

# Nrf2/HO-1/NQO1 Pathway-Mediated Regulation of Mitophagy in Renal Ischemia-Reperfusion Injury

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## CITATION

Zelin G, Zexin W. et al. Nrf2/HO-1/NQO1 Pathway-Mediated Regulation of Mitophagy in Renal Ischemia-Reperfusion Injury. *Psycho-Oncologie*.

## ARTICLE INFO

Received: 14 July, 2025

Revised: 15 July, 2025

Accepted: 16 July, 2025

Available online: 26 August, 2025

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**Abstract:** Objective: To investigate the mechanism by which the nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1)/NAD(P)H quinone oxidoreductase 1 (NQO1) signaling pathway mediates mitophagy to protect against renal ischemia-reperfusion injury (RIRI).

Methods: A total of 40 rats were randomly divided into four groups. Ten rats were assigned to the control group and were given normal saline. The remaining 30 rats were used to establish a RIRI model, with 28 rats successfully modeled. These were then divided into three groups: the model group (n = 10), which received normal saline; the agonist group (n = 9), which received an Nrf2 agonist; and the inhibitor group (n = 9), which received an Nrf2 inhibitor. After 14 days of intervention, renal function (blood urea nitrogen (BUN) and serum creatinine (Scr)), oxidative stress indicators (malondialdehyde (MDA) and superoxide dismutase (SOD)), expression levels of mitophagy-related proteins (BCL-2/BNIP3/LC3-II), and expression levels of Nrf2, HO-1, and NQO1 were measured.

Results: Compared with the control group, the model, agonist, and inhibitor groups showed significantly increased levels of BUN, Scr and MDA, while the levels of SOD, the expression of mitophagy-related proteins (Bnip3 and LC3-II), and the mRNA and protein expression levels of Nrf2, HO-1, and NQO1 were significantly decreased ( $P < 0.05$ ). Compared with the model group, the agonist group showed significantly decreased BUN, Scr, and MDA levels, and significantly increased SOD levels, BNIP3 and LC3-II protein expression, as well as mRNA and protein expression of Nrf2, HO-1, and NQO1 ( $P < 0.05$ ); whereas the inhibitor group showed increased BUN, Scr, and MDA levels and decreased SOD levels, BNIP3 and LC3-II protein expression, and Nrf2, HO-1, and NQO1 mRNA and protein levels ( $P < 0.05$ ). Compared with the agonist group, the inhibitor group exhibited significantly higher BUN, Scr, and MDA levels and lower SOD levels, Bnip3 and LC3-II protein expression, and Nrf2, HO-1, and NQO1 mRNA and protein expression ( $P < 0.05$ ).

Conclusion: Activation of the Nrf2/HO-1/NQO1 signaling pathway enhances mitophagy, improves renal function, and alleviates oxidative stress with RIRI.

**Keywords:** Nrf2/HO-1/ NQO1, Mitophagy, Renal ischemia-reperfusion injury, Oxidative stress

## 1 Introduction

Renal ischemia-reperfusion injury (RIRI) was known as a clinically acquired complication characterized by high incidence, acute onset, and rapid progression. It was frequently occurred after hemorrhagic shock, cardiopulmonary resuscitation, renal surgery, and severe infections. RIRI induced damage to DNA, lipids, and cellular proteins, thereby activating inflammatory pathways and cellular stress responses that ultimately culminate in cell necrosis and apoptosis. This condition poses a significant threat to patient survival. Consequently, the prevention and mitigation of reperfusion injury have become critical objectives in renal protection research. However, effective therapeutic strategies remain largely elusive<sup>[1-3]</sup>.

The pathogenesis and progression of RIRI involve multiple mechanisms, including vascular endothelial dysfunction, oxidative stress, inflammation, and renal tubular injury. Among these mechanisms, mitophagy emerges as a pivotal factor. Mitophagy participates in the regulation of apoptosis and the generation of reactive oxygen species (ROS), playing a critical role in maintaining renal tubular cell homeostasis and preserving normal epithelial function. Consequently, this process contributes significantly to the amelioration of RIRI[4, 5]. Mitochondrial function is closely linked to the body's oxidative stress response. Activation of the Nrf2/HO-1/NQO1 signaling pathway elicits antioxidant effects by ROS, thereby mitigating oxidative damage<sup>[6]</sup>.

