

Research Article

Inhibition of Homeobox D10 Alleviates Acute Kidney Injury by Upregulating PI3K/AKT Signaling Proteins

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Purpose. To observe the protective effect of homeobox D10 (HOXD10) on acute kidney injury (AKI) by regulating PI3K/AKT signaling pathway is the purpose of this study. **Methods.** 30 rats were randomly divided into three groups: blank control group, model group, and HOXD10 interference group. The kidney function indexes, HOXD10 protein expression, histopathological features, tubulointerstitial injury, and PI3K and AKT protein expression levels of the three groups were analyzed. **Results.** Compared with the blank control group, the kidney weight, BUN and SCr in model group increased significantly, and TIL score was higher ($P > 0.05$). The expression of HOXD10 in model group and HOXD10 interference group were higher than blank control group, and the expression of HOXD10 in HOXD10 interference group was lower than model group ($P < 0.05$). After we administered HOXD10 blocker to AKI rats, pathological sections by HE staining showed that the kidney tissue damage was significantly reduced compared with the model group, and the expression levels of BUN and SCr in kidney tissue decreased, and the TIL score decreased. The expression of p-PI3K and p-AKT decreased after kidney injury. Compared with the model group, the phosphorylation levels of PI3K and AKT in HOXD10 interference group were significantly increased ($P < 0.05$). **Conclusion.** Downregulation of HOXD10 can play a protective role on AKI by activating PI3K/AKT signaling pathway, which can reduce tubulointerstitial injury and improve kidney function.

1. Introduction

Acute kidney injury (AKI) is an acute and critical disease in which the body has sustained kidney function damage and decline in a short period of time. It is caused by insufficient renal perfusion, changes in cell metabolism, oxidative stress, apoptosis, and other factors, which can lead to acid-base balance disorder, decreased urine output, and accumulation of nitrogen metabolites in blood, and then cause systemic complications [1, 2]. In recent years, the global incidence of AKI has gradually increased, and the prognosis of AKI patients is poor, with a high mortality rate of about 28%-90%, especially the mortality rate of hospital-acquired AKI patients in intensive care unit is as high as 60%, which seriously threatens people's life and health [3]. At present, the treatment methods of AKI at home and abroad are mainly symptomatic support therapy and renal replacement therapy.

Clinicians can significantly improve the survival rate and prognosis of AKI patients by early intervention therapy aiming at energy metabolism disorders, calcium overload, free radical damage, abnormal hemorheology, and other pathogenesis [4]. However, the pathogenesis of AKI is very complicated, and the research on the pathogenesis of AKI has always been the focus of clinical discussion.

The homeobox (HOX) was originally discovered during the study of the growth and development of *Drosophila*. It exists in almost all eukaryotic cells and is mainly responsible for the development of animal limbs and morphology and is crucial in the development of embryos [5]. HOX family encodes a series of important transcription factors, which have a non-negligible role in different developmental stages, and participate in the process of regulating cell proliferation, differentiation, invasion, apoptosis, angiogenesis and receptor signal transduction, and also play an important role in

TABLE 1: TIL score standard.

Items	0 points	1 points	2 points	3 points
Interstitial fibrosis	Without	Mild (<25%)	Moderate (25%-50%)	Severe (>50%)
Interstitial edema	Without	Mild (mild focal tubule separation)	Moderate (mild diffuse or focal moderate tubular separation)	Severe (severe renal tubular separation)
Renal tubular dilatation	Without	Mild (<25%)	Moderate (25%-50%)	Severe (>50%)
Vacuolar degeneration of renal tubular cells	Without	Mild focal	Severe focal or mild diffuse	Extensive or moderate diffuse
Inflammatory cell infiltration	Without	Mild (<25%)	Moderate (25%-50%)	Severe (>50%)
Red cell cast	Without	Mild (occasionally)	Moderate (<10% of renal tubules)	Severe (>10% of renal tubules)
Protein cast	Without	Mild (occasionally)	Moderate (<10% of renal tubules)	Severe (>10% of renal tubules)
Renal tubular atrophy	Without	Mild (<25%)	Moderate (25%-50%)	Severe (>50%)

