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LncRNA SOX2OT alleviates the high glucose-induced podocytes injury through autophagy induction by the miR-9/SIRT1 axis

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ABSTRACT

Objectives: Podocytes injury is a major contributor to the progression of diabetic nephropathy (DN). This study aims to investigate the role of long non-coding RNA SOX2OT in the high glucose (HG)-induced injury of human podocytes cells (HPCs) and the underlying mechanism.

Methods: HPCs proliferation and apoptosis were examined using MTT assay and flow cytometry assay, respectively. The protein levels of SIRT1 and autophagy-associated proteins (Beclin-1, LC3-II, Atg7, and p62) were determined using western blot. The interactions among SOX2OT, miR-9, and SIRT1 were investigated using luciferase activity assay.

Results: SOX2OT overexpression significantly alleviated the HG-induced HPCs injury and induced autophagy, which was abrogated by the autophagy inhibitor 3-MA and SIRT1 knockdown. Mechanistically, SOX2OT acted as a ceRNA by sponging miR-9 to facilitate SIRT1, and thus induce autophagy.

Conclusion: SOX2OT overexpression alleviates the HG-induced podocytes injury through autophagy induction by the miR-9/SIRT1 axis.

1. Introduction

Diabetic nephropathy (DN) is one of the most common complications of diabetes and is the leading cause of end-stage renal disease (ESRD). The main feature of DN is persistent albuminuria of 30–299 mg/24 h (microalbuminuria) (Wada et al., 2012). Podocytes injury is positively associated with proteinuria and has been considered as a major contributor to the development and progression of DN (Dai et al., 2017). The reasons for podocytes loss include podocytes apoptosis, detachment, as well as lack of podocyte proliferation (Tharaux and Huber, 2012). Especially, podocytes apoptosis is an important contributing reason to the pathogenesis of DN (Wang et al., 2012; Winn et al., 2005).

Autophagy is a highly conserved cellular process that delivers macromolecules and other impaired cell organelles to lysosomes for degradation and recycle to maintain intracellular homeostasis (Liu et al., 2017). Autophagy plays a critical role in maintaining lysosome homeostasis in podocytes under diabetic conditions. Emerging evidence has shown that impaired podocytes autophagy is involved in the pathogenesis of podocytes loss, leading to massive proteinuria in DN (Liu et al., 2017; Tagawa et al., 2016). Recent studies have suggested that activation of autophagy in podocytes may be a potential therapeutic option to prevent the progression of DN (Liu et al., 2017).

Long non-coding RNAs (lncRNAs) play an important role in the pathogenesis of various human diseases (Li et al., 2019). However, their roles in DN remain largely unknown. A recent study showed that the lncRNA SOX2-overlapping transcript (SOX2OT) is significantly down-regulated in DN mice and high glucose (HG)-treated human podocytes cells (HPCs) (Zhang et al., 2018b). This indicates that SOX2OT may act as an important regulator in the pathogenesis of DN. However, the exact role of SOX2OT in DN has not yet been clearly documented.

LncRNAs play crucial roles in regulating various biological processes by functioning as a competitive endogenous RNA (ceRNA) by competitively binding miRNAs (Dong et al., 2019; Gu et al., 2018). Our bioinformatics analysis revealed that SOX2OT harbors predicted binding sites of miR-9 and sirtuin 1 (SIRT1) might act as a putative target of miR-9. Importantly, SIRT1 is a deacetylase and can induce autophagy *via* deacetylation of autophagy-related marker Beclin-1 and other autophagy mediators (Qiu et al., 2016). Accordingly, we hypothesized that SOX2OT might function as a ceRNA by sponging miR-9 to facilitate SIRT1 expression, thereby inducing the impaired podocytes autophagy and then alleviating the podocytes injury under the HG environment.

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2. Materials and methods

2.1. Cell culture

The immortalized HPCs are maintained in RMPI 1640 medium (Gibco) containing 10% fetal bovine serum (FBS; Gibco), 5 mg/L insulin, 5 mg/L transferrin, 5 μg/L sodium selenite, 100 μg/mL streptomycin, and 100 IU/mL penicillin. The cells were propagated under a permissive condition at 33 °C in a humidified air with 5% CO_2. For propagation of cells, interferon-γ (IFN-γ, 50 U/mL; Santa Cruz Biotechnology, Dallas, TX, USA) was added to the culture medium. After the passage of the two generations, the concentration of IFN-γ was reduced to 20 U/mL and finally maintained at 10 U/mL. When the cells grew to 70–80% confluence, cells were switched to 37 °C (non-permissive condition) without the addition of IFN-γ for 10–14 days for induction of differentiation.

