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Accelerated onset of senescence of endothelial progenitor cells in patients with type 2 diabetes mellitus: Role of dimethylarginine dimethylaminohydrolase 2 and asymmetric dimethylarginine

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ABSTRACT

The risk of cardiovascular complications in diabetic patients is mainly associated with endothelial dysfunction. Reduced number of EPCs and impaired function of EPCs in diabetes result in imbalance of endothelial homeostasis and dysfunction of vessels. In patients with diabetes mellitus, plasma levels of asymmetric dimethylarginine (ADMA) were elevated, while the expression and activity of dimethylarginine dimethylaminohydrolase (DDAH) were reduced. In the present study, we investigated the role of the DDAH2/ADMA pathway in the senescence of EPCs in type 2 diabetic patients and cultured EPCs treated with high glucose. The results showed that the percentage of senescent EPCs increased while the expression of *DDAH2* decreased concomitantly with an increase in the plasma levels of ADMA in patients with type 2 diabetes mellitus (T2DM). Similar results were seen in cultured EPCs treated with high glucose. Exogenous application of ADMA accelerated the senescence of EPCs in a dose-dependent manner, and overexpression of DDAH2 inhibited high glucose-induced EPCs senescence. In addition, it has also been reported that DDAH/ADMA pathway is regulated by silent information regulator 1 (SIRT1) in endothelial cell. In the present study, we found decreased expression of SIRT1 both in T2DM patients and EPCs pretreated with high glucose. And resveratrol (activating SIRT1) inhibited high glucose-induced EPCs senescence by upregulating the expression of DDAH2 and decreasing the levels of ADMA. Taken together, we concluded that DDAH2/ADMA is involved in the accelerated senescence of EPCs in diabetes, which is associated with the activation of SIRT1.

1. Introduction

Diabetes mellitus is a serious disease affecting about 5% of people worldwide, and nearly 50% of diabetic patients die from cardiovascular complications. The maintenance of an intact endothelial layer and improvement of endothelial function are essential for blood vessels to function properly and prevent the development of cardiovascular complications associated with diabetes [1]. Circulating endothelial progenitor cells (EPCs) play a key role in the maintenance of endothelial homeostasis and promote neovascularization [2]. Emerging evidence showed that reduced number of circulating EPCs and impaired function of EPCs are involved in endothelial dysfunction in diabetes [3–5]. Asymmetric dimethylarginine (ADMA), as a novel risk factor for endothelial dysfunction, has been reported to predict adverse cardiovascular events in diabetic patients and accelerate endothelial cell senescence [6–8]. ADMA is metabolized to L-citrulline and dimethylamine by dimethylarginine dimethylaminohydrolase (DDAH). DDAH has two isoforms, DDAH1 and DDAH2 [6,7]. Our previous study showed that DDAH2, predominantly expressed in EPCs, regulated the differentiation of EPCs, decreased the senescence of EPCs, and improved function of EPCs [9]. These results suggest that DDAH2/ADMA may account for, at least in part, the accelerated EPCs senescence and dysfunction in diabetes, and it is therefore

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likely that increasing the expression of DDAH2 could be a novel way to improve EPCs function by inhibiting senescence in diabetes.

The silent information regulator 1 (SIRT1), a NAD^+-dependent protein deacetylases, is central to the lifespan and vascular health. In cultured endothelial cells, high glucose accelerated the onset of senescence of endothelial cells by down- regulating SIRT1 [10,11]. Our previous work demonstrated that interrupting SIRT1 expression affected EPCs differentiation by decreasing DDAH2 expression [9]. Whether DDAH2/ADMA may regulate the senescence of EPCs by SIRT1 in diabetes is unknown.

In the present study, we observed the correlation between DDAH2/ADMA pathway and the number of circulating senescent EPCs in patients with T2DM, and then confirmed the effects of DDAH2/ADMA pathway on high glucose-induced EPCs senescence by exogenous application of ADMA or overexpression of DDAH2. Finally, we investigated the effects of resveratrol (RSV), a SIRT1 activator, on high glucose-induced EPCs senescence.

2. Materials and methods

2.1. Reagents

Endothelial basal medium-2 (EBM-2) was purchased from Lonza (Basel, Switzerland). Lymphocyte separation medium was purchased from Sigma (St. Louis, USA), and Matrigel was purchased from BD Bioscience (MA, USA). Fibronectin was purchased from Millipore (Jaffrey, USA). SYBR Green real-time polymerase chain reaction (PCR) master mix was purchased from Takara (Shiga, Japan). Goat anti-hDDAH2 and goat anti-SIRT1 antibodies were purchased from Abcam (Cambridge, USA), and rabbit anti-β-actin, HRP-anti-goat, and HRP-anti-rabbit antibodies were purchased from Santa Cruz (CA, USA).