regulating the proliferation and differentiation of mature somatic cells [6]. As a member of the HOX gene family, HOXD10 can keep endothelial cells in a silent and highly differentiated state by inhibiting cell migration-related genes and regulating extracellular matrix remodeling and can affect the development of Alzheimer's disease, rheumatoid arthritis, and other diseases [7, 8]. HOXD10 expression level is often abnormal in tumors, and its abnormal expression can interfere with the development of normal tissues and organs, leading to abnormal morphology of tissues and cells, and even malignant transformation leading to tumor formation. As a cancer-promoting or cancer-suppressing factor, HOXD10 gene has been proved to be closely related to the occurrence and development of various human tumors, including endometrial cancer, colon cancer, gastric cancer, and renal cell carcinoma [9–12].

Phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) signal pathway is involved in the regulation of various biological behaviors in cells. It participates in protein synthesis, regulates cell cycle, accelerates angiogenesis, and plays a key role in regulating cell growth and survival [13]. PI3K/AKT signaling pathway mediates the cell survival of many cell types, including kidney cells, and it can protect the liver and kidney by regulating the inflammatory response and preventing body damage [14]. Currently, the potential role of HOXD10 in AKI has not been reported. Whether HOXD10 can alleviate AKI through PI3K/AKT signaling pathway needs further study. Therefore, the purpose of this study is to observe the protective effect of HOXD10 on AKI by regulating PI3K/AKT signaling pathway.

2. Materials and Methods

2.1. Methods. 30 healthy male rats (Wistar rats, 12 weeks old) were selected, all from the Animal Experiment Department of our hospital. The temperature in the animal laboratory is 20°C–25°C, the relative humidity is 40%–70%, the cycle of light and darkness is 12 hours, and standard food and water are provided to the laboratory animals. The treatment of animals in all experiments followed the standards of animal ethics.

Animal grouping and model establishment: All rats were randomly divided into 3 groups, blank control group, model group and HOXD10 interference group, with 10 rats in each group. The experiment was conducted after 1 week of adaptive feeding. Blank control group: 1 ml normal saline was injected via tail vein, and 0.2 ml dimethyl sulfoxide+18 ml normal saline was injected via right abdominal cavity. Model group: 1 ml lipopolysaccharide (LPS) was injected via tail vein, and 0.2 ml dimethyl sulfoxide+18 ml normal saline was injected via right abdominal cavity. HOXD10 interference group: 1 ml LPS was injected via tail vein, and 0.2 ml HOXD10 blocker (siRNA transfection complex: containing 3 μ g HOXD10 siRNA and 7.5 μ g transfection reagent) +18 ml normal saline was injected via right abdominal cavity.

Kidney index detection: All rats were observed for 12 weeks, and then, specimens were collected. After 8 h on an empty stomach, 2 ml of blood was taken from the eyeball of rats and centrifuged at 3000 rpm at low temperature. The upper serum was taken after 15 min of centrifugation. Blood urea nitrogen (BUN) and serum creatinine (SCr) were detected by automatic biochemical analyzer.

Histopathological examination: The rats were sacrificed by dislocation method. The kidneys were taken out, freed and weighed. Part of the kidney tissue fixed in 4% paraformaldehyde was taken, dehydrated, and embedded in paraffin. The sections were cut at 4 μ m thick intervals and stained with hematoxylin-eosin (H&E). Histological evaluation of the rats was performed by a designated pathologist blinded to the experiment, and the histopathological characteristics of the rats were observed.

The tubulointerstitial lesions (TIL) score of rats under a light microscope was observed and calculated: 10 glomerular interstitial visual fields were randomly selected of each specimen under a low-power microscope. The sum of each score was the final score of a field of view, and the tubulointerstitial TIL score of each specimen = the average of 10 visual field scores. TIL score standard is shown in Table 1.

In western blotting test: About 50 mg of kidney tissue was taken and placed in a homogenizer. After homogenization on ice, protein lysate and PMSF were added, placed on ice for 40 min, and centrifuged at 4°C and 12000 r/min for 40 min, and the supernatant was taken. Using BSA as the

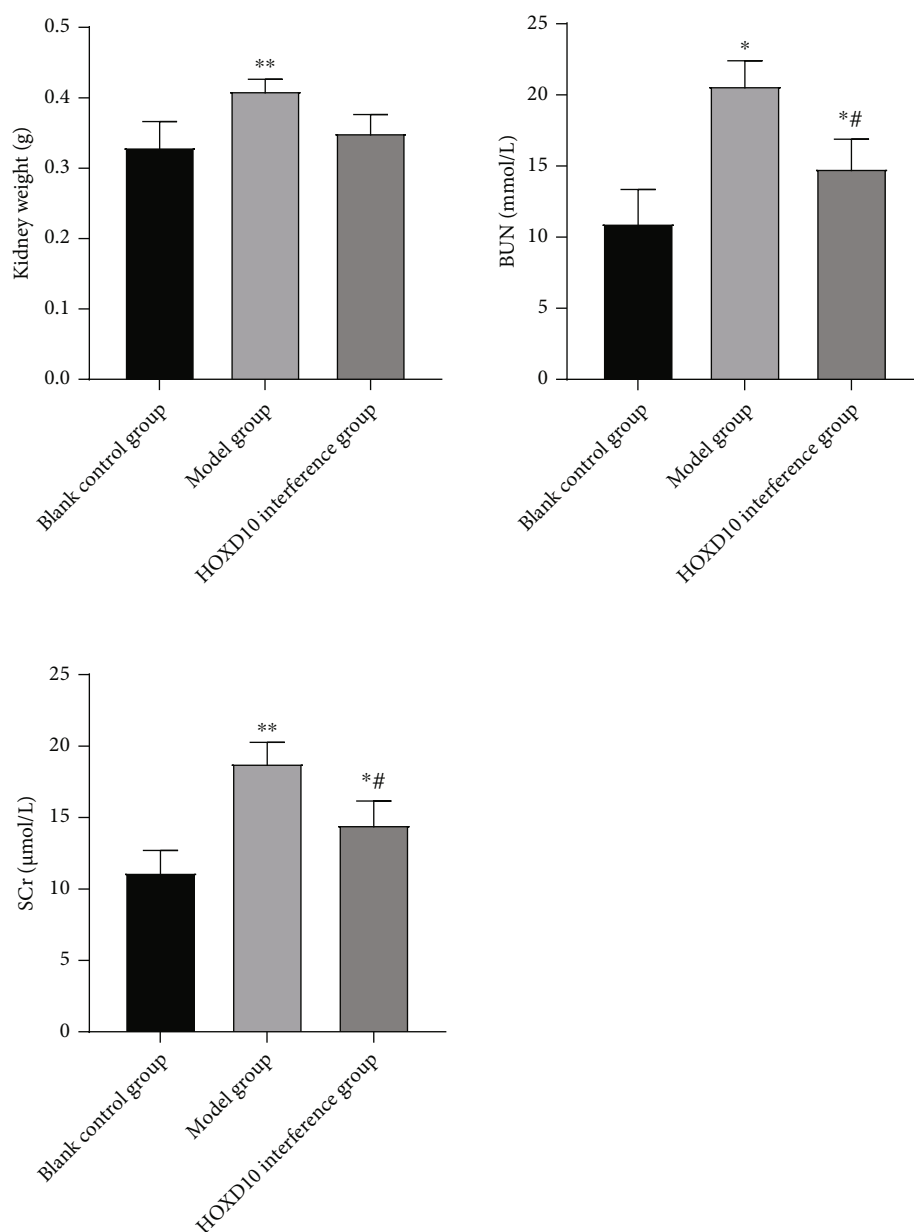


FIGURE 1: General situation and kidney function indexes of the three groups. Note: compared with the blank control group, * $P < 0.05$. Compared with model group, # $P < 0.05$.

