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Protection of Parkin over-expression on lung in rats with exertional heat stroke by activating mitophagy

Jiaxing Wang[1†], Ran Meng[2†], Zhengzhong Sun[2†], Lyv Xuan[2], Jiao Wang[3], Yan Gu[1*] and Yuxiang Zhang[1*]

Abstract

Objective To investigate the role of Parkin overexpression-induecd mitophagy in alleviating acute lung injury of exertional heat stroke(EHS) rats.

Methods Eighty SD rats were divided into four groups: Control group (CON group), Control Parkin overexpression group (CON + Parkin group), exertional heat stroke group (EHS group), and exertional heat stroke Parkin overexpression group (EHS + Parkin group). Adeno-associated virus carrying the Parkin gene was intravenously injected into the rats to overexpress Parkin in the lung tissue. An exertional heat stroke rat model was established, and survival curves were plotted. Lung Micro-CT was performed, and lung coefficient and pulmonary microvascular permeability were measured. Enzyme-linked immunosorbent assays(ELISA) were used to determine the levels of interleukin-6(IL-6), interleukin-1β(IL-1β), Tumor necrosis factor-α(TNF-α), and reactive oxygen species(ROS). The morphology of mitochondria in type II epithelial cells of lung tissue was observed using transmission electron microscopy. The apoptosis of lung tissue, the level of mitophagy, and the co-localization of Pink1 and Parkin were determined using immunofluorescence. The expression of Pink1, Parkin, MFN2, PTEN-L, PTEN, p62, and microtubule associated protein 1 light chain 3 (LC3) in rat lung tissue was measured by western blot.

Results Compared with the CON group, there were more severe lung injury and more higher levels of IL-6, IL-1β, TNF-α in EHS rats. Both of the LC3-II/LC3-I ratio and the co-localization of LC3 and Tom20 in the lung tissue of EHS rats decreased. Compared with the EHS group, the survival rate of rats in the EHS + Parkin overexpression group was significantly increased, lung coefficient and pulmonary microvascular permeability were reduced, and pathological changes such as exudation and consolidation were significantly alleviated. The levels of IL-6, IL-1β, TNF-α, and ROS were significantly decreased; the degree of mitochondrial swelling in type II alveolar epithelial cells was reduced, and no vacuolization was observed. Lung tissue apoptosis was reduced, and the colocalization fluorescence of Pink1 and Parkin, as well as LC3 and Tom20, were increased. The expression of Parkin and LC3-II/LC3-I ratio in lung tissue were both increased, while the expression of P62, Pink1, MFN2, and PTEN-L was decreased.

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Conclusion Pink1/Parkin-mediated mitophagy dysfunction is one of the mechanisms underlying acute lung injury in rats with EHS, and activation of Parkin overexpression induced-mitophagy can alleviate acute lung injury caused by EHS.

Keywords Exertional heat stroke, Lung injury, Mitophagy, Pink1, Parkin

Introduction

Heat stroke (HS) is a heat illness associated with high temperature and humidity, and has a high rate of disability and death if not treated effectively [1]. It is divided into "classic heat stroke" and "exertional heat stroke" depending on the cause of heat [2]. Exertional heat stroke (EHS) occurs in people who work and train outdoors in summer and has a high mortality rate [3], which is characterized by a core body temperature > 40 °C and is associated with central nervous system dysfunction, which progresses to multi-organ impairment in severe cases [2]. The lung is susceptible to heat stress, which leads to acute lung injury (ALI)/or acute respiratory distress syndrome (ARDS) [4, 5].

Organ damage due to EHS is associated with mitochondrial damage [4]. Studies have confirmed that heat stroke can directly cause damage to mitochondria and activate apoptosis [6, 7]. In addition, damage to mitochondria generates large amounts of reactive oxygen species (ROS), which enhance intracellular oxidative stress and induce an inflammatory response [8]. