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Peroxiredoxin 1 inhibits lipopolysaccharide-induced oxidative stress in lung tissue by regulating P38/JNK signaling pathway

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Abstract. – OBJECTIVE: To investigate the potential role of peroxiredoxin 1 in lipopolysaccharide (LPS) induced acute lung injury (ALI) in mice and the possible mechanism.

MATERIALS AND METHODS: Male Prdx1 knockout mice (Prdx1 (-/-)) and C57BL/6 wild-type mice with the same genetic background were used in this experiment. Primary culture of peritoneal macrophages was performed to measure the level of reactive oxygen species. The acute lung injury (ALI) model was induced by intraperitoneal injection of LPS (5 mg/kg). The mice were sacrificed at 6 h and 24 h after the treatment. The pathological changes of the lungs, wet/dry ratio and protein levels in bronchoalveolar lavage fluid (BALF) were measured. The levels of hydrogen peroxide (H_2O_2), malondialdehyde (MDA), superoxide dismutase (SOD) activity and total antioxidant capacity (TAOC) were also measured in lung tissue homogenates.

RESULTS: Our study found that the knockout of Prdx1 gene significantly increased the ROS content in mouse macrophages after LPS treatment, and the lung wet/dry ratio and BALF protein concentration were also increased, indicating the increased lung pathological damage. Prdx1 gene knockout significantly reduced the antioxidant capacity of lung tissue, increased its oxidative capacity and oxidative stress in lung. Prdx1 knockdown also significantly increased p38 mitogen-activated protein kinases (P38) and c-Jun N-terminal protein kinase (JNK) protein phosphorylation levels, leading to the activation of P38/JNK signaling pathway.

CONCLUSIONS: Prdx1 knockout can aggravate the oxidative stress and lung injury by increasing the level of Reactive Oxygen Species (ROS), and also activate P38/JNK signaling pathway. Therefore, the anti-oxidative of Prdx1 reduced LPS-induced acute lung injury in mice.

Key Words:
Peroxiredoxin 1, Lipopolysaccharide, Oxidative stress, P38/JNK, Signaling pathway.

Introduction

Oxidative stress, which is defined as the imbalance between the production of antioxidant and free radicals, is caused by the abnormal production of reactive oxygen species (ROS) in cells[1,2]. Previous studies[3] showed that oxidative stress is closely related to the innate immune system in the process of the elimination of foreign pathogens. Oxidative stress plays pivotal regulation roles in the development of a variety of human disease including Parkinson's disease, Alzheimer's disease and vascular disease[4-6]. The uncontrolled oxidative stress can usually lead to the inflammation response, vascular barrier dysfunction and damage in various tissues including lung tissue[7-9]. Acute lung injury (ALI), which is a disease bringing extremely high mortality and morbidity to the patients, can usually be induced by uncontrolled oxidative stress[10]. However, up to now, no efficient method has been developed for the treatment of ALI. So it will be with great clinical values to identify molecular targets that involved in the pathological processes of ALI to facilitate the development of new treatment method. As a component of gram-negative bacteria cell walls, LPS has been proved to be able to induce the release of ROS, which in turn cause the uncontrolled oxidative stress, leading to the occurrence of ALI. So, LPS stimulation is widely used in the studies on ALI. Peroxiredoxin 1, which is also called Prdx1, is a member of peroxiredoxin family that encodes antioxidant enzymes[11]. As an enzyme that can reduce oxidative stress, Prdx1 plays a pivotal role in many physiological processes of the body and the development of various human diseases[12,13]. It has been proved that the expression level of Prdx1 protein can be significantly increased by LPS treatment[14], indicating that Prdx1 may be involved

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in the regulation of LPS induced oxidative stress. So, it will be reasonable to hypothesize that Prdx1 may also be involved in the pathological processes of LPS-Induced lung injury.

In our work, Prdx1 knockout mice were included to investigate the potential roles of Prdx1 in ALI induced by LPS. The acute lung injury model was established by intraperitoneal injection of LPS. The pathological changes of the lungs, wet/dry (W/D) ratio and protein levels in broncho-alveolar lavage fluid (BALF) of both wild-type mice and Prdx1 knockout mice were measured before and after treatment. Also, the oxidative stress-related factors in lung tissue were detected. Our study found that ROS content in mouse macrophages, the lung W/D ratio and BALF protein concentration can all be increased by LPS treatment in both wild-type mice and Prdx1 knockout mice, while the Prdx1 knockout mice showed even higher levels of the above mentioned three indicators that those of the wild-type mice after LPS treatment. Also, Prdx1 knockdown significantly increased P38 and JNK protein phosphorylation levels, leading to the activation of P38/JNK signaling pathway. So, Prdx1 plays a positive role in the regulation of Prdx1 reduced LPS-induced acute lung injury in mice.