standard, protein quantification in the supernatant was performed using the Bradford method. 20-40 μg protein samples were taken. After denaturation, electrophoresis was performed on a 10% SDS-PAGE gel, transferred to PVDF membrane by wet method, and placed in a blocking solution at 37°C for 1 h, and then, the primary antibody was added at 4°C overnight. The next day, TBST buffer was used to wash the membrane, HRP-labeled secondary antibody was added, and the membrane was incubated at room temperature for 1 h. TBST buffer solution was used to wash the membrane, and enhanced chemiluminescence method was used to expose the membrane. The absorbance values were determined by image analysis for quantitative analysis. With GADPH as internal reference,

semiquantitative analysis was carried out by calculating the gray ratio of target protein to GADPH. Meanwhile, the expression levels of PI3K and AKT in kidney tissue were detected by western blotting.

2.2. Statistical Methods. With SPSS22.0 statistical software, the data was expressed as (mean \pm SD), and the variance analysis and LSD t test showed that the difference was statistically significant with $P < 0.05$.

3. Results

3.1. General Situation and Kidney Function Indexes of the Three Groups. The kidney weight of the model group was

larger than that of the blank control group ($P < 0.05$), while the kidney weight of the HOXD10 interference group had no significant difference compared with the blank control group ($P > 0.05$). The BUN and SCr of model group and HOXD10 interference group are higher than those of blank control group, and those of HOXD10 interference group are lower than model group ($P < 0.05$), as shown in Figure 1.

3.2. Expression of HOXD10 Protein in Kidney Tissues of the Three Groups. Western blotting results showed that the expression of HOXD10 in model group and HOXD10 interference group are higher than blank control group, and the expression of HOXD10 in HOXD10 interference group is lower than model group ($P < 0.05$), as shown in Figures 2 and 3.

3.3. Histopathological Features of the Three Groups. HE staining results show that in the blank control group, the cytoplasm of renal tubular epithelial cells in rat kidney tissue was abundant, the structure of glomerulus and renal tubules in kidney tissue was normal, the wall of proximal convoluted renal tubules was completely filled, and the nucleus was blue-stained. In the model group, the glomeruli were congested and swollen, the renal tubule lumen was formed in a tube shape, and part of it was occluded; the glomerulus sac was expanded; the proximal tubular epithelial cells were swollen; and a large number of inflammatory cells infiltrated. In the HOXD10 interference group, the partial glomeruli were congested, the proximal tubular epithelial cells were slightly swollen, the glomerulus was slightly dilated, and a small amount of inflammatory cells were infiltrated. As shown in Figure 4.

3.4. TIL Score of the Three Groups. TIL score of model group and HOXD10 interference group is higher than those of blank control group, and TIL score of HOXD10 interference group is lower than model group ($P < 0.05$), as shown in Figure 5.

3.5. Relative Expression Level of PI3K and AKT Protein of the Three Groups. The expression levels of p-PI3K and p-AKT in HOXD10 interference group are higher than those in model group ($P < 0.05$), as shown in Figures 6 and 7.

4. Discussion

AKI is one of the most common severe syndromes in clinic. Its pathological changes include renal hypertrophy, interstitial fibrosis, thickening of the basement membrane of glomerular capillaries, and renal tubular hypertrophy. It has the characteristics of acute onset, rapid disease progression, and high mortality [15]. The occurrence of AKI mainly leads to cellular inflammatory reaction and nonbenign repair, which mediates the chronic kidney injury and long-term renal insufficiency, resulting in poor prognosis, prolonged hospitalization, and increased medical expenses [16].