2.2. Clinical subjects

We recruited 42 patients with T2DM from the outpatient clinic of Xiangya Hospital, Hunan, China. The fasting blood glucose level in diabetic patients was ≥7.8 mmol/L, and none of diabetic patients was under insulin, and all were treated only with diet (no other medication was used in diabetic patients). 41 healthy controls from individuals attending a routine health screening at the same hospital were recruited. To make the cases and controls matched better in age, gender and coronary artery disease risk factors, the recruitment of the controls was started when general information about the demographic characters and distribution of T2DM risk factors in the initially collected cases were obtained. The controls were apparently healthy and had a negative history of hypertension, diabetes mellitus, ischemic heart disease and chronic heart failure. Information on age, gender, cigarette smoking and alcohol consumption was collected by questionnaire. From all the participants, we took peripheral venous blood samples before breakfast for EPCs isolation and routine blood and biochemistry tests including serum total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and fasting blood glucose (FBG). The relevant characteristics were summarized in Table 1. The study was approved by the local Ethics Committee at Xiangya Hospital of Central South University (Changsha, China), and written informed consent was obtained from all subjects.

Table 1
Characteristics of control and T2DM individuals.

	Control (n = 41)	T2DM (n = 42)
Sex (male/female)	26/15	23/19
Age (years)	53 ± 2	54 ± 3
Smoking	12	8
Drinking	15	17
FBG (mM)	5.6 ± 0.3	13.3 ± 2**
SBP (mm Hg)	111 ± 2	135 ± 4**
DBP (mm Hg)	75 ± 2	80 ± 2
TG (mM)	2.16 ± 0.26	2.45 ± 0.31
TC (mM)	4.73 ± 0.13	4.03 ± 0.34
HDL-C (mM)	1.34 ± 0.05	1.27 ± 0.11*
LDL (mM)	2.44 ± 0.13	3.08 ± 0.29*

*$P < 0.05$, **$P < 0.01$ vs. Control. FBG: fasting blood glucose; SBP: systolic blood pressure; DBP: diastolic blood pressure; TG: triglycerides; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL: low-density lipoprotein.

2.3. EPC isolation

EPCs were cultured according to previously described techniques [12,13]. We have successfully isolated and identified EPCs in our laboratory [9,14]. In brief, mononuclear cells were isolated from the peripheral blood of volunteers by density-gradient centrifugation with Ficoll–Paque™ PREMIUM. The isolated cells were cultivated on six-well plates coated with fibronectin in endothelial basal medium-2 supplemented with endothelial growth medium-2 Single-Quots. After 3 days of culture, non-adherent cells were removed by washing with phosphate-buffered saline (PBS), and adherent cells were reseeded. Thereafter, the medium was changed every 3 days.

2.4. AD-hDDAH2-overexpression

Briefly, the recombinant AD-*hDDAH2*-overexpression (Genechem Shanghai, China) was constructed by homologous recombination between the parental virus genome and the expression cosmid cassette or shuttle vector. To established optimum conditions for EPC lentivirus gene transfer, serum concentration, virus incubation time and virus were measured. Day-3 cultured EPCs were transduced with 20 MOI of AD-*hDDAH2*-overexpression, or AD-GFP for 24 h in 20% serum medium. After transduction, the cells were washed with PBS and incubated in EPC medium that was changed every 3 days. The DDAH2 gene expression was detected on day 6.

2.5. β-Galactosidase activity assay

Cell senescence was determined by senescence-associated β-galactosidase (SA-β-Gal) activity assay as previously described [14]. The quantification of SA-β-gal–positive cells was performed by counting cells at four random fields per dish and assessing the percentage of SA-β-gal–positive cells from at least 1000 cells per field.

2.6. Determination of ADMA level

The protein in plasma or medium was removed using 5-sulfosalicylic acid (5-SSA). The level of ADMA was measured by high-performance liquid chromatography (HPLC) as described previously [15].

2.7. Real-time reverse transcriptase PCR

The mRNA expression of DDAH2 and SIRT1 in EPCs were analyzed by using the ABI 7300 real-time PCR system (Applied Biosystems, Foster City, Calif., USA). The specific primer pairs were shown in Table 2. Reverse transcription reaction was performed with 1 μg total RNA isolated from the cells of each group. For PCR amplification, cDNA was amplified using SYBR Green Real-time PCR

Table 2
Sequences of real-time PCR primers.

Primers	Sense
DDAH2	P+ : 5′-ACAAGGACCCCCGCTAAAA-3′
	P− : 5′-AAGGGAGTCCCCGTCTTCAA-3′
SIRT1	P+ : 5′-GCCTCACATGCAAGCTCTAGTGAC-3′
	P− : 5′-TTCGAGGATCTGTGCCAATCATAA-3′
GAPDH	P+ : 5′-CTGCACCACCAACTGCTTAG-3′
	P− : 5′-AGGTCCACCACTGACACGTT-3′

Master Mix and 0.4 μM of each primer pair. Amplification was carried out starting with an initial step for 30 s at 94 °C, followed by 40 cycles of the amplification step (94 °C 30 s, 60 °C 60 s, and 72 °C 1 min) for DDAH2, SIRT1 and glyceraldehyde 3-phosphate dehydrogenase (GAPDH). All amplification reaction for each sample were carried out in triplicates and the means of the threshold cycles were used to interpolate curves using ABI 7300 SDS software (Applied Biosystems). Results were expressed as the ratio of DDAH2, SIRT1 to GAPDH mRNA, and the value of control group was set at 1.

2.8. Western blot analysis

For Western blotting, the primary antibodies to DDAH2 (1:1000), SIRT1 (1:1000) and β-actin (1:2000). HRP-anti-goat (1:2000) and HRP-anti-rabbit (1:2000) antibodies were also used. Band intensities were densitometrically analyzed, and the results were expressed as the ratio of DDAH2 or SIRT1 to β-actin.

2.9. Statistical analysis

Results are expressed as mean ± S.E.M. The Data were analyzed by *t*-test for 2-group comparisons or one-way analysis of variance, followed by Tukey's test for multiple comparisons. Results were considered statistically significant at $P < 0.05$.

3. Results

3.1. General characteristics of the study participants

Table 1 showed the general characteristics of the study participants. Compared with controls, patients with T2DM had significantly higher FBG ($p < 0.01$), higher systolic blood pressure ($P < 0.001$), lower HDL-C ($P < 0.05$) and higher LDL ($P < 0.05$). The two study groups did not differ with regard to age, gender, smoking, drinking, DBP, TG and TC.

3.2. The accelerated senescence of EPCs in T2DM

The SA-β-Gal staining was used to evaluate the senescence of EPCs. EPCs senescence was accelerated in T2DM group, as characterized by the increased percentages of SA-β-gal positive cells ($P < 0.01$, Fig. 1A), in comparison with those in control group.

3.3. The decreased ADMA and increased DDAH2 in T2DM patients

We observed the plasma levels of ADMA, the expression of DDAH2 in peripheral blood EPCs from T2DM and control

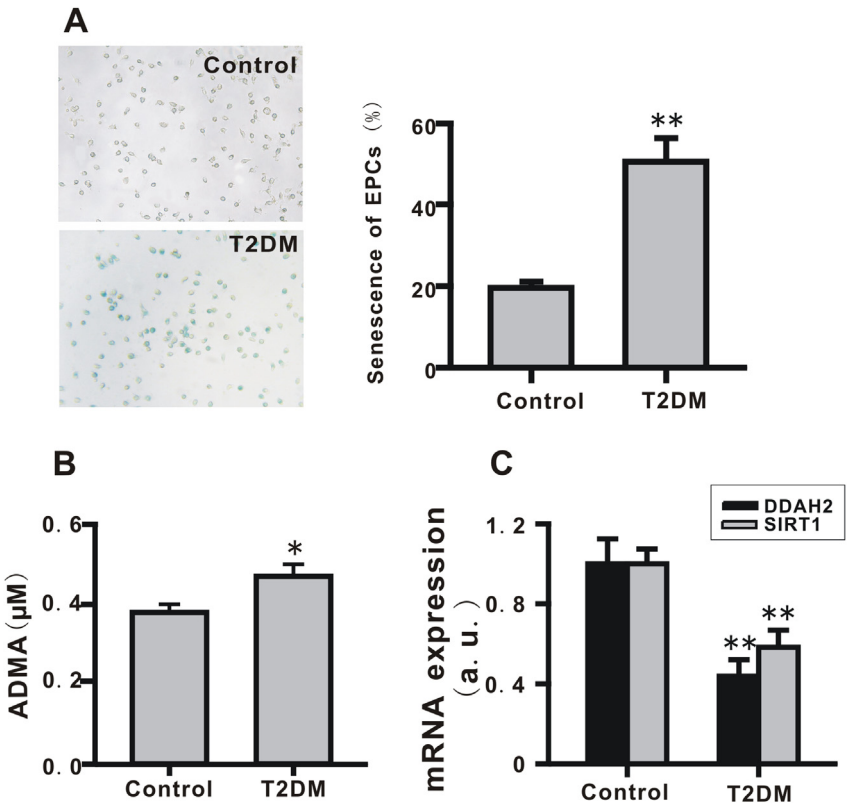

Fig. 1. The senescence of EPC, the plasma levels of ADMA and the mRNA expression of DDAH2 and SIRT1 in EPCs in T2DM patients. (A) Representative images of EPCs senescence in control and T2DM patients. (B) The plasma levels of ADMA in control and T2DM patients. (C) The mRNA expression of DDAH2 and SIRT1 in EPCs from control and T2DM patients. The senescence-associated SA-β-gal positive cells (blue) in EPCs were shown in the representative images, and senescence of cells were increased in T2DM patients. Values are expressed as mean ± SEM ($n = 41–42$). $^{*}P < 0.05$, $^{**}P < 0.01$ vs. control. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

individuals. The plasma levels of ADMA were significantly increased in T2DM group ($P < 0.01$, Fig. 1B). Our previous study showed that EPCs predominantly expressed DDAH2 rather than DDAH1 [9]. Therefore, in the present study, we only detected the mRNA expression of DDAH2 of EPCs. The mRNA expression of DDAH2 of EPCs from T2DM group was markedly decreased compared to control group (Fig. 1C).

3.4. Increased EPCs senescence, decreased ADMA levels and increased DDAH2 expression in EPCs stimulated by high glucose

In cultured EPCs, high glucose accelerated the onset of senescence of EPCs in concentration-dependent manner, and reached a maximal effect at concentration of 30 mmol/L for 48 h (Fig. 2A). Mannitol, as osmotic pressure control, had no effect on EPCs.

To study whether DDAH2/ADMA pathway is involved in the senescence of EPCs in diabetic milieu, we detected the levels of ADMA in the medium, and the expression of DDAH2 in cultured EPCs exposed to high glucose (30 mmol/L, 48 h). The levels of ADMA in cultured EPCs pretreated with high glucose markedly increased (Fig. 2B). Simultaneously, the mRNA and protein expression of DDAH2 of EPCs pretreated with high glucose were markedly decreased (Fig. 2C and D). These results were in consistence with in vivo, indicating that DDAH2/ADMA pathway is involved in the senescence of EPCs in T2DM.

3.5. The role of DDAH2/ADMA in EPCs senescence stimulated by high glucose

To further confirm the role of DDAH2/ADMA pathway in high glucose-induced EPCs senescence, DDAH2 overexpression and exogenous ADMA were used. The efficiency of lentivirus for DDAH2-overexpression was determined by immunofluorescence and real-time PCR. The immunofluorescence analysis of the green fluorescent protein (in the web version) expression was 80%, and DDAH2 mRNA expression successfully increased (Fig. 3A and B). Overexpression of DDAH2 inhibited the increase in EPCs senescence and ADMA levels induced by high glucose (Fig. 3C and D). Furthermore, we also observed the direct effect of exogenous ADMA on EPCs. Exogenous ADMA increased the senescence of EPCs (Fig. 3E) in concentration-dependent manner, similar to that we had observed in high glucose-treated EPCs (Fig. 2A).

3.6. The expression of SIRT1 in T2DM patients and EPCs stimulated by high glucose

To study the role of SIRT1 in the senescence of EPCs in T2DM, we observed the expression of SIRT1 in peripheral blood EPCs from T2DM patients and cultured EPCs exposed to high glucose. Real-time PCR analysis showed that the mRNA expression of SIRT1 in peripheral blood EPCs from T2DM patients was markedly