Following synchronization with sequential serum starvation for 24 h, the culture medium of HPCs was replaced with medium containing normal glucose (NG group; 5.6 mmol/L D-glucose), high glucose (HG group; 30 mmol/L D-glucose), or high mannitol (MA, purchased from Shanghai Longsheng Chemical Co., Ltd.; osmotic control group; 5.6 mmol/L D-glucose plus 24.4 mmol/L mannitol). After 24 h of incubation, relative SOX2OT expression was examined by qRT-PCR to assess the effect of glucose on SOX2OT expression.

2.2. Quantitative real-time PCR (qRT-PCR)

Total RNA was extracted from HPCs using a TRIzol reagent (Invitrogen) according to the manufacturer's instructions. Subsequently, total RNA was reverse transcribed using the iScript kit (Bio-Rad Laboratories, Inc., Hercules, CA, USA),. The cDNAs were amplified through qRT-PCR by SYBR Green Realtime PCR Master Mix (TOYOBO, Japan). The relative expression of SOX2OT, miR-9, and SIRT1 was calculated by the $2^{-\Delta\Delta Ct}$ method. β-Actin served as internal control.

2.3. Plasmid construction and cell transfection

To overexpress SOX2OT, the SOX2OT cDNA fragments were cloned into the pcDNA 3.1 vector (Invitrogen, USA). An empty pcDNA3.1 vector was used as the control. To knockdown SOX2OT and SIRT1, small interfering RNA (siRNA)-SOX2OT (si- SOX2OT), si-SIRT1, and a scramble control siRNA (si-Ctrl) were designed and synthesized by GenePharma (Shanghai, China). To overexpress miR-9 mimic, has-miR-9 mimic was purchased from Sigma-Aldrich. When HPCs grew to 70%–80% confluence, cells were transfected with these vectors using Lipofectamine™ 3000 (Invitrogen), siRNAs and mimic using Lipofectamine™ RNAiMAX Transfection Reagent (Invitrogen), respectively, following the manufacturer's instructions. After 48 h of transfection, cells were harvested for qRT-PCR to examine the overexpression or knockdown efficiency.

2.4. Cell proliferation assay

The HPCs proliferation was assessed by an MTT assay kit (Beyotime, Shanghai, China) according to the manufacturer's instructions. Briefly, the treated cells were seeded into 96-well plates at a density of 5×10^3 cells/well. After 24 h of incubation, 20 μL of 5 mg/mL MTT was added into each well. Following another 4 h of incubation at 37 °C, the culture medium was replaced with 150 μL DMSO to solubilize the crystals for 10 min. Cellular viability was determined by measuring the optical density (OD) at 490 nm by a spectrophotometer (Multiskan MK3, Thermo, USA). Cellular viability was normalized to control well.

2.5. Cell apoptosis assay

The HPCs apoptosis was qualified using an Annexin V-fluorescein isothiocyanate (FITC)/propidium iodide (PI) cell apoptosis kit (Invitrogen, Thermo Fisher Scientifc, Inc.) according to the instructions. Briefly, the treated cells were digested with EDTA-free trypsin (Solarbio, Beijing, China) and washed twice with PBS, and re-suspended at a density of 1×10^6 cells/mL in the Annexin Binding Buffer provided in the kit. After this, 5 μL Annexin V-FITC and 5 μL PI were mixed with the cells. After 15 min of incubation at room temperature, the mixtures were analyzed using the FACScan flow cytometry equipped with CELLQuest software (BD Biosciences).

2.6. Western blot

Total protein from HPCs was extracted in RIPA lysis buffer (Beyotime). The protein concentrations were determined using Bradford assay (Beyotime). Then equal protein from cell lysates was separated by 10% SDS-PAGE gels and transferred onto PVDF membrane (Millipore, USA). After being blocked with 5% non-fat milk, the membranes were incubated at 4 °C overnight with the following primary antibodies against: Caspase-3 (1:1000, Abcam), Bax (1:1000, Abcam), Bcl-2 (1:1000, Abcam), Beclin-1 (1:1000, Abcam), LC3-I and LC3-II (both from anti-LC3B antibodies, 1:1000, Sigma-Aldrich), p62 (1:1000, Abcam), Atg7 (autophagy related 7; 1:1000, Abcam), SIRT1 (1:1000, Abcam) and β-Actin (1:1000, Abcam). The membranes were then washed with TBST three times and incubated with horseradish peroxidase (HRP)-labeled secondary antibodies (Beyotime) at room temperature for 1 h. The protein was detected with an enhanced chemiluminescence kit (Pierce; Thermo Fisher Scientific, In). The band intensity was analyzed by Image-Pro Plus 6.0 software (Media Cybernetics Inc., Bethesda, MD, USA). β-Actin served as the loading control.

