Tropical Journal of Pharmaceutical Research September 2022; 21 (9): 1885-1891
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v21i9.11

Original Research Article

Dexmedetomidine alleviates high glucose-induced podocyte damage by inhibiting EDA2R

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Sent for review: 6 June 2022 *Revised accepted: 1 September 2022*

Abstract

Purpose: *To investigate the effect and mechanism of action of dexmedetomidine (Dex) on podocyte injury.*
Methods: *Cells were incubated with high glucose (50 mM) to induce a podocyte injury model in vitro. Cell viability, apoptosis, the expression of related protein related in podocyte injury and albumin permeability were evaluated by 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide (MTT), flow cytometry, western blot and Transwell assays.*
Results: *Dex administration enhanced HG-induced cell viability and the relative protein expression of Bcl-2, but reduced the HG-induced relative protein level of Bax and apoptosisrate in podocytes ($p < 0.05$). Besides, Dex incubation compensated HG-induced relative protein expressions of nephrin and podocin in podocytes but did the reverse with regard to relative protein expression of desmin and albumin permeability ($p < 0.05$). Moreover, Dex treatment resulted in a decrease in ectodysplasin A2 receptor (EDA2R) expression in HG-induced podocytes. The level of EDA2R was upregulated by the transfection of overexpression plasmid containing the EDA2R sequences. Overexpression of EDA2R reversed Dex-induced increase in cell viability, apoptosis, expression of nephrin, podocin and desmin, as well as albumin permeability in HG-stimulated podocytes ($p < 0.05$).*
Conclusion: *Dex ameliorates HG-induced podocyte injury via inhibition of EDA2R, indicating that Dex is a potential alternative drug for the treatment of podocyte injury.*

Keywords: *Diabetic nephropathy, Dexmedetomidine, Podocyte, ectodysplasin A2 receptor (EDA2R)*

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INTRODUCTION

Diabetic mellitus (DM) is a major health issues with an estimated 6.4 % prevalence in 2010 and 7.7 % prevalence projected in 2030 worldwide [1]. About one-third of DM patients develop diabetic nephropathy (DN), the leading cause of end-stage renal disease. The pathogenesis of DN is linked to genetic factors, podocyte damage, oxidative stress, aberrant glucose and

lipid metabolism and immune response [2]. Podocytes are terminally differentiated epithelial cells of glomeruli with unrestrained regenerative on capacity and are a major contributor of the renal glomerular filtration barrier. It has been reported that podocyte injury driven by high sugar and fat, and diverse cytokines result in proteinuria, indicating that podocyte damage plays a pivotal role in DN. Thus, alleviation of podocyte injury is one of the promising approaches to DN treatment.

Dexmedetomidine (Dex) is an α2-adrenergic agonist with high selectivity. Evidence has shown that Dex also possesses other potential effects, such as anti-inflammation and anti-apoptosis, based on its organoprotective properties [3]. More importantly, several studies have examined the protective roles of Dex in renal injury. For instance, Dex acts on alpha 2 adrenal receptor (α2-AR) to prevent acute kidney injury (AKI) induced by lipopolysaccharide (LPS) through the inhibition of iNOS/NO signaling axis [4].

Kang *et al* [5] reports that Dex exerts anti-inflammatory and anti-apoptotic activities thereby playing a protective role against LPS-induced AKI via α7 nAChR-dependent signaling axis. Besides, Dex promotes autophagy through α2-AR and attenuation of PI3K/AKT/mTOR axis, which causes the dislodgement of impaired mitochondria and the reduction of apoptosis and oxidative stress, thereby preventing LPS-induced AKI [6]. Furthermore, Dex protects against renal injury via the suppression of inflammation and apoptosis mediated by NF-κB axis in DN rats [7]. Also, Dex relieves diabetic neuropathic pain by suppressing microglial activation through the modulation of miR-618/P2Y12 axis [8].

However, the effect of Dex on podocyte injury remains unclear. Thus, the aim of the present study was to investigate the effect and mechanism of action of Dex on podocyte injury in high glucose (HG)-induced MPC-5 cells.

