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Alleviation of Acute Lung Injury in Rats with Sepsis by Resveratrol via the Phosphatidylinositol 3-Kinase/Nuclear Factor-Erythroid 2 Related Factor 2/Heme Oxygenase-1 (PI3K/Nrf2/HO-1) Pathway

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Resveratrol (Res) is a type of polyphenol found in many plants, which can protect important organs from the damage induced by sepsis. However, the exact mechanism of its protective effect has not been established. This study investigated the effect of Res on the PI3K/Nrf2/HO-1 signaling pathway in rats with sepsis-induced acute lung injury (ALI).

Material/Methods: Male Wistar rats were treated with 30 mg/kg Res by intraperitoneal administration for 1 hour immediately after cecal ligation and puncture. Levels of MIP-2, IL-18, and IL-10 in bronchoalveolar lavage fluid (BALF) were determined. Lung tissues were collected to measure the wet-to-dry (W/D) ratios, oxidative stress index, and lung injury scores. Expression levels of Akt, p-Akt, HO-1, Nrf-2, and active caspase-3 proteins were determined by western blotting; expression of HO-1 mRNA was determined by RT-PCR.

Results: Treatment with Res significantly decreased the levels of MIP-2 and IL-18 and increased IL-10 in the BALF of rats with sepsis-induced ALI. In addition, Res also effectively reduced the W/D lung weight ratio, lung injury score, and the levels of MDA (malondialdehyde) and 8-OHdG. Conversely, Res increased SOD (superoxide dismutase) activity in the lung tissue. Moreover, Res significantly induced higher HO-1 mRNA expression, upregulated HO-1 and Nrf-2 protein expression, and the phosphorylation of Akt in the lung tissue. In contrast, the levels of activated caspase-3 protein were decreased in Res-treated rats ($P<0.05$).

Conclusions: Res could inhibit inflammation, oxidative stress, and cell apoptosis to alleviate ALI in septic rats through the inhibition of the PI3K/Nrf2/HO-1 signaling pathway.

MeSH Keywords: Acute Lung Injury • Sepsis • Signal Transduction

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Background

Sepsis is a reactive state of disorder in response to infection which can cause life-threatening organ dysfunction. The lung is the first organ to be injured in the course of sepsis, and the appearance of acute lung injury (ALI) indicates the occurrence and progress of multi-organ dysfunction [1]. An uncontrolled inflammatory response is one of the most important pathophysiological factors that can cause ALI. The PI3K/Akt pathway is one of the signal pathways involved in the endogenous regulation of the inflammatory response, which can provide negative feedback to regulate the inflammatory response and chemotaxis. It can promote cell-proliferation and cytoskeleton recombination, and it can inhibit apoptosis [2]. The N-E2 relative factor 2 (Nrf2)/anti-oxidation sequence element (ARE) signaling pathway is an important endogenous antioxidative stress pathway [3]. The PI3K/Akt signaling pathway is involved in the activation of Nrf2. Once activated, Nrf2 dissociates from Kelch-like epichlorohydrin associated protein-1 (Keap1) and translocates to the nucleus where it binds to the ARE to regulate the expression of target genes, including heme oxygenase-1 (HO-1) [4]. The upregulation of HO-1 expression reduces the mortality of sepsis in rats. Therefore, HO-1 has a negative regulatory effect on the inflammatory response and oxidative stress of ALI [5].

The chemical name of resveratrol (Res) is 3, 5, 4'-trihydroxydiphenyl. It is a non-flavonoid phenolic substance with antitumor, anti-oxidative, and anti-inflammatory properties which can reduce the synthesis and secretion of various inflammatory mediators [6]. *In vitro*, Res, which inhibits cellular events associated with tumor initiation, promotion, and progression, is particularly relevant as a chemopreventive agent [7]. In recent years, it was discovered that Res had a protective effect against the organ damage caused by sepsis [8]. Hao et al. [9] found a protective effect against cardiac injury induced by lipopolysaccharide (LPS) in rats. Xu et al. [10] discovered that Res could reduce the level of serum high mobility group protein-1 (HMGBl) and inhibit the nuclear translocation of hepatocyte HMGBl, which could effectively inhibit liver injury in rats with sepsis. Mechanisms of Res have been demonstrated to be associated with reducing oxidative stress and inflammation and improving microcirculation perfusion status. Therefore, we speculated that Res could also have a protective effect against lung injury caused by sepsis, although the exact mechanism has not been established. In this study, a sepsis rat model was established by cecal ligation and puncture (CLP) to investigate the effects of Res on the PI3K/Nrf2/HO-1 signaling pathway in sepsis-induced ALI.

Material and Methods

Experimental animals and animal sepsis model

Healthy adult male Wistar rats (clean-grade; 220±20 g) were purchased from Charles River Laboratories (Beijing, China). All experimental procedures were performed in accordance with the legislation on the protection of animals and were approved by the Local Ethical Committee for Animal Experimentation. Polymicrobial sepsis was induced in rats by CLP as previously described [11]. Briefly, the animals were anesthetized by intraperitoneal injection of 5% chloral hydrate (0.6 mL/100 g), and a midline incision was made to expose the cecum. The cecum was filled with feces by milking the stool backward from the ascending colon, and 50% of the cecum was ligated with a 5-0 silk suture. The cecum was then punctured twice with an 18-gauge needle on the antimesenteric border. The cecum was returned to the peritoneal cavity, and the abdominal incision was sutured. Sham-operated rats underwent identical laparotomy and resuscitation procedures, but the cecum was neither ligated nor punctured. The severity of abdominal infection in sepsis rat was assessed using Simon celiac infection classification criteria [12].