Materials and Methods

Primary Culture of Mice Peritoneal Macrophages

This study has been approved by the Ethics Committee of our institute. Male Prdx1 knockout mice (Prdx1 (-/-)) (29/svJ, Korea) and C57BL/6 wild-type mice (SPF grade, National Genetics Engineering Mouse Resource Library of Nanjing University, Nanjing, Jiangsu, China) with the same genetic background were used in this experiment. The mice were 8 to 12 weeks old and the weight ranged from 22 g to 28 g. All the mice were reared in sterile environment (22-24ºC, 50-60% relative humidity, 12 h light/12 h dark) with free access to food and water. Mice were sacrificed by cervical dislocation, and the skin of mice was disinfected with ethanol, about 3.5 ml BALF was extracted from abdominal wall. After centrifugation (1000 g) for 10 min at 4°C, the supernatant was discarded. The cells were counted and 5×10^5 cells were seeded in each well of the 6-weel plate and cultured with Dulbecco's Modified Eagle Medium (DMEM) (Sigma-Aldrich, St. Louis, MO, USA) supplemented with 10% fetal bovine serum (FBS), 100 U/ml penicillin and 100 U/ml streptomycin in incubator (50 ml/L CO_2, 37°C) from 2 to 3 h. The supernatant was discarded and the cells were washed 3 times with phosphate buffer solution (PBS). Unbound cells were removed and 2 ml of DMEM containing 10% FBS, 100 U/ml penicillin and 100 U/ml streptomycin was added.

Detection of ROS in Peritoneal Macrophages

The ROS level of peritoneal macrophages was measured using 2,7-dichlorofluorescein diacetic acid (DCFH-DA). Both of the two types of mouse peritoneal macrophages were divided into two subgroups: LPS treated group (1 ug/ml LPS) and control group [equal volume of phosphate buffered saline (PBS)]. The cells were treated with LPS for 6 h and 24 h respectively. After treatment, the cells were digested with 0.25% trypsin to prepare a single cell suspension. DCFH-DA was added to the final concentration of 10 μmol/L. After incubation at 37°C for 20 min, the cells were washed 3 times with phosphate-buffered saline (PBS). DCFH-DA outside the cells was removed. The fluorescence intensity of 10000 cells at excitation wavelength of 488 nm and emission wavelength of 525 nm were determined by a fluorescent microplate reader.

Establishment of Animal Model of Acute Lung Injury

Healthy mice were selected and reared for 1 week. All the mice were fasted for 12 h before the surgery. Ketamine (100 mg/kg) and chlorpromazine (2.5 mg/kg) intraperitoneal injection were performed for anesthesia; then, 5 min later, the mice were fixed in the supine position, and the skin was disinfected. Lipopolysaccharide (LPS) (5 mg/kg) or equal volume of normal saline was then injected intraperitoneally.

Animal Grouping and Specimen Collection

The experimental animals were randomly divided into 4 groups: C57BL/6 negative control group, Prdx1 (-/-) knockout negative control group (Prdx1 (-/-)), C57BL/6 + LPS group and Prdx1 (-/-) + LPS group, 16 rats in each group. Mice in the two LPS groups were injected with LPS intraperitoneally with a dose of 5 mg/kg for the induction of acute lung injury, while same volume of saline was used for the two negative control groups. Eight mice were randomly selected at 6 h and 24 h after LPS injection; the mice were sacrificed by intraperito-

neal injection of pentobarbital sodium with a dose of 50 mg/kg. BALF and lung tissues were collected for the follow-up test.

Detection of Protein in BALF

The left lung was taken and subjected to bronchoalveolar lavage with 0.5 ml saline for 4 times. The BALF was recycled and injected into test tubes followed by centrifugation (2500 r/min) for 10 min to collect the supernatant. The protein concentration in the supernatant was measured by automatic biochemical analyzer (Beckman-Coulter Co., Brea, CA, USA).

The Calculation of Lung Wet/Dry Weight Ratio (W/D)

The wet weight of the right lung tissue was measured. The tissue was then placed in 80°C oven for 48 h until the lung was completely dry. The ratio of W/D lungs was calculated to assess the degree of pulmonary edema.

Pathological Examination

Middle lobe of right lung was taken and washed with saline solution. The tissue was cut into small pieces and kept in 10% neutral formaldehyde solution for 2 h. After gradient ethanol dehydration, the tissue was embedded in paraffin and sliced into 10 intermittent slices with a thickness of about 4-5 μm. The paraffin-embedded kidney sections were put into xylene for dewaxing, followed by washing with 95%, 80%, and 70% ethanol for 5 min, respectively. Then the tissue was hydrated with tap water. After hematoxylin staining the slides were washed with tap water. The nucleus staining was observed under microscope. After treatment with ethanol containing 0.5% hydrochloric acid, the slides were washed with water followed by eosin staining and treatment with 50%, 75%, 95%, and 100% ethanol for dehydration. Xylene treatment (5 min, 2 times) was applied to make the tissue transparent. Then slides were sealed with neutral gum and microscopic observation was performed.

