Role and Mechanism of NUP160-regulated Autophagy in Pathogenesis of Diabetic Nephropathy

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Keywords. NUP160, autophagy, diabetic nephropathy, podocytes

Introduction. Diabetes mellitus (DM) is one of the most common chronic diseases worldwide, and diabetic nephropathy (DN) is the most significant complication of DM, which is highly prevalent and difficult to cure. This research project aims to investigate the role and mechanism of Nucleoporin 160kDa (NUP160)-regulated autophagy in the pathogenesis of DN.
Methods. NUP160 levels in diabetic and non-diabetic kidney tissues were measured by Western blot, and the connection between NUP160 and renal function of DN patients was analyzed. The podocytes were divided into four groups, namely the standard group (culture medium: standard glucose solution), high glucose (HG) group (HG solution), HG+si-NUP160 group (HG solution+si-NUP160 transfection) and HG+si-NC group (HG solution+si-NUP 160 transfection) for the determination of apoptosis by flow cytometry and measurements of LC3B, Prostacyclin-62 (P62), Janus kinase 2 (JAK2) and Signal transducer and activator of transcription3 (STAT3) by Western blot.
Results. In DN patients, NUP160 decreased in podocytes and was inversely proportional to Blood urea nitrogen (BUN), Serum creatinine (Scr) and β2-Microglobulin (β2-MG) ($P < .05$). Compared with a standard group, the apoptosis rate, P62 level, and the ratios of phosphorylation-JAK2 (p-JAK2)/JAK2, phosphorylation-STAT3 (p-STAT3)/STAT3, and LC3B-II/LC3B-I elevated in the other three groups ($P < .05$). Apoptosis rate and P62 level, p-JAK2/JAK2 and p-STAT3/STAT3 ratios increased, and LC3B-II/LC3B-I ratio decreased in the HG+si-NUP160 group ($P < .05$), while those in HG+si-NC group showed no evident changes, compared with HG group ($P > .05$).
Conclusion. NUP160 is downregulated in DN and can affect cellular autophagy through the activation of JAK2/STAT3 signaling pathway.

IJKD 2023;17:327-34
www.ijkd.org
DOI: 10.52547/ijkd.7884

Original Paper

INTRODUCTION

As people's living standards continue to improve, the prevalence of diabetes mellitus (DM) also increases. According to a survey, the global prevalence rate of diabetes was 9.3% in 2019 and is expected to rise to 10.2% by 2030.[1] Diabetic nephropathy (DN) is one of the common complications of diabetes mellitus and the main cause of end-stage kidney disease (ESKD). In the absence of effective intervention, the rate of progression to ESKD is 14 times faster than other kidney diseases.[2,3] However, the treatment of ESKD

is demanding, and kidney replacement therapy is usually initiated to prolong the life of patients, which brings a massive burden to individuals and the health care system.[4] Hence, it is necessary to clarify the pathogenesis of DN and find the potential therapeutic targets to improve the effectiveness of preventive and therapeutic measures in DN.

Nucleoporin 160kDa (NUP160), an essential part of NUP, is located on human chromosome 11 and expressed in human kidney cells.[5] Podocytes, also known as glomerular visceral epithelial cells, are attached to the lateral aspect of the glomerular basement membrane and form a filtration protection barrier in combination with the glomerular basement membrane and endothelial cells. This filtration barrier plays a pivotal role in maintaining the selective permeability of glomerular filtration.[6] In the setting of diabetic nephropathy, oxidative stress and advanced glycation end products (AGEs) induced by high glucose (HG) contribute to the mass apoptosis of podocytes, thereby increasing the incidence of renal failure.[7] A previous study showed that NUP160 knockdown can cause damage to mouse podocytes, manifesting as cell growth arrest, apoptosis, autophagy and migration enhancement, as well as interfering with the distribution of podocyte-related molecules,[8] indicating that NUP160 may interfere with the development of DN.

In this study, we will explore the expression of NUP160 in DN and conduct a preliminary analysis of its mechanism of action, which can confirm the relationship between NUP160 and DN, and lay a reliable foundation for future molecular immunotherapy through NUP160 to protect the health of DN patients.