EXPERIMENTAL

Cell culture and treatments

Conditionally immortalized mouse podocytes MPC-5 cell line was bought from the National infrastructure of Cell Line resource (Wuhan, China). The MPC-5 cells were maintained in RPMI 1640 media (Procell, Wuhan, China) supplemented with 10 % fetal bovine serum (FBS, Gibco, Rockville, MD, USA), 1 % streptomycin-penicillin (Procell) and 10 U/ml recombinant mouse γ-interferon (γ-IFN, P6137, Beyotime, Shanghai, China) at 33 ^{o}C with 5 % carbon dioxide (CO_2) for cell proliferation. For differentiation, MPC-5 cells were cultured with RPMI 1640 culture medium only including 10 % FBS and 1 % streptomycin-penicillin without γ-IFN at 37 ^{o}C with 5 % CO_2 for 10-14 days. Cells were incubated with high glucose (50 mM, ST1227, ≥99.5 %, Beyotime) to induce the podocyte injury model *in vitro*, in which conventional glucose (5.6 mM) acted as the control group. Then, the cells were treated with different concentrations of Dex (0, 0.5, 1 and 1.5 μM, Hengrui Medicine Co. Ltd, Jiangsu, China) for 24 h. In addition, podocytes were transfected with vector plasmids pcDNA (Vigene Biosciences, Rockville, MD, USA) containing EDA2R sequences using Lipofectamine 3000 (Invitrogen, Carlsbad, CA), while the empty vector plasmid, pcDNA, was also transfected into cells which acted as the control treatment. Cells were collected for subsequent analysis following 24 h of transfection.

MTT assay

Following the preceding treatments, podocytes were administered 10 μL MTT solution (Sigma) for 4 h, and then the supernatant was discarded. Subsequently, the crystals were dissolved in DMSO and the absorbance was determined at 570 nm in a microplate reader (Thermo Fisher Scientific, Waltham, MA, USA).

Western blotting

Total protein was treated with a RIPA lysis buffer (Beyotime) and quantified with a BCA protein quantification kit (23225, Thermo Fisher Scientific) according to the kit manufacturer's operating instructions. Protein samples were dissolved by 10 % SDS-PAGE, and then electrically transferred onto a PVDF membrane for 4 h at 150 V. After blocking with skim milk (Anchor, Switzerland) for 1 h at room temperature, the membrane was treated with the primary antibody (Bcl-2, 1:2000, ab196495; Bax, 1:200, ab216494; nephrin, 1:500, ab216692; podocin, 1:1000, ab177242; desmin, 1:1000, ab8592; EDA2R, 1:1000, ab167224 and GAPDH, 1:2500, ab9485) at 4 °C overnight.

Subsequently, the membrane was washed thrice and incubated with appropriate secondary antibodies at 37 °C for 1 h. DAB kit (Sigma, St Louis, MO, USA) was used to visualize the bands. The expressions were calculated after normalization to glyceraldehyde-3-phosphate dehydrogenase (GAPDH).

Flow cytometry

The apoptosis of podocytes was assessed by flow cytometry. Briefly, podocytes obtained as described above, were collected, rinsed and resuspended in 500 µL bind buffer. Subsequently, the cells were stained with 5 µL Annexin V/FITC and 5 µL propidium iodide (PI) (both from Thermo Fisher Scientific) for 15 min at room temperature. Podocytes were determined using a FACScan flow cytometer with CellQuest software (BD Biosciences, NJ, USA) to analyze the apoptosis rate.

Podocyte permeability

The differentiated podocytes were plated in Transwell filters (Corning Company, New York, NY, USA) and treated with high glucose and Dex for 48 h. Then, 600 µL of RPMI 1640 culture medium including FITC albumin (1.5 mg/ml, Solarbio, Beijing, China) was added io lower chamber, while 600 µL of RPMI 1640 culture medium was placed in the top chamber. After incubation for 6 h at 37 °C, 30 µL of media was taken from the top chamber. The albumin influx through the podocyte monolayer was determined by measuring the absorbance at 490 nm using a fluorescence multi-well plate reader (SpectraMax M3, Molecular Devices, Sunnyvale, CA, USA).