2.7. Luciferase activity assay

For construction of SOX2OT-WT, SOX2OT-Mut, SIRT1-WT, and SIRT1-Mut reporter vectors, the fragments of SOX2OT and 3'-UTR of SIRT1 containing the predicted wild-type (WT) binding sites of miR-9 or mutated miR-9 binding sites (Mut) were amplified by PCR and inserted into a pMIR-REPORT luciferase reporter vector (Ambion, Austin, TX, USA), respectively. For the luciferase reporter assay, cells were co-transfected with the constructed luciferase reporter vectors, pRL-TK (expressing renilla luciferase as the internal control) and miR-9 mimic or mimic NC using Lipofectamine 2000™. At 24 h post-transfection, the luciferase activities were analyzed using a luciferase reporter assay system (Promega Corporation, Fitchburg, WI, USA).

2.8. Statistical analysis

Statistical analysis was performed using Prism software (GraphPad, San Diego, CA) version 7. The differences between groups were analyzed using the Student's *t*-test and one-way ANOVA. The data are presented as the mean ± standard deviation (SD) from three independent experiments. $p < 0.05$ was considered to indicate a statistically significant difference.

3. Results

3.1. SOX2OT overexpression alleviated the HG-induced HPCs injury

First, we assessed the effect of high glucose on SOX2OT expression. Data revealed that HG treatment significantly decreased SOX2OT expression in HPCs (Fig. 1A). Next, we determined the potential role of SOX2OT in HPCs injury under HG stimulation. Data showed that SOX2OT overexpression significantly promoted cell proliferation (Fig. 1B) and inhibited cell apoptosis (Fig. 1C) under HG stimulation.

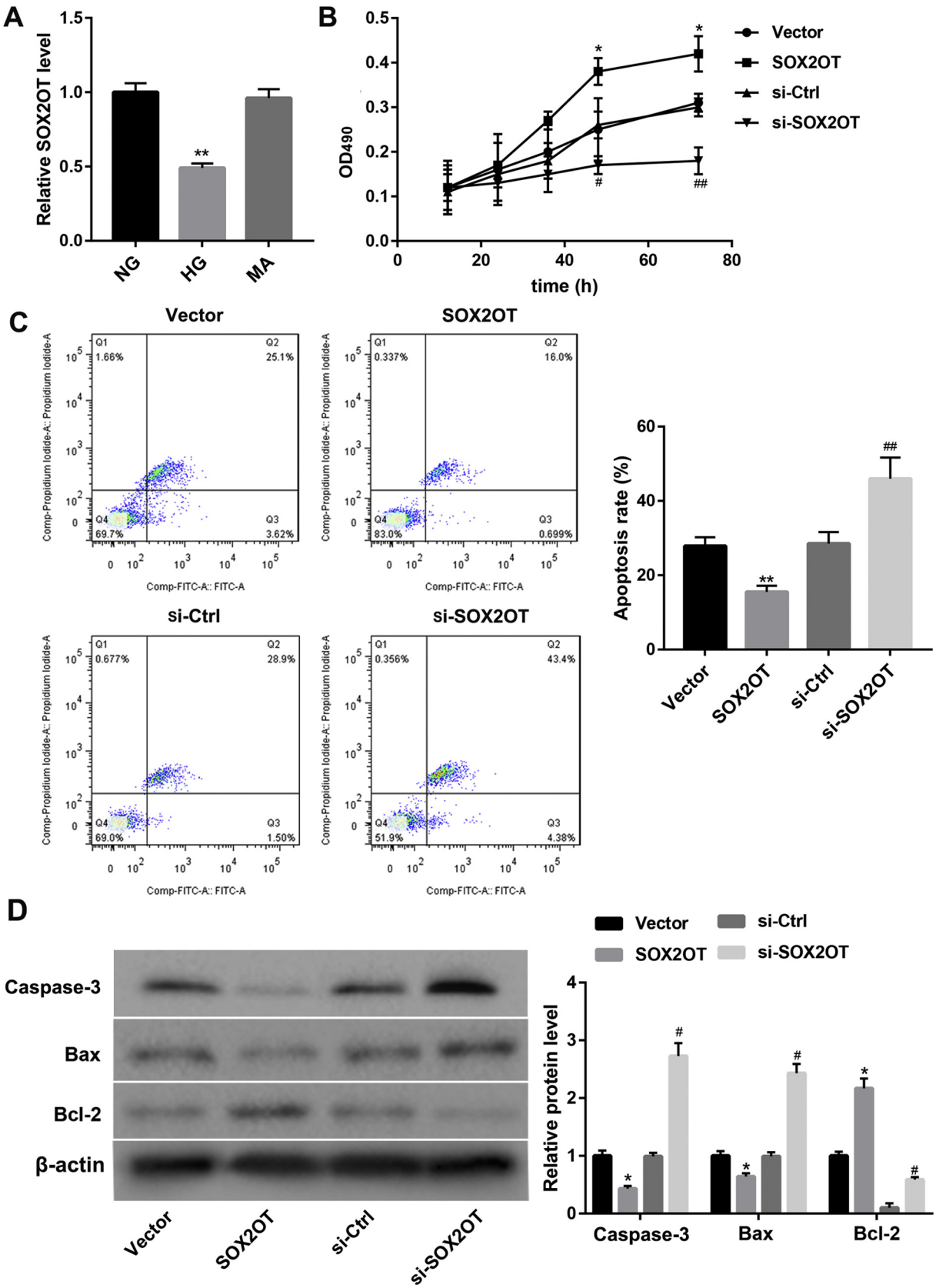

Fig. 1. SOX2OT alleviated the HG-induced HPCs injury.