MATERIALS AND METHODS

Sample Source

From January 2019 to October 2020, 36 patients who underwent kidney biopsy and were diagnosed as DN in the Department of Nephrology of Xinghua People's Hospital were enrolled in the DN group. The inclusion criteria included patients who met the diagnostic criteria of DN[9] and had complete clinical data and pathological data. The exclusion criteria included malignant tumor(s) and autoimmune disease(s), severe disturbance of endocrine function, use of drugs harmful to the kidney within the past 30 days and acute kidney injury. Additionally, 18 patients who had undergone surgery for renal hamartoma were selected as the control group. They had no history of chronic diseases such as diabetes mellitus and hypertension nor abnormalities in heart, liver and kidney function. Renal tissue samples from both groups were immediately rinsed with sterile normal saline to remove blood stains and fixed in 40 mL/L formalin solution for subsequent tests. Measurements of renal function indices such as blood urea nitrogen (BUN), serum creatinine (Scr) and β2-microglobulin (β2-MG) of both groups were performed with an automatic biochemical analyzer. All clinical samples were used with informed consent signed by patients, and the hospital ethics committee approved this study (ethical no. KD2021). Furthermore, the study was conducted in strict compliance with the Declaration of Helsinki.

Cell Intervention

Cell cultivation. The mouse podocytes offered by the ATCC of the United States were grown in a 10% bovine fetal serum-containing RPMI 1640 medium (Gibco, US) in an incubator at 37 ℃ (5% CO_2).

Cell transfection. The cells adjusted to $2*10^5$ /well were inoculated into wells of a 6-well plate in an incubator at 37 ℃ overnight. The NUP160 inhibitory plasmid (si-NUP160) and the corresponding negative control (si-NC) were established by using pcDNA 3.1 plasmids as the vector and were then transfected into cells respectively by using Lipofectamine™ 2000 kits (Invitrogen, US).

Cell grouping. Podocytes were divided into four groups: regular group, HG group, HG+si-NUP160 group and HG+si-NC group. In the standard group, 5.6 mmol/L glucose-containing RPMI1640 medium was used for culture; the HG group was cultivated in 30 mmol/L glucose medium; the HG+si-NUP160 group and HG+si-NC group were transfected with si-NUP160 and si-NC based on the treatment in HG group, respectively.

Quantitative RT-PCR (qRT-PCR)

Measurements of NUP160 mRNA levels in collected tissues and cells were performed by employing qPCR. The total RNA in the samples was extracted according to the manufacturer's instructions for Trizol Kit (Invitrogen, USA), and the samples' purity, concentration and integrity

were checked. Then, 2 μg of total RNA was reversely transcribed into cDNA with the reverse transcription kit (Invitrogen, US) for subsequent PCR amplification with the PrimeScript RT Master Mix kit (Takara Japan). The amplification system was 10 μL SYBR qPCR Mix, 0.8 μL each of upstream and downstream primers, 2 μL cDNA product, 0.4 μL 50×ROX reference dye, and RNase-free water in a final volume of 20 μL. PCR reaction conditions: 95°C, 60 s; 95°C, 30 s; 60°C, 40 s, for 40 cycles. Gene expression profiles were normalized to GADPH and calculated by using $2^{-\Delta\Delta ct}$.

Western Blot (WB)

Total protein isolation and determination of protein concentration were perfomed by using RIPA lysis (Thermo Scientific, US) and BCA method (Thermo Fisher, US), respectively. The 4 μg/μL proteins were separated on 10% SDS-PAGE and shifted to PVDF membranes (Life Technologies, US). After immersion in PBST for five minutes of washing and two hours of blocking with 5% skimmed milk powder, the membranes were added with LC3B, Prostacyclin-62 (P62), Janus kinase 2 (JAK2), phosphorylation-JAK2 (p-JAK2), Signal transducer and activator of transcription3 (STAT3), phosphorylation-STAT3 (p-STAT3) and β-catenin (Abcam, US) primary antibodies to seal at 4°C for a night. The membranes were then washed to remove the primary antibodies and put them in the horseradish peroxidase labelled goat anti-rabbit (Abcam, US) for cultivation at 37 °C for one hour, followed by three PBS rinses, each for 5 min. After developing in a dark room with ECL reagents, Quantity One software analyzed the grey value to calculate the target proteins' relative expression.

Cell Multiplication Assay

Cell multiplication was determined by CCK-8 (Beijing Transgen, CHN). Twenty-four hours after transfection, the target cells were cultured in wells of a 96-well plate at 2.5×10^3 per well. After that, 10 μL CCK-8 was dripped into wells at 24, 48, 72, and 96 hours, respectively. After incubation at ambient temperature for 2 hours, the absorption of each well was detected by a microplate reader at 490 nm, and the growth curve was drawn.

Apoptosis Assay

The transfected cells were gathered to digest with 0.25% trypsin. After that, they were prepared into a 1×10^6 cells/mL suspension, successively mixed with 10 μL AnnexinV-FITC/PI (Shanghai Yisheng Biotech, CHN), and incubated for 5 min at ambient temperature away from light. The cells were analyzed by flow cytometry (BD CantoII), and the apoptosis rate was calculated.

Statistical Methods

The experimental data came from three independent experiments. SPSS18.0 software package and GraphPad 7 software package were used for data analysis and image rendering. The mean and standard deviation (Mean ± SD) were obtained, and the differences between groups were analyzed by the independent samples t-test, and one-way ANOVA and LSD-t post-test were used for the differences among multiple groups, with $P < 0.05$ as the significance level. Pearson correlation coefficient was employed for correlation analysis.

RESULTS

NUP160 Is Decreased in DN Patients

NUP160 protein content in the collected tissues and cells was found to decrease by using WB, not only in tissues of DN patients but also in podocytes induced by HG ($P < .05$). Similarly, decreased NUP160 mRNA expression in samples of DN patients and HG-induced podocytes were determined by qPCR ($P < .05$) (**Figure 1).**

NUP160 Is Significantly Correlated with Renal Function Indexes of Patients

DN patients showed higher BUN, Scr, and β2-MG levels than controls ($P < .05$). Pearson analysis identified that NUP160 protein expression in the DN group was inversely correlated with BUN, Scr and β2-MG ($P < .05$) (Figure 2**).**

