterior, inter-ventricular-septum, lateral, and left ventricular posterior walls] was evaluated on short axis 2D images. Every animal was tested in similar conditions (room temperature, breath, heart rate and blood pressure), and all scans of echocardiographic investigation were performed by two experienced sonographers to ensure the reproducibility.

2.3. TUNEL staining

Isolated cardiac tissues were fixed in 4% paraformaldehyde for 48 h at 4 °C and incubated in 30% sucrose for 2 days. Each cardiac tissue was embedded in paraffin. The paraffin-embedded sections (5 μm thick) were placed on poly-l-lysine-coated slides. The slides were air-dried overnight at room temperature, wrapped, and stored at −70 °C until immunostaining.

Assessment for apoptosis was conducted using a commercially available TUNEL assay kit (Beyotime Biotech Inc., Jiangsu, China). Detailed procedures of TUNEL staining are presented in the Supplementary materials.

Fig. 2. Expression of SERCA2α, SIRT1, GRP 78 B.P. and CHOP in experimental animals. (A) Representative immunohistochemical staining images of the cardiac tissues of rats. (B) Densitometric analysis shows that SERCA2α expression was lower in diabetic group, but its level is higher in rats treated with resveratrol. (C) mRNA expression of SERCA2α in three groups. (D) SIRT1 expression in diabetic group is reduced and resveratrol treatment increases SIRT1 expression. (E) GRP 78 BiP is higher in diabetic rats treated with or without resveratrol. However, there is no difference between diabetic untreated group and resveratrol-treated group. (F) Resveratrol decreases CHOP level in diabetic rats. Values are expressed as means ± SD from triplicate experiments. R: resveratrol (RSV). *p < 0.05 indicates significant differences between control and untreated diabetic group. #p < 0.05 indicates significant differences between untreated diabetic group and resveratrol-treated diabetic group.
2.4. Immunohistochemistry assay

Slides were immersed in 0.3% H2O2 (hydrogen peroxide) for 10 min to abolish endogenous peroxidase activity and rinsed with PBS. The slides were then incubated with 10% non-immune goat serum for 1 h at room temperature to block non-specific staining, before overnight incubation with the murine anti-SERCA2α antibodies (1:50 dilutions; Cell Signaling Technology, Danvers, Massachusetts, USA), in humidified chambers at 4 °C. All slides were incubated with biotinylated secondary antibody for 1 h at room temperature and HRP-conjugated streptavidin for 20 min at room temperature, followed by detection with a commercial kit (Beyotime).

For quantitative analysis, the average score of 10–20 randomly selected areas was calculated using the National Institutes of Health (NIH) Image Pro Plus 6.0 software.

2.5. Real-time quantitative PCR

Total RNA was extracted from homogenized cardiac tissues (50 mg) by dissolving in TRIzol reagent (Life Technologies, Grand Island, NY, USA) and reversed transcribed to cDNA using PrimeScript RT Reagent Kit (Takara, Tokyo, Japan). SYBR Premix Ex TaqTMII (Takara) and primer pairs were designed for specific genes. The real-time PCR system (Applied Biosystems, Life Technologies) was used to perform real-time quantitative PCR. Detailed information and the oligonucleotide primers for target genes are listed in the Supplementary materials.

2.6. Cell culture and cell viability assay

H9C2 cells were cultured in high glucose Dulbecco’s modified Eagle medium, supplemented with 10% fetal bovine serum, 100 U/mL of penicillin and 100 μg/mL streptomycin at 37 °C in a humidified atmosphere of 5% CO2. The cardiomyocytes were then divided into the following groups: (1) BSA group, in which cardiomyocytes were incubated in BSA for additional 48 h; (2) AGE 400 μg/mL group, in which cardiomyocytes were exposed to 400 μg/mL AGES; (3) AGE 400 μg/mL + SIRT1 siRNA group, in which cells were transfected with SIRT1 siRNA (10 nM; Santa Cruz Biotechnology, Inc., CA, USA) and exposed to AGE 400 μg/mL; (4) resveratrol group, in which 10 μM resveratrol was added to the medium before exposure to 400 μg/mL AGES for 2 h.