Detection of Oxidative Stress Indicators in Lung Tissue

The lung tissue was washed with precooled saline to remove blood, and the fluid was blotted with filter paper. About 0.2 g lung tissue was added into 1.8 ml pre-cooling 0.9% saline. After homogenization, the tissue was centrifuged at 3000 g for 10 min at 4°C. The supernatant was collected and used as 10% homogenate of lung tissue. The supernatant was stored in refrigerator at -20°C. The levels of MDA, H_2O_2, SOD and TAOC in lung tissue homogenate were measured by colorimetric enzyme kit (Nanjing Jiancheng Bioengineering Institute, Nanjing, Jiangsu, China) to reflect the oxidation and antioxidant activity of lung tissue.

The Detection of P38/JNK Pathway Related Proteins in Lung Tissue by Western Blot

The total proteins were extracted from right lung tissue according to the instructions, and the concentration of the protein was detected by bicinchoninic acid (BCA) protein quantification kit (Tiangen Biotech Co., Ltd., Beijing, China). 40 μg of each sample were added and separated by sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE), then transferred to polyvinylidene fluoride (PVDF) membrane. The primary antibody of each protein (JNK, p-JNK, p38, p-p38) (Santa Cruz, CA, USA) were added at 1:500 dilution and incubated at 4°C overnight. After washing, horse radish peroxidase (HRP)-labeled secondary antibody (1:5000) (Sigma-Aldrich, St. Louis, MO, USA) was added and incubated at room temperature for 1 h. After washing, the ECL luminescent substrate was used for color development, and the results were analyzed with a Quantity-One gel electrophoresis image analyzer. The protein expression level was normalized by the proportion to that of endogenous control (β-actin).

Statistical Analysis

Statistical analysis was performed using SPSS19.0 statistical software (SPSS Inc., Chicago, IL, USA). The data were expressed as mean ± standard deviation (SD). Multivariate analysis of variance was used to compare the differences between more than two groups. The *t*-test was used to compare the differences between two groups, $p<0.05$ was considered to be statistically significant.

Results

Effect of Prdx1 Gene Knockout on Pulmonary Function

The effect of Prdx1 knockout on the BALF protein concentration (Figure 1A) and lung W/D ratio (Figure 1B) in LPS-induced acute lung injury mice was examined. There was no signi-