Quantitative reverse transcription-polymerase chain reaction (qRT-PCR)

The cells' total RNA was extracted with TRIzol reagent (TaKaRa Biotechnology Co., Ltd., Dalian, China) and then used for reverse transcription with Bio-Rad ScripTM cDNA Synthesis Kit (Bio-Rad Laboratories, Inc, Hercules, CA, USA) following the procedure in the operating manual. RT-qPCR was carried out with the aid of Bio-Rad CFX Manager software (Bio-Rad Laboratories, Inc.). The primer sequences were shown in Table 1. The qRT-PCR conditions were as follows: 5 min at 95 °C, followed by 40 cycles at 95 °C for 10 s and 62 °C for 20 s, and 72 °C for 30 s. The relative mRNA expression level of EDA2R was determined using $2^{-\Delta\Delta CT}$ method and normalized to GAPDH.

Statistical analysis

Comparison between two groups was determined with Student's t-test, while multiple data comparison was by one-way analysis of variance and Duncan's test for multiple groups using SPSS 22.0 package (SPSS Inc, Chicago, IL, USA), and then followed by *Post Hoc* Bonferroni test. All data are presented as mean ± standard deviation (SD). Differences were considered significant when $p < 0.05$.

RESULTS

Dex enhanced cell viability with decreased apoptosis in HG-induced podocytes

To evaluate the effect of Dex on podocyte injury, cell viability and apoptosis were determined in HG-treated podocytes after introduced with Dex. As shown in Figure 1 A, HG stimulation significantly reduced the viability of podocytes compared with that of podocytes treated with low glucose, which was evidently rescued by Dex administration in a concentration-dependent manner, suggesting that Dex enhanced the HG-induced cell viability of podocytes. In addition, Dex incubation significantly increased HG-induced relative protein expression of Bcl-2, but whereas diminished HG-induced relative protein level of Bax of podocytes in a concentration-dependent manner (Figure 1 B). Moreover, Dex treatment also prominently counteracted the HG-induced apoptosis rate of podocytes (Figure 1 C). Thus, these results suggest that Dex enhanced HG-induced cell viability, but inhibited HG-induced apoptosis of podocytes.

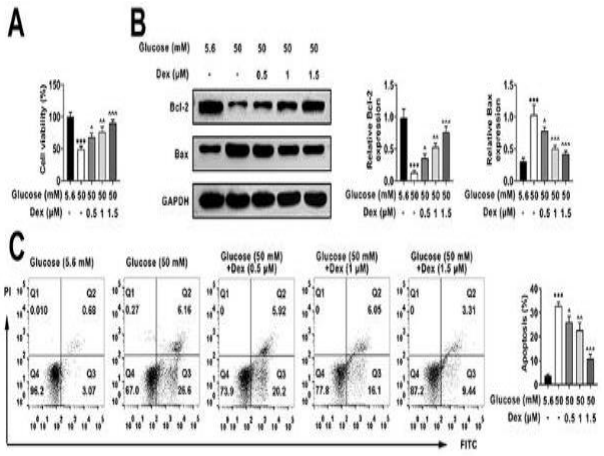

Figure 1: Dex increased cell viability with the reduced apoptosis in HG-induced podocytes. (A) Cell viability after treatment with 5.6 mM glucose or 50 mM glucose along with different concentrations of Dex (0, 0.5, 1 and 1.5 µM) for 24 h. (B) Relative protein expressions of Bcl-2 and Bax in podocytes after treatment with 5.6 mM glucose or 50 mM glucose along with different concentrations of Dex (0, 0.5, 1 and 1.5 µM) for 24 h. The data were normalized to GAPDH. (C) Cell apoptosis after treatment with 5.6 mM glucose or 50 mM glucose at different concentrations of Dex (0, 0.5, 1 and 1.5 µM) for 24 h. *** $p < 0.001$ *vs.* 5.6 mM glucose; ^$p < 0.05$, ^^$p < 0.01$, ^^^$p < 0.001$ *vs.* 50 mM glucose

Table 1: Primer sequences used in PCR

Item	Forward primer (5′-3′)	Reverse primer (5′-3′)
EDA2R	CCAGCTAATGAGGGCATCTTG	CCCATTGAGAATGGCTCTCTG
GAPDH	GGGAAGCTCACTGGCATGGCCTTCC	CATGTGGGCCATGAGGTCCACCAC

Dex attenuated HG-induced podocyte injury

Dex compensated the HG-induced relative protein expression of nephrin in a concentration-dependent fashion (Figure 2 A, $p < 0.05$). Besides, the relative protein level of podocin of HG-stimulated podocytes was reduced compared with that of low glucose-treated conditions, which was significantly reversed after incubation with 1.5 µM Dex (Figure 2 A, $p < 0.05$). On the other hand, Dex administration significantly counteracted HG-induced relative protein expression of desmin (Figure 2 A, $p < 0.05$). More importantly, Dex treatment consistently neutralized the HG-induced albumin permeability (Figure 2 B). Overall, therefore, Dex suppressed HG-induced podocyte injury.