Animal groups

Thirty-six Wistar rats (n=12 rats per group) were randomly divided into 3 groups: a sham group, a CLP (sepsis) group, and a CLP+Res (Res) group. Res (Sigma-Aldrich) was dissolved in DMSO to a final concentration of 20 mg/mL. Res was administered intraperitoneally to the Res group for 1 hour after CLP at a dose of 30 mg/kg. Rats in the sham and sepsis groups were given an equal volume of sterile saline. Subsequent studies were performed on each group at 24 hours after model establishment.

Detection of MIP-2, IL-18, and IL-10 in bronchoalveolar lavage fluid (BALF)

Rats were euthanized 24 hours after CLP surgery. Tracheal intubation was performed after the separation of the trachea and main bronchus. The left lung was washed 3 times with 0.5 mL precooled phosphate-buffered saline. The BALF was collected and centrifuged at 1500×g for 10 min at 4°C. The supernatant was collected, and the concentrations of MIP-2, IL-18, and IL-10 in the BALF were detected using ELISA kits according to the manufacturer's instructions (R&D Systems Inc., Minneapolis, MN, USA). The levels of MIP-2, IL-18, and IL-10 in the samples were calculated based on a standard curve. The detection ranges of the MIP-2, IL-18, and IL-10 ELISA assays were 15.6–1000 pg/mL respectively. Samples that had a concentration that exceeded the limit of the standard curve were measured after dilution.

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Detection of oxidative stress response of lung tissue

The malondialdehyde (MDA) level was determined in lung tissue using the thiobarbituric acid colorimetric method and superoxide dismutase (SOD) activity was detected by the yellow purine oxidase method, using a kit (Nanjing Jiancheng Bioengineering Institute, Nanjng, China), in strict accordance with the manufacturer's instructions. The level of 8-OHdG was assessed using a commercial ELISA kit according to the manufacturer's instructions (Bio Legend, Inc., San Diego, CA, USA). The levels of 8-OHdG in the samples were calculated based on a standard curve. The detection ranges of the 8-OHdG ELISA assays were 0.312–20 ng/ml.

Determination on the ratio of wet weight/dry weight (W/D) of lung tissue

The surface water and blood on the upper lobe of the right lung of each rat was absorbed by filter paper. The wet weight (W) was measured using an electronic balance, put in a dryer at 80°C for 24 hours, and then the dry weight (D) was determined. The ratio of the wet weight of the wet lung to the dry weight of the lung was calculated.

Lung histopathology

The right lung tissue was fixed with 10% paraformaldehyde and the specimens were sliced into tissue blocks with a thickness of 0.5 cm. Conventional gradient alcohol dehydration, paraffin-embedding, serial sectioning, and hematoxylin and eosin (H&E) staining were carried out and histopathological changes in lung tissue were observed under an optical microscope. The lung injury score consisted of determining the amount of edema, congestion, neutrophil infiltration, bronchial hemorrhage and debris, and cell proliferation. Each score based on the degree of lung injury was divided into 0, 1, 2, and 3 points, and the total score was the sum of the scores of the five injury categories [13].

Quantitative reverse transcriptase-polymerase chain reaction

Total RNA was extracted from lung tissue using the RNeasy Plus Mini Kit following the manufacturer's protocol (Qiagen, Frankfurt, German). cDNA was synthesized using the GoScript™ Reverse Transcription System (Promega, Madison, WI, USA) using 2 μg of total RNA. Real-time polymerase chain reaction (RT-PCR) was performed using the GoTaqP® qPCR Master Mix (Promega, Madison, WI, USA) and the Line-Gene 9600 Plus QPCR system (Bioer, Hangzhou, China) with LineGene 9600 Plus software. The oligonucleotide primer sequences used for HO-1 and β-actin are as follows: HO-1 (224 bp), forward primer: 5' AAACAAGCAGAACCCAGTC3', reverse primer: 5' AGAGGTCACCCAGGTAGCG 3'; β-actin (203 bp), forward primer: 5'TTCCTTCTTGGGTATGGAAT3' and reverse primer 5'GAGCAATGATCTTGATCTTC3'. The RT-PCR procedures were as follows: 10 min 95°C hot-start followed by 35 cycles of amplification (95°C for 10 sec, 60°C for 20 sec, 72°C for 15 sec). The relative differences in the HO-1 expression levels between the groups were determined by using cycle threshold (Ct) values.