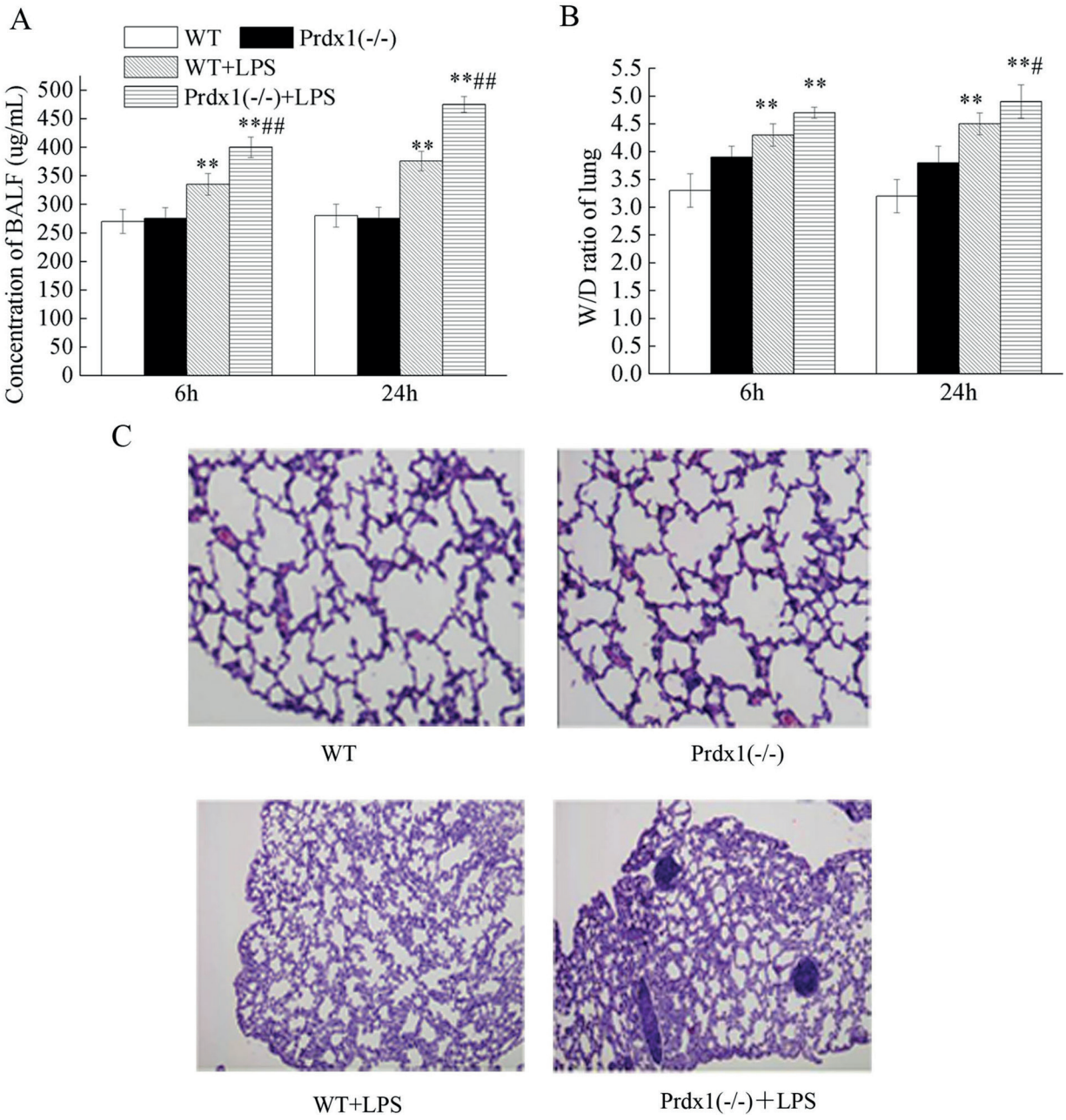

Figure 1. Effect of Prdx1 gene knockout on pulmonary function (×100). ***A,*** Effect of Prdx1 gene knockout on BALF protein concentration. ***B,.*** Effect of Prdx1 gene knockout on lung W/D; C. Effect of Prdx1 gene knockout on pulmonary pathological damage at 24 h after LPS-treated.
Notes: Compared with wild-type group, $^{*}p<0.05$, $^{**}p<0.01$; compared with wild-type +LPS group, $^{\#}p<0.05$, $^{\#\#}p<0.01$.

ficant difference in BALF protein concentration and W/D between wild-type control group and Prdx1 knockout control group at both time points (6 h and 24 h) ($p>0.05$). Compared with the control groups, LPS treatment significantly increased BALF protein concentration and W/D at both time points (6 h and 24 h) ($p<0.01$). The levels of BALF protein in LDR-treated Prdx1 knockout mice were significantly higher than those in wild-type mice after LPS treatment ($p<0.01$). No significant difference was found in W/D between wild-type mice and Prdx1 knockout mice at 6 h after LPS treatment ($p>0.05$), while the W/D in Prdx1 knockout

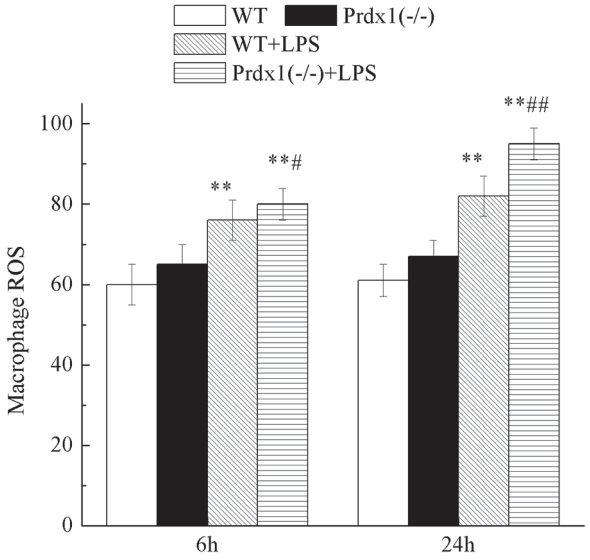

Figure 2. Effect of Prdx1 knockout on ROS level in peritoneal macrophages of mice with LPS-induced acute lung injury. Notes: Compared with wild-type group, $^{*}p<0.05$, $^{**}p<0.01$; compared with wild-type +LPS group, $^{\#}p<0.05$, $^{\#\#}p<0.01$.

mice was significantly higher than that in wild-type mice at 24 h after LPS treatment ($p<0.01$). Histopathological examination of the lung tissue at 24 h after treatment showed that the alveolar contour of the wild-type control group and Prdx1 knockout control group was clear without obvious lesions (Figure 1C). Compared with the control group, lipopolysaccharide (LPS) increased the thickness of alveolar wall. Inflammatory cell infiltration and capillary hemorrhage also occurred after treatment. The pathological damage of Prdx1 knockout mice was more severe than that of wild-type mice after LPS treatment (Figure 1C).