Table 1. Primer Sequences

	F (5'-3')	R (5'-3')
NUP160	CACGGACTGCACGGAAACA	GAGTTCGAGGGATAACCTGGT
GAPDH	CTGGGCTACACTGAGCACC	AAGTGGTCGTTGAGGGCAATG

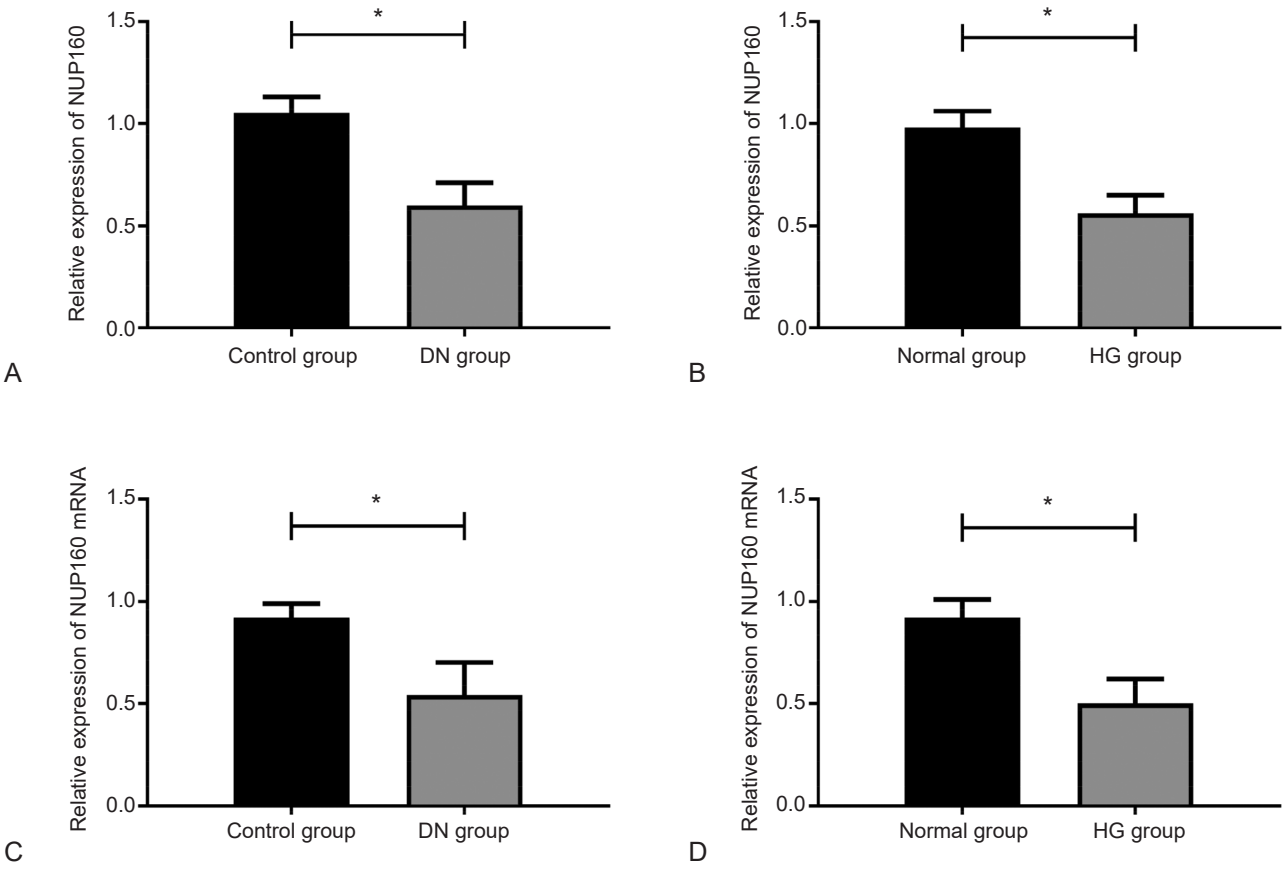

Figure 1. The Decrease of NUP160 in Tissues of Patients with DN [A: NUP160 elevated in tissues of patients with DN; B: NUP160 increased in podocytes induced by HG; C: NUP160 mRNA elevated in tissues of patients with DN; and D: NUP160 mRNA increased in HG-induced podocytes ($P < .05$) (note: * indicates $P < .05$)]