In this study, we investigate the protective effects of Nrf2/HO-1/NQO1 pathway-mediated mitophagy in the context of RIRI, aiming to elucidate its underlying mechanisms and provide new insights into potential therapeutic strategies for the prevention and treatment of this challenging clinical condition.

## 2 Materials and Methods

### 2.1 Experimental animals

Forty SPF SD rats (550–680 g; sourced from Guangzhou Gino Biotechnology Co., Ltd. (SYXK(Yue)2019-0514)) underwent 5-day acclimatization in ventilated cages maintained at 22–26 °C with 40–50% humidity under 12-h light/dark cycles.

### 2.2 Group Assignment and RIRI Modeling

After 5-day acclimatization, 40 rats were divided into control group (n=10) and RIRI modeling groups (n=30). RIRI was induced in the modeling cohort according to the surgical protocol established by Meng et al.<sup>[7]</sup>: Under ketamine anesthesia, bilateral renal pedicles were isolated through laparotomy and occluded for 45 min. Reperfusion was confirmed by left renal erythema following clamp removal, with concurrent right nephrectomy. Twenty-eight validated IRI models were randomly assigned to model control (n=10), agonist-treated (n=9), and inhibitor-treated (n=9) groups.

Following model validation (Day 2 post-RIRI), therapeutic interventions were administered as follows: The agonist group (n=9) received intravenously delivered Nrf2 agonist ( $2 \times 10^{12}$  vg/kg; Hanheng Bio, China), while the inhibitor group (n=9) was given equivalent-dose Nrf2 inhibitor. Control (n=10) and RIRI model (n=10) groups received volume- normal saline (10 mL/kg). All treatments were delivered daily via caudal vein injection for 14 days.

## 2.3 Histopathological Examination

Following 14 days interventions, blood samples (4 mL) were collected and processed for serum isolation through incubation (37°C, 60 min) and centrifugation (3,000 rpm, 10 min). After euthanasia under anesthesia, kidneys were excised. Tissue sections from 4% dehyde-fixed (Richjoint, China) specimens underwent paraffin embedding, microtome sectioning (4  $\mu$ m), and H&E staining (C-reagent Bio, China). Histopathological evaluation of cortical and outer medullary regions, focusing on tubular necrosis, dilatation, and cast formation, was conducted using light microscopy (Inspectis U30, Sweden).

## 2.4 BUN and Scr assay

Renal functional parameters were evaluated through serum biochemistry on a Dirui CS-1600 automated analyzer. BUN and Scr concentrations were determined enzymatically according to manufacturer protocols, with results expressed in mg/dL.

## 2.5 Oxidative stress assessment

Serum MDA and SOD concentrations were quantified using species-specific ELISA kits (Bairade Biotechnology, China). Briefly, 10  $\mu$ L serum aliquots diluted 1:5 in assay buffer were loaded into secondary antibody-coated wells. Following 37°C incubation (60 min), plates underwent  $5 \times 1$ -min wash cycles. After TMB/ $H_2O_2$  substrate development (37°C, 15 min, dark), reactions were stopped with 2M  $H_2SO_4$ . Absorbance was measured at 450 nm with reference at 630 nm.

## 2.6 Western blotting assay

Renal tissues were homogenized in RIPA lysis buffer containing protease inhibitors (Umibio, China). After centrifugation (12,000 rpm, 20 min), supernatants were quantified by BCA assay. Proteins (30  $\mu$ g) were separated on 10% SDS-PAGE and transferred to 0.45  $\mu$ m PVDF membranes. Following blocking with 5% BSA, membranes were probed with primary antibodies anti-BNIP3, anti-LC3-II, anti-Nrf2, anti-HO-1, anti- NQO1, and anti-GAPDH overnight at 4°C. HRP-conjugated secondary antibodies were applied for 2 h at room temperature. Protein bands quantified by densitometry (ImageJ)

## 2.7 RNA extraction and real-time quantitative polymerase chain reaction (qRT-PCR)

Total RNA was isolated from renal samples using TRIzol-chloroform ex-

traction (Biotnt, China). CDNA was synthesized from 1 µg RNA using M-MLV reverse transcriptase (Zhennuo Biotechnology, China). QRT-PCR reactions contained 2× SYBR Green Master Mix (Bio-Rad, USA). Data analysis was performed using the  $\Delta\Delta C_t$  method to compare relative RNA expression levels.

## 2.8 Statistical analysis

Statistical analyses were performed using SPSS 19.0. The mean  $\pm$  standard ( $\bar{x} \pm s$ )

deviation was used to describe the continuous data, the homogeneity test of variance was used for comparison between multiple groups, and the analysis of variance was used for repeated measures between two groups, and  $P < 0.05$  was statistically significant.

## 3 Results

### 3.1 Nrf2 Modulation Attenuates Renal Tubular Injury in RIRI

In **Figure 1**, H&E staining revealed that renal tissues in the control group exhibited normal morphology, with intact renal tubular epithelial cells and no inflammatory cell infiltration in the interstitium. In contrast, both the model group and inhibitor groups displayed significant renal tubular damage, characterized by necrotic and atrophic epithelial cells, swollen epithelial tissue, marked interstitial inflammatory cell infiltration, and dilated lumina. Notably, renal lesions in the inhibitor group appeared more severe than those observed in the model group. By comparison, the agonist-treated group showed markedly attenuated pathological changes, characterized by reduced tubular dilation, mild epithelial cell swelling, limited cell detachment, and minimal inflammatory cell infiltration.

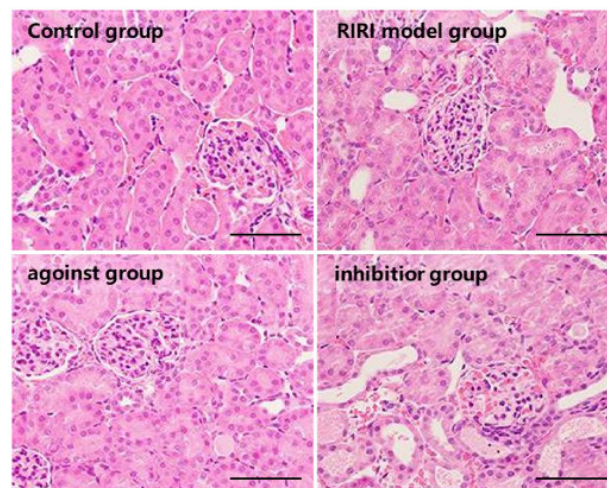


**Figure 1.** Histopathological features of renal tissues by H&E staining ( $\times 400$  magnification).

### 3.2 Nrf2 Modulation Significantly Alters Renal Function Bio-markers in RIRI

Compared to the control group, both BUN and Scr levels were significantly elevated in the model, agonist, and inhibitor groups ( $P < 0.05$ ). Notably, relative to the model group, BUN and Scr levels were significantly reduced in the agonist group, whereas the inhibitor group showed further increases in these markers, with the differences reaching statistical significance ( $P < 0.05$ ). These results are summarized in Table 1, and the corresponding statistical analyses are illustrated in Figure 2.

**Table 1.** Comparison of renal function in rats in each group ( $\bar{x} \pm s$ )

| Constituencies   | Samples |  | BUN (mmol/L)        | Scr( $\mu$ mol/L)    |
|------------------|---------|--|---------------------|----------------------|
| Control group    | 10      |  | 4.60 $\pm$ 0.36     | 46.12 $\pm$ 4.89     |
| RIRI model group | 10      |  | 26.12 $\pm$ 2.58a   | 82.01 $\pm$ 9.10a    |
| Agonist group    | 9       |  | 6.14 $\pm$ 0.59ab   | 55.89 $\pm$ 5.03ab   |
| Inhibitor Group  | 9       |  | 32.14 $\pm$ 3.88abc | 95.45 $\pm$ 10.28abc |
| F                |         |  | 578.800             | 76.634               |
| P                |         |  | <0.001              | <0.001               |

Note: aP < 0.05 compared to the blank group, bP < 0.05 compared to the model group, and cP < 0.05 compared to the agonist group

