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Hippo-YAP Signalling Pathway Promotes Apoptosis of Renal Tubular Epithelial Cells in Contrast-Induced Acute Kidney Injury

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KEYWORDS Hippo Signalling Pathway. HK-2 Cells. Iohexol. Kidney Injury. Programmed Cell Death

ABSTRACT The Hippo-YAP pathway drives kidney injury, but its function in contrast-induced acute kidney injury (CI-AKI) is uncertain. The researchers examined how the Hippo-YAP signalling pathway affects iohexol-induced apoptosis in CI-AKI. Iohexol treatment was applied to human HK-2 renal tubular epithelial cells. The Hippo-YAP pathway was inhibited using XMU-MP-1. CCK-8, TUNEL, flow cytometry, and Western blot analyses were employed to evaluate cell viability and apoptosis. A CI-AKI mouse model was established to evaluate renal injury. The results showed that iohexol reduced cell viability, induced apoptosis, and activated the Hippo-YAP pathway. Blocking this pathway using XMU-MP-1 reversed these effects in vitro. In vivo, XMU-MP-1 attenuated iohexol-induced renal tubular injury, improved kidney function, and suppressed apoptosis in the kidney. In conclusion, activating the Hippo-YAP pathway triggers renal tubular epithelial cell apoptosis, while its inhibition protects against iohexol-induced kidney injury, suggesting that targeting this pathway may present a potential therapeutic approach for CI-AKI.

INTRODUCTION

Contrast-induced acute kidney injury (CI-AKI) is a widespread health concern that occurs after using iodinated contrast agents in diagnostic or interventional procedures (Chandiramani et al. 2020; McCullough et al. 2016). Ranked as the third most common cause of AKI acquired in hospital settings, this condition represents a major threat to patient well-being (Li and Wang 2024). CI-AKI is linked to higher rates of in-hospital illness and mortality, progressive deterioration of renal function and long-term heart-related issues (Ribitsch et al. 2019). The emergence of CI-AKI differs widely depending on patient risk profiles, with reported rates ranging from 2 percent to 50 percent among different groups of people, such as those with diabetes, chronic kidney disease, or congestive heart failure (Iranirad et al. 2024). However, since the pathogenesis behind CI-AKI has not been fully elucidated, effective treatment strategies to improve prognosis remain limited.

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CI-AKI pathogenesis is influenced by various factors, involving direct cytotoxic effects, ischemic injury to tubular cells, and the generation of reactive oxygen species (Bansal and Patel 2020). Contrast media has been reported to directly damage renal tubular epithelial cells, causing mitochondrial malfunction, cell death, and inflammatory responses (Bansal and Patel 2020). However, the precise intracellular signalling cascades underlying this apoptotic process following contrast media exposure remain incompletely understood, hindering the development of targeted therapeutic strategies.

The Hippo signalling cascade, together with its downstream molecules YAP and TAZ, constitutes an evolutionarily conserved kinase pathway that is key to managing biological activities, including cell proliferation, tissue repair and renewal, and cell death (Fu et al. 2022; Zhong et al. 2024; Ma et al. 2019). The Aberrant Hippo-YAP pathway is involved in numerous diseases. Therefore, targeting this pathway may represent an effective therapeutic approach for these conditions (Fu et al. 2022). Recent evidence has revealed the connection between the Hippo pathway and AKI. Specifically, during the initial phase of AKI, transient activation of YAP/TAZ contributes to kidney healing and regeneration, while continuous activation harms kidney function and leads to the onset of

chronic kidney disease (Zhang et al. 2022). Nevertheless, the exact function and regulatory dynamics of this pathway in CI-AKI have not yet been well-documented.

Objectives

In the current study, the researchers identified how the Hippo pathway influences renal tubular injury in CI-AKI. The hypothesis was that this pathway could govern the progression of CI-AKI by modulating renal tubular epithelial cell apoptosis. By critically evaluating the roles of the Hippo pathway in CI-AKI, this study clarifies its potency as a novel therapeutic target.