(A) HPCs were cultured with media containing normal glucose (NG group; 5.6 mmol/L D-glucose), high glucose (HG group; 30 mmol/L D-glucose), or high mannitol (MA, osmotic control group; 5.6 mmol/L D-glucose plus 24.4 mmol/L mannitol) for 24 h. Relative SOX2OT expression was examined by qRT-PCR. $^{**}p < 0.01$ *vs.* the MA group. In another experiment, HPCs were transfected with pcDNA3.1-SOX2OT, si-SOX2OT, or their corresponding controls. After 24 h of incubation in HG medium (30 mmol/L D-glucose), cell proliferation (B) and apoptosis (C) in HPCs were examined using MTT assay and flow cytometry assay, respectively. (D) The protein levels of apoptosis-related proteins (Caspase-3, Bax, Bcl-2) were examined using western blot. $^{*}p < 0.05$, $^{**}p < 0.01$ *vs.* the Vector group; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ *vs.* the si-Ctrl group.

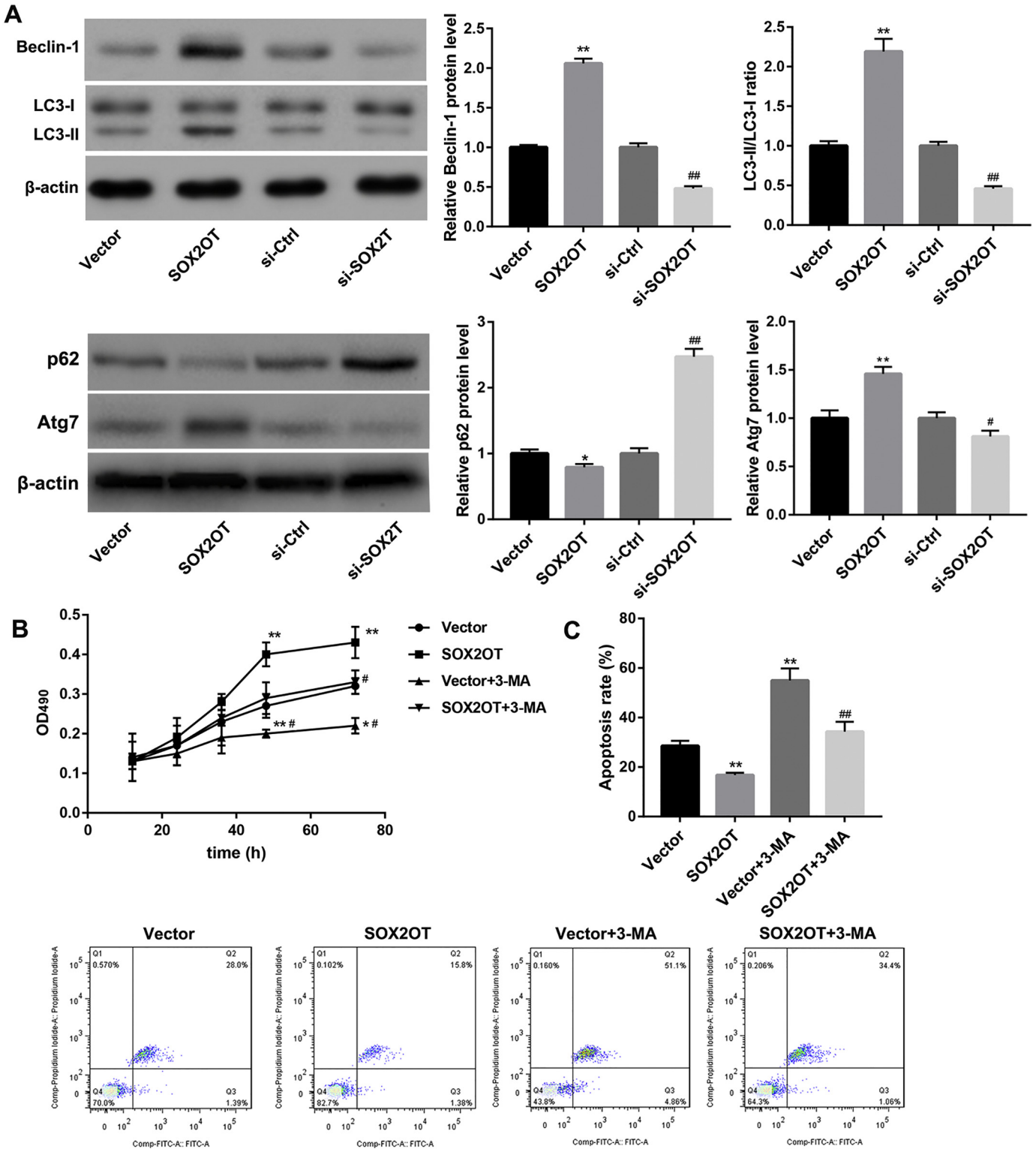

Fig. 2. Autophagy inhibition abrogated the SOX2OT-mediated alleviation of the HG-induced HPCs injury.
(A) HPCs were transfected with pcDNA3.1-SOX2OT, si-SOX2OT, or their corresponding controls. After 24 h of incubation in HG medium (30 mmol/L D-glucose), the protein levels of LC3-I, LC3-II, Beclin-1, p62, and Atg7 in HPCs were examined using western blot and their quantitative analysis was normalized β-Actin. $^{*}p < 0.05$, $^{**}p < 0.01$ *vs.* the Vector group; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ *vs.* the si-Ctrl group. In another experiment, 3-methyladenine (3-MA; an autophagy inhibitor, 5 mM; Sigma-Aldrich) was added into the pcDNA3.1-SOX2OT- and empty vector-transfected HPCs at 1 h before HG stimulation (30 mmol/L D-glucose). After 24 h of incubation in HG medium, cell proliferation (B) and apoptosis (C) in HPCs were examined using MTT assay and flow cytometry assay, respectively. $^{*}p < 0.05$, $^{**}p < 0.01$ *vs.* the Vector group; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ *vs.* the SOX2OT group.