Detection of Akt, p-Akt, HO-1, Nrf-2, and activated caspase-3 in lung tissue by western blotting

Total protein and nucleoprotein were extracted from the middle lobe of the right lung using the Thermo protein extraction kit (Thermo, Waltham, MA, USA). Protein concentrations were determined using a bicinchoninic acid assay kit (Beyotime Institute of Biotechnology, Haimen, China). Proteins were separated by sodium dodecyl sulfate polyacrylamide gel electrophoresis and transferred to polyvinylidene fluoride membranes (Millipore, Bedford, MA, USA). The membranes were incubated overnight at 4°C with rabbit polyclonal antibodies against total Akt, p-Akt (Cell Signaling Technology, Inc. Danvers, MA, USA), Nrf2 (Biotechnology Inc, Dallas, TX, USA), HO-1 and activated caspase-3 (Santa Cruz Biotechnology Inc, Dallas, TX, USA). The membranes were then incubated with a horseradish peroxidase-conjugated goat anti-rabbit secondary antibody (Beyotime, Jiangsu, China) at 37°C for 45 min. An enhanced chemiluminescence (ECL) imaging system was used to visualize the protein bands. The Akt phosphorylation level was determined by the ratio of p-Akt to total Akt expression.

Statistical analysis

SPSS Statistics software version 17.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Numeric data are presented as the mean ±SD. One-way analysis of variance was used to compare the means of the 3 groups, and a least significant difference *t*-test was used for pairwise comparisons between the groups. A $P<0.05$ was considered statistically significant.

Results

Characteristics of the rats in each study group

According to the Simon grading system, the intraperitoneal infection in the sepsis group was grade 3–4 and the infection grade in the treatment group was 2–3. The infection grade in the sham-operated group was 0. The 24-hour survival rate for the CLP rats was 83.3%.

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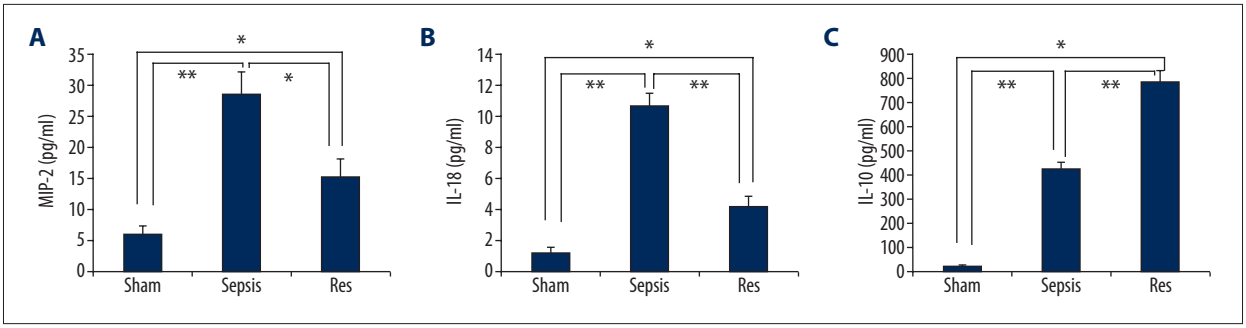

Figure 1. Resveratrol decreased the MIP-2 and IL-18 levels and increased the IL-10 levels in the BALF of rats with CLP-induced acute lung injury. Data are presented as the mean ±SD (n=10 for each group). * $P \leq 0.05$, ** $P \leq 0.01$. BALF – bronchoalveolar lavage fluid; CLP – cecal ligation and puncture.

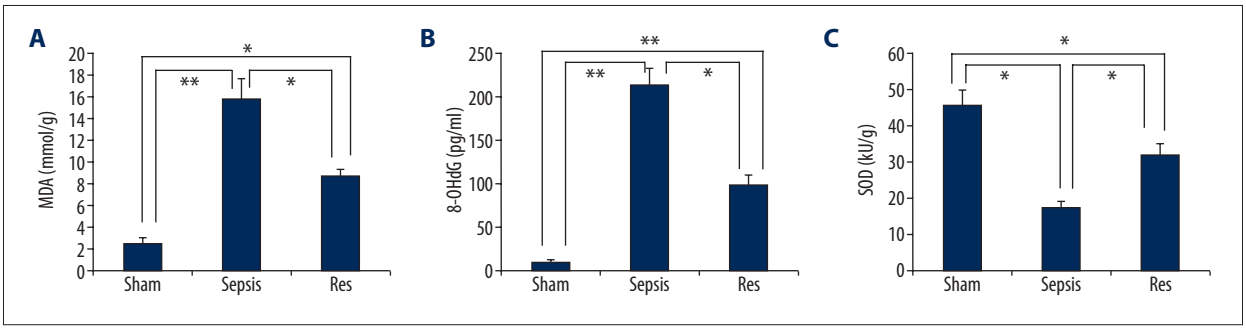

Figure 2. Resveratrol reduced MDA and 8-OHdG levels and increased SOD activity in lung tissues. Data are presented as the mean ±SD (n=10 for each group). * $P \leq 0.05$, ** $P \leq 0.01$. MDA – malondialdehyde; SOD – superoxide dismutase.

Detection indexes in BALF

The levels of MIP-2 and IL-18 in BALF were significantly higher in the sepsis group (28.6±3.5 pg/mL and 10.6±0.9 pg/mL, respectively) than those of the sham group. In contrast, these 2 indices were significantly lower in the Res group (15.3±2.8 pg/mL and 4.2±0.5 pg/mL, respectively) compared to the sepsis group ($P<0.05$, Figure 1). Thus, Res significantly decreased the concentrations of MIP-2 and IL-18 by 47% and 60% respectively, in the BALF during CLP-induced ALI. In contrast, Res increased the IL-10 levels from 425.6±26.4 pg/mL observed in the sepsis group to 783.4±45.3 pg/mL ($P<0.05$, Figure 1).