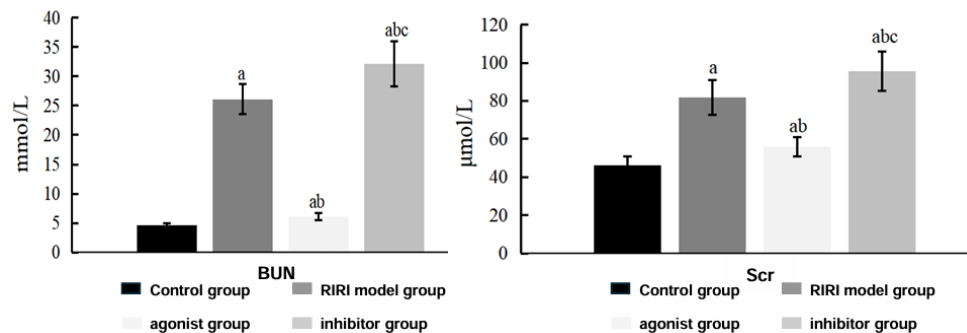


**Figure 2.** Histogram of renal function indexes in each group

### 3.3 Nrf2 Reduces MDA and Elevates SOD in RIRI.

As shown in Table 2 and Figure 3, compared with the control group, the RIRI model, agonist, and inhibitor groups exhibited significantly increased MDA levels and decreased SOD levels ( $P < 0.05$ ). Compared with the model group, the agonist group showed a significant decrease in MDA levels and an increase in SOD levels ( $P < 0.05$ ), whereas the inhibitor group showed a significant increase in MDA levels and a decrease in SOD levels ( $P < 0.05$ ).

**Table 2.** Oxidative Stress Response Comparison Across Groups( $\bar{x} \pm s$ )

| Constituencies   | Samples | MDA(mmol/dL) | SOD(U/mL)    |
|------------------|---------|--------------|--------------|
| Control group    | 10      | 2.60±0.25    | 4.58±0.48    |
| RIRI model group | 10      | 4.60±0.58a   | 1.60±0.12a   |
| Agonist group    | 9       | 3.01±0.33ab  | 4.07±0.39ab  |
| Inhibitor Group  | 9       | 5.12±0.61abc | 1.14±0.09abc |
| F                |         | 64.575       | 191.439      |
| P                |         | <0.001       | <0.001       |

Note: aP < 0.05 compared to the blank group, bP < 0.05 compared to the model group, and cP < 0.05 compared to the agonist group

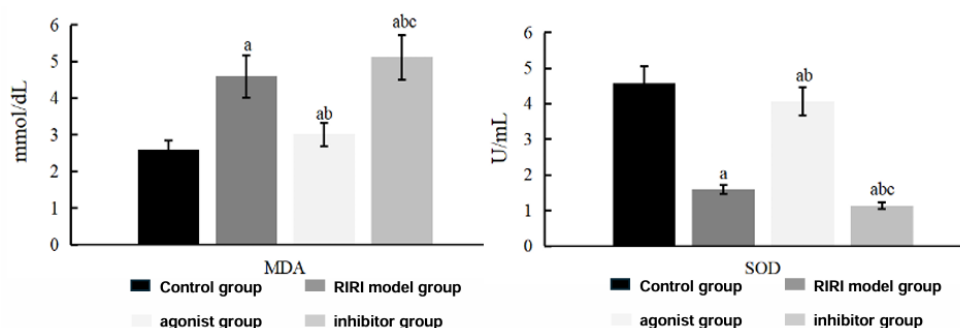


**Figure 3.** Oxidative Stress Parameters Across Groups was shown by histogram.

### 3.4 Nrf2 mediated mitophagy through BNIP3 pathway in RIRI.

As presented in **Table 3** and **Figure 4**, the expression levels of BNIP3 and LC3-II proteins were significantly reduced in the model, agonist, and inhibitor groups compared with the control group ( $P < 0.05$ ). Relative to the model group, the agonist group exhibited significantly increased expression of BNIP3 and LC3-II, whereas the inhibitor group showed further reduction ( $P < 0.05$ ).

