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Role of Tisp40/Smad2 Protein in High Glucose-induced Renal Interstitial Fibrosis

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Abstract: *Objective:* To observe the effect of high glucose staining on human renal tubular epithelial cells (HKC) and to investigate the role of Tisp40/Smad2 protein in diabetes-induced renal fibrosis. *Methods:* Human renal tubular epithelial cells (HKC) were cultured in vitro and cells were incubated with a final concentration of 25, 50, and 100 mM high glucose for 24 h. The cell viability was detected by the CCK-8 assay; cells were treated with a final concentration of 50 mM high glucose for 6, 8, 12, 24, 48, and 72 h, and the degree of cell damage by high glucose at different time points was detected. Cells were treated with final concentrations of 25, 50, and 100 mM glucose for 24 h. Tisp40 protein expression was detected by enzyme-linked immunosorbent assay (ELISA) and Tisp40 mRNA expression was detected by polymerase chain reaction (RT-PCR). To observe the effect of high glucose on Tisp40/Smads signaling proteins, the Tisp40 cells were divided into six groups: (1) the normal control group; (2) the 25 mM high glucose group; (3) 50 mM high glucose group; (4) 100 mM high glucose group; (5) Tisp40-positive control group; (6) Tisp40-stimulated group (100 mM high glucose + 50 mM Tisp40), and the expression level of phosphorylated Smad2 protein (p-Smad2) was detected by immunoblotting (Western blot). *Results:* Compared with the control group, the survival rate of HKC cells decreased significantly with the increase of high glucose staining dose and time ($P < 0.05$) in a dose-dependent and time-dependent manner. ELISA results showed that the expression of Tisp40 protein was elevated to 44.3, 63.7, and 82.6 μg/ml after 24 h of high glucose action on HKC cells and the induction was in a dose-dependent manner. RT-PCR showed that the expression level of Tisp40 mRNA increased significantly with increasing glucose concentration, which was 2.75, 5.42 and 9.67 times higher than that of the control group, respectively, and the induction was in a dose-dependent manner ($P < 0.05$). The Western blot showed that the expression level of p-Smad2 protein increased significantly after 24h of glucose action in the cells at concentrations of 25, 50 and 100 mM glucose ($P < 0.05$), and the amount of p-Smad2 protein reached the maximum under the co-stimulation of 100 mM high glucose + 50 mM Tisp40 given to the cells ($P < 0.05$). *Conclusion:* Abnormal expression of Tisp40 and p-Smad2 was involved in the process of high glucose-induced HKC cell injury and Tisp40-induced high expression of Smads proteins played an important role in high glucose-induced renal fibrosis.

Keywords: HKC cells; Renal interstitial fibrosis; Tisp40/Smad protein

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1. Introduction

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia, which has become one of the most lethal chronic diseases, with the most prominent and significant renal damage [1]. Diabetic nephropathy (DN) presents early with persistent microalbuminuria and proteinuria and eventually progresses to renal failure [2]. It is the most common single etiology in patients with nephropathy in the United States and Europe, up to 44.5%, and about 25% in China [3]. Pathological findings show that interstitial fibrosis and glomerulosclerosis have become the first manifestation and the mechanism of high glucose-induced renal fibrosis is unknown so far. Renal fibrosis is characterized by fibroblast (FB) proliferation and excessive deposition of extracellular matrix (extracellular matrix, ECM), which leads to changes in normal renal tissue organization and loss of function [4]. It is characterized by interstitial collagen deposition, inflammatory cell infiltration, loss of renal tubular cell damage, fibroblast accumulation, and peritubular microvascular sparing. Smads play an important role in cell proliferation, development, differentiation, apoptosis, immunomodulation, and regulation of ECM accumulation. The most sensitive receptor-regulated protein in Smad protein is Smad2, and its phosphorylation marks the activation of this protein [5]. Based on this, this study intends to simulate the model of diabetes-induced renal fibrosis by culturing HKC cells in vitro, to detect the expression of key gene proteins after different high-glucose staining, to elucidate the expression of Tisp40/Smads in the renal fibrosis induced by diabetes, and to provide a theoretical basis for patients with diabetes-induced renal injury in the later stage.

1.2. Research questions

Diabetic renal fibrosis (DNF) is a key pathological process in the progression of diabetic nephropathy to end-stage renal disease, and its core mechanisms include cellular injury, inflammatory response, and extracellular matrix deposition. However, the roles of Tisp40 and p-Smad2 in the development of DNF are still not fully elucidated. The present study focuses on the following questions.

(1) What are the expression changes and interrelationships of Tisp40 and p-Smad2 in diabetic renal fibrosis?

(2) Is the expression of Tisp40 and p-Smad2 up-regulated in HKC cells and renal tissues of patients with diabetic renal fibrosis in a high-glucose environment?

(3) Does Tisp40 contribute to the activation of the Smads signaling pathway through direct or indirect regulation of p-Smad2?

1.3. Objectives

Diabetic renal fibrosis is a key pathology in the progression of diabetic nephropathy to end-stage renal disease and its development involves the regulation of multiple signaling pathways. Among them, the specific roles and interrelationships of Tisp40 and p-Smad2 in renal fibrosis have not been fully clarified. This study aimed to investigate the expression changes of Tisp40 and p-Smad2 in diabetic renal fibrosis and to analyze the expression levels and localization of Tisp40 and p-Smad2 in a high glucose-induced renal tubular epithelial cell (HKC) model. To assess the correlation between Tisp40 and p-Smad2 and to explore their possible roles in diabetic renal fibrosis.

2. Materials and methods

(1) Human renal tubular epithelial cells (HKC) (Cell Resource Center, Shanghai Institutes for Life Sciences,

Chinese Academy of Sciences)
(2) Glucose, CCK-8 cell proliferation kit (4980-050k, Trevigen)
(3) DMSO (Sigma Aldrich)
(4) Fetal bovine serum (Sigma Aldrich)
(5) DMEM medium (Sigma Aldrich)
(6) Penicillin-streptomycin antibiotic (HyClone Cell Culture and Bioprocessing)
(7) Rabbit anti-human Phospho-Smad2 antibody
(8) Rabbit anti-human Smad2 antibody
(9) TRIzol kit
(10) Sigma-Aldrich quantitative PCR kit
(11) Taq DNA polymerase probe kit (Wuhan Doctoral Biotechnology Co., Ltd.)
(12) ELISA reagent test kits (Wuhan Doctoral Biotechnology Co., Ltd.)
(13) Whole protein extraction Kit (Beijing Solebao Technology Co., Ltd.)
(14) Bio-Rad DC Protein Assay Kit (Beijing Boao Sen Biotechnology Co., Ltd.)
(15) Primers (Shanghai Sangon Bioengineering Co., Ltd.)

2.1. Methods

2.1.1. Cell culture

HKC cells are cultured using F12/DMEM (1: 1) medium (37 ℃ constant temperature incubator with 5% CO2, Thermo Fisher) for 3–7 generations for experiments. After 24 hours of incubation, the cells are digested using pre-formulated trypsin to make a cell suspension, which is counted under the microscope and evenly distributed into two culture flasks according to the ratio of 1: 2~3. Logarithmic proliferating cells were selected (to prove no mycoplasma contamination) and continued to be incubated for 24 hours using DMEM to prepare for the experiments. HKC cells were divided into six groups: (1) Normal control group (control); (2) 25 mM high glucose group; (3) 50 mM high glucose group; (4) 100 mM high glucose group; (5) Tisp40 positive control group; and (6) Tisp40 stimulation group (100 mM high glucose + 50 mM Tisp40), and the proteins were extracted as described above.

2.1.2. CCK-8 detection of cell viability

The ultra-clean bench is sterilized and disinfected before and after the operation, and after the working conditions are reached, the cells are removed from the incubator to observe the cell growth. According to the cell growth status, the logarithmic growth phase cells that are favorable for the experiment are selected. Trypsin (0.25% by mass) is used to digest the adherent cells, and the cells are mixed from the bottom of the dish with a micropipette repeatedly. All the cells are resuspended under the microscope, counted, and then cultured for the experiment (1: 3 or 4), and counted under the microscope. The cell density is adjusted using 100 μl/well inoculation in a sterilized 96-well cell culture plate in a 5% CO_2 incubator incubation, at 37 ℃ for 24h, the plate is removed and the cell growth status is observed under the microscope, to observe if it is fused around 80%–90%, then the plate waste is discarded. Around 100 μL of the intervention reagent is added to each well, so that the cells are exposed to the final concentration of 0 (blank control), 25, 50, and 100 mM of high-sugar DMEM medium, respectively, and incubated at 37°C in a 5% CO_2 incubator. After 24 h of incubation, the intervention solution in each well was discarded, and then 80 μl of fresh DMEM medium and 20 μl of CCK-8 reagent with a mass volume fraction of 5