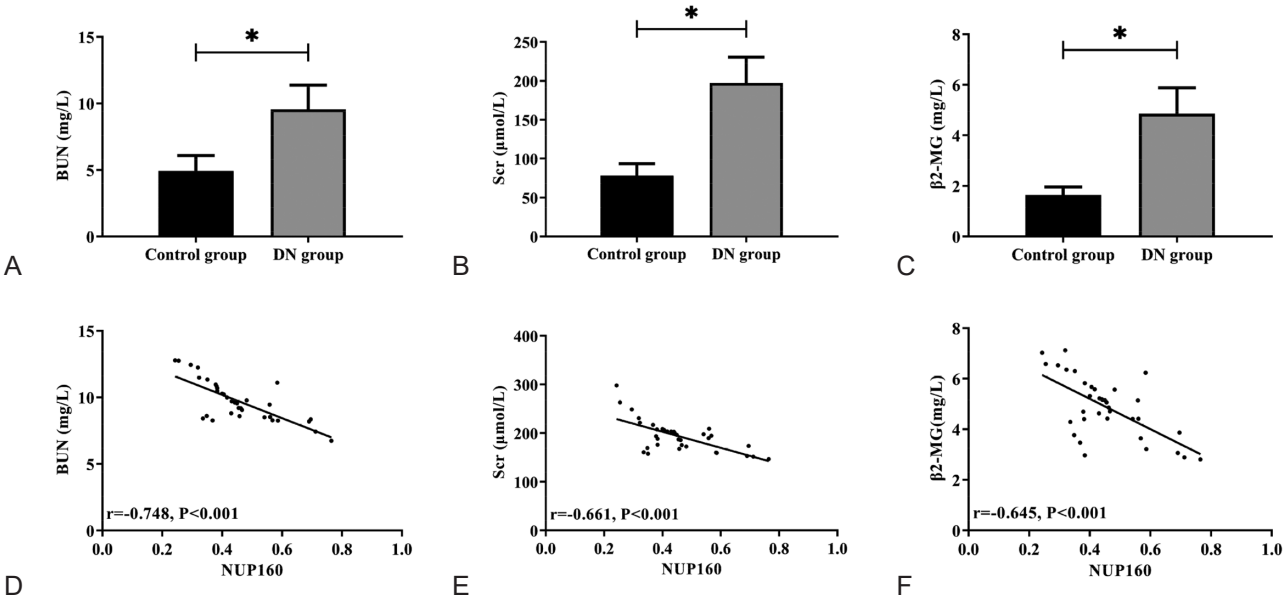

Figure 2. The Significant Correlation Between NUP160 and Renal Function Indexes of Patients

According to Figure 2, NUP160 is significantly correlated with indexes of kidney function in patients which could are presented in A, B, C, D, E, and F [A: BUN level in DN group was higher than that of the control group; B: Scr level in DN group was higher than that of the control group; C: β2-MG level in DN group was higher than that of the control group; D: NUP160 protein level in DN group was negatively correlated with BUN; E: NUP160 protein level in DN group was negatively correlated with Scr; and F: NUP160 protein level in DN group was negatively correlated with β2-MG (note: * indicates $P < .05$ between the two groups)]

Quantitative PCR (qPCR) Analysis

Quantitative PCR (qPCR) analysis exhibited that NUP160 protein and mRNA in the HG+si-NUP160 group decreased ($P < .05$), while those in HG+si-NC differed insignificantly ($P > .05$), compared to HG group, indicating that NUP160 in podocytes was knocked down successfully. The subsequent flow cytometry revealed higher podocyte apoptosis in the other three groups compared to the standard group ($P < .05$). As compared with the HG group, the apoptosis rate of the HG+si-NUP160 group was higher ($P < .05$), while no change was observed in HG+si-NC ($P > .05$), which indicates that NUP160 knockdown could promote the apoptosis of HG-stimulated podocytes (Figure 3).

Figure 3 shows that NUP260 knockdown promotes apoptosis of HG simulated podocytes, presented in A, B, D [A: Transfection of si-NUP160 reduced NUP160 protein in podocytes; B: Transfection of si-NUP160 reduced NUP160 miRNA in podocytes; and C: Transfection of si-NUP160 promoted podocyte apoptosis (note: $^{*}P < .05$ vs. normal group, $^{\#}P < .05$ vs. HG group, and $^{\&}P < .05$ vs. HG+si-NC group)].

Reduction of Autophagy Level of HG-treated Podocytes by NUP160 Knockdown

WB detected the alterations of autophagy-related proteins LC3B and P62 in the podocytes of each group. The other three groups showed elevated P62 and reduced LC3B-II/LC3B-I compared with the standard group ($P < .05$). P62 in the HG+si-NUP160 group increased ($P < .05$), and LC3B-II/LC3B-I decreased ($P < .05$), while HG+si-NC showed no evident change ($P > .05$), compared with HG group. Therefore, NUP160knockdown can reduce the autophagy level of HG-treated podocytes (Figure 4).

As Figure 4 shows, NUP160 knockdown reduces autophagy level of HG-treated podocytes which is presented in A and B [A: Transfection of si-NUP160 increased P62 protein content in podocytes; B: Transfection of si-NUP160 decreased the ratio of LC3B-II/LC3B-I in podocytes (note: $^{*}P < .05$ vs. normal group, $^{\#}P < .05$ vs. HG group, and $^{\&}P < .05$ vs. HG+si-NC group)].