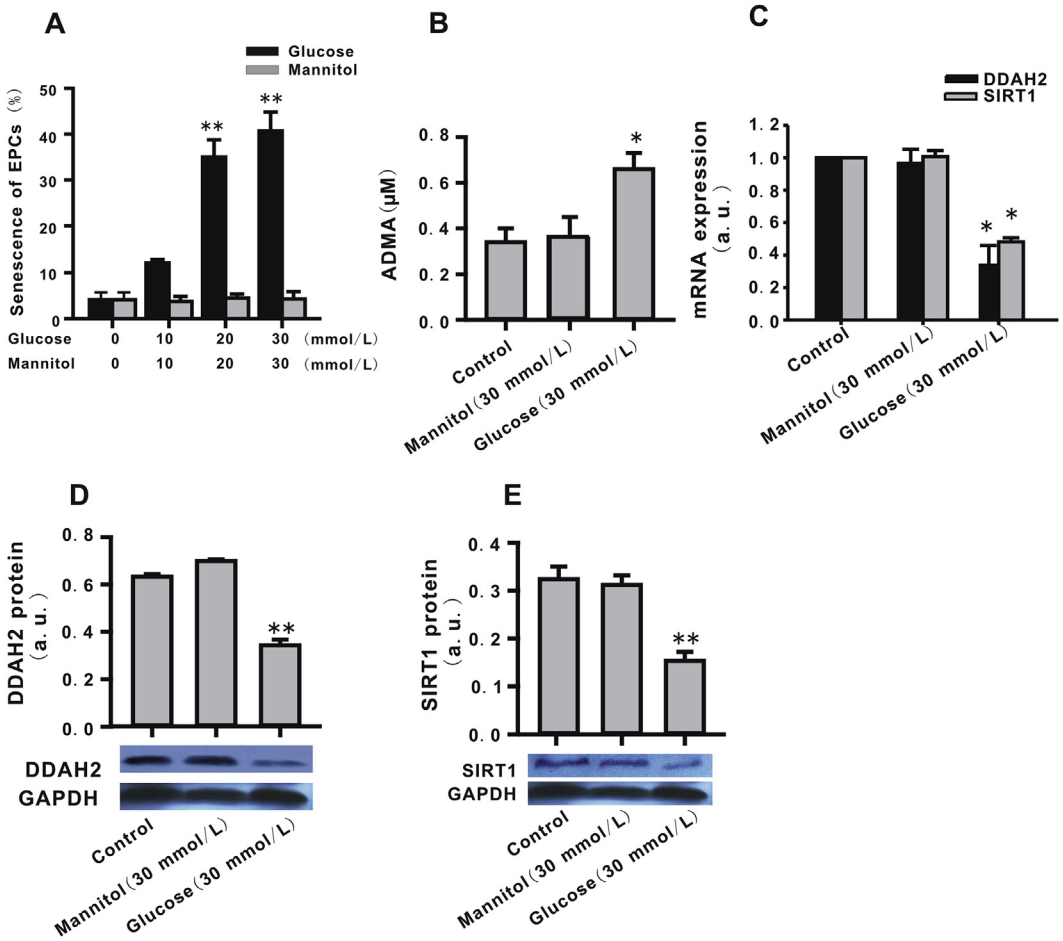

Fig. 2. The senescence of EPC, the levels of ADMA and the expression of DDAH2 and SIRT1 in cultured EPCs pretreated with high glucose. (A) High glucose induced EPCs senescence in a dose-dependent manner. (B) High glucose (30 mmol/L, 24 h) increased the levels of ADMA in the culture medium. (C) The mRNA expression of DDAH2 and SIRT1 in EPCs stimulated by high glucose were decreased. The protein expression of DDAH2 (D) and SIRT1 (E) in EPCs stimulated by high glucose were also decreased. Values are expressed as mean ± SEM (n = 3–4). $^{*}P < 0.05$, $^{**}P < 0.01$ vs. control.