MATERIAL AND METHODS

Cell Culture

HK-2 cell line was purchased from ATCC (Manassas, VA, USA) and maintained in Keratinocyte Serum-Free Medium (K-SFM; Gibco, Grand Island, NY, USA) added with 0.05 mg/mL bovine pituitary extract (BPE) and 5 ng/mL human recombinant epidermal growth factor (EGF) at 37°C with 5 percent CO_2.

Cell Stimulation

HK-2 cells in the logarithmic growth phase were separated into the control and iohexol groups. The latter was subsequently exposed to iohexol (75 mg iodine/mL; MedChemExpress, Monmouth Junction, NJ, USA), whereas the control group was exposed to the same volume of PBS.

To inactivate the Hippo-YAP pathway, 5 μM XMU-MP-1 (MedChemExpress) was applied to stimulate cells for 6 hours before iohexol or PBS treatment. Dimethyl sulfoxide (DMSO; MedChemExpress) served as the negative control for XMU-MP-1.

Cell Counting Kit-8 (CCK-8) Assay

Cells were placed in 96-well plates (2,000 cells/well) and exposed to iohexol or PBS for 0, 24, 48, and 72 hours. At each designated time, cells were harvested for incubation for 2 hours with 10 ìL of CCK-8 reagent (Dojindo, Kumamoto, Japan). Optical density was then determined using a microplate reader at 450 nm.

TUNEL Assay

To evaluate apoptosis, the TUNEL FITC Apoptosis Detection Kit (Vazyme, Nanjing, China) was employed following 2 days of iohexol treatment. HK-2 cells were rinsed and resuspended in PBS. Cell suspension (100 μL, 2 × 10v cells/mL) was spread on polylysine-coated slides. Then, 4 percent paraformaldehyde was utilised for fixation for 25 minutes, and then permeabilised for 5 minutes using 0.2 percent Triton X-100. Following a 20-minute incubation in 1× equilibration buffer, the cells were treated with TdT incubation buffer (50 μL) for 60 minutes at 37°C. Subsequently, cell nuclei staining was carried out using 2 μg/mL 4',6-diamidino-2-phenylindole (DAPI; Sigma-Aldrich, St. Louis, MO, USA) for 5 minutes. Following PBS washing, the cells were observed under a fluorescence microscope.

Flow Cytometry

After being exposed to iohexol, 2 × 10u cells were digested with trypsin without EDTA. After centrifuging at 300 × g for 5 minutes and washing with PBS, cells were resuspended in 100 μL of 1× binding buffer. They were then stained with Annexin V-PE (5 μL) and 7-AAD (5 μL) from the Annexin V-PE/7-AAD Apoptosis Detection Kit (Vazyme) in the dark for 10 minutes. Apoptotic cells were analysed with a flow cytometer after being mixed with 400 μL of 1× binding buffer, with data analysis conducted via FlowJo software.

Western Blot

HK-2 cells and kidney tissues were disrupted in a radioimmunoprecipitation assay (RIPA) buffer. Protein content in the lysates was measured using the Bicinchoninic Acid Kit (Vazyme). Each lane was loaded with the same quantity of protein and separated using sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), then transferred to polyvinylidene fluoride (PVDF) membranes. After a 5 percent non-fat milk block, the membranes were labelled with primary antibodies against Bcl-2 (ab82858, Abcam, Cambridge, MA, USA), Bax (5059-2-Ig, Proteintech, Wuhan, China), cleaved caspase-3 (2512-1-AP, Proteintech), MST1 (ab245190, Abcam), MST2 (ab52641, Abcam), phospho (p)-MST1/2 (ab76323, Abcam), LATS1 (17049-1-AP, Proteintech), p-LATS1 (28998-

1-AP, Proteintech), YAP1 (ab52771, Abcam), p-YAP1 (ab76252, Abcam), and µ-actin (ab213262, Abcam) at 4°C overnight. The membranes were then exposed to the secondary antibody (ab6721, Abcam) for 60 minutes at room temperature. Protein bands were made visible using the ECL Western Blotting Substrate (Solarbio, Beijing, China).