Promoting Activation of JAK2/STAT3 Axis by NUP160 Knockdown

JAK2/STAT3 is an overactivated axis in DN. The activation of the JAK2/STAT3 axis in podocytes of each group was determined by WB. The other three groups showed higher ratios of p-JAK2/JAK2 and p-STAT3/STAT3 than the normal group ($P < .05$). The ratios of p-JAK2/JAK2 and p-STAT3/STAT3 in the HG+si-NUP160 group increased ($P < .05$), while these ratios showed no distinct change in HG+si-NC ($P > .05$), compared with HG group. Therefore, NUP160 knockdown can promote the activation of the JAK2/STAT3 axis (Figure 5).

According to Figure 5, NUP160 knockdown promotes the activation of JAK2/STAT3 axis, represented in A and B [A: Transfection of si-

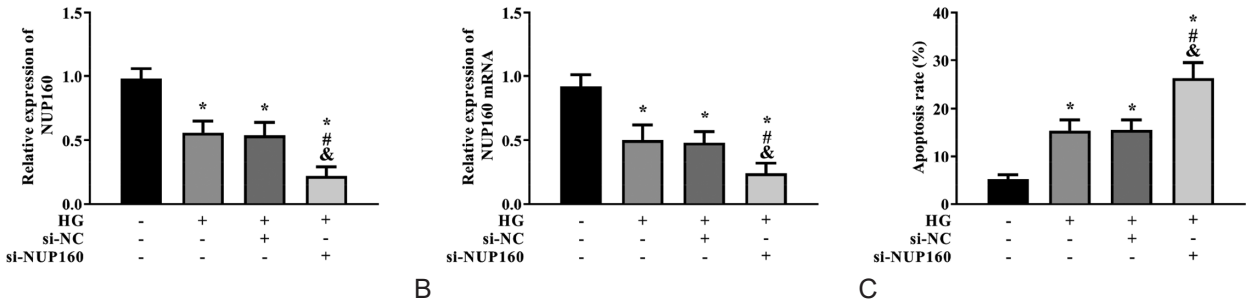

Figure 3. Promoting Apoptosis of HG-stimulated Podocytes by NUP160 Knockdown

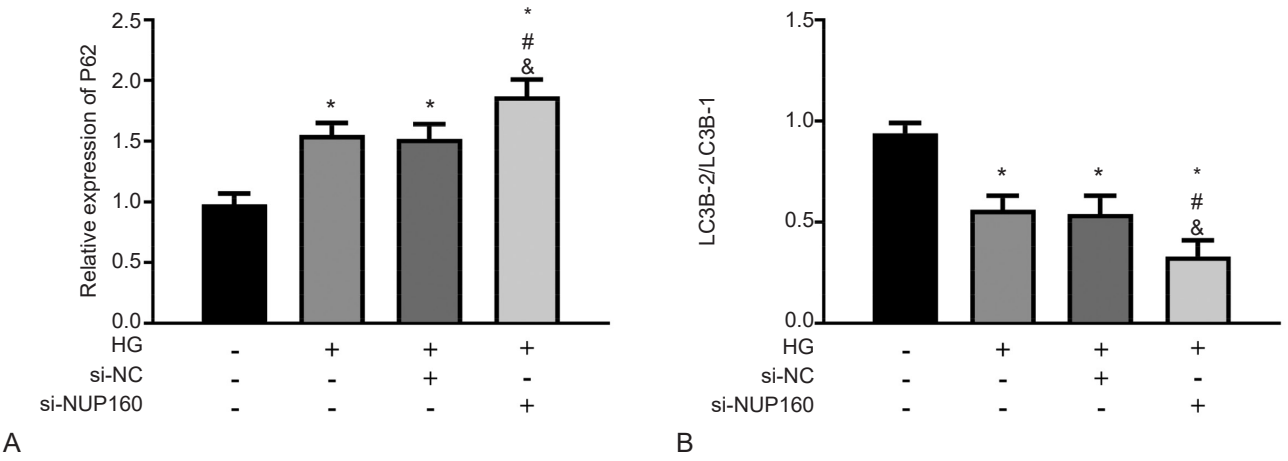

Figure 4. Reduction of Autophagy Level of HG-treated Podocytes by NUP160 Knockdown