μg/μL (which had been prepared 4 h in advance), are added to each well of each experimental group and shaken at a low speed for 3 min, and the absorbance (OD) are detected by the enzyme marker at 490 nm. The average OD value of each group is quoted. Cell inhibition rate = (mean value of OD in the solvent control group - mean value of OD in the intervention group)/(mean value of OD in the solvent control group - mean value of OD in the blank control group) × 100%. Five parallel samples are set up in each group and the experiment was repeated thrice.

2.1.3. Protein extraction

The culture solution is poured out and the bottle is held upside down on the blotting paper to allow the blotting paper to absorb the culture solution. Around 3 ml of 4°C pre-cooled PBS (0.01M pH = 7.2–7.3) is added to each bottle of cells. The cells are washed by gently shaking for 1 min on a flat surface and then the washings are discarded. The above operation is repeated twice, and the cells are washed three times in total to wash away the culture fluid. The culture flask is placed on ice after discarding the PBS. Around 10 μl of PMSF (100 mM) is added to 1 ml of lysate and shaken well on ice. Around 400 μl of lysate containing PMSF is added to each bottle of cells and lysed on ice for 30 min. To make the cells fully lysed, the culture bottle is shaken back and forth frequently. After lysis, a clean scraper is used to scrape the cells on one side of the culture flask, and the cell fragments are quickly transferred to a 1.5 ml centrifuge tube with a pipette. The cells is centrifuge at 12000 rpm for 5 min at 4°C. The supernatant is transferred after centrifugation to a 0.5 mL centrifuge tube and stored at -20°C.

2.1.4. Western blot detection of Tisp40, p-Smad2 protein expression

The preparation of the SDS-PAGE gel electrophoresis includes: Preparation of separator gel (10% PAGE gel, 4 ml) (Solution A: 0.5 ml; Solution B: 0.75 ml); deionized water: 1.75 ml (10% APS: 30 μl; TEMED: 10 μl). After mixing thoroughly, the solution is transferred into the gel-making tank to the corresponding scale and seal with deionized water. A total of 40 μg of protein is extracted into 80 ml of buffer solution, which needs to be denatured for 11 min at 100 ℃. Pre-prepared PVDF membranes with the same quality as the separator gel are immersed into the solution containing 1 × Transfer Buffer for 16 min. Previously prepared separator gels are placed in the 1 × Transfer Buffer solution at 4 ℃. Drops of pre-prepared rabbit anti-human p-Smad2 (1: 200), rabbit anti-human Smad2 (1:200), rabbit anti-human Tisp40 primary antibody are added, refrigerated overnight at 4°C, washed 3 times with TBST for 5 min and then incubated with (HRP)-labeled IgG secondary antibody (1:1000) for 1 h. In addition to the ECL liquid, Solution A and Solution B of the above ECL kit are taken, mixed well, and put on the plastic wrap. The membrane is placed with the protein side facing up. Add ECL solution to the top of the membrane and incubate for 6 minutes. After incubation, the excess ECL solution is discarded and the membrane is wrapped in clean plastic wrap and set aside. The plastic wrap, completed in the above process, is put into the Kodak Gel Imaging Image Station 4000MM imager, the gray and dark bands are observed and the clear bands are selected to take pictures.