Immunofluorescence

HK-2 cells underwent fixation and permeabilisation. After blocking nonspecific binding sites with 5 percent bovine serum albumin (BSA; Sigma-Aldrich). The cells were treated overnight at 4°C with primary antibody against YAP1 (ab52771, Abcam), followed by a 1-hour incubation at 37°C with the secondary antibody (ab150078, Abcam). For nuclear visualisation, DAPI at 1 ìg/mL was applied to counterstain the cells for 10 minutes, and the signals were then observed with a fluorescence microscope.

In Vivo Study

Male C57BL/6 mice (18-20 g, SPF grade) were purchased from Vital River Company (Beijing, China). Mice were assigned to four groups at random, that is, control, iohexol, iohexol + DMSO, and iohexol + XMU-MP-1 (5 mice/group). The mouse model was established following previous descriptions (Tian et al. 2025). Mice underwent right uninephrectomy under isoflurane anaesthesia. After three weeks, mice were deprived of water for 48 hours and then intraperitoneally injected with furosemide (MedChemExpress). After 30 minutes, iohexol (350 mg iodine/mL, 20 mL/kg/day) was injected via the tail vein. Instead of iohexol, the control group of mice was given tail vein injections with normal saline in the same quantity. To analyse the contribution of the Hippo-YAP pathway, mice were administered 2 mg/kg of XMU-MP-1 through intraperitoneal injection for 5 consecutive days prior to iohexol injection. DMSO was administered intraperitoneally as the negative control. 24 hours after iohexol or normal saline injection, mice were euthanised by isoflurane inhalation. Blood and kidney samples were collected.

Histological Staining

Paraffin sections of mouse kidneys with 4-ìm-thick were prepared after fixation. Once dewaxing and rehydration were completed, they were stained using the hematoxylin and eosin (H&E) staining kit (Solarbio) and then photographed under a light microscope. Tubular injury was scored as a previous study (Tian et al. 2025), that is, 0 points = normal, 1 point for 0-10 percent damaged tubules, 2 points for 11-25 percent damaged tubules, 3 points for 26-50 percent damaged tubules, 4 points for 51-75 percent damaged tubules, and 5 points for 76-100 percent damaged tubules. Scoring was conducted in a blinded manner.

Measurement of Kidney Function

Serum was isolated from mouse blood by centrifugating at 2,000 ×g for 10 minutes. Serum creatinine (SCr) and blood urea nitrogen (BUN) were subsequently quantified on an automated biochemical analyser (Hitachi, Tokyo, Japan).

Statistical Analysis

Statistical evaluations were carried out with the GraphPad Prism 8 software. Quantitative data are presented as mean ± standard deviation (SD). The analysis of differences between two groups was conducted using Student's t-test, while one-way ANOVA was utilised to assess differences among multiple groups. For cell viability measurements, a two-way ANOVA was performed. $P < 0.05$ was regarded as statistical significance.

RESULTS

Iohexol Promotes Apoptosis of HK-2 Cells

To assess whether iohexol affects HK-2 cell functions, they were treated with iohexol. As illustrated in Figure 1A, iohexol markedly reduced HK-2 cell viability. The researchers then found that iohexol significantly increased TUNEL stained cells (5.14 vs. 30.2) and apoptosis rate (4.24 vs. 22.54) (Fig. 1B and C). A reduction of Bcl-2 protein levels and an increase of Bax and cleaved caspase-3 levels were found in cells following iohexol treatment (3.88, 3.78 and 3.68 folds; Fig. 1D). Collectively, these results demonstrate that iohexol inhibits viability and facilitates apoptosis of HK-2 cells.

Iohexol Treatment Activates the Hippo-YAP Pathway

Subsequently, the researchers assessed whether the iohexol could affect the Hippo-YAP path-