Oxidative stress indexes of lung tissue

The levels of MDA and 8-OHdG in the lungs of the sepsis group rats were significantly higher than those in the sham group. In addition, SOD activity was significantly decreased in the sepsis group. In contrast, Res reduced the levels of MDA by 45% and 8-OHdG by 54% during CLP-induced ALI. Moreover, Res significantly increased the CLP-induced SOD activity by 46% ($P<0.05$, Figure 2).

W/D ratio of lung tissue

The W/D ratio in the sepsis group was significantly higher than that of the sham group. However, the W/D ratio in the Res treatment group was significantly lower than that of the sepsis group ($P<0.05$, Figure 3).

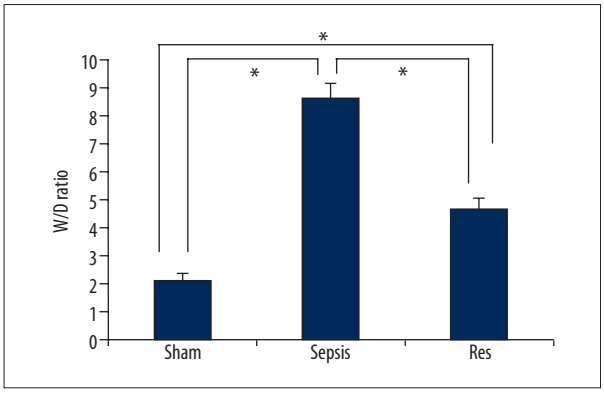

Figure 3. Resveratrol reduced the lung wet-to-dry ratio in rats with CLP-induced acute lung injury. Data are presented as the mean ±SD (n=10 for each group). * $P \leq 0.05$, ** $P \leq 0.01$. CLP – cecal ligation and puncture.

Pulmonary histopathological changes

The alveolar structure in the lungs of rats in the sham group was intact, the alveolar interval was normal, the pulmonary interstitium was not significantly edematous, and there was no inflammatory cell infiltration in the alveolar cavity. The alveolar

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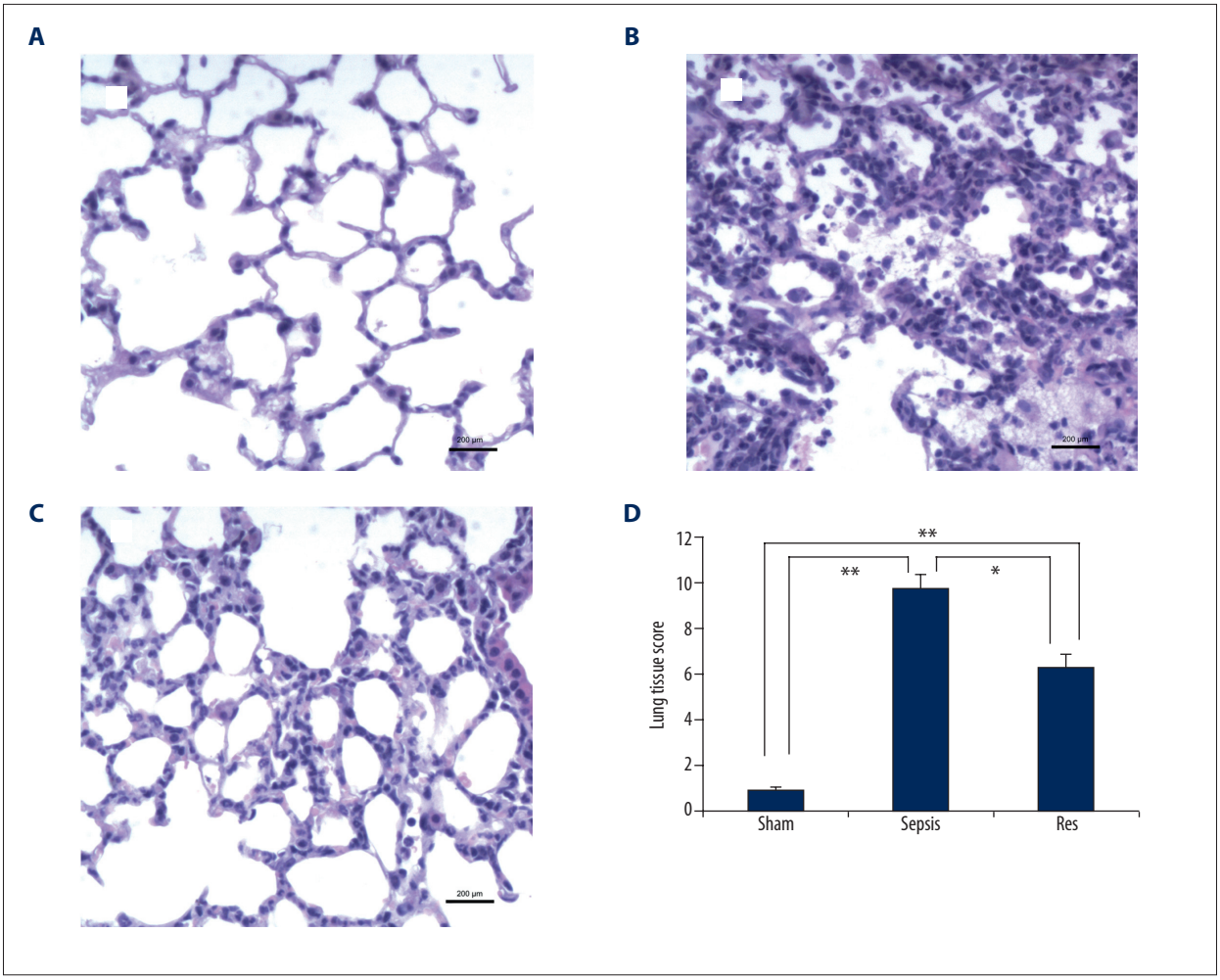