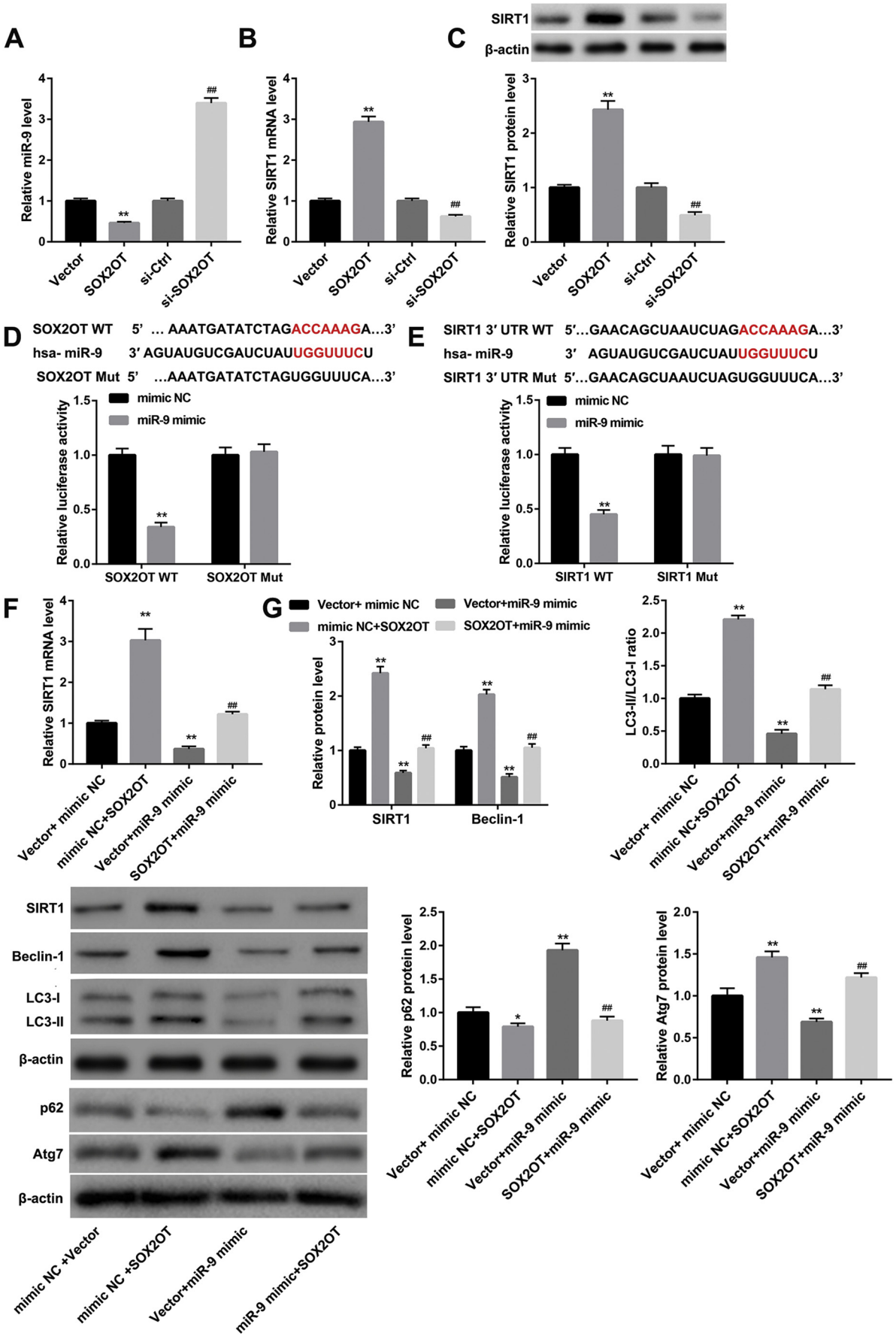

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Fig. 3. SOX2OT acts as a ceRNA by sponging miR-9 to facilitate SIRT1 and induce autophagy.
HPCs were transfected with pcDNA3.1-SOX2OT, si-SOX2OT, or their corresponding controls. After 24 h of incubation in HG medium (30 mmol/L D-glucose), relative miR-9 expression (A) and SIRT1 mRNA expression (B) were examined using qRT-PCR. (C) The protein level of SIRT1 was measured using western blot. $^{**}p < 0.01$ *vs.* the Vector group; $^{\#\#}p < 0.01$ *vs.* the si-Ctrl group. (D) Results of the luciferase activity assay verified the direct binding between SOX2OT and miR-9. $^{**}p < 0.01$ *vs.* the mimic NC + SOX2OT WT group. (E) Results of luciferase activity assay showed that the 3'-UTR of SIRT1 is directly targeted by miR-9. $^{**}p < 0.01$ *vs.* the mimic NC + SIRT1 WT group. (F-G) HPCs were co-transfected with pcDNA3.1-SOX2OT or empty vector, and miR-9 mimic or mimic NC. After 24 h of incubation in HG medium (30 mmol/L D-glucose), (F) relative SIRT1 mRNA expression was examined using qRT-PCR, (G) and the protein levels of SIRT1, LC3-I, LC3-II, Beclin-1, p62, and Atg7 were examined using western blot. $^{*}p < 0.05$, $^{**}p < 0.01$ *vs.* the Vector + mimic NC group; $^{\#\#}p < 0.01$ *vs.* the mimic NC + SOX2OT group.

Furthermore, SOX2OT overexpression notably decreased protein levels of pro-apoptotic Caspase-3 and Bax, whereas increased levels of anti-apoptotic Bcl-2 under HG stimulation (Fig. 1D). In contrast, SOX2OT knockdown exerted the opposite effect (Fig. 1B–D). These data indicate that SOX2OT overexpression alleviates the HG-induced HPCs injury.

3.2. SOX2OT overexpression alleviated the HG-induced HPCs injury through autophagy induction

Next, we explored the effect of SOX2OT expression on the autophagy level in HPCs under HG stimulation. Data revealed that SOX2OT overexpression led to a significant increase in protein expression of Beclin-1, Atg7, and LC3-II, as well as the LC3-II/LC3-I ratio, but a decrease in levels of p62 (Fig. 2A). In contrast, SOX2OT knockdown exerted the opposite effect (Fig. 2A). Beclin-1 and Atg7 are autophagy-related markers. Furthermore, LC3-II is also an indicator of autophagy because LC3 protein converts from LC3-I to LC3-II during autophagosome formation. p62 is an autophagy substrate that is used as a reporter of autophagy activity. Accordingly, our results suggest that SOX2OT induces autophagy upregulation.