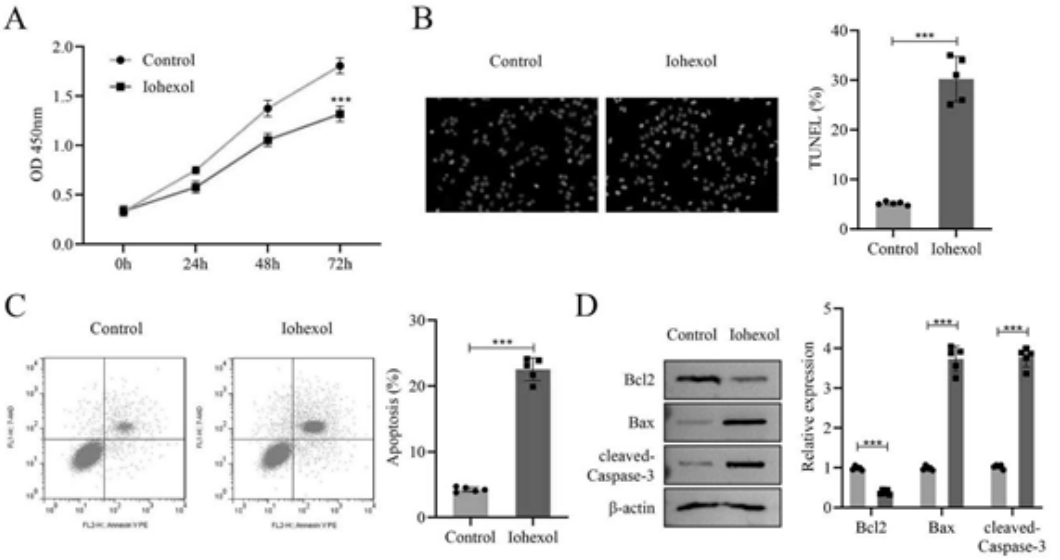

Fig. 1. Iohexol inhibits apoptosis of HK-2 cells. (A) HK-2 cells were treated with iohexol for 0, 24, 48, and 72 hours, and cell viability was detected using CCK-8. After HK-2 cells were treated with iohexol for 48 hours. (B) TUNEL assay, and (C) Flow cytometry were performed to determine cell apoptosis. (D) The levels of apoptosis markers Bcl-2, Bax, and cleaved caspase-3 were measured using Western blot. ***P<0.001

way. Iohexol induced upregulation of p-MST1/2/MST1/2 (4.16 folds), p-LATS1/LATS1 (5.60 folds), and p-YAP1 levels, along with downregulation of total YAP1 protein levels (p-YAP1/YAP1: 7.94 folds; Fig. 2A). Additionally, YAP1 nuclear translocation was assessed using immunofluorescence. The results demonstrated that iohexol decreased nuclear YAP1 levels and increased its cytoplasmic accumulation (Fig. 2B). In summary, iohexol treatment triggers the activation of the Hippo-YAP pathway.

Inactivating the Hippo-YAP Pathway Inhibits Iohexol-induced Apoptosis

To explore if the Hippo-YAP pathway affects cell behaviours, XMU-MP-1, a specific MST1/2 inhibitor, was used to pretreat cells before iohexol treatment. The decline in cell viability due to iohexol was counteracted by XMU-MP-1 (Fig. 3A). Furthermore, while iohexol promoted apoptosis, XMU-MP-1 treatment notably lessened apoptosis in iohexol-treated cells, manifesting as a 64.20 percent decrease in TUNEL cells and a 44.92 percent reduction in apoptosis rate (Fig. 3B and C). Additionally, XMU-MP-1 upregulated Bcl-2 levels and concurrently lowered Bax and cleaved caspase-3 levels in cells stimulated with iohexol (2.84, 0.37 and 0.25 folds; Fig. 3D). In short, suppressing the Hippo-YAP pathway pharmacologically enhances HK-2 cell viability and inhibits apoptosis.

Inactivating the Hippo-YAP Pathway Ameliorates Iohexol-induced Renal Injury in Mice

The in vivo function of the Hippo-YAP pathway was investigated using a murine CI-AKI model with iohexol treatment, and XMU-MP-1 was administered to inactive this pathway. Renal histology was evaluated using H&E staining. The researchers found that iohexol induced significant renal tubular injury (0.76 vs. 3.74), whereas the impact was markedly diminished with XMU-MP-1 treatment (3.58 vs. 1.98; Fig. 4A and D). In addition, iohexol treatment significantly elevated SCr (25.55 vs. 193.72) and BUN (16.93 vs. 71.52) levels, and these effects were abrogated following XMU-MP-1 administration (SCr: 188.19 vs. 119.57, BUN: 72.82 vs. 37.30; Fig. 4B and C). Furthermore, Bcl-2 levels were downregulated, while cleaved caspase-