Viability of H9C2 cells was evaluated using Cell Counting Kit-8 (CCK-8; Dojindo Molecular Technologies, Kumamoto, Japan), according to the manufacturer’s instructions. 100 μL of H9C2 cells was seeded in 96-well plates at a density of 1–2 × 10⁴ cells/well for 24 h and subsequently treated with BSA, AGES, SIRT1 siRNA, and resveratrol for 12, 24 h, and 48 h in complete medium. Wells were incubated with CCK-8 reagent for 2 h, and absorbance at 450 nm was measured with a microplate reader (BioTek, Winooski, VT, USA).

2.7. Cell apoptosis measurements

Apoptosis was detected using an annexin V-FITC/propidium iodide Apoptosis Detection kit (Roche, IN, USA). Cardiomyocytes (1 × 10⁵ cells/well) were double stained with FITC-conjugated annexin V and propidium iodide for 15 min at 20 °C in Ca²⁺-enriched binding buffer, and fluorescence was detected using a flow cytometer (EPICS-XL, Beckman Coulter, Fullerton, USA). At least 10,000 cells were analyzed in each of the three independent experiments.

2.8. Western blot and caspase activities

The total proteins in H9C2 were analyzed by using western blot. Anti-α-actin and anti-ATF6 were purchased from Santa Cruz Biotechnology (Santa Cruz Biotech Inc., CA, USA). Anti-SIRT1, anti-SERCA2α, anti-phosphorylated protein kinase like-endoplasmic reticulum kinase (anti-p-PERK), anti-PERK, anti-phosphorylated eukaryotic initiation factor 2α (anti-p-eIF2α), anti-eIF2α, anti-CCAAT/enhancer-binding protein homologous protein (CHOP), anti-phosphorylated inositol-requiring transmembrane kinase and endonuclease 1α (anti-p-IRE1α), anti-IRE1α, anti-phosphorylated Jun-amino-terminal kinase (anti-p-JNK), and anti-Caspase 12 were purchased from Cell Signaling Technology (Danvers, Massachusetts, USA). Detailed procedures of western blot are described in the Supplementary materials.

The bioactivity of caspase-3 and caspase-9 was measured with a Fluorometric Assay Kit (Abcam, Cambridge, UK). In brief, cell homogenates were incubated with the caspase-3 substrate, DEVD-AFC, or the caspase-9 substrate, LEHD-AFC. The fluorescence of the cleaved substrates was determined at an excitation wavelength of 400 nm and an emission wavelength of 505 nm.

2.9. Statistical analysis

All data are expressed as mean ± SD, and analyzed with Graph-Pad Prism 6.0 software (GraphPad Software, San Diego, CA). All data were tested for Gaussian- or non-Gaussian-distribution. In brief, one-way ANOVA was performed for Gaussian-distributed data, and non-parametric test was performed for non-Gaussian-distributed data. Differences with p < 0.05 were considered statistically significant.

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Fig. 3. Effects of siRNA, resveratrol, and AGES on SIRT1 expression in H9C2 cells. (A) SIRT1 siRNA transfection significantly represses SIRT1 expression in H9C2 cells, and resveratrol increases SIRT1 level at 10 μM. (B) AGE further inhibits SIRT1 level in H9C2 cardiomyocytes. Values are expressed as means ± SD from triplicate experiments. R: resveratrol (RSV). *p < 0.05 indicates significant differences from the control group.
3. Results

3.1. In vivo study

3.1.1. Effect of resveratrol, a SIRT1 activator, on cardiac mass and function in STZ-induced diabetic rats

To investigate the role of SIRT1 in the cardiac hypertrophy and cardiac dysfunction, we used resveratrol, a SIRT1 activator, to treat the animals. The final body weights of rats were significantly higher in diabetic rats treated with resveratrol compared to untreated diabetic rats (Supplemental Table 2, *p < 0.05*). However, a significant elevation of the heart/body weight ratio was observed in diabetic rats without resveratrol treatment (*Fig. 1A, p < 0.05*).

The hearts of the diabetic untreated rats exhibited an increase of the left ventricular posterior wall, inter-ventricular-septum thickness, as well as deceleration time, and a reduction of the left ventricular ejection fraction and ratio of the early (E) to late (A) ventricular filling velocities (E/A ratio) (*Fig. 1B–F, p < 0.05*) as compared to the resveratrol treated rats/control rats.