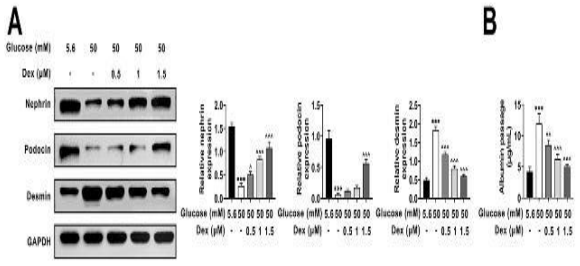

Figure 2: Dex ameliorated HG-induced podocyte injury. (A) The relative protein expressions of nephrin, podocin and desmin of podocytes after treatment with 5.6 mM glucose or 50 mM glucose at different concentrations of Dex (0, 0.5, 1 and 1.5 µM) for 24 h. (B) Albumin influx through the podocyte monolayer after treatment with 5.6 mM glucose or 50 mM glucose at different concentrations of Dex (0, 0.5, 1 and 1.5 µM) for 24 h. ***$P < 0.001$ *vs.* 5.6 mM glucose, and ^$p < 0.05$, ^^$p < 0.01$ and ^^^$p < 0.001$ *vs.* 50 mM glucose

Dex inhibited the expression of EDA2R

Since EDA2R is closely associated with podocyte injury, the effect of Dex on the expression of EDA2R was examined by qRT-PCR and western blot assay. The results showed that relative mRNA (Figure 3 A) and protein (Figure 3 B) levels of EDA2R of HG-induced podocytes were significantly enhanced when compared with these of low glucose-stimulated podocytes, which were reversed after Dex treatment in a concentration-dependent manner. The results indicate that Dex down-regulated the expression of EDA2R in HG-induced podocytes.

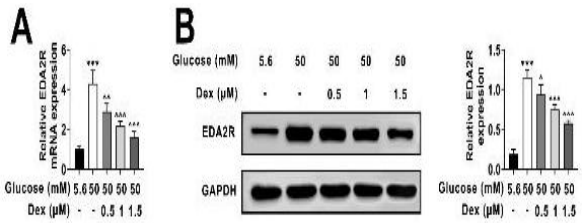

Figure 3: Dex decreased the expression of EDA2R in HG-induced podocytes. (A and B) Relative mRNA (A) and protein (B) expressions of EDA2R of podocytes after treatment with 5.6 mM glucose or 50 mM glucose at different concentrations of Dex (0, 0.5, 1 and 1.5 µM) for 24 h. ***$P < 0.001$ *vs.* 5.6 mM glucose, and ^$p < 0.05$, ^^$p < 0.01$ and ^^^$p < 0.001$ *vs.* 50 mM glucose

Dex mitigated HG-induced podocyte injury by inhibiting EDA2R

Expression of EDA2R was overexpressed with transfection of vector plasmid, pcDNA, was inserted in EDA2R sequences (Figure 4 A). Overexpression of EDA2R evidently decreased the Dex-rescued the cell viability (Figure 4 B), but enhanced the Dex-antagonized apoptosis (Figure 4 C) in HG-stimulated podocytes. Moreover, Dex treatment significantly increased HG-induced relative protein levels of nephrin and podocin, but were notably reversed with upregulation of EDA2R (Figure 4 D). The reverse was observed for the relative protein levels of desmin (Figure 4 D). Furthermore, overexpression of EDA2R enhanced Dex-induced albumin permeability in HG-stimulated podocytes (Figure 4 E). Thus, overexpression of EDA2R counteracted the mitigating effect of Dex on HG-induced podocyte injury.