To further validate whether autophagy induction was involved in the SOX2OT-mediated attenuation of HPCs injury under HG stimulation, HPCs were transfected with pcDNA3.1-SOX2OT to overexpress SOX2OT, followed by treatment with 3-MA (an autophagy inhibitor) before 24 h of HG stimulation. Data revealed that 3-MA significantly reversed the SOX2OT overexpression-mediated promotion of cell proliferation (Fig. 2B) and inhibition of cell apoptosis (Fig. 2C) in HPCs under HG stimulation. These data indicate that SOX2OT overexpression attenuates the HG-induced HPCs injury, at least in part, through autophagy induction.

3.3. SOX2OT acted as a ceRNA by sponging miR-9 to facilitate SIRT1 and induce autophagy

We then investigated the mechanism underlying the SOX2OT-mediated autophagy induction. SIRT1 is a deacetylase and can induce autophagy *via* deacetylation of autophagy-related marker Beclin-1 and other autophagy mediators (Qiu et al., 2016). Thus, we explored the interaction between SOX2OT and SIRT1. Data revealed that SOX2OT overexpression significantly decreased miR-9 expression (Fig. 3A), but notably increased SIRT1 mRNA (Fig. 3B) and protein levels (Fig. 3C). By contrast, SOX2OT knockdown exerted the opposite effect (Fig. 3A–C). Furthermore, the results of the luciferase reporter assay showed that the miR-9 mimic caused a marked decrease in luciferase activity in the SOX2OT-WT group compared with the mimic NC group, but had no significant effect on luciferase activity in the SOX2OT-Mut group. These data verified the direct binding between SOX2OT and miR-9 (Fig. 3D). Moreover, the luciferase activity in cells co-transfected with miR-9 mimic and SIRT1 WT 3'-UTR luciferase reporter plasmids was decreased, indicating that the SIRT1 3'-UTR was directly targeted by miR-9 (Fig. 3E). In addition, miR-9 mimic effectively abolished the SOX2OT overexpression-mediated upregulation of SIRT1 mRNA (Fig. 3F) and protein levels (Fig. 3G) in HPCs under HG stimulation. Together, these results indicate that SOX2OT acts as a ceRNA of miR-9 to facilitate SIRT1 expression.