3.1.2. Changes of SERCA2α, SIRT1, GRP78 B.P. and CHOP in cardiomyocytes of diabetic rats

In order to investigate whether the expression levels of ER stress markers change in the cardiomyocytes of diabetic rats, we compared the levels of these markers in diabetic untreated, resveratrol-treated, and control rats. *Fig. 2A* to *C* shows that the protein and mRNA levels of SERCA2α, SIRT1, GRP78 B.P., and CHOP were significantly altered in diabetic rats compared to control rats.

![Graph](image1.png)

*Fig. 4. Cell apoptosis analysis by flow cytometer. (A) H9C2 cells incubated with AGEs (400 μg/ml) for 6, 12, 24 and 48 h. (B) Cells treated with 50, 100, 200, and 400 μg/ml of AGEs for 24 h prior to analysis of apoptosis. (C) Flow cytometry dot plots show necrotic and apoptotic cell populations, based on annexin V and propidium iodide staining. In each figure, the upper left quadrant corresponds to necrotic cells (annexin V−/propidium iodide +), the upper right quadrant contains the late apoptotic cells (annexin V+/propidium iodide +), the lower left quadrant shows viable cells (annexin V−/propidium iodide −), and the lower right quadrant represents the early apoptotic cells (annexin V+/propidium iodide −). (D) The rate of apoptosis as quantified by flow cytometry. *p < 0.05* indicates significant differences from the control group. *#p < 0.05* indicates significant differences from resveratrol-treated cells.

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expression of SERCA2α, a marker of ER stress, were reduced in the left ventricular cardiomyocytes of diabetic untreated rats compared to the control rats and resveratrol-treated rats \( (p < 0.05) \). Similarly, SIRT1 expression was significantly decreased in cardiac tissue of diabetic untreated rats, and resveratrol treatment could markedly restore SIRT1 expression \( (Fig. 2D, p < 0.05) \). GRP78 BiP was significantly increased in diabetic rats treated with or without resveratrol \( (Fig. 2E, p > 0.05) \). However, resveratrol markedly decreased CHOP expression in cardiomyocytes of diabetic rats \( (Fig. 2F, p > 0.05) \).

3.2. In vitro study

3.2.1. Effects of SIRT1 siRNA and resveratrol on SIRT1 expression in H9C2 cardiomyocytes

To test whether SIRT1 expression was affected by SIRT1 siRNA transfection and resveratrol activation, western blotting analyses were performed in H9C2 cells to examine protein expression of SIRT1. Fig. 3A shows that the SIRT1 protein expressions in H9C2 cells were significantly inhibited by SIRT1 siRNA silencing technique, and resveratrol significantly increased SIRT1 expression at 10 μM. Moreover, SIRT1 expression levels were further decreased by siRNA transfection and AGE treatment at 400 μg/mL for 24 h \( (Fig. 3B) \). However, resveratrol could increase the SIRT1 protein levels in H9C2 cardiomyocytes treated with 400 μg/mL AGEs \( (Fig. 3B) \).

3.2.2. Effect of resveratrol, a SIRT1 activator, on AGE-induced cell apoptosis

Next, we investigated whether AGE-BSA could induce apoptosis in cells. Cardiomyocytes were incubated with 400 μg/mL of AGE-BSA for 6, 12, 24, and 48 h or treated with 50, 100, 200, and 400 mg/mL of AGE-BSA for 24 h. Apoptosis was determined by flow cytometer. As shown in Fig. 4A, exposure of H9C2 cells to AGE-BSA induced a dose-dependent increase in apoptosis for 24 h.

To further confirm the inhibitory effect of SIRT1 on AGEs-induced apoptosis, annexin V/propidium iodide dual staining and flow cytometer analysis were performed. Representative images from flow cytometer assays and summarized data are presented in Fig. 4C and D. These analyses revealed that, compared to the control, AGES increased the late apoptosis rate and early apoptosis rate, from 0.8 ± 0.3% to 72.5 ± 2.5%, respectively \( (p < 0.05) \). Silencing of SIRT1 with siRNA exhibited an increasing rate of apoptosis after AGE simulation \( (Fig. 4C and D, p < 0.05) \). Resveratrol significantly reduced the late apoptosis rate and early apoptosis rate of cardiomyocytes compared to AGE treated cells \( (Fig. 4C and D, p < 0.05) \).