2.1.5. RNA extraction and reverse transcription synthesis of cDNA

According to the pre-determined groups, the concentration of high glucose staining required for the experiment is added and incubated for 24h. The cells are collected after and 1 ml of Trizol reagent is added for digestion. The cells are lysed after the staining at a low temperature for 5 minutes and trichloromethane is added before mixing repeatedly with a pipette. The above homogenate is left at room temperature for 5 min to allow nucleic acids and proteins to fully dissociate. Around 0.2 ml of chloroform per 1 ml of TRIzol reagent dosage of homogenate

is added and the cap of the tube is closed tightly, manually shaken vigorously for 15 s, before being left to stand at room temperature for 2–3 min and centrifuged at 10,000 g at 4°C for 10 min. The carefully aspirated upper aqueous phase (colorless) is added it to a new tube and the volume of the aspirated aqueous phase is calculated at the same time. An equal volume of pre-cooled isopropanol is added to the aspirated aqueous phase, the tube tightly is capped tightly, and gently shaken. The RNA is left to settle by centrifugation at 10,000 g for 10 min at 4°C. The supernatant is discarded, each tube is rinsed with 1 ml of 75% ethanol, cap tightly, and gently shaken to remove residual isopropanol and salts. The tubes is centrifuged at 7,500 g for 5 min at 4°C. The supernatant is disposed, the tubes are un capped and the RNA precipitates are dried (either by evaporation at room temperature or by vacuum drying). The RNA precipitate is dissolved in an appropriate amount of RNase-free water. The appropriate amount of DEPC is added and fully dissolved. An A260 /A280 ratio assay is performed and the sample is placed between 1.8 and 2.1, before being stored at -80°C for backup. Extracted RNA is subjected to agarose gel electrophoresis, and the following mixture is prepared in RNase-free centrifuge tubes, reacted at 65°C for 5 min, and cooled in an ice bath. The reverse transcription reaction conditions are set up as follow: 30°C, 10 min; 42°C for 30 min; 95°C for 5 min, then cooled in an ice bath. The product is stored in the refrigerator at -20°C.

2.1.6. Real-time fluorescence quantitative reverse transcription-polymerase chain reaction (Real-time PCR)

The frozen lysed cells are taken and left at room temperature for 5 minutes to make them completely soluble. The cDNA sequences of the target gene and the internal reference β-actin are obtained from Genbank NCBI Reference Sequences (RefSeq), and the primer design software Primer Premier 5.0 (primer5) and Primer blast are used to design primers based on the genomic reference assemblies of the selected organisms. Primer5 is used to verify the characteristics of the primers themselves, hairpin structure, primer self-dimerization, mismatch, and inter-primer dimerization, and the absolute value of △ G.

The upstream primer sequence for Tisp40 is 5'-TTACGATCGGTACGAC-3', and the downstream primer is 5'-AATCTAGGCTATGCTG-3'. For the internal reference gene β-actin, the upstream primer is 5'-TCACACCCACGATAATGGC-3' and the downstream primer is 5'-CGGAGTTATCGACTGATCG-3'. For each sample, 1 μL of cDNA was used. PCR is conducted with an initial denaturation at 93°C for 2 minutes, followed by 40 cycles of 93°C for 1 minute, 55°C for 1 minute, and 72°C for 1 minute. A final extension is carried out at 72°C for 7 minutes. The peak plot of the solubilization curve is used to determine the presence of non-specific amplification: the GC content of the products and the order of the bases make each product have different peaks, which can distinguish the specific products. The ΔΔCt method is used to analyze the concentration of template DNA, based on the principle that the Ct value is linearly related to the logarithm of the initial template copy number.

2.2. Statistical processing

SPSS 22.0 software is applied to analyze the data statistically, and the test results are expressed as (± s). ANOVA is used for multiple group comparisons, and SNK and Fisher LSD-t tests are used for group comparisons of multi-sample means. The results are expressed as $P < 0.05$ to indicate that the differences are statistically significant.

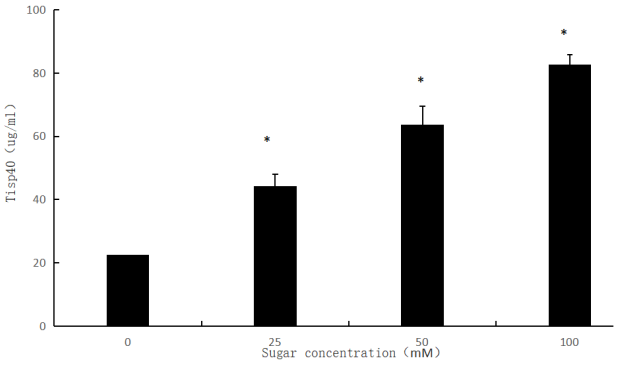
2.3. Ethics approval

Research ethics provided by the Ethics Committee of Ningxia Medical University (License No.: 2024-N066) is used.