**Table 3.** Expression of Mitophagy-Related Proteins in Different Groups

| Constituencies   | Samples | BNIP3        | LC3-II       |
|------------------|---------|--------------|--------------|
| Control group    | 10      | 1.73±0.12    | 1.89±0.20    |
| RIRI model group | 10      | 0.80±0.06a   | 0.83±0.07a   |
| Agonist group    | 9       | 1.41±0.13ab  | 1.38±0.14ab  |
| Inhibitor Group  | 9       | 0.62±0.05abc | 0.65±0.04abc |
| F                |         | 194.869      | 130.266      |
| P                |         | <0.001       | <0.001       |

Note: aP < 0.05 compared to the blank group, bP < 0.05 compared to the model group, and cP < 0.05 compared to the agonist group

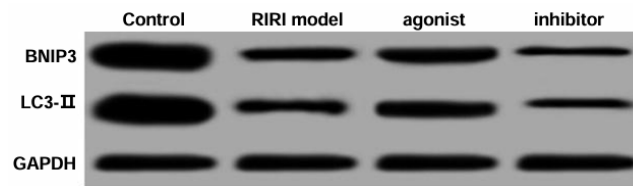


**Figure 4.** WB assay of expression of mitophagy-related proteins.

### 3.5 Effects of Agonist and Inhibitor on Nrf2, HO-1, and NQO1 mRNA Expression

According to Table 4 and Figure 5, the mRNA levels of Nrf2, HO-1, and NQO1 were significantly lower in the model, agonist, and inhibitor groups compared to the control group ( $P < 0.05$ ). Relative to the model group, the agonist treatment significantly upregulated the mRNA expression of these genes, while the inhibitor treatment further suppressed their expression ( $P < 0.05$ ).

**Table 4.** MRNA Expression of Nrf2, HO-1, and NQO1 in Different Groups ( $\bar{x} \pm s$ )

| Constituencies   | Samples | Nrf2         | HO-1         | NQO1         |
|------------------|---------|--------------|--------------|--------------|
| Control group    | 10      | 1.92±0.18    | 1.84±0.16    | 1.82±0.20    |
| RIRI model group | 10      | 0.72±0.08a   | 0.69±0.06a   | 0.85±0.10a   |
| Agonist group    | 9       | 1.60±0.15ab  | 1.52±0.13ab  | 1.49±0.12ab  |
| Inhibitor Group  | 9       | 0.51±0.06abc | 0.42±0.04abc | 0.53±0.05abc |
| F                |         | 188.825      | 229.169      | 111.638      |
| P                |         | <0.001       | <0.001       | <0.001       |

Note: aP < 0.05 compared to the blank group, bP < 0.05 compared to the model group, and cP < 0.05 compared to the agonist group

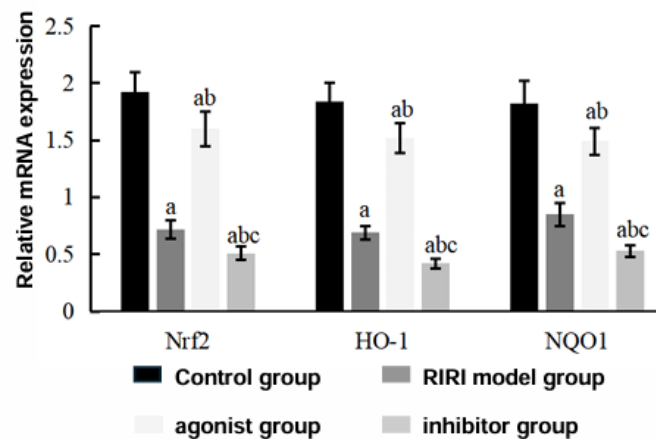


**Figure 4.** Bar Graph of Nrf2, HO-1, and NQO1 mRNA Expression Levels in Different Groups

### 3.6 Effects of Agonist and Inhibitor on Nrf2, HO-1, and NQO1 Protein Expression

Data depicted in Table 5 and Figure 6 was demonstrated that significant decreases in the protein levels of Nrf2, HO-1, and NQO1 were observed in the

model, agonist, and inhibitor groups relative to the control group ( $P < 0.05$ ). Furthermore, compared to the model group, protein expression of Nrf2, HO-1, and NQO1 was significantly elevated in the agonist group, while a further significant reduction was noted in the inhibitor group ( $P < 0.05$ ).