Effect of Prdx1 Gene Knockout on ROS Level

In this work, the ROS levels of macrophages in Prdx1 knockout mice and wild-type mice at 6 h and 24 h after LPS treatment were analyzed. No significantly difference was found in the ROS level between the macrophages of the 2 control groups at both time points (6 h and 24 h) (Figure 2). The level of ROS in macrophages was increased significantly at 6 h and 24 h after LPS treatment ($p<0.01$) and the ROS level in macrophages of Prdx1 knockout mice was significantly higher than that in macrophages of wild-type mice at both 6 h ($p<0.05$) and 24 h ($p<0.01$) after treatment (Figure 2).

Effect of Prdx1 Gene Knockout on Oxidative Stress-related Indicators

We examined the effects of Prdx1 knockout on oxidative stress indicators (MDA and H_2O_2) and antioxidant stress indicators (SOD and TAOC) in lung tissue of the mice with LPS-induced acute lung injury. There was no significant difference in the above-mentioned four indicators between wild-type control group and Prdx1 knockout control group at both time points (6 h and 24 h) ($p>0.05$) (Figure 3). Compared with the control group, the levels of MDA and H_2O_2 in lung homogenate was significantly increased by LPS treatment at both 6 h and 24 h ($p<0.01$), while the levels of SOD and TAOC were significantly decreased at both time points ($p<0.01$) (Figure 3). MDA and H_2O_2 levels were significantly higher in the Prdx1 knockout group than in the wild-type group at both time points (6 h and 24 h) after LPS treatment ($p<0.01$) (Figure 3A and 3B), while the level of TAOC was significantly lower in the Prdx1 knockout group than in the wild-type group at both time points (Figure 3D). No difference was found in SOD level between Prdx1 knockout group and wild-type group at 6 h after LPS treatment, while the level of SOD was significantly lower in the Prdx1 knockout group than in the wild-type group at 24 h after treatment (Figure 3D).

Effects of Prdx1 Gene Knockout on P38/JNK Pathway

The expression levels of p-JNK, JNK, p-p38 and p38 protein involved in P38/JNK pathway were detected by Western blot. There was no significant difference in p-JNK/JNK and p38/p-p38 ratios between wild-type control and Prdx1 knockout control at both time point (6 h and 24 h) ($p>0.05$) (Figure 4). Compared with control group, the ratios of p-JNK/JNK and p38/p-p38 in lung tissue were both significantly increased by LPS treatment at both 6 h and 24 h after treatment ($p<0.01$) (Figure 4). The ratios of p-JNK/JNK and p38/p-p38 were significantly higher in the Prdx1 knockout group than those of wild-type group at both 6 h ($p<0.05$) and 24 h ($p<0.01$) after LPS treatment (Figure 4).

Discussion

With the ability of combating oxidative stress, Prdx1 plays a pivotal role in many physiological