3. Results

3.1. Effects of different high glucose staining on HKC cell viability

HKC cells were treated with glucose at final concentrations of 25, 50, and 100 mM for 24 hours. The resulting cell survival rates were 91.7%, 79.5%, and 49.3%, respectively. The differences were statistically significant ($P < 0.05$) when compared with the control group. A dose-dependent pattern was observed, with the higher the staining concentration, the lower the survival rate of the cells (refer to **Figure 1**).

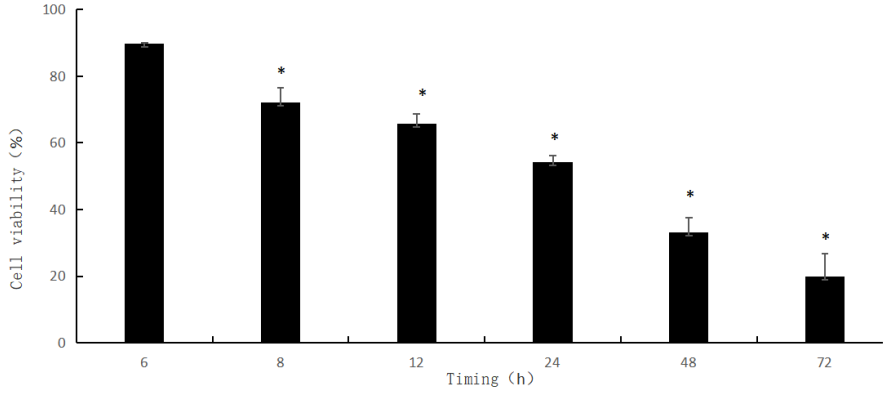


Note: * indicates that the difference between the high glucose group and the control group was statistically significant ($P < 0.05$)

Figure 1. Changes in 24h relative cell survival of HKC cells stained with different concentrations of high sugar.

3.2. Effect of the duration of high glucose staining on the survival of HKC cells

The cells were stained with glucose at a final concentration of 100 mM, and HKC cells were stained for 6 h, 8 h, 12 h, 24 h, 48 h, and 72 h. The survival rate of HKC cells decreased to 89.7%, 72.1%, 65.8%, 54.3%, 33.1%, and 19.9%, respectively, when compared with that of the control group (the survival rate of the control group was set to 1). The differences were all statistically different ($P < 0.05$) when compared with the control group. A time-dependent pattern was observed, with longer dyeing time, lower cell survival, and greater damage (refer to **Figure 2**).



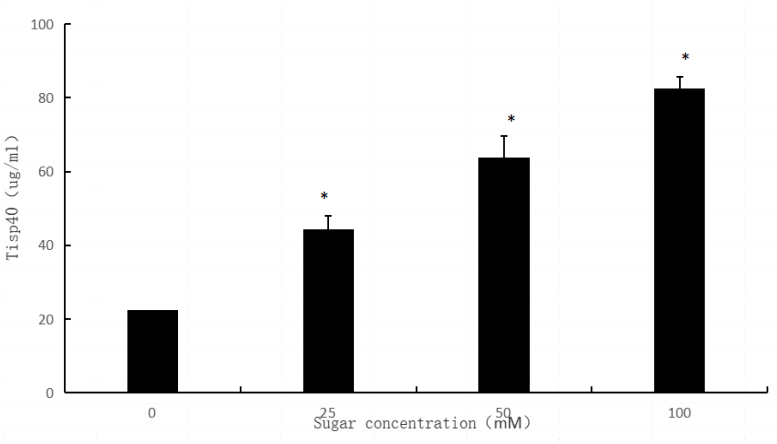
Note: * indicates that the difference between the intervention group and the control group was statistically significant ($P < 0.05$)

Figure 2. Changes in relative survival of HKC cells at different time points under 100 mM concentration staining.