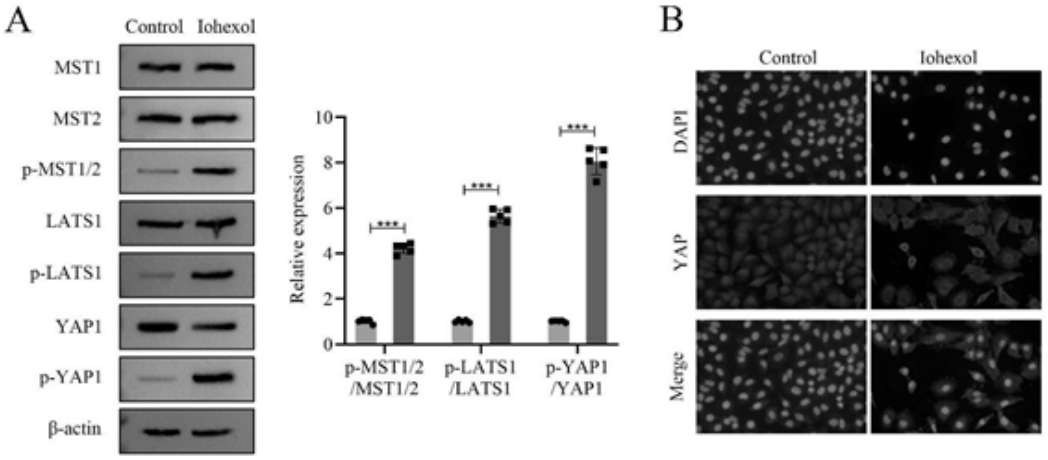

Fig. 2. The Hippo-YAP signalling pathway is activated after iohexol treatment. (A) HK-2 cells were treated with iohexol for 48 hours, and Western blot was performed to detect the protein levels of the factors in the Hippo-YAP pathway. (B) Immunofluorescence was conducted to assess YAP1 nuclear translocation. ***P<0.001

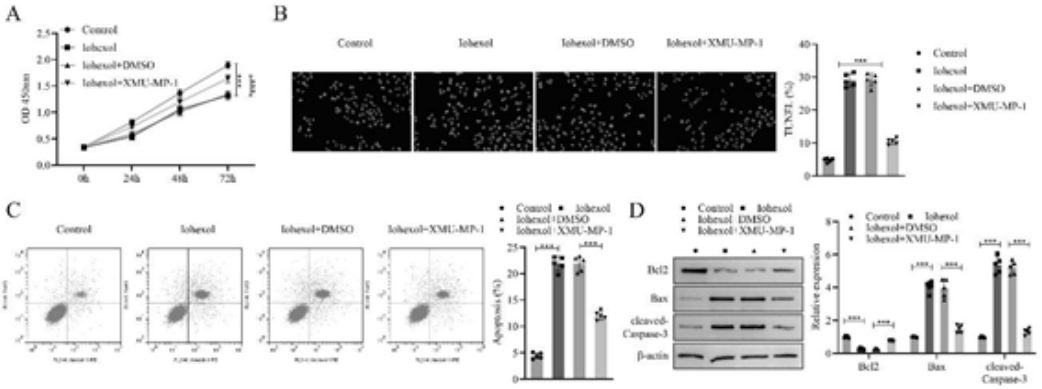

Fig. 3. Inactivation of the Hippo-YAP pathway inhibits apoptosis of iohexol-induced cells. HK-2 cells were treated with iohexol and XMU-MP-1, and the following cellular behaviours were measured. (A) Cell viability was evaluated using CCK-8. Cell apoptosis was evaluated using the (B) TUNEL assay, and (C) Flow cytometry. (D) The levels of apoptosis markers Bcl-2, Bax, and cleaved caspase-3 were measured using Western blot. ***P<0.001

3 and Bax levels were elevated in the iohexol group (0.29, 3.77, 4.34 folds). XMU-MP-1 rescued the iohexol-induced alterations in apoptosis marker expression (2.61, 0.45, 0.33 folds; Fig. 4E). Together, suppressing the Hippo-YAP pathway ameliorates iohexol-induced kidney injury.