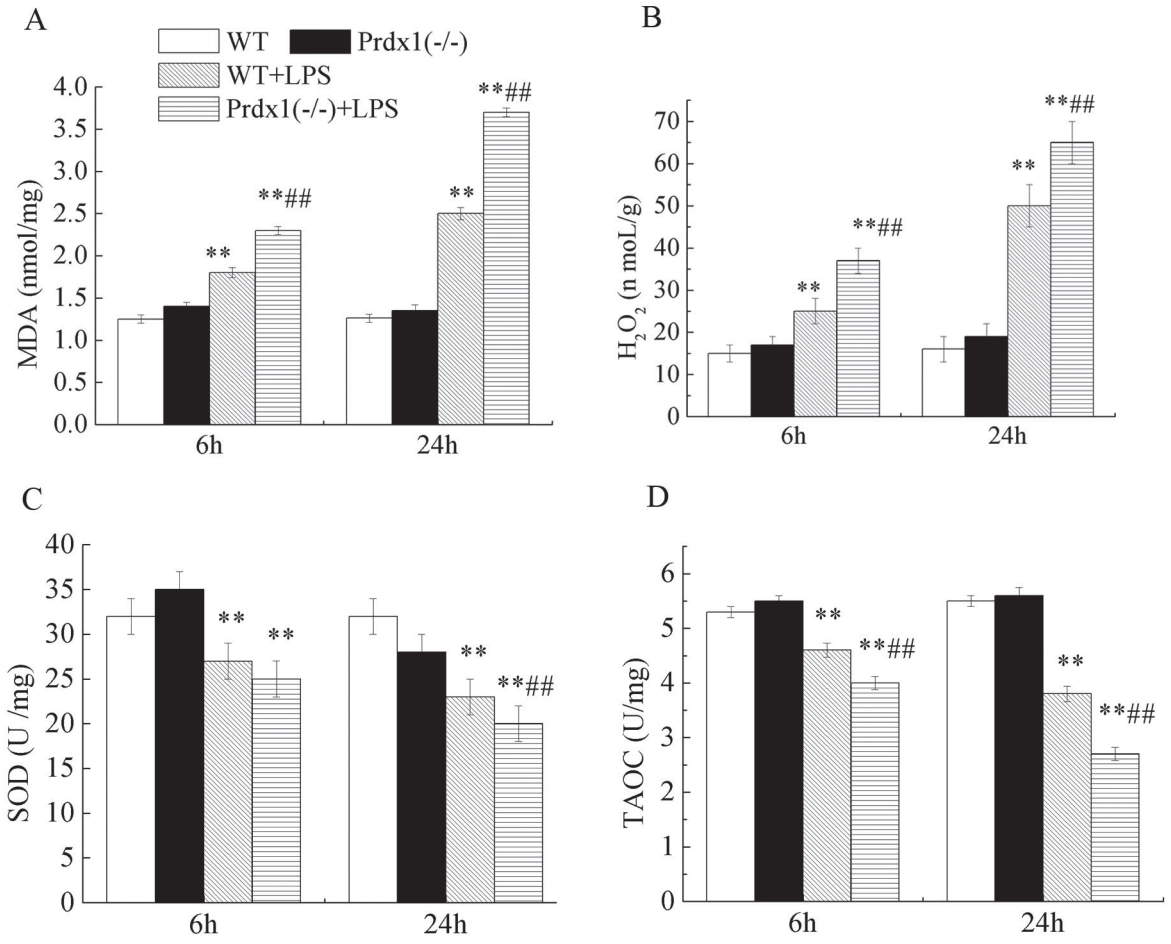

Figure 3. Effect of Prdx1 gene knockout on oxidative stress-related indicators in mice with LPS-induced acute lung injury. Notes: Compared with wild-type group, $^{*}p<0.05$, $^{**}p<0.01$; compared with wild-type +LPS group, $^{\#}p<0.05$, $^{\#\#}p<0.01$.

processes of the body and the development of various human diseases through different signaling pathways[12,13,15-17]. In our study, the important role of Prdx1 in LPS-Induced in lung injury was also identified. We found that LPS treatment significantly increased BALF protein concentration and W/D ratio of both wild-type mice and Prdx1 knockout mice. However, the Prdx1 knockout mice showed much higher increase in BALF protein concentration and W/D ratio than that of the wild-type mice after LPS treatment (Figure 1A and 1B). In addition, LPS increased the thickness of alveolar wall in both wild-type mice and Prdx1 knockout mice, and inflammatory cell infiltration and capillary hemorrhage also occurred in both of the two types of mice. However, the pathological damage of Prdx1 knockout mice was more severe than that of wild-type mice after LPS treatment. These results indicate that Prdx1 knockout can increase the permeability of alveolar epithelial cells, promote lung tissue edema, and aggravate pathological lung injury. So, Prdx1 can improve the pathological damage of lung tissue by protecting the integrity of alveolar epithelial cells and reducing the pulmonary edema. Previous reports[18,19] have shown that LPS treatment can induce the release of ROS. Consistent results were found in our study – the level of ROS in macrophages was increased significantly at 6 h and 24 h after LPS treatment ($p<0.01$). Also, the ROS level in macrophages of Prdx1 knockout mice was significantly higher than that in macrophages of wild-type mice at both 6 h ($p<0.05$) and 24 h ($p<0.01$) after treatment (Figure 2), indicating that Prdx1 protein can reduce the level of ROS cause by LPS treatment. MDA and H_2O_2 are two oxidative stress indicators, and SOD and TAOC are two-antioxidant stress indicators[20]. Those four indicators are widely used in the estimation of oxidative conditions. In our study, the levels of MDA and H_2O_2 in lung homogenate were found to be significantly increased by LPS