In contrast to SOX2OT overexpression, miR-9 mimic significantly decreased protein levels of LC3-II, Beclin-1, and Atg7, but increased protein levels of p62 (Fig. 3G) in HPCs under HG stimulation, indicating that miR-9 inhibited autophagy. Importantly, miR-9 mimic effectively abolished the SOX2OT overexpression-mediated upregulation of induction of autophagy (Fig. 3G). These findings indicated that SOX2OT induced autophagy *via* sponging miR-9.

3.4. SOX2OT alleviated the HG-induced HPCs injury and induced autophagy through upregulating SIRT1

Finally, we performed rescue experiments to elucidate whether SOX2OT alleviated the HG-induced HPCs injury and induced autophagy through upregulating SIRT1. To this end, HPCs were co-transfected with pcDNA3.1-SOX2OT or empty vector, and si-SIRT1 or si-Ctrl, followed by HG stimulation. Data showed that in contrast to SOX2OT overexpression, SIRT1 knockdown significantly inhibited cell proliferation (Fig. 4A) and promoted cell apoptosis (Fig. 4B) under HG stimulation, as well as decreased Beclin-1 protein levels and the LC3-II/LC3-I ratio (Fig. 4C). Of note, SIRT1 knockdown efficiently impaired the SOX2OT overexpression-mediated alleviation of HG-induced HPCs injury (Fig. 4A and B) and induction of autophagy (Fig. 4C). Collectively, these data suggest that SOX2OT alleviated the HG-induced HPCs injury and induced autophagy through upregulating SIRT1.

4. Discussion

The results in the present study showed that SOX2OT overexpression significantly alleviated the HG-induced podocytes injury by enhancing cell viability and suppressing cell apoptosis. Furthermore, to our knowledge, this study is the first to show the protective role of SOX2OT in HG-induced podocyte injury was through induction of autophagy *via* the miR-9/SIRT1 axis.

Emerging studies have highlighted the important roles of lncRNAs in DN (Long and Danesh, 2018; Wang et al., 2018; Zhang et al., 2018c). For example, lncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is dysregulated in streptozocin (STZ)-induced DN mice and involved in HG-induced podocyte injury (Hu et al., 2017). LINC01619 regulates miR-27a/forkhead box protein O1 (FOXO1) and endoplasmic reticulum stress-mediated podocyte injury in DN (Bai et al., 2018). To date, studies concerning lncRNA SOX2OT mainly focus on cancer (Li et al., 2018; Qu and Cao, 2018; Wu et al., 2018). Here, we show for the first time the protective role of SOX2OT in HG-induced podocytes injury in DN.

Recent studies have indicated that activation of autophagy in podocytes may be a potential therapeutic option to prevent the progression of DN (Liu et al., 2017). Importantly, the results in this study indicate that the protective role of SOX2OT in HG-induced podocyte injury may be mediated through autophagy induction. In accordance with the induction of autophagy by SOX2OT, a previous study showed that suppression of SOX2OT inhibited hydrogen peroxide (H_2O_2)-induced injury in pheochromocytoma (PC-12) cells partially by decreasing autophagy (Yin et al., 2018).

SIRT1 is a deacetylase that relies on nicotinamide adenine dinucleotide (NAD^+). Studies show that SIRT1 promotes renal energy cell homeostasis in the HG environment and contributes to renoprotective effects in DN (Shi and Huang, 2018; Zhang et al., 2018a).