DISCUSSION

Podocyte damage is one of the most crucial features of the pathogenesis of DN. Ectodysplasin A2 receptor (EDA2R) belongs to the tumor necrosis factor receptor (TNFR) family and resides on X chromosome. EDA2R is expressed in a variety of tissues such as heart, artery, lung, skin, lung and aging adipose that is relevant in the cellular apoptosis. In addition, the expression of EDA2R is upregulated in the kidneys of both types 1 and 2 diabetic mice based on microarray and RNA-seq assays [9,10].

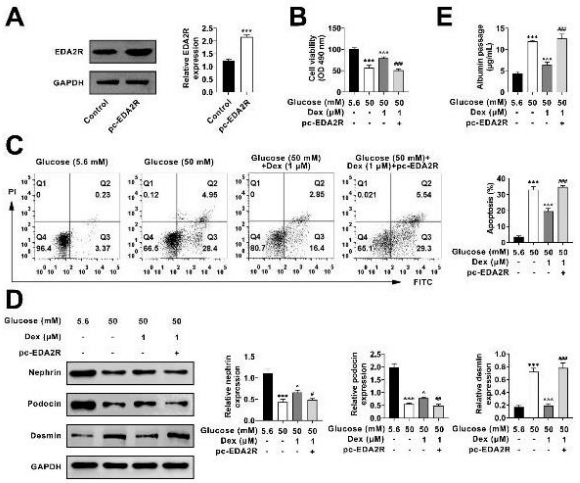

Figure 4: Dex alleviated HG-induced podocyte injury by inhibiting the expression of EDA2R. (A) Relative protein expressions of EDA2R of podocytes after transfection with vector plasmid, pcDNA, that was inserted in EDA2R sequences. (B) Cell viability after treatment with 5.6 mM glucose, 50 mM glucose, 50 mM glucose plus 1 μM Dex or 50 mM glucose plus 1 μM Dex and pc-EDA2R. (C) Cell apoptosis following treatment with 5.6 mM glucose, 50 mM glucose, 50 mM glucose plus 1 μM Dex or 50 mM glucose plus 1 μM Dex and pc-EDA2R. (D) Relative protein expressions of nephrin, podocin and desmin in podocytes with 5.6 mM glucose, 50 mM glucose, 50 mM glucose plus 1 μM Dex or 50 mM glucose plus 1 μM Dex and pc-EDA2R. (E) Albumin influx through podocyte monolayer following treatment with 5.6 mM glucose, 50 mM glucose, 50 mM glucose plus 1 μM Dex or 50 mM glucose plus 1 μM Dex and pc-EDA2R. ***P < 0.001 *vs.* Control (A) or 5.6 mM glucose (B-E), ^p < 0.05 and ^^^p < 0.001 *vs.* 50 mM glucose, and #p < 0.05, ##p < 0.01, ###p < 0.001 *vs.* 50 mM glucose plus 1 μM Dex

Another study has confirmed that high levels of EDA2R lead to dedifferentiation and apoptosis of podocyte via increase of ROS production [11], thus indicating the direct connection between EDA2R and podocyte injury. Although the mitigatory roles of Dex in renal injury has been reported in DN rats [7], its specific effect on podocyte injury is still not clear.

In the present study, Dex administration increased HG-induced cell viability and relative protein expression of Bcl-2, but decreased HG-induced relative protein level of Bax and apoptosis in podocytes, suggesting Dex enhanced cell viability but reduced apoptosis in HG-induced podocytes. In addition, Dex incubation compensated the HG-induced relative protein expression of nephrin and podocin in podocytes but reversed relative protein expression of desmin and albumin permeability. This indicates that Dex mitigated HG-induced podocyte injury. Moreover, Dex treatment elicited a decrease in EDA2R expression in HG-induced podocytes. Overexpression of EDA2R reversed Dex-induced amelioration of cell viability, apoptosis, expressions of nephrin, podocin and desmin, as well as albumin permeability in HG-stimulated podocytes. Therefore, these findings demonstrate that Dex ameliorated HG-induced podocyte injury via inhibition of EDA2R.

Loss of podocytes is one of the characteristics of podocyte injury. Although podocyte injury can result from a variety of factors, HG stimulation is the most common laboratory method verified in extensive studies [12]. Thus, in the current study, podocytes were treated with 50 mM glucose, which induced a remarkable reduction of cell viability, similar to previous findings [13]. A substantial fraction of studies has demonstrated that agents that rescued HG-induced decrease in podocyte viability can protect against podocyte injury. For instance, catalpol [13], tetrahydroxy stilbene glucoside [14] and hispidulin [15] exert protective role against HG-induced podocyte injury accompanied with enhancement of cell viability of podocytes. Corroborating these reported findings, the results of the present study also reveal that Dex treatment reversed HG-induced attenuation of podocytes viability. Furthermore, it has been found that apoptosis is the primary mechanism of podocyte death in DM and other progressive glomerular syndromes.