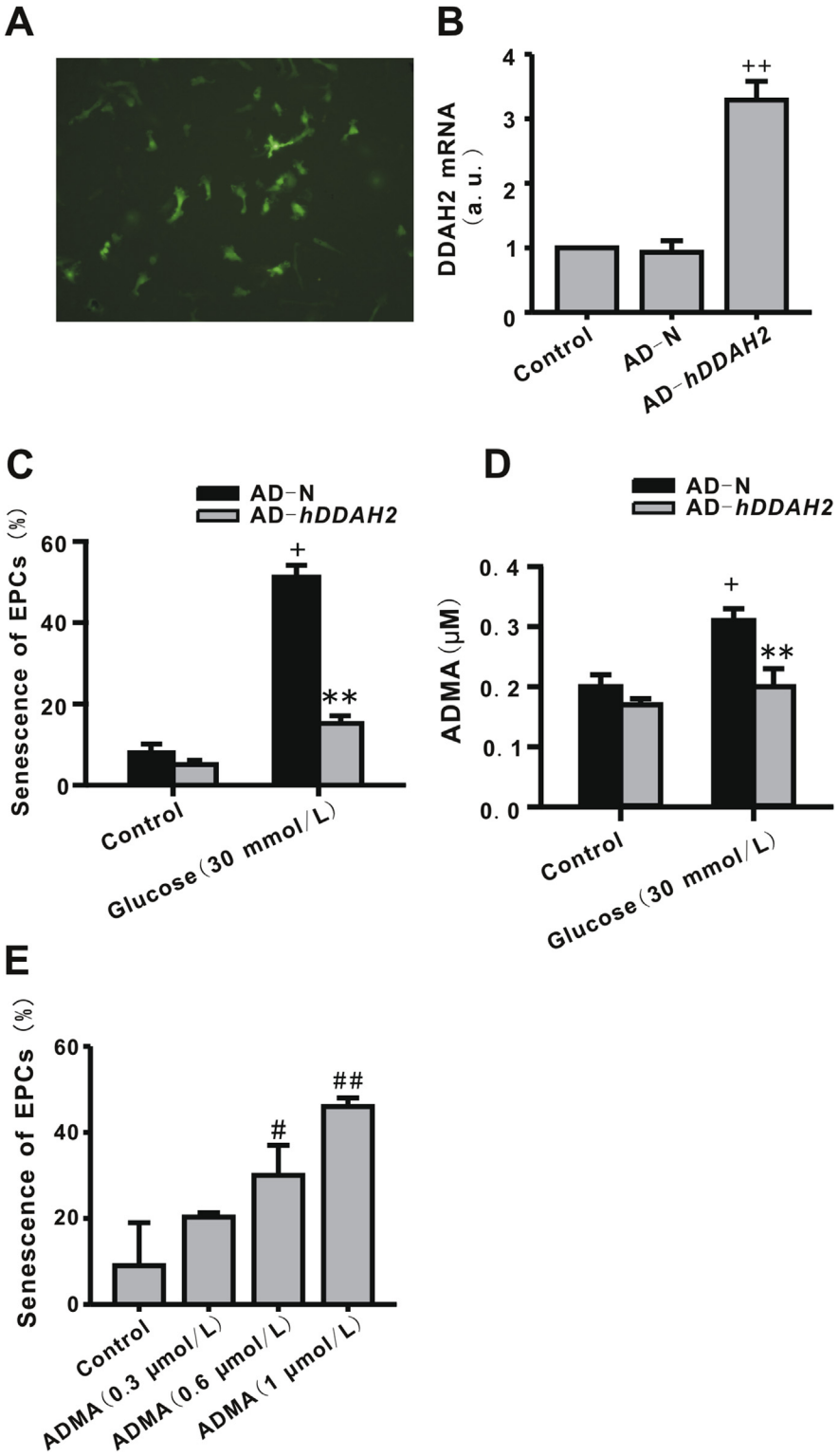

Fig. 3. Effects of DDAH2 overexpression and exogenous ADMA on EPCs senescence. (A) Immunofluorescence detected the DDAH2 overexpression transfection, and the positive rate was nearly 80%. (B) Real-time PCR analyzed the mRNA expression of DDAH2 in AD-hDDAH2 overexpression transduction EPCs. The mRNA expression of DDAH2 was dramatically upregulated by AD-hDDAH2 overexpression transduction. (C) DDAH2 overexpression inhibited EPCs senescence induced by high glucose. (D) DDAH2 overexpression decreased ADMA levels. pGC-FU had no effect on DDAH2 expression and ADMA levels. (E) ADMA (0.3, 0.6, and 1 μmol/L, 48 h) induced the senescence of EPCs in a dose-dependent manner. Values are expressed as mean ± SEM (n = 3–4). $^{+}P < 0.05$ vs. AD-N; $^{*}P < 0.05$, $^{**}P < 0.01$ vs. AD-N + glucose; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ vs. control.

decreased (Fig. 1C). Similar to in vivo, the mRNA and protein expression of SIRT1 in EPCs stimulated by high-glucose were also markedly decreased (Fig. 2C and E), indicating that SIRT1 is involved in the accelerated senescence of EPCs in T2DM.

3.7. Effects of RSV on EPCs senescence, ADMA levels and DDAH2 expression in EPCs stimulated by high-glucose

To test the role of endogenous SIRT1 in EPCs senescence induced by high glucose, we used RSV, an activator of SIRT1. As shown in Fig. 4A, pretreatment with RSV 30 min attenuated markedly high glucose-induced senescence of EPCs.