**Table 5.** Protein Levels of the Nrf2/HO-1/NQO1 Signaling Pathway in Different Groups( $\bar{x} \pm s$ )

| Constituencies   | Samples | Nrf2         | HO-1         | NQO1         |
|------------------|---------|--------------|--------------|--------------|
| Control group    | 10      | 1.95±0.20    | 1.82±0.21    | 1.84±0.22    |
| RIRI model group | 10      | 0.75±0.09a   | 0.70±0.08a   | 0.80±0.11a   |
| Agonist group    | 9       | 1.50±0.14ab  | 1.58±0.14ab  | 1.51±0.14ab  |
| Inhibitor Group  | 9       | 0.52±0.07abc | 0.45±0.05abc | 0.51±0.06abc |
| F                |         | 161.804      | 146.898      | 104.402      |
| P                |         | <0.001       | <0.001       | <0.001       |

Note: aP < 0.05 compared to the blank group, bP < 0.05 compared to the model group, and cP < 0.05 compared to the agonist group

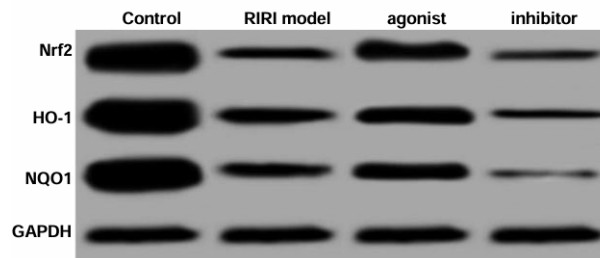


**Figure 5.** Protein Expression of Nrf2/HO-1/NQO1 Signaling Pathway in Different Groups

## 4 Discussion

RIRI induces renal degeneration and necrosis, resulting in the deterioration of renal function and delayed recovery of graft function following transplantation. In severe cases, it can lead to multiple organ dysfunction syndrome and ultimately mortality<sup>[8-10]</sup>. Studies have shown that due to the kidney's abundant oxygen supply and rich blood flow, it is highly susceptible to oxidative stress-induced injury. Oxidative stress, in turn, triggers activation of the immune system, apoptosis, DNA damage, and increased release of inflammatory factors, ultimately exacerbating renal tissue damage<sup>[11, 12]</sup>. In this study, a rat model of RIRI was established by transient occlusion of the renal artery followed by reperfusion. The model induced significant renal tissue damage, as evidenced by elevated serum levels of BUN, Scr, and MDA, along with a reduction in SOD activity. Treatment with an Nrf2 agonist significantly attenuated these changes, reducing BUN, Scr, and MDA levels while restoring SOD activity. These findings suggest that activation of the Nrf2/HO-1/NQO1 signaling pathway plays a protective role in mitigating renal injury in rats. Previous studies have demonstrated that elevated MDA levels and decreased SOD activity can induce oxidative stress injury, leading to excessive accumulation of ROS. The excessive ROS damages the biological functions and structural integrity of cell membranes, triggering a cascade

of pathological changes. BUN is commonly used to assess renal excretory function, while Scr, due to its low molecular weight and partial tubular reabsorption, also correlates positively with the severity of renal injury<sup>[13, 14]</sup>.

Studies have identified mitochondria as critical regulators of apoptosis and ROS production. Mitophagy selectively removes dysfunctional and damaged mitochondria, thereby maintaining intracellular homeostasis. In RIRI, mitophagy plays a pivotal role; impairment of mitophagy reduces ATP production, increases pro-apoptotic proteins and ROS release, and exacerbates inflammatory responses. These changes ultimately lead to renal tubular epithelial cell dysfunction and apoptosis, aggravating kidney injury<sup>[15-17]</sup>. BNIP3 function as an inducer of mitophagy and apoptosis. LC3-II, the predominant intracellular form of LC3, localizes to both the inner and outer membranes of autophagosomes and serves as a marker of autophagosome formation. Fission and fusion dynamics of the mitochondrial network regulate mitochondrial morphology and structure, thereby maintaining mitophagy stability. During mitophagy, the expression levels of BNIP3 and LC3-II are significantly upregulated<sup>[18-20]</sup>. In this study, compared to the RIRI model group, the agonist group exhibited decreased protein expression levels of BNIP3 and LC3-II, whereas the inhibitor group showed increased expression of these proteins, suggesting that activation of the Nrf2/HO-1/NQO1 signaling pathway enhances mitophagy. Under normal physiological conditions, the oxidative-antioxidant system maintains a dynamic balance. Nrf2 is a critical regulator of the antioxidant response as well as cellular autophagy and apoptosis. Upon oxidative stress activation, Nrf2 stimulates downstream effectors such as HO-1 and NQO1. HO-1 exerts anti-inflammatory and antioxidant effects by catalyzing the degradation of heme into carbon monoxide, iron ions, and biliverdin, thereby maintaining redox homeostasis. NQO1, which is widely distributed, inhibits ROS production by blocking the quinone single-electron redox cycle and removes superoxide radicals through regulation of vitamin E and ubiquinone metabolism, ultimately alleviating oxidative stress-induced damage<sup>[21-23]</sup>.