3.3. Different concentrations of glucose-induced Tisp40 protein and Tisp40 mRNA expression

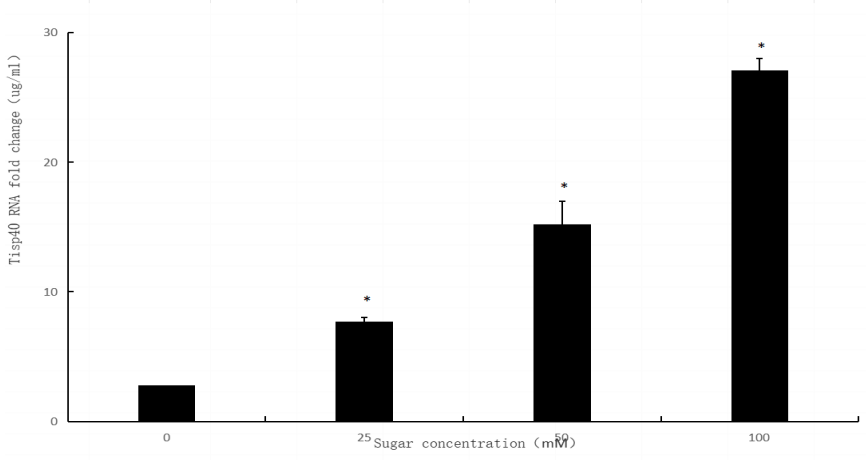
After acting on HKC cells at final concentrations of 25, 50, and 100 mM high glucose for 24 h, the expression of

Tisp40 protein and Tisp40 mRNA was significantly increased compared with that of the control group, and the difference was statistically significant ($P < 0.05$), as shown in **Figure 3** and **Figure 4**.



Note: * indicates that the difference between the intervention group and the control group was statistically significant ($P < 0.05$)

Figure 3. Different concentrations of high glucose induced Tisp40 protein expression



Note: * indicates that the difference between the intervention group and the control group was statistically significant ($P < 0.05$)

Figure 4. Different concentrations of high glucose induced Tisp40 gene expression

3.4. High sugar-induced p-Smad2 protein expression

Compared with the control group, high glucose 25, 50 and 100 mM toxicity doses were able to induce an increase in p-Smad2 protein in HKC cells, and the cell survival rate decreased with the increase of the concentration in a dose-dependent manner ($P < 0.05$). When cells were given Tisp40 stimulation alone, the amount of cellular expression of p-Smad2 protein was very small, whereas when cells were given 100 mM high glucose + 50 mM Tisp40 co-stimulation, the cells expressed the maximum amount of p-Smad2 protein ($P < 0.05$) (refer to **Figure 5**).

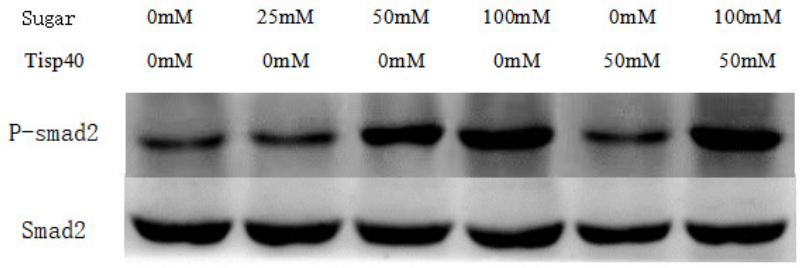


Figure 5. p-Smad2 protein expression in each group of cells

4. Discussion

The pathogenesis of renal fibrosis in diabetic patients is unknown so far. Studies have shown that Tisp40 is closely related to apoptosis, proliferation, and differentiation [6]. In hepatocellular carcinoma tissues, the expression level of Tisp40 is also upregulated compared with normal tissues [7]. Xiao *et al.* found that the expression of Tisp40 protein was significantly higher than that of the control group in animal models, both in I/R-induced human renal tubular epithelial cell (HK-2) fibrosis and in TGF-β1 stimulation-induced renal tubular epithelial cells [8]. In addition to this, the process of Smad2 phosphorylation, including promoter gene 4 (URG4), transforming growth factor (TGF-β I), zinc finger transcription protein (Snail I), α-smooth muscle actin (α-SMA), epithelial calreticulin (E-cadherin), and inhibition of E-cadherin expression were also regulated.