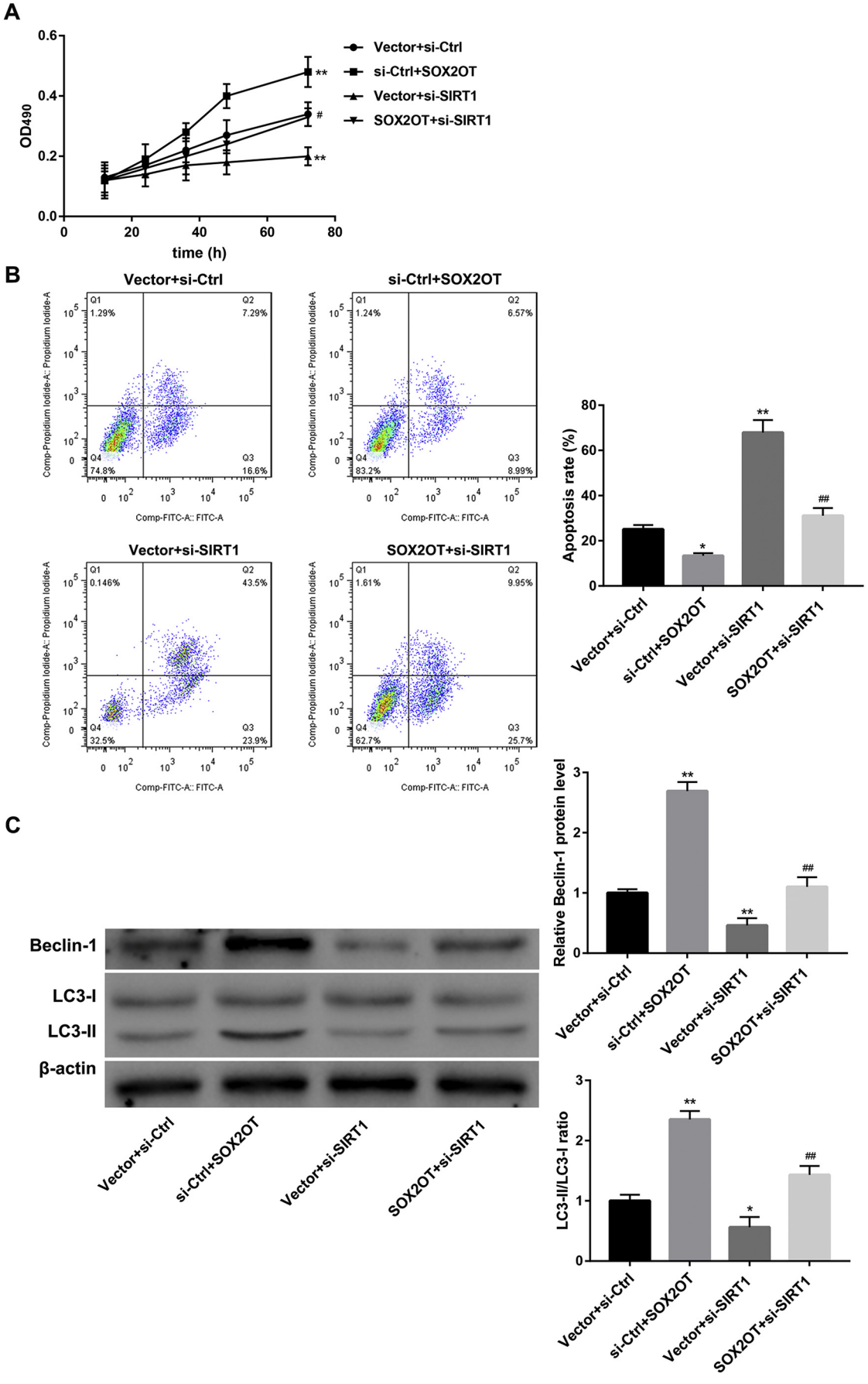

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Fig. 4. SOX2OT alleviated the HG-induced HPCs injury and induced autophagy through upregulating SIRT1.
HPCs were co-transfected with pcDNA3.1-SOX2OT or empty vector, and miR-9 mimic or mimic NC. After 24 h of incubation in HG medium (30 mmol/L D-glucose), cell proliferation (A) and apoptosis (B) in HPCs were examined using MTT assay and flow cytometry assay, respectively. (C) The protein levels of Beclin-1, LC3-I, LC3-II, were examined using western blot. $^{*}p < 0.05$, $^{**}p < 0.01$ *vs.* the Vector + si-Ctrl group; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ *vs.* the si-Ctrl + SOX2OT group.

Mechanistically, SIRT1 has its renoprotective effects by modulating metabolic homeostasis and autophagy, resisting apoptosis and oxidative stress, and inhibiting inflammation (Wang et al., 2019). Especially, SIRT1 can induce autophagy *via* deacetylation of autophagy-related marker Beclin-1 and other autophagy mediators (Qiu et al., 2016). Accordingly, we verified whether SOX2OT induced autophagy through regulating SIRT1. SIRT1 can be regulated by various lncRNAs. For example, lncRNA SNHG12 promoted the expression of SIRT1 by inhibiting miR-199a (Yin et al., 2019); HOTAIR protected against diabetic cardiomyopathy by competitively binding to miR-34a (Gao et al., 2019). Interestingly, our results showed that SOX2OT serves as a "sponge" for miR-9 to upregulate SIRT1 expression and thus induce autophagy.

5. Conclusion

In conclusion, SOX2OT overexpression alleviates the HG-induced podocytes injury. The protective effects of SOX2OT on podocytes injury were mediated through autophagy induction by the miR-9/SIRT1 axis. This study may provide novel insights for DN therapy.

Decalaration of Competing Interest

The authors declare no conflicts of interest.

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