DISCUSSION

The present study demonstrates that iohexol exposure activates the Hippo-YAP signalling pathway in renal tubular epithelial cells. Inhibiting this pathway pharmacologically with XMU-MP-1 notably reduces tubular cell apoptosis and thus ameliorates kidney damage in CI-AKI mice, which indicates the key role of the Hippo-YAP pathway y during CI-AKI progression.

The onset of AKI after administering iohexol is linked to various pathophysiological processes, including inflammation, oxidative stress, damage to the proximal renal tubules, and vascular injury (Li et al. 2022). The extent and occurrence rate of

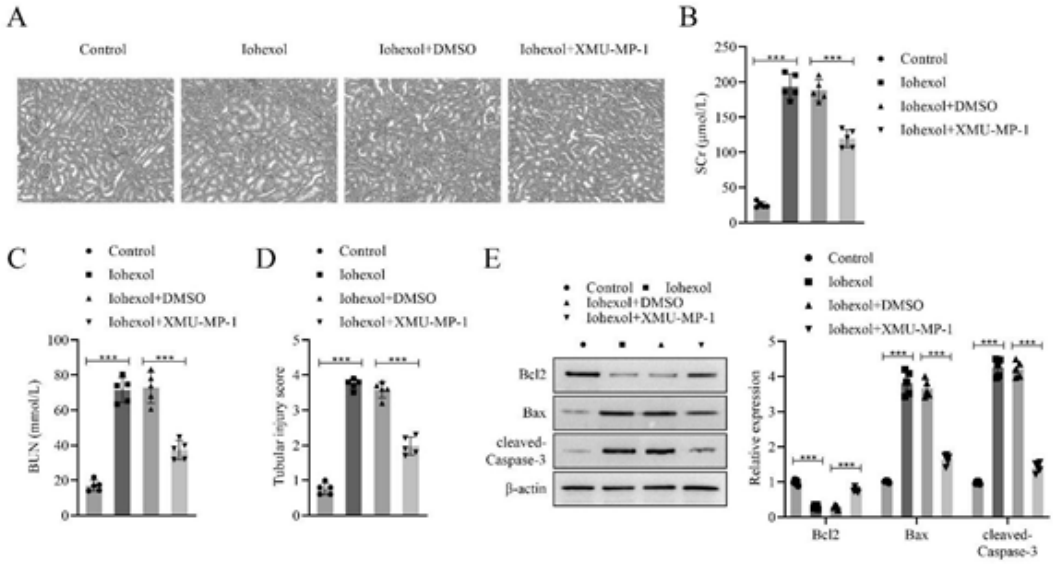

Fig. 4. Inactivation of the Hippo-YAP pathway inhibits iohexol-induced renal injury via the apoptosis-inhibitory effects. (A) Renal histology was evaluated using H&E staining assay. (B) SCr and (C) BUN levels were measured to assess renal function. (D) Tubular injury score. (E) Apoptosis markers in the kidneys were measured by Western blot. ***P<0.001

proximal tubular injury are key determinants of prognosis in patients with AKI (Takaori et al. 2016). Apoptosis of tubular epithelial cells represents a critical manifestation of proximal tubular injury. This study involved treating HK-2 cells with iohexol, which led to decreased cell viability and triggered apoptosis, aligning with past reports (Li et al. 2022; Liu et al. 2017). Moreover, in the animal study, iohexol treatment significantly increased the tubular injury score. These findings confirm the damaging effects of iohexol on renal tubular cells.