PI3K/AKT signaling pathway is ubiquitous in organism cells, which is an important pathway for transmitting internal and external signals. It participates in the regulation of tumor growth and metastasis and has become the focus of

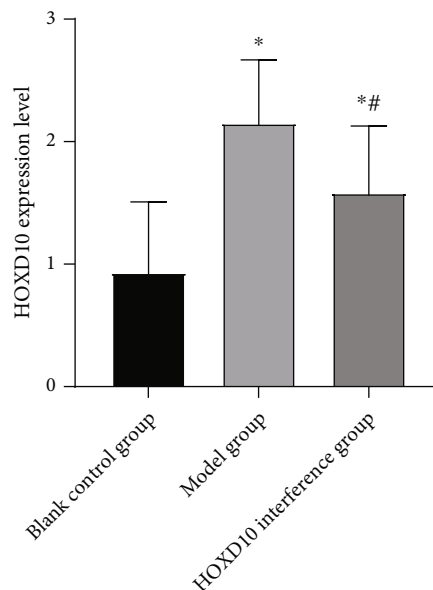


FIGURE 2: Expression of HOXD10 protein in kidney tissues of the three groups. Note: compared with the blank control group, * $P < 0.05$, Compared with model group, # $P < 0.05$.

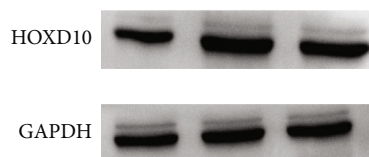


FIGURE 3: Western blotting result.

clinical research in the field of cancer [17]. Miricescu's research found that the abnormalities of renal clear cell carcinoma at the molecular level of gene protein mainly include the abnormal changes of epigenetic regulatory factors/chromatin remodeling genes and the disturbances of PI3K/AKT signaling pathway, and the activation of PI3K/AKT signaling pathway can significantly inhibit cell apoptosis [18]. PI3K is a phospholipid kinase that exists in various cells and is activated by growth factors and upstream factors. It further activates AKT by converting phosphatidylinositol diphosphate to phosphatidylinositol triphosphate (PIP3), resulting in phosphorylation of various substrate proteins. AKT is the downstream target protein of PI3K, and its amino terminal contains a PH domain, with which PIP3 can interact, resulting in full activation of AKT, which in turn initiates its downstream substrates. There have been many studies on PI3K/AKT signaling pathway at home and abroad, which greatly promoted the clinical application of targeted drugs and opened up a new way for disease treatment.

The protein encoded by HOX gene is an important transcription factor, which can be used as both activator and inhibitor of transcription, and is closely related to the differentiation and development of embryonic cells and adult cells. When the normal expression of HOX gene is disturbed, cell differentiation and growth will be affected to some extent. The expression disorder of HOX gene is

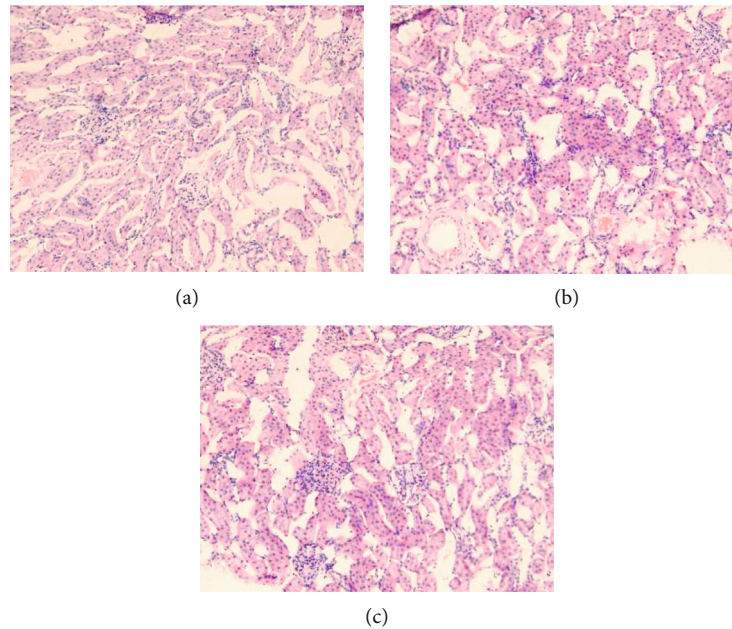


FIGURE 4: HE staining result. (a) Blank control group. (b) Model group. (c) HOXD10 interference group.