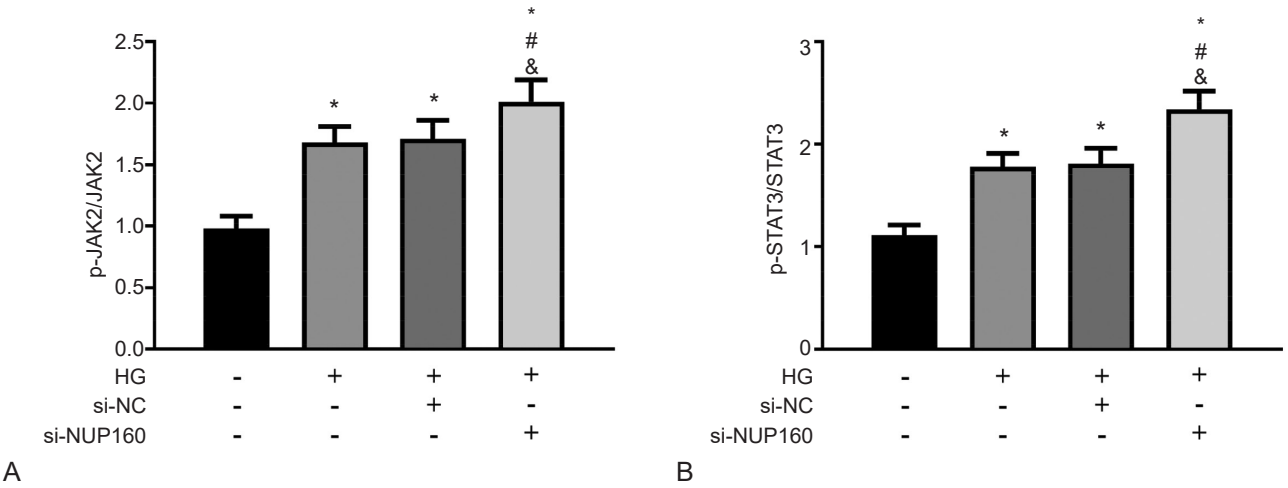

Figure 5. Promoting Activation of JAK2/STAT3 Axis by NUP160 Knockdown

NUP160 increased the ratio of p-JAK2/JAK2 in podocytes; B: Transfection of si-NUP160 increased the ratio of p-STAT3/STAT3 in podocytes (note: $^{*}P < .05$ vs. normal group, $^{\#}P < .05$ vs. HG group, and $^{\&}P < .05$ vs. HG+si-NC group)].

DISCUSSION

The present study showed that NUP160 was under expressed in DN. In addition, HG-induced histiocyte autophagy could be inhibited after knockdown the expression of NUP160, which fully demonstrated the promising clinical significance of NUP160 in both the diagnosis and treatment of DN in the future.

DN is one of the most severe complications of diabetes and is also among the prime reasons for death in diabetic patients.[10] Despite recent advances in the pathogenesis of DN in recent years, the high incidence and poor prognosis resulting from DN have not significantly been ameliorated.[11] Therefore, it carries enormous implications to find new therapeutic targets for DN. NUP160 is a NUP that is highly expressed in human kidney cells. It can change a number of biological processes in podocytes and is considered as a possible therapeutic target for DN.[8] In this research study, NUP160 was shown to elevate in DN patients and HG-induced podocytes. The subsequent Pearson analysis revealed an inverse association between NUP160 protein and BUN, Scr and β2-MG in the DN group, suggesting that NUP160 was closely bound up with DN progression. In HG settings, renal podocyte apoptosis is a critical triggering factor for the

onset and development of DN.[12] However, the mechanism of podocyte injury is not fully defined, and there is still a lack of effective intervention means. Herewith, finding effective intervention measures to reduce podocyte apoptosis in an HG environment is essential. In the present study, we knocked down NUP160 gene expression in podocytes and observed the apoptosis rate. It was found that podocyte apoptosis increased after si-NUP160 transfection, indicating that knocking down NUP160 can enhance podocyte apoptosis.