In conclusion, the present study demonstrates that activation of the Nrf2/HO-1/NQO1 signaling pathway significantly enhances mitophagy and mitigates oxidative stress in a rat model of RIRI, thereby exerting a protective effect on renal function. However, further research is warranted to elucidate the temporal interplay between RIRI and mitophagy, and to identify additional signaling cascades that may participate in this regulatory network. Such insights could ultimately facilitate the development of innovative therapeutic strategies for the clinical management of RIRI.

## References

- [1] GUO Z, CHEN D, YAO L, et al. The molecular mechanism and therapeutic landscape of copper and cuproptosis in cancer [J]. *Signal transduction and targeted therapy*, 2025, 10(1): 149.
- [2] 高建辉, 薛莹, 张佳齐, et al. 瑞马唑仑对大鼠急性肾缺血再灌注损伤的影响及机制 [J]. *山西医*

科大学学报, 2024, 55(5): 621-616.

[3] ZHOU X, ZHAO S, LI W, et al. Tubular cell-derived exosomal miR-150-5p contributes to renal fibrosis following unilateral ischemia-reperfusion injury by activating fibroblast in vitro and in vivo [J]. International journal of biological sciences, 2021, 17(14): 4021-4033.

[4] 陈明环, 王咏兰, 李相国, et al. 鬼箭羽醇提取物通过阻止氧化应激和抑制 TNF- $\alpha$ -NF- $\kappa$ B 及 T $\beta$ R1-Smad2/3 通路减轻兔肾缺血再灌注损伤 [J]. 中国病理生理杂志, 2022, 38(4): 688-697.

[5] FENG R, XIONG Y, LEI Y, et al. Lysine-specific demethylase 1 aggravated oxidative stress and ferroptosis induced by renal ischemia and reperfusion injury through activation of TLR4/NOX4 pathway in mice [J]. Journal of cellular and molecular medicine, 2022, 26(15): 4254-4267.

[6] 胡彦, 王锁刚, 翟琼瑶, et al. 积雪草苷调控 SIRT1-FOXO3-PINK1-Parkin 通路介导的线粒体自噬保护肾缺血再灌注损伤的机制研究 [J]. 天津医药, 2021, 49(11): 1148-1153.

[7] 孟巧云, 王雪, 邱国萍, et al. 雌激素对肾缺血再灌注损伤大鼠 Th17/Treg 平衡、氧化应激及肾组织 NF- $\kappa$ B、TGF- $\beta$ 1 表达的影响 [J]. 现代生物医学进展, 2021, 21(10): 1844-1848.

[8] JIANG J, WEN C, LI Y, et al. IFC-305 attenuates renal ischemia-reperfusion injury by promoting the production of hydrogen sulfide (H<sub>2</sub>S) via suppressing the promoter methylation of cystathionine  $\gamma$ -lyase (CSE) [J]. Bioengineered, 2022, 13(5): 12045-12054.

[9] 陈家辉, 张燕子, 张艾莎, et al. 缺血预处理的肾小管细胞来源外泌体对肾缺血再灌注损伤大鼠 PI3K/AKT/mTOR 信号通路的调控机制 [J]. 中华肾脏病杂志, 2024, 40(9): 732-740.