Figure 4. Resveratrol ameliorated the histopathological changes in the lung tissues of rats with CLP-induced acute lung injury. (**A**) Photomicrograph of lung tissue from a sham rat. (**B**) Photomicrograph of lung tissue from a septic rat. (**C**) Photomicrograph of lung tissue from a septic rat treated with resveratrol. (**D**) Histopathologic scoring of lung injury in the 3 groups. Data are presented as the mean ±SD (n=10 for each group). * $P \leq 0.05$, ** $P \leq 0.01$. CLP – cecal ligation and puncture.

structure in the lungs of rats in the sepsis group was severely damaged, the alveolae and interstitium were significantly edematous, the alveolar interval was widened, a large number of inflammatory cells infiltrated into the alveolar cavity, and there was hyperemia in the pulmonary capillary. There was some improvement in the inflammatory cell infiltration, and the pulmonary interstitial hyperemia and edema caused by Res treatment (Figure 4A–4C). Furthermore, the Res group showed a significantly lower score than the sepsis group ($P<0.05$, Figure 4D).

HO-1 mRNA expression in lung tissue

HO-1 mRNA expression in the sham group was extremely low, but increased slightly in the sepsis group, there was no statistical difference between the 2 groups. HO-1 mRNA expression markedly increased in the Res treatment group compared with the sepsis group ($P < 0.05$ versus sepsis group, Figure 5).

HO-1, Nrf-2, p-Akt, and activated caspase-3 protein levels in lung tissue

The HO-1 protein level in the lung tissue from the sham group was extremely low. Its level in the sepsis group was slightly increased, but there was no statistical difference between the 2 groups. In contrast, HO-1 protein level in the Res treatment group was significantly higher than that in the sepsis group ($P<0.05$ versus the sepsis group). The changes in Nrf-2 protein expression paralleled that of HO-1. The p-Akt level was decreased by 42.0% in the sepsis group compared to the sham group ($P<0.05$, Figure 6). Interestingly, the CLP-induced decrease in Akt phosphorylation was significantly attenuated by Res as indicated by a 50.1% increase in the p-Akt level in the septic rat with Res treatment ($P<0.05$, Figure 6). The level of active caspase-3 was upregulated in the lung tissue from rats of the sepsis group compared to the sham group.

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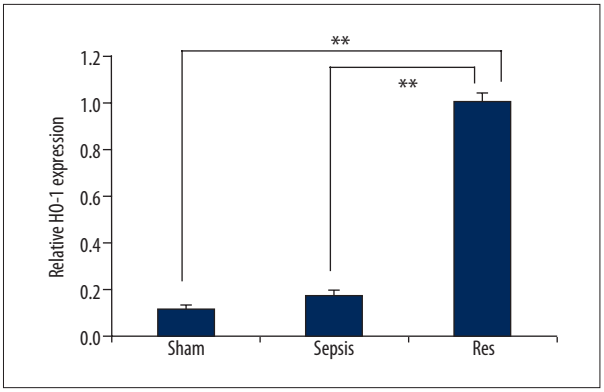

Figure 5. Resveratrol upregulates HO-1mRNA expression in rats with sepsis-induced acute lung injury. Data are presented as the mean ±SD (n=10 for each group). * $P \leq 0.05$, ** $P \leq 0.01$.

This upregulation was reduced with Res treatment ($P<0.05$) (Figure 7).

Discussion

Res was identified in an extract from the rhizome of Polygonum cuspidatum. Recent studies have shown that Res has protective effects on the brain, lung, kidney, and intestines in the treatment of sepsis. The mechanism was mainly related to its anti-oxidative stress, anti-inflammatory, and anti-apoptosis properties [14]. Pulmonary edema and inflammatory cell infiltration are the main features of ALI. In the current study, Res could effectively reduce the W/D ratio of the lung, alleviate internal alveolar bleeding, inflammatory cell infiltration, and pulmonary interstitial hyperemia and edema, which indicated that Res could effectively improve the degree of the local inflammatory response. We found that Res could reduce the levels of MIP-2 and IL-18 in the rats with ALI, suggesting that multiple effector cells and inflammatory mediators were involved in ALI. The exudation and aggregation of neutrophils in the lung have been a cytologically important link in the incidence of ALI. MIP-2 is a powerful neutrophil chemokine, which can be released through the stimulation of macrophages by TNF-α. Its specific target cells are neutrophils [15]. MIP-2 participates in the inflammatory response through chemical chemotaxis and activation [16]. As an important pre-inflammatory factor, IL-18 can induce the generation and release of other inflammatory mediators, such as TNF-α, which leads to uncontrolled inflammation. In addition, IL-18 can upregulate the expression and activity of NF-κB, the pivotal factor in the regulation of the cascade reaction of inflammation leading to ALI [17]. This study also found that Res could increase the level of IL-10 in BALF. IL-10 has an inhibitory effect on inflammation and can negatively regulate the septic shock induced by microorganisms [18].