Previous research has established that the Hippo signalling cascade participates in several types of AKI, including those induced by sepsis, cisplatin, and ischemia-reperfusion (Chen et al. 2023; Sun et al. 2024; Xu et al. 2016). Central components of this signalling network consist of the kinase module comprising MST1/2 and LATS1/2, together with the downstream regulators YAP and TAZ (Ma et al. 2019). Activating this pathway leads to MST1/2 phosphorylation through its interaction with Sav1, which then drives the phosphorylation followed by activation of LATS1/2 (Callus et al. 2006). In its active state, LATS1/2 adds phosphate groups to distinct serine residues on YAP and TAZ (Zhao et al. 2007). Upon inactivating the Hippo pathway, YAP/TAZ undergoes dephosphorylation and enters the nucleus, where it triggers target gene transcription by binding TEAD transcription factors (Zhao et al. 2008). Here, the results revealed that iohexol increased p-MST1/2, p-LATS1, and p-YAP1 levels. Furthermore, YAP1 exhibited increased cytoplasmic retention with reduced nuclear localisation. These findings collectively demonstrate that iohexol activates the Hippo-YAP signalling in vitro.

XMU-MP-1 acts as a specific pharmacological agent that specifically blocks MST1/2 kinases, which was applied to treat HK-2 cells to inactivate the Hippo-YAP pathway (Fan et al. 2016). The results showed that XMU-MP-1 attenuated apoptosis in iohexol-induced HK-2 cells, suggesting that reducing renal tubular injury is linked to the inactivation of the Hippo-YAP signalling cascade. Moreover, utilising an iohexol-induced CI-AKI mouse model, XMU-MP-1 was effective in decreasing renal function marker SCr and BUN levels and lowering the tubular injury score, accompanied by inhibiting apoptosis in the kidney tissues. These observations indicate that inactivating the Hippo-

YAP pathway reduces kidney damage caused by iohexol by preventing apoptosis. The research results are consistent with those in previous studies on AKI. For example, MCD1 accelerates sepsis-induced AKI by activating the Hippo-YAP pathway and promoting ferroptosis (Zhang et al. 2025). Similarly, renal ischemia-reperfusion leads to the continuous activation of Hippo-YAP signalling, and pharmacological inhibiting YAP helps alleviate renal inflammation (Zheng et al. 2021). On the contrary, a previous indicates that after a brief induction of AKI, YAP/survivin expression is elevated in proximal tubular cells, thereby inhibiting apoptosis and leading to resistance to urea-acetate until the proximal tubular cells recovered (Iwakura et al. 2017). The researchers speculate that this difference may depend on the stage of kidney injury or different types of kidney injury. It is necessary to systematically verify this hypothesis through further staged and model-specific experiments to clarify its specific mechanism of action under different pathological conditions.

The clinical implications of the findings are potentially significant. Currently, preventive strategies for CI-AKI are very limited, focusing primarily on contrast agent dilution and minimisation of contrast retention time (Li and Wang 2024). The study reveals that CI-AKI is largely influenced by the Hippo-YAP pathway, which could be a potential target for therapy. However, it is important to recognise several limitations of this study. First, the researchers only investigated the effect of the Hippo-YAP pathway on apoptosis, and hence, whether this pathway confers long-term benefits by mitigating inflammation or subsequent fibrosis following CI-AKI, was not examined. Second, the upstream activators of Hippo signalling in this context are yet to be clarified. Third, in the animal study, XMU-MP-1 was administered prior to iohexol treatment, suggesting that targeting this pathway may be more suitable for preventive rather than therapeutic applications.

CONCLUSION

The findings provide evidence that activating the Hippo-YAP pathway is critical for mediating renal tubular apoptosis in CI-AKI. Inhibition of this pathway alleviates CI-AKI by suppressing tubular cell apoptosis, highlighting its potential as a novel intervention target.

RECOMMENDATIONS

Upcoming studies need to concentrate on confirming these results in models that are more applicable to clinical settings and investigating the therapeutic potential of inhibiting Hippo-YAP after injury, thereby clarifying the role of this signalling pathway more comprehensively.

ETHICAL APPROVAL

This study was approved by the Ethics Committee of The Jiangyin Clinical College of Xuzhou Medical University. All animal experiments should comply with the ARRIVE guidelines.

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COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Zhuowen Xu, Jinfeng Zhou, Yukun Xu, Chenggao Jia, Lingyun Gu, Hua Zhang and Weizhang Li. The first draft of the manuscript was written by Zhuowen Xu and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

DATA AVAILABILITY

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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