[10] HOU Y, XIN Y, LIU S, et al. A biocompatible nanoparticle-based approach to inhibiting renal ischemia reperfusion injury in mice by blocking thrombospondin-1 activity [J]. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons, 2022, 22(9): 2246-2253.

[11] 刘钰林, 陈珮如, 梁毅敏, et al. 米诺地尔联合地塞米松对肾缺血再灌注损伤大鼠肾功能指标和氧化应激指标的影响 [J]. 现代药物与临床, 2020, 35(06): 1064-1068.

[12] AL-SULTANY H H A, ALTIMIMI M, QASSAM H, et al. Cardamonin mitigates kidney injury by modulating inflammation, oxidative stress, and apoptotic signaling in rats subjected to renal ischemia and reperfusion [J]. Journal of medicine and life, 2023, 16(12): 1852-1856.

[13] 曾蕾, 席晓荣, 孙承霞, et al. 基于氧化应激及其相关凋亡蛋白研究苓桂术甘汤预处理对大鼠心肌缺血再灌注损伤的保护作用及机制 [J]. 中华中医药学刊, 2024, 42(06): 60-4+267-270.

[14] 刘庆亮, 杨自生, 曹保江. 芍药苷预处理对大鼠心肌缺血-再灌注损伤氧化应激的保护作用及对 Nrf-2/TXNIP/NLRP-3 信号通路的影响 [J]. 中国循证心血管医学杂志, 2023, 15(03): 352-356.

[15] 邓新琦, 熊永红, 李维. PINK1/Parkin-溶酶体相关膜蛋白 2 通路介导的线粒体-溶酶体自噬在肾缺血再灌注损伤后上皮-间充质转化中的作用 [J]. 中华实验外科杂志, 2022, 39(12): 2331-2334.

[16] 王华, 谭超, 王子焱, et al. 三七总皂苷基于 PI3K/Akt/mTOR 通路调控自噬和泛素蛋白积累对大鼠肾缺血再灌注损伤的影响 [J]. 现代中西医结合杂志, 2023, 32(11): 1461-7+72.

[17] 赖轻舟, 吴小琴, 龚玉萍. 激酶锚定蛋白 12/蛋白原转化酶枯草杆菌蛋白酶/kexin 型 6 信号通路对糖尿病肾脏疾病小鼠足细胞线粒体自噬保护作用的研究 [J]. 中国糖尿病杂志, 2024, 32(10): 770-777.

[18] 曹蛟, 刘建和, 张杼惠, et al. 柴胡三参胶囊调控 HIF-1 $\alpha$ /BNIP3/NIX 介导的线粒体自噬通路减轻心肌缺血再灌注损伤作用的研究 [J]. 世界科学技术-中医药现代化, 2023, 25(03): 993-1001.

[19] 王妮妮, 丁昱, 王琳, et al. 灯盏花素通过转录因子 cAMP 反应元件结合蛋白磷酸化促进细胞自噬保护心肌细胞缺血-再灌注损伤的机制研究 [J]. 解放军医学院学报, 2023, 44(01): 43-49.

[20] 梁荣珍, 王太成, 林德文, et al. 艾帕素 13(apelin-13) 通过阻断 PINK1/parkin 信号通路促进线粒体自噬改善大鼠心肌缺血再灌注损伤 [J]. 细胞与分子免疫学杂志, 2023, 39(11): 981-987.

[21] 庞鹏飞, 冯达云, 黄涛, et al. 氧化槐果碱上调 Nrf2/HO-1/NQO1 通路及抑制 NF- $\kappa$ B 的活化缓解脑缺血再灌注大鼠氧化损伤和炎症反应 [J]. 医学分子生物学杂志, 2020, 17(2): 85-90.

[22] 潘建立, 郑良英, 叶成杰. 右美托咪定通过核转录因子红系 2 相关因子 2/ 重组人血红素加氧酶-1

信号转导通路对小鼠肾缺血再灌注损伤的保护作用 [J]. 中国临床药理学杂志, 2023, 39(02): 251-255.

[23] 李雪, 李博, 谈彬, et al. 槲皮素预处理 ALI 大鼠肺组织损伤、炎症 / 氧化应激反应、铁死亡及 Nrf2/HO-1 信号通路激活情况观察 [J]. 山东医药, 2024, 64(15): 13-18.