In addition to apoptosis, autophagy is one of the primary causes of the decrease in cell number. Autophagy is a general term for the process of cell degradation of abnormal intracellular substances. As an intracellular degradation system, autophagy is a conservative steady-state process.[13] Podocytes are terminally differentiated cells with limited self-renewal ability, so autophagy is pivotal in maintaining the number of podocytes.[14] Several previous studies have shown that the autophagy activity of podocytes will decrease in an HG environment, thereby reducing the number of podocytes. [15,16] Therefore, it is suggested that stimulating autophagy in podocytes may be a feasible treatment option to prevent DN progression.[17] To explore whether knocking down the NUP160 gene would affect podocyte autophagy, we detected the alterations of autophagy-related proteins LC3B and P62. LC3B is a specific marker of autophagosome formation, and its content is proportional to the number of cytophagosomes.[18] The ratio of LC3B-II/LC3B-I shows a positive association with the number of autophagosomes. P62 is a specific substrate and regulatory protein in intracellular autophagy. As the level of autophagy increases, P62 will be consumed continuously.[19] Our research findings showed that the ratio of LC3B-II/LC3B-I decreased and P62 increased after transfecting si-NUP160 into podocytes, suggesting that NUP160 knockdown can hamper podocyte autophagy.

Besides, the Janus kinase-signal transducer and activator of transcription (JAK/STAT) axis is an extensively studied signal pathway participating in many cellular biological events, in which JAK2 and STAT3 are pivotal in the onset and development of DN.[20] Past evidence has shown that JAK2 and STAT3, stimulated by various substances such as hyperglycemia, reactive oxygen species (ROS) and AGEs, will undergo phosphorylation to enter the nucleus and act on downstream target genes such as Bax and Bcl-2, thereby regulating cell multiplication, differentiation, and apoptosis, and finally accelerating the occurrence and development of DN.[21,22] JAK2/STAT3 is a common axis involved in various critical cell biological processes, such as cell multiplication, apoptosis and invasiveness.[23] It is shown that the JAK2/STAT3 axis is over-activated in an HG environment and causes damage to podocytes.[24,25] Therefore, we hypothesized that NUP160 may modulate podocyte apoptosis and autophagy by activating the JAK2/STAT3 axis. To prove this conjecture, we examined this pathway's marker proteins in each group's podocytes. The results identified increased ratios of p-JAK2/JAK2 and p-STAT3/STAT3 after si-NUP160 transfection, indicating that NUP160 knockdown may damage podocytes via activating the JAK2/STAT3 axis.

Similar to other studies, many limitations exist in this study. For example, we still need to further explore the relationship between NUP160 and the pathological progression of DN. Also, we need to conduct a prognostic follow-up of all the study participants to analyze the prognostic significance of NUP160 in the prognostic assessment of DN patients. Finally, the mechanism of NUP160's effect on DN also needs to be confirmed by more experiments. In the follow-up study, we will carry out a more in-depth and comprehensive analysis to address the above limitations, in order to provide more reliable clinical references.

CONCLUSION

NUP160 is down-regulated in DN patients, and its knockdown can promote podocyte apoptosis and reduce autophagy, which is linked to the activation of the JAK2/STAT3 axis.

CONFLICT OF INTEREST

The author(s) declare no potential conflicts of interest concerning this article's research data, authorship, and publication.

FUNDINGS

This work supported by Taizhou Science and Technology Support Plan (Social Development) Project (No: SSF20200028), Scientific Research and Development fund of Kangda College of Nanjing Medical University (NO: KD2021KYJJZD062

AVAILABILITY OF DATA AND MATERIALS

The datasets used during the present study are available from the corresponding author upon reasonable request.

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Received July 2023
Revised August 2023
Accepted September 2023