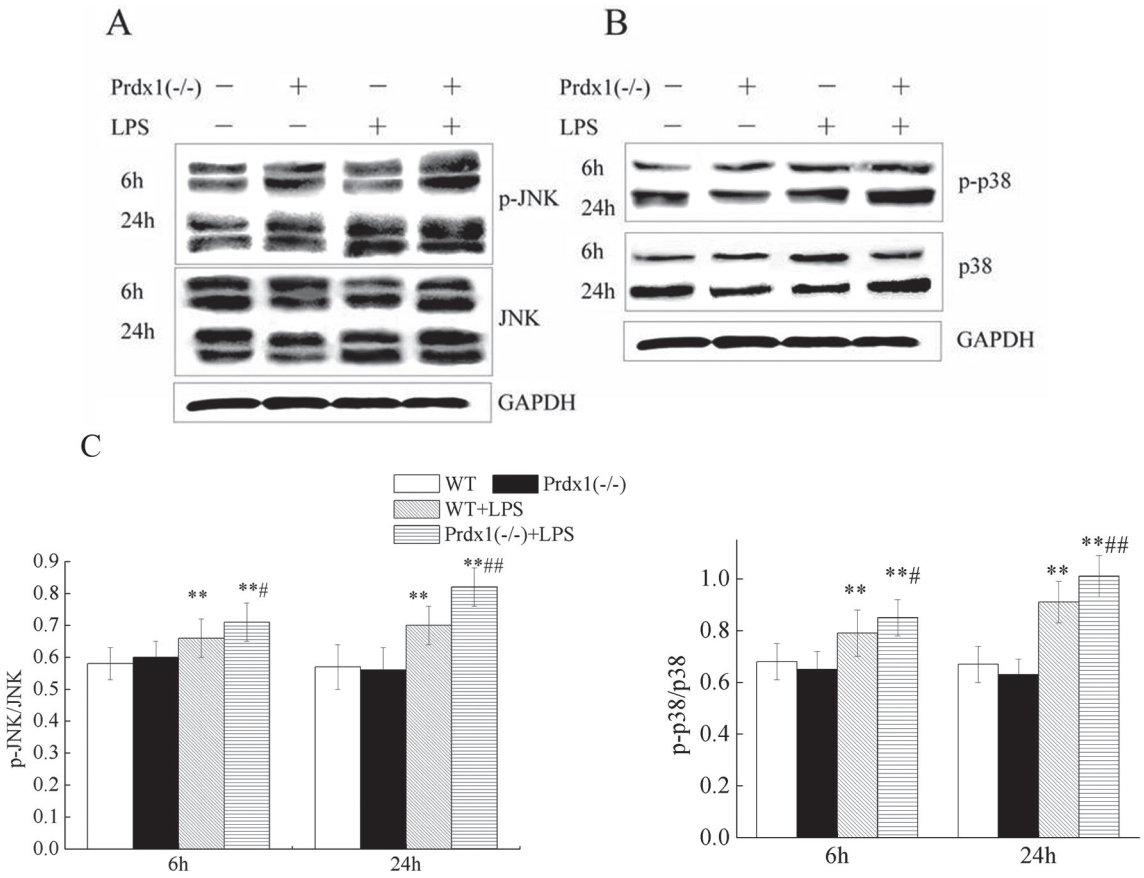

Figure 4. Effects of Prdx1 gene knockout on P38/JNK pathway. Notes: Compared with wild-type group, $^{*}p<0.05$, $^{**}p<0.01$; compared with wild-type +LPS group, $^{\#}p<0.05$, $^{\#\#}p<0.01$.

treatment ($p<0.01$), while the levels of SOD and TAOC were significantly decreased after treatment ($p<0.01$) (Figure 3). In addition, MDA and H_2O_2 levels were found to be significantly higher in Prdx1 knockout group than in the wild-type group after LPS treatment ($p<0.01$), while TAOC and SOD levels were found to be significantly lower Prdx1 knockout group than in the wild-type group at 24 h after LPS treatment ($p<0.01$). These results suggest that LPS can induce oxidative stress in lung tissue. Moreover, the knockout of Prdx1 gene may increase oxidative stress and decrease antioxidant capacity in lung tissue, which in turn aggravate oxidative stress-induced lung injury, indicating that Prdx1 plays an important role in improving the antioxidant capacity of lung tissue and protecting the lung from oxidative stress. JNK and p38, which can be activated by various stress stimuli, are two key factors in the regulation of apoptosis[21]. Previous studies[22-24] have shown that JNK and p38 can participate in chlorpyrifos-induced apoptosis the by regulating oxidative stress and the inflammatory response. In our study, the ratios of p-JNK/JNK and p38/p-p38 in lung tissue were both significantly increased by LPS treatment at both 6 h and 24 h after treatment ($p<0.01$) (Figure 4), indicating that LPS treatment can activate JNK/P38 signaling pathway. Also, the ratios of p-JNK/JNK and p-p38/p38 were significantly higher in the Prdx1 knockout group than those of wild-type group at both 6 h ($p<0.05$) and 24 h ($p<0.01$) after LPS treatment (Figure 4), indicating that Prdx1 can inhibit the activation of JNK/P38 signaling pathway caused by LPS treatment.

Conclusions

Prdx1 gene knockout increased the levels of ROS, which in turn increased oxidative stress. Prdx1 gene knock can also activate P38/JNK signaling pathway, leading to the increased LPS-induced lung injury. Therefore, the anti-oxidative effects of Prdx1 can reduce the LPS-induced acute lung injury in mice.

Conflict of interest

The authors declare no conflicts of interest.