To further verify whether renal tubular fibrosis is involved in the development of the disease, this study took human renal tubular epithelial cells (HKC) as the research object. The results of this study showed that different concentrations of high glucose, as well as different time interventions in HKC cells could significantly elevate the expression levels of Tisp40 protein and Tisp40 mRNA, and showed a positive correlation between the time and the dose of expression. The high expression of Tisp40 induced morphological changes in the cells, remodeling the microenvironment of HKC cells to make it suitable for new HKC cell survival and proliferation sites. The main changes were α-smooth muscle actin (α-SMA) expression and fibronectin (FN) in the renal tubule-mesenchyme, which were transformed into myofibroblasts that characteristically expressed α-SMA in the presence of high glucose-stimulating factor, and the expression of Tisp40 mRNA was significantly increased.

TGF-β1 is a key signal transduction factor that plays a critical role in the activation of Smads. However, it is a "double-edged sword," and some studies to validate the role of TGF-β1 in fibrosis have found that mice were killed by systemic inflammatory infections after genetically silencing TGF-β1 [9, 10]. To further verify whether Tisp40 could affect the expression of TGF-β1, Tisp40 knockout mice and I/R-induced mice were constructed, which showed that TGF-β1 protein expression was not differential, and it was hypothesized that Tisp40 could not directly induce the expression of TGF-β1.

The Smad family of proteins are common signaling protein factors that induce fibrosis, especially the presence of Smad2 protein as a key factor. Smad2 is composed of the highly conserved MH1 and MH2 linked by a proline-rich strand region. Smad2 has 2 more amino acid fragments than Smad3. Its activation can be phosphorylated by the TβRI receptor on the membrane of downstream cell lines, and the phosphorylated P-Smad2 separates from the receptor TβRI at this time and is transcriptionally activated with target genes on the other copolymer. The results of this study showed that comparing the different concentrations of the high glucose staining group with the control group, the intervention of staining with concentrations of 25mM, 50mM, and

100mM could make the p-Smad2 protein highly expressed, and the difference was statistically significant.

Without high glucose stimulation, simply giving cells Tisp40 intervention, the cells expressed less amount of p-Smad2 protein. Whereas, giving cells 100mM high glucose + 50mM Tisp40 combined intervention, HKC cells showed a significant increase in p-Smad2, which was the highest among all groups, indicating that P-Smad2 was due to high expression of Tisp40 protein and was positively correlated with the dose. Smad2 is overactivated in both experimental animal models and human renal fibrosis [11]. In previously constructed models of renal fibrosis, knockdown of the Smad2 gene significantly alleviated the degree of renal fibrosis [12], and overexpression of Smad2 was shown to inhibit the activity of MMP-1 in fibroblasts [13].

In summary, activation of the Tisp40 protein plays an important role in renal tubular fibrosis caused by high glucose intervention. Based on this, explicitly inhibiting the expression activity of Tisp40, p-Smad2, in this signaling protein, may be a new way to treat renal fibrosis in diabetic patients. However, there may be numerous intermediate synergistic intervention pathways for the high expression of p-Smad2 induced by Tisp40, and it is particularly urgent to explore and precisely inhibit the activating factors affecting its synergistic pathways.

5. Conclusion

Aberrant expression of Tisp40 and p-Smad2 is significantly involved in HKC cell injury under a high glucose environment. It was shown that high glucose conditions induced the upregulation of Tisp40 expression and further promoted the activation of the Smads signaling pathway, especially the aberrant phosphorylation of p-Smad2. Tisp40 may play an important role in key pathological processes, such as renal tubular epithelial cell-to-fibroblast transition (EMT), extracellular matrix (ECM) deposition, and inflammatory response through enhancing the expression of Smads and its signaling, inflammatory response and other key pathological processes. This mechanism may accelerate the process of high glucose-induced renal fibrosis, which ultimately leads to renal impairment. Therefore, Tisp40 may be an important target to regulate the Smads-mediated renal fibrosis signaling pathway, which may provide a new theoretical basis and potential therapeutic strategy for the intervention of diabetic nephropathy (DN) and other related diseases.

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Disclosure statement

The authors declare no conflict of interest.

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