3.2.3. Changes in SERCA2α in the SIRT1-silenced and AGE-incubated H9C2 cardiomyocytes

We used AGES to induce ER stress in cardiomyocytes similar to a previous report \[17\]. In this study, AGES \( (400 \mu g/mL) \) significantly decreased SERCA2α expression in a time-dependent manner, while silencing SIRT1 further reduced SERCA2α expression. Resveratrol \( (10 \mu M) \) treatment restored the SERCA2α protein expression in H9C2 cardiomyocytes \( (Fig. 5A and B) \).

3.2.4. Effect of resveratrol, a SIRT1 activator, on ER stress-related signaling pathways

ATF6-mediated pathway and PERK pathway are well-known pathways related to ER stress. In this study, the level of ATF6 p50 was markedly increased after AGES \( (400 \mu g/mL) \) treatment and SIRT1 siRNA silencing at 6, 12, and 24 h \( (Fig. 5C and D, p < 0.05) \). Resveratrol \( (10 \mu M) \) treatment reduced ATF6 p50 expression at 12 h compared to AGES and SIRT1 siRNA treated cells \( (Fig. 5C, p < 0.05) \). Additionally, the level of phosphorylated PERK was markedly increased after AGE \( (400 \mu g/mL) \) treatment and SIRT1 siRNA silencing at 6, 12, and 24 h \( (Fig. 5D and E, p < 0.05) \).

Moreover, the level of phosphorylated eIF2α, downstream molecules of ATF6 and PERK, was increased by AGE treatment and SIRT1 silencing \( (Fig. 5D and E) \). However, resveratrol treatment significantly reduced the expression of phosphorylated eIF2α at 12 and 24 h \( (p < 0.05, Fig. 5D and F) \). Similarly, the level of phosphorylated IRE1α and phosphorylated JNK 1/2 was significantly increased after AGE \( (400 \mu g/mL) \) treatment and SIRT1 siRNA silencing at 6, 12, and 24 h \( (Fig. 5G and I) \). The levels of phosphorylated IRE1α and phosphorylated JNK 1/2 were markedly reduced at 12 and 24 h in cells treated with resveratrol \( (Fig. 5G and L, p < 0.05) \).

CHOP was increased after 6 h of AGE incubation and SIRT1 silencing, and these changes were abrogated by treatment with resveratrol \( (Fig. 5J) \) and K \( (p < 0.05) \). The expression of GRP78 BiP was also markedly increased after AGE treatment. However, its level did not reduce in cells treated with resveratrol at 10 μM \( (Fig. 5J and L) \).

3.2.5. Caspase-12, caspase-3, and caspase-9 activities

We observed that the expression of cleaved caspase-12 was increased after AGE incubation and SIRT1 RNA interference at 6, 12, and 24 h, while resveratrol could significantly decrease its expression in a time-dependent manner \( (Fig. 6A and B, p < 0.05) \). Moreover, caspase-3 and caspase-9 were measured to confirm the activities of downstream apoptosis-related proteins of caspase-12. Both caspase-3 and caspase-9 activities were elevated after AGE treatment and SIRT1 silencing at 24 h, which was reduced by resveratrol incubation \( (Fig. 6C and D, p < 0.05) \).

4. Discussion

Growing evidence suggests that SIRT1 can be regarded as a new therapeutic target for the prevention of diseases related to insulin resistance and diabetes \[18\]. However, the exact role of SIRT1 in the prevention and treatment of diabetes and its complications is still poorly understood. The main finding of the present study is the reduction of DCM induced cardiomyocyte apoptosis due to SIRT1 activation in vivo and in vitro. This could be explained by the amelioration of ER stress in cardiomyocytes, and complement findings from our previous study \[12\], which suggested that the SIRT1 activator, resveratrol, might improve diabetic vascular inflammation by inhibiting NF-κB pathway.