References

1) Finkel T. Signal transduction by reactive oxygen species. J Cell Biol 2011; 194: 7-15.
2) Lushchak VI. Free radicals, reactive oxygen species, oxidative stress and its classification. Chem Biol Interact 2014; 224: 164-175.
3) Cannizzo ES, Clement CC, Sahu R, Follo C, Santambrogio L. Oxidative stress, inflamm-aging and immunosenescence. J Proteomics 2011; 74: 2313-2323.
4) Hwang O. Role of oxidative stress in Parkinson's disease. Exp Neurobiol 2013; 22: 11-17.
5) Wang X, Wang W, Li L, Perry G, Lee HG, Zhu X. Oxidative stress and mitochondrial dysfunction in Alzheimer's disease. Biochim Biophys Acta 2014; 1842: 1240-1247.
6) Drummond GR, Selemidis S, Griendling KK, Sobey CG. Combating oxidative stress in vascular disease: NADPH oxidases as therapeutic targets. Nat Rev Drug Discov 201; 10: 453-471
7) Lavie L. Oxidative stress inflammation and endothelial dysfunction in obstructive sleep apnea. Front Biosci (Elite Ed) 2012; 4: 1391-1403.
8) Lu Q, Sakhatskyy P, Grinnell K, Newton J, Ortiz M, Wang Y, Sanchez-Esteban J, Harrington EO, Rounds S. Cigarette smoke causes lung vascular barrier dysfunction via oxidative stress-mediated inhibition of RhoA and focal adhesion kinase. Am J Physiol Lung Cell Mol Physiol 2011; 301: L847-L857.
9) Kratzer E, Tian Y, Sarich N, Wu T, Meliton A, Leff A, Birukova AA. Oxidative stress contributes to lung injury and barrier dysfunction via microtubule destabilization. Am J Respir Cell Mol Biol 2012; 47: 688-697.
10) Parekh D, Dancer RC, Thickett DR. Acute lung injury. Clin Med (Lond) 2011; 11: 615-618.
11) Neumann CA, Krause DS, Carman CV, Das S, Dubey DP, Abraham JL, Bronson RT, Fujiwara Y, Orkin SH, Van Etten RA. Essential role for the peroxiredoxin Prdx1 in erythrocyte antioxidant defence and tumour suppression. Nature 2003; 424: 561-565.
12) Riddell JR, Bshara W, Moser MT, Spernyak JA, Foster BA, Gollnick SO. Peroxiredoxin 1 controls prostate cancer growth through Toll-like receptor 4-dependent regulation of tumor vasculature. Cancer Res 2011; 71: 1637-1646.
13) Watanabe A, Yoneda M, Ikeda F, Sugai A, Sato H, Kai C. Peroxiredoxin 1 is required for efficient transcription and replication of measles virus. J Virol 2011; 85: 2247-2253.
14) Mullen L, Hanschmann EM, Lillig CH, Herzenberg LA, Ghezzi P. Cysteine oxidation targets Peroxiredoxins 1 and 2 for exosomal release through a novel mechanism of redox-dependent secretion. Mol Med 2015; 21: 98-108.
15) Jarvis RM, Hughes SM, Ledgerwood EC. Peroxiredoxin 1 functions as a signal peroxidase to receive, transduce, and transmit peroxide signals in mammalian cells. Free Radic Biol Med 2012; 53: 1522-1530.
16) Watanabe A, Yoneda M, Ikeda F, Sugai A, Sato H, Kai C. Peroxiredoxin 1 is required for efficient transcription and replication of measles virus. J Virol 2011; 85: 2247-2253.
17) Kim JH, Bogner PN, Baek SH, Ramnath N, Liang P, Kim HR, Andrews C, Park YM. Up-regulation of peroxiredoxin 1 in lung cancer and its implication as a prognostic and therapeutic target. Clin Cancer Res 2008; 14: 2326-2333.
18) Hsu HY, Wen MH. Lipopolysaccharide-mediated reactive oxygen species and signal transduction in the regulation of interleukin-1 gene expression. J Biol Chem 2002; 277: 22131-22139.
19) Egler R A, Fernandes E, Rothermund K, Sereika S, de Souza-Pinto N, Jaruga P, Dizdaroglu M, Prochownik EV. Regulation of reactive oxygen species, DNA damage, and c-Myc function by peroxiredoxin 1. Oncogene, 2005; 24: 8038-8050.
20) Finkel T, Holbrook NJ. Oxidants, oxidative stress and the biology of ageing. Nature 2000; 408: 239-247.
21) Sui X, Kong N, Ye L, Han W, Zhou J, Zhang Q, He C, Pan H. p38 and JNK MAPK pathways control the balance of apoptosis and autophagy in response to chemotherapeutic agents. Cancer Lett 2014; 344: 174-179.
22) Ki YW, Park JH, Lee JE, Shin IC, Koh HC. JNK and p38 MAPK regulate oxidative stress and the inflammatory response in chlorpyrifos-induced apoptosis. Toxicol Lett 2013; 218: 235-245.
23) Zhou Y, Wu PW, Yuan XW, Li J, Shi XL. Interleukin-17A inhibits cell autophagy under starvation and promotes cell migration via TAB2/TAB3-p38 mitogen-activated protein kinase pathways in hepatocellular carcinoma. Eur Rev Med Pharmacol Sci 2016; 20: 250-263.
24) Chen XH, Ling XM, Shi S. microRNA-106a induces the proliferation and apoptosis of glioma cells through regulating JNK/MAPK pathway. Eur Rev Med Pharmacol Sci 2015; 19: 3412-3417.