Feng *et al* [16] reported that perilipin 5 inhibits apoptosis, inflammation and oxidative stress, thereby protecting podocytes from HG-induced damage. Catalpol relieves HG-challenged podocyte injury through the inhibition of apoptosis and inflammation [13]. Here, the present results demonstrate that Dex treatment enhanced HG-induced relative protein expression of Bcl-2, but lowered HG-induced relative protein level of Bax and apoptosis in podocytes, thus indicating that Dex reduced apoptosis in HG-induced podocytes. Therefore, these findings suggest that Dex antagonized HG-induced podocyte loss.

HG stimulation induced a decrease in relative protein expressions of nephrin and podocin, and enhancement of relative protein level of desmin, which indicate that HG resulted in epithelial-to-mesenchymal transition (EMT) of podocytes, as also reported in a previous study [15]. EMT is a closely modulated process by which epithelial cells drop epithelial features and acquire mesenchymal characteristics. Thus, it has been recognized that the expression levels of epithelial markers, such as nephrin and podocin, are downregulated, while these mesenchymal markers, such as desmin are upregulated during podocyte EMT.

Diabetic neuropathy (DN) has been known to accompany the process of podocyte EMT, in which EMT may be a potential cause of podocyte depletion [17]. In the present study, Dex incubation reversed the HG-induced alteration in relative protein expressions of nephrin, podocin and desmin, which suggests that Dex mitigated HG-induced podocyte injury through EMT. In addition, several signaling pathways have been confirmed to evoke the podocyte EMT process, including TGF-β/Smad, Wnt/β-catenin, MAPKs, NF-κB signaling axis. Hence the signaling signaling pathways involved in the mitigatory effect of Dex on HG-induced podocyte injury via EMT may need further identification. Taken together with the results that Dex treatment neutralized HG-induced albumin permeability, it is clear that Dex restored HG-induced podocyte injury *in vitro*.

High expression of EDA2R has been demonstrated in hyperglycemia-related animal models [9,10], kidneys of diabetic mice [11], as well as HG-induced human podocytes [11]. Consistent with these outcomes, the findings of the present study also show that HG stimulation induced upregulation of both transcriptional and translational levels of EDA2R. The treatment of neutralized this effect. EDA2R is a member of TNFR family whose signals are transduced by the TNFR-associated factors (TRAFs). A recent study reported that Dex treatment enhanced H/R-induced increase in TRAF3 expression in HT-22 cells [18], suggesting a possible regulative effect of Dex on the TNFR. Here, the results showed that overexpression of EDA2R reversed Dex-induced the alleviation in cell viability, apoptosis, EMT, as well as the albumin permeability in HG-stimulated podocytes. Considered together with these findings, Dex ameliorated HG-induced podocyte injury via inhibition of EDA2R. Besides, EDA2R is closely associated with the regulation of apoptosis in a variety of cells, including human podocytes [11]; thus, the specific relationship between EDA2R and apoptosis in HG-induced podocytes after Dex introduction should be analyzed in the future.

CONCLUSION

The findings of this study show that Dex enhances cell viability but reduces apoptosis in HG-induced podocytes, as well as mitigates HG-induced podocyte injury. Mechanically, Dex treatment induces a decrease in EDA2R expression in HG-induced podocytes, and this was confirmed by gain-of-function assays. Therefore, these findings demonstrate that Dex ameliorates HG-induced podocyte injury via inhibition of EDA2R. Thus, EDA2R is a potential therapeutic target for podocyte injury, and Dex is an alternative drug for the treatment of podocyte injury.

DECLARATIONS

Acknowledgements

None provided.

Funding

None provided.

Ethical approval

None provided.

Availability of data and materials

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Yongqiang Lin and Xiang Chen designed the experiments and carried them out. Zaizai Lin analyzed and interpreted the data, and Weiwei Yan prepared the manuscript with contributions from all the co-authors.

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