Dissection of the pathophysiology of DCM and the understanding of the disease-related remodeling in the heart have progressed considerably in recent years. As a result, unfolded protein response (UPR) has been considered as a novel mechanism \[19\]. Accumulating evidence indicates the disruption of ER homeostasis in DCM \[20–22\]. ER is the central organelle for secretory/transmembrane protein folding, calcium storage, and lipid synthesis. When ER homeostasis disrupted generating adaptive signaling pathways in its lumen (ER stress), the UPR is activated \[23,24\]. If ER stress remains unresolved, apoptosis is triggered as part of the terminal UPR. This involves CHOP, but in some cell types, other pathways downstream of IRE1 have also been implicated \[7\]. These include activation of the protease, caspase 12, and a signaling cascade initiated via the adaptor protein TNF receptor–associated factor 2 (TRAF2), and the apoptosis signal-regulating kinase 1 (ASK1)/c-Jun N-terminal kinase (JNK) protein kinase pathway \[25,26\].

Excess of AGES is one of the most important mechanisms involved in the pathophysiology of chronic diabetic complications \[27\]. Adamopoulos C et al. reported that AGES directly induce ER stress in human aortic endothelial cells, playing an important role in endothelial cell apoptosis \[28\]. Some other studies indicated that blocking RAGE-ER stress scavenging pathways might efficiently inhibit cell death \[29,30\]. In this study, we found that AGES could significantly induce ER stress in H9C2 cardiomyocytes and maybe associated with cell apoptosis. Thus, we provided a novel evidence for the relationship between AGES and ER stress in diabetes-induced cardiomyocyte apoptosis.

SIRT1 deacetylates a diverse array of cellular proteins, including histones, transcription factors, DNA repair proteins, autophagy factors, and others, to modulate metabolism, stress responses, and other cellular processes \[31\]. Many studies demonstrated that SIRT1 activation could increase mammalian lifespan \[32,33\]. Resveratrol, a potent SIRT1
activator, and its related polyphenolic compounds had been documented as possessing health-enhancing effects [34], due to their antioxidant properties [35]. Emerging evidence showed that SIRT1 activation and resveratrol treatment could improve various metabolic health parameters and might have beneficial effect on numerous degenerative diseases at different stages of pathogenesis [12,36,37]. For example, resveratrol also could protect endothelium against high glucose and high fat-induced hyperpermeability via endothelial nitric oxide synthase pathway [38]. Several mechanisms of resveratrol are involved in the treatment for heart failure and cardiomyopathy in vivo and in vitro. Some studies showed that resveratrol ameliorated cardiac dysfunction through AMPK pathway, modulation of calcium handling proteins, and restoration of the SERCA2α expression in cardiomyocytes [39–41]. In our study, we further explored the effect of SIRT1 on ER stress-mediated cardiac dysfunction and apoptosis.

Lee J et al. found that the inhibition of SIRT1 significantly increased the expression of ER stress marker genes in cells [42]. Furthermore, Liu L et al. reported that ethanol-induced cell apoptosis was alleviated via resveratrol by inhibiting ER stress and caspase-12 activation in a SIRT1-dependent manner [43]. A rodent study showed that overexpression of SIRT1 in the liver attenuated hepatic steatosis, ameliorated insulin resistance, and restored glucose homeostasis through inhibition of ER stress [44]. These results suggest that ER stress may be regulated by SIRT1, and hence, SIRT1 can be regarded as a novel therapeutic target.
candidate. Therefore, we suggest that SIRT1 might have an anti-apoptotic function, contributing to the prevention of diabetic cardiac complications.

Although we have observed anti-apoptosis effect of SIRT1 in the cardiomyocytes in the diabetic rat heart, the exact mechanism of SIRT1 regulation of ER stress is more complicated than previously reported. Little is known about the contributions of SIRT1 or resveratrol interaction with other signaling networks in response to the development of DCM. Therefore, further identification of SIRT1 in cardiomyocytes in diabetes will be required to gain more comprehensive information about the beneficial effects of SIRT1 on diabetic heart.

5. Conclusion

In summary, we found that ER stress was enhanced and associated with cell apoptosis in the heart of STZ-induced diabetic rat. SIRT1 may attenuate ER stress-induced cardiomyocyte apoptosis via PERK/eIF2α, ATF6/CHOP, and IRE1α/JNK-mediated pathways (Fig. 7). This study may provide insight into a novel underlying mechanism and a treatment strategy for DCM.

Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2015.04.245.

References