involved in the occurrence and development of various solid tumors [19]. HOXD10 can regulate the invasion, metastasis, and apoptosis of tumor cells by regulating some target genes. The stable expression of HOXD10 can make vascular endothelial cells in a stable state of differentiation, while the expression of HOXD10 will be lost or silenced in newly generated vascular endothelial cells of some malignant tumors. Zhang's team showed that overexpression of HOXD10 inhibited cell proliferation and migrated and invaded esophageal squamous cell carcinoma cells by regulating PI3K/AKT/mTOR signaling pathway. Therefore, targeting HOXD10 may be considered as a therapeutic strategy for esophageal squamous cell carcinoma [20]. Yang's team found that lncRNA HOXD-AS1 can regulate the growth and metastasis of colorectal cancer by inhibiting HOXD3-induced transcription activation of integrin β 3 and MAPK/AKT signaling pathway [21]. Yang et al. suggested that the increased expression of HOXD10 may lead to reduce the release of matrix metalloproteinase-2 (MMP2) and MMP9 in cholangiocarcinoma, thus accelerating tumor apoptosis, and the RHOC/AKT/MAPK pathway is involved in the tumor inhibition function of HOXD10 [22]. In addition, Hakami's team found in the study of squamous cell carcinoma of the head and neck that HOXD10 was highly expressed in primary tumors, but the expression level of HOXD10 decreased in lymph node metastasis cells. Overexpression of HOXD10 can reduce the invasiveness of cells, but also increase the proliferation and adhesion of cells [23].

Studies have shown that excessive release of bacterial endotoxin and its inflammatory factors is one of the key causes for inducing AKI [24]. LPS is an endotoxin and an important group-specific antigen, which can directly acts on the epithelial cells of renal tubules, resulting in AKI [25]. LPS can stimulate the body to initiate an inflammatory response, often producing a large number of proinflamma-

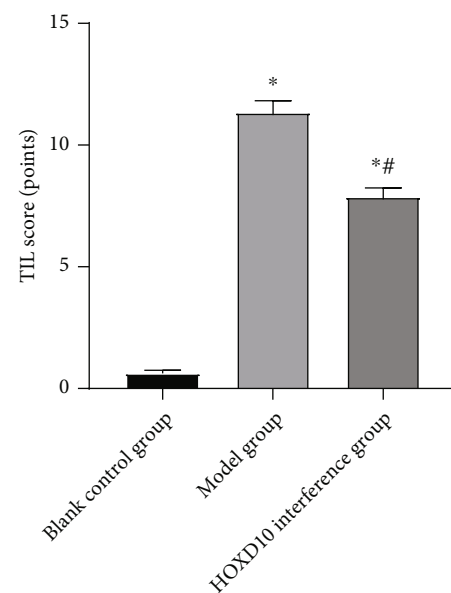


FIGURE 5: TIL score of the three groups. Note: compared with the blank control group, * $P < 0.05$. Compared with model group, # $P < 0.05$.

tory factors, resulting in oxidative stress, mitochondrial damage, and energy depletion. This study found that the intraperitoneal injection of LPS can rapidly lead to renal insufficiency and pathological damage of kidney tissue in rats and pathological changes such as glomerular congestion and swelling, renal balloon expansion, and swelling of proximal tubular epithelial cells. Compared with blank control group, the kidney weight, BUN, and SCr in model group increased significantly, and TIL score was higher, which indicated that the rat model of endotoxin-induced AKI was