We also observed the effect of SIRT1 on DDAH2/ADMA pathway. The results showed that RSV markedly reversed increased ADMA (Fig. 4C) and reduced DDAH2 (Fig. 4B) induced by high glucose.

4. Discussion

In this study, we investigated the molecular mechanisms involved in EPCs senescence in diabetes. The major findings of this work included: (1) Diabetic milieu accelerated EPCs senescence, decreased DDAH2 expression and increased ADMA concentrations; and (2) Exogenous application of ADMA mimicked high glucose-induced EPCs senescence, and DDAH2 overexpression reversed the senescence of EPCs induced by high glucose; and (3) Diabetic milieu decreased SIRT1 expression in EPCs, and activation of SIRT1 by RSV decreased high glucose-induced EPCs senescence, and increased DDAH2 expression accompanied by a decrease in ADMA concentration.

It has been well documented that diabetes mellitus impairs endothelial cells and attenuates endothelial repair and angiogenesis, which are closely associated with the increased prevalence of cardiovascular diseases [1]. Circulating EPCs play an essential role in endothelial maintenance and repair. There were reports that in both experimental models of diabetes mellitus and patients with type 1 or type 2 diabetes mellitus, the function of EPCs was impaired [3–5]. In consistent with these results, our present study also showed that the senescence of EPCs was accelerated in patients with T2DM, and high glucose accelerated the onset of senescence of EPCs in a dose-dependent manner. The senescence of EPCs limits the ability of proliferative potential and contributes to endothelial dysfunction and cardiovascular complications in diabetes [2–5]. However, the mechanisms responsible for the senescence of EPCs in diabetic mellitus are not fully understood.

ADMA, as an endogenous nitric oxide synthase inhibitor, participates in regulating vascular function under physiological and