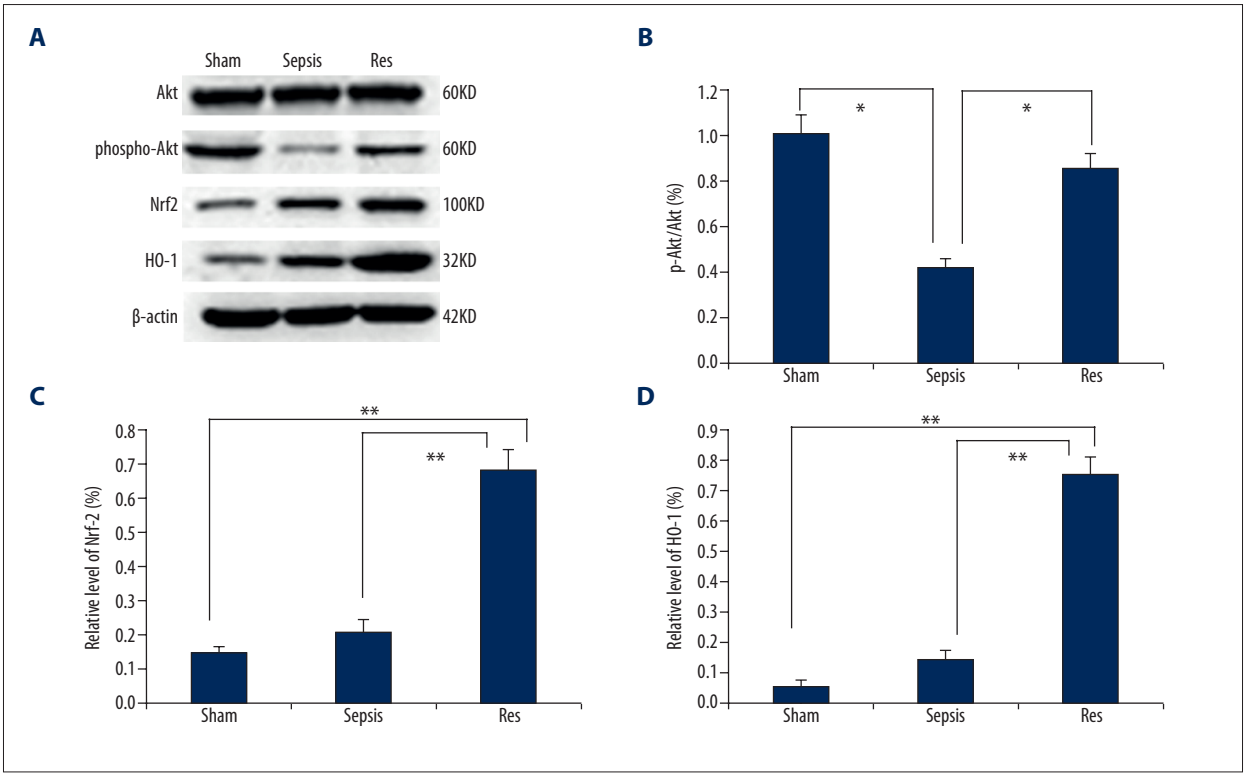

Figure 6. Resveratrol significantly upregulated HO-1 and Nrf-2 protein expression and increased Akt phosphorylation in rats with sepsis-induced acute lung injury. Data are presented as the mean ±SD (n=10 for each group). * $P \leq 0.05$, ** $P \leq 0.01$.

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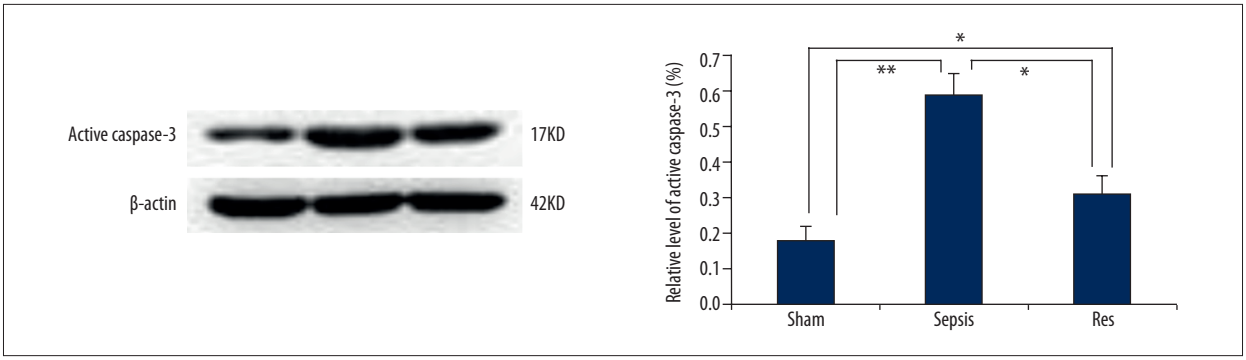

Figure 7. Resveratrol significantly decreased the expression of activated caspase-3 in rats with sepsis-induced acute lung injury. Data are presented as the mean ±SD (n=10 for each group). * $P \leq 0.05$, ** $P \leq 0.01$.