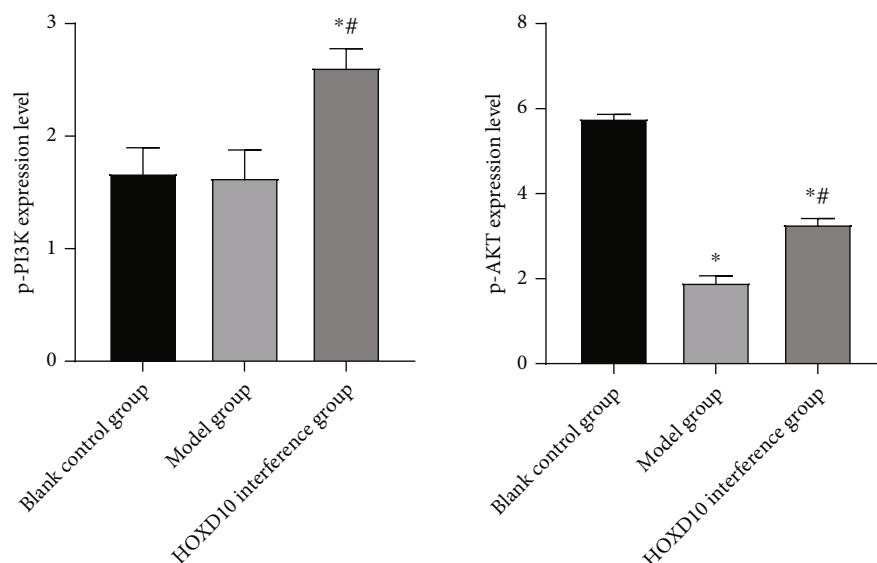


FIGURE 6: Relative expression level of PI3K and AKT protein of the three groups. Note: compared with the blank control group, $*P < 0.05$. Compared with model group, $\#P < 0.05$.

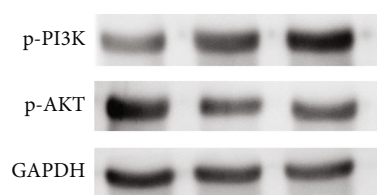


FIGURE 7: Western blotting result.

successfully established. We believe that the reason is that the endothelial cells of kidney can release inflammatory factors under the stimulation of LPS, forming a vicious circle and eventually causing kidney damage. In addition, our results showed that the expression of HOXD10 in the model group was higher than that in the blank control group, suggesting that the expression of HOXD10 gene protein in AKI rats was significantly upregulated. After we administered HOXD10 blocker to AKI rats, pathological sections by HE staining showed that the kidney tissue damage was significantly reduced compared with the model group, and the expression levels of BUN and SCr in kidney tissue decreased, and the TIL score decreased. In this study, the expression of p-PI3K and p-AKT decreased after kidney injury. Compared with the model group, the phosphorylation levels of PI3K and AKT in HOXD10 interference group were significantly increased. The above results indicate that HOXD10 can affect the signal transmission of PI3K/AKT signaling pathway, thereby inhibiting excessive inflammatory response, reducing the degree of AKI, and thus increasing the kidney weight of rats. The possible reason is that HOXD10 can regulate the expression of p-PI3K and p-AKT signal transduction pathways in kidney tissue and affect the apoptosis ability of cells. Downregulation of HOXD10 alleviates morphological renal injury, activates PI3K/AKT signaling pathway, and corrects the activation of apoptotic pathways, improving kidney function. On the other hand, low expres-

sion of HOXD10 can increase the protein levels of PI3K and AKT and reduce the release of related inflammatory factors, thereby protecting kidney tissue.

5. Conclusion

To sum up, downregulation of HOXD10 can play a protective role on AKI by activating PI3K/AKT signaling pathway, which can reduce tubulointerstitial injury and improve kidney function. In this study, only part of the role of HOXD10 in LPS-induced AKI was preliminarily discussed, but the specific mechanism of influence is still unclear, and further experimental research is needed, in order to better provide new ideas for clinical AKI treatment.

Data Availability

The data used and/or analyzed during the current study are available from the corresponding author.

Ethical Approval

This study was approved by the ethics committee of our hospital.

Conflicts of Interest

The authors declare no conflict of interest, financial or otherwise.

Acknowledgments

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