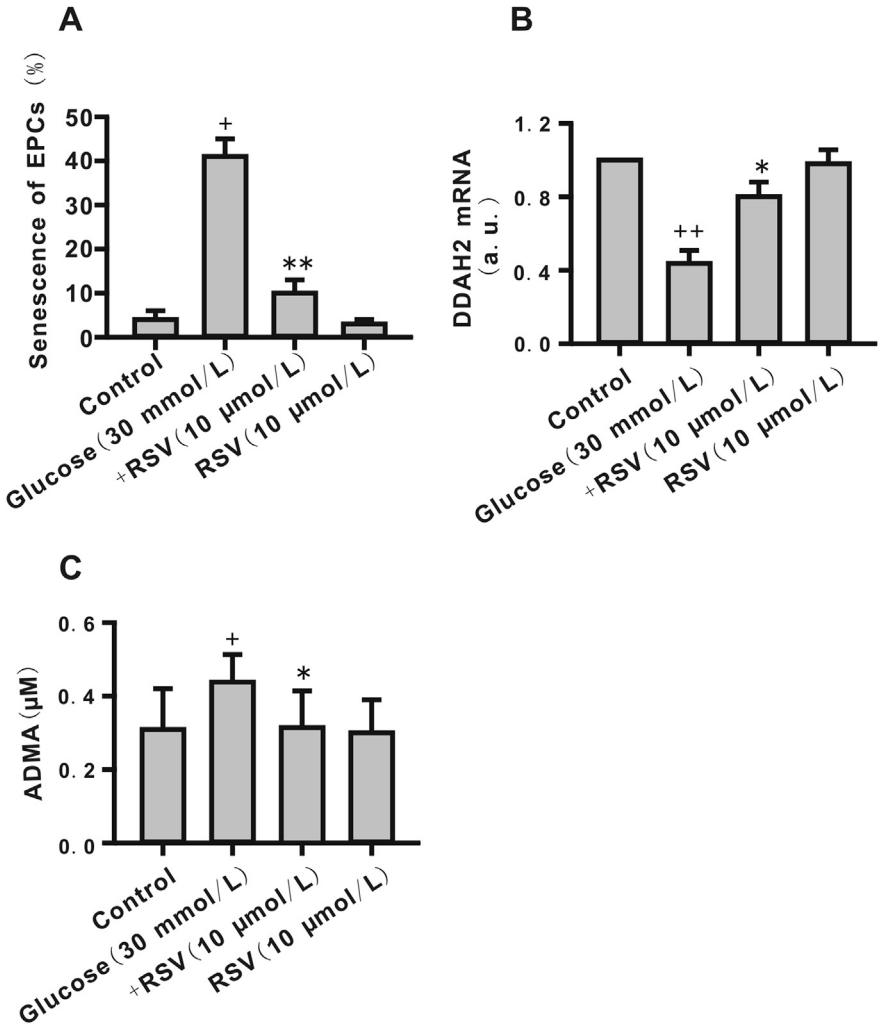

Fig. 4. Effects of RSV on EPCs senescence and DDAH/ADMA pathway in cultured EPCs stimulated by high glucose. (A) RSV (10 μmol/L), the specific activator of SIRT1, attenuated the senescence of EPCs induced by high glucose. The effects of high glucose on DDAH2 expression (B) and ADMA levels (C) were reversed by RSV. Values are expressed as mean ± SEM (n = 4). $^{+}P < 0.05$, $^{++}P < 0.01$ vs. control; $^{*}P < 0.05$, $^{**}P < 0.01$ vs. high glucose.

pathophysiological conditions. A variety of studies have demonstrated that elevated ADMA contributed to endothelial dysfunction, the common characteristic of diabetes, atherosclerosis and hypertension [6,16]. In the older population, ADMA was thought to be a strong independent predictor of mortality, and plasma ADMA concentrations increased with age [17]. In cultured endothelial cells, exogenous ADMA accelerated endothelial cell senescence through increasing oxidative stress [8,18]. Moreover, it has been reported that high glucose accelerated the senescence of endothelial cells as well as decreasing the activity and expression of DDAH2, one of the major isoforms of DDAH in endothelial cell, indicating that DDAH2/ADMA pathway play important role in endothelial cell senescence in diabetes. ADMA has also been reported to be associated with decreased EPC proliferation, mobilization and recruitment [19]. Clinical studies showed increased ADMA and decreased circulating EPCs in coronary artery disease [19], renal transplantation [20] and rheumatoid arthritis [21]. In our present study, diabetic milieu accelerated the senescence of EPCs and this is also in agreement with the results of others [22,23]. Our previous study showed that EPCs isolated from peripheral blood predominantly express DDAH2 that increased with EPCs differentiation. Therefore, we considered that DDAH2/ADMA pathway may be involved in EPCs senescence in diabetes. The results of the present study showed that the levels of ADMA markedly increased concomitantly with the downregulation of DDAH2 mRNA expression in the EPCs from patients with T2DM and in high glucose-treated EPCs. To confirm the role of DDAH2/ADMA in EPCs senescence in diabetic milieu, exogenous ADMA and DDAH2 overexpression were used to stimulate EPCs. The results showed that similar to high glucose, exogenous ADMA also induced EPCs senescence in a dose-dependent manner, and DDAH2 overexpression reversed high glucose-induced EPCs senescence and increased ADMA.

SIRT1 is closely associated with diabetes mellitus. It has been documented that SIRT1 protected endothelial function in the aortas of type 2 diabetic (db/db) mice by upregulation of eNOS [24]. In cultured endothelial cells, introduction of SIRT1 inhibited high glucose-induced endothelial senescence and dysfunction [25]. Recently, a novel and an unexpected role for SIRT1 as a critical modulator of EPC function governing postnatal vascular growth has been noted. There was evidence that SIRT1 downregulation impaired EPC formation and increased EPCs senescence [27]. Moreover, high glucose-induced EPCs dysfunction has also been reported to be associated with the reduced SIRT1 expression [28,29]. In this study, we found that SIRT1 expression was decreased in EPCs from patients with T2DM and in EPCs stimulated by high glucose, which was in agreement with the results of these reports [29]. Moreover, it has been reported that red wine (rich in resveratrol, an activator of SIRT1) inhibited accelerated endothelial senescence by increasing DDAH activity and decreasing ADMA concentration [26], which was further confirmed by our previous study showing that RSV or RSV derivative BTM-0512 exerted the inhibitory effects on high glucose-induced endothelial cell senescence through DDAH/ADMA pathway [15]. Our previous study also showed that interruption of SIRT1 attenuated EPCs differentiation and function by inhibiting DDAH2 expression [10]. These supported a possible interaction between the SIRT1 and DDAH2/ADMA pathways. Therefore, we hypothesized that SIRT1 reversed high glucose induced-EPCs senescence by regulating DDAH2/ADMA pathway. By using high glucose-induced senescence model of EPCs, we found that RSV was able to reduce the senescence of EPCs by increasing DDAH2 expression and decreasing ADMA concentrations.

In summary, the DDAH2/ADMA pathway participates in the accelerated onset of senescence of EPCs in diabetic milieu, which is associated with the activation of SIRT1.

Conflicts of interest

We declared that authors have no conflict of interest.

Acknowledgments

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