Another important biological function of IL-10 is to increase the expression of HO-1. HO-1 is the rate-limiting enzyme that catalyzes heme degradation into CO, Fe^{2+}, and bilirubin, and plays an important role in the anti-inflammatory and anti-oxidative damage responses [19]. This study found that Res could not only increase HO-1 mRNA, but also increase HO-1 protein expression. HO-1 works mainly through its metabolites. CO and bilirubin can inhibit inducible nitric oxide synthase (iNOS) expression, the generation of TNF-α in macrophages, and increase the expression of the anti-inflammatory cytokine IL-10. They also form a positive feedback loop to regulate the inflammatory response [20]. The mortality rate from sepsis of mice with a HO-1 gene deficiency is significantly higher than that of the wildtype strain during sepsis [21]. Studies have found that when sepsis occurs, inflammation of lung tissue can be reduced when the HO-1 gene is transfected into the mice with a HO-1 gene deficiency through the increased expression of HO-1 in the mouse lung endothelial cells, which could inhibit MIP-2 expression in the BALF [22]. Li et al. [23] found that puerarin could increase the expression of HO-1 in the lung tissue of mice with ALI, thus minimizing the damage to the injury organs.

LPS can activate neutrophils, monocytes/macrophages, induce the excessive release of oxygen free radicals and inflammatory factors, and promote the aggregation of inflammatory cells in tissues, such as polymorphonuclear neutrophils (PMN). A large number of PMN gather and release a mass of oxygen free radicals, which causes oxidative stress injury by lipid peroxidation and damage to protein and nucleic acids. At the same time, LPS can activate caspase-mediated apoptosis pathways and induced apoptosis and ALI during sepsis [24]. Caspase-3 directly participates in the early initiation of apoptosis, apoptosis signal transmission, and late apoptotic events. This study found that Res could reduce the amounts of MDA and 8-OhdG, increase SOD activity, and reduce the levels of activated caspase-3 in lung tissue. The data obtained from this study suggest that the mechanism of reduced ALI mediated by Res in rats with sepsis is related to the alleviation of the inflammatory and oxidative stress responses and cell apoptosis.

HO-1 is regulated by multiple mechanisms, including mitogen-activated protein kinase, protein kinase C, active oxygen, PI3 kinase (P13K), and Nrf2 [25]. P13K is a complex consisting of p85, p55, p110, and other subunits. Among them, p85α is the regulatory subunit that can activate the downstream protein kinase B after phosphorylation (that is Akt), resulting in a variety of biological effects. This study confirmed that Res induced Akt phosphorylation, suggesting that Res could activate PI3K. Another effect of activated PI3K is to activate Nrf2. In resting cells, Nrf2 is bound to its inhibitory factor Keap1 and located in the cytoplasm. Multiple exogenous stimuli can induce the degradation of Keap1, which allows Nrf2 to translocate to the nucleus where it can bind to the HO-1 promoter to induce expression [26]. Reddy et al. [27] showed that if the Nrf-2 gene was knocked out in mouse alveolar epithelial cells, the progress of ALI could be accelerated. The Nrf-2 signaling pathway is an important target for the protection of lungs from ALI. This study confirmed that Res could induce the expression of Nrf2 protein in lung tissues. Thus, the activation of Nrf2 may be the mechanism responsible for the induction of HO-1 expression by Res.

Conclusions

Our study suggests that Res has a protective effect on rats with sepsis-induced ALI. It could activate the PI3K/Nrf2 signal pathway and induce the expression of HO-1, which results in anti-inflammatory, anti-oxidative stress, and anti-apoptotic effects to alleviate lung injury. The study provides an experimental basis for the clinical treatment of sepsis by Res.

Acknowledgement

We thank all the people who helped us to carry out this work.

Conflict of interest

The authors declare that they have no conflict of interest.

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References:

1. Ornellas DS, Maron-Gutierrez T, Ornellas FM et al: Early and late effects of bone marrow-derived mononuclear cell therapy on lung and distal organs in experimental sepsis. Respir Physiol Neurobiol, 2011; 178: 304–14
2. Eisenreich A, Raueh U: PI3K inhibitors in cardiovascular disease. Cardiovasc Ther, 2011; 29: 29–36
3. Motohashi H, Yamamoto M: Nrf2-Keapl defines a physiologically important stress response mechanism. Trends Mol Med, 2004; 10: 549–57
4. Shen G, Jeong WS, Hu R, Kong AN: Regulation of Nrf2, NF-kappaB, and AP-1 signaling pathways by chemopreventive agents. Antioxid Redox Signal, 2005; 7: 1648–63
5. Cao TH, Jin SG, Fei DS et al: Artesunate protects against sepsis-induced lung injury Via Heme Oxygenase-1 Modulation. Inflammation, 2016; 39: 651–62
6. Guo R, Liu B, Wang K et al: Resveratrol ameliorates diabetic vascular inflammation and macrophage infiltration in db/db mice by inhibiting the NF-κB pathway. Diab Vasc Dis Res, 2014; 11: 92–102
7. Jang M, Cai L, Udeani GO et al: Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. Science, 1997; 275: 218–20
8. Zhang HX, Duan GL, Wang CN et al: Protective effect resveratrol of against endotoxemia-induced lung injury involves the reduction of oxidative/nitrative stress. Pulm Pharmacol Ther, 2014; 27: 150–55
9. Hao E, Lang F, Chen Y et al: Resveratrol alleviates endotoxin-induced Myocardial toxicity via the Nrf2 transcripcion factor. PLoS One, 2013; 8: e69452
10. Xu W, Lu Y, Yao J et al: Novel role of resveratrol: Suppression of high-mobility group protein box 1 nucleocytoplasmic translocation by the upregulation of sirtuin 1 in sepsis-induced liver injury. Shock, 2014; 42: 440–47
11. Rittirsch D, Huber-Lang MS, Flierl MA, Ward PA: Immunodesign of experimental sepsis by cecal ligation and puncture. Nat Protoc, 2009; 4: 31–36
12. Skrupky LP, Kerby PW, Hotchkiss RS: Advances in the management of sepsis and the understanding of key immunologic defects. Anesthesiology, 2011; 115: 1349–62
13. Wu R, Dong W, Zhou M et al: Ghrelin attenuates sepsis-induced acute lung injury and mortality in rats. Am J Respir Crit Care Med, 2007; 176: 805–13
14. Yu HP, Hwang TL, Hsieh PW, Lau YT: Role of estromgen receptor-dependent upregulation of p38 MAPK/heme oxygenase l in resveratrol mediated attenuation of intestinal injury after trauma hemorrhage. Shock, 2011; 35: 517–23
15. De Lima FM, Villaverde AB, Albertini R et al: Low-level laser therapy associated to Nacetylcysteine lowers macrophage inflammatory protein-2 (MIP-2) mRNA expression and generation of intracellular reactive oxygen species in alveolar macrophages. Photomed Laser Surg, 2010; 28: 763–771
16. Lee BH, Lee TJ, Jung JW et al: The role of keratinocyte derived chemokine in hemorrhage induced acute lung injury in mice. J Korean Med Sci, 2009; 24: 775–81
17. Kaplanski G: Interleukin-18: Biological properties and role in disease pathogenesis. Immunol Rev, 2018; 281: 138–53
18. Belperio JA, Keane MP, Lynch JP 3rd, Strieter RM: The role of cytokines during the pathogenesis of ventilator-associated and ventilator-induced lung injury. Semin Respir Crit Care Med, 2006; 27: 350–64
19. Constantin M, Choi AJ, Cloonan SM, Ryter SW: Therapeutic potential of heme oxygenase-1/carbon monoxide in lung disease. Int J Hypertens, 2012; 2012: 859235
20. Zhang FH, Sun YH, Fan KL et al: Protective ffects of heme oxygenase-1 against severe acute pancreatitis via inhibition of tumor necrosis factor-α and augmentation of interleukin-10. BMC Gastroenterol, 2017; 17: 100
21. Yeh DY, Fu YH, Yang YC, Wang JJ: Resveratrol alleviates lung ischemia and reperfusion-induced pulmonary capillary injury through modulating pulmonary mitochondrial metabolism. Transplant Proc, 2014; 46: 1131–34
22. Hashiba T, Suzuki M, Nagashima Y et al: Adenovirus- mediated transfer of heme oxygenase-1 cDNA attenuates severe lung injury induced by the influenza virus in mice. Gene Ther, 2001; 8: 1499–507
23. L i XH, Gong X, Zbang L et al: Protective effects of polydafin on septic lung injury in mice via upregulation of HO-1. Mediators Inflamm, 2013; 2013: 354087
24. Hai Y, Zhou X, Dai Q et al: Hydrogen rich saline ameliorates lung injury associated with cecal ligation and puncture induced sepsis in rats. Exp Mol Pathol, 2015; 98: 268–76
25. Lv H, Yu Z, Zheng Y et al: Isovitexin exerts anti-inflammatory and antioxidant activities on lipopolysaccharide-Induced acute lung injury by inhibiting MAPK and NF-κB and activating HO-1/Nrf2 pathways. Int J Biol Sci, 2016; 12: 72–86
26. Zhang Z, Cui W, Li G et al: Baicalein protects against 6-OHDA-induced neurotoxicity through activation of Keap1/Nrf2/HO-1 and involving PKCalpha and PI3K/AKT signaling pathways. J Agric Food Chem, 2012; 60: 8171–82
27. Reddy NM, Potteti HR, Mariani TJ et al: Conditional deletion of Nrf2 in airway epithelium exacerbates acute lung injury and impairs the resolution of inflammation. Am J Respir Cell Mol Biol, 2011; 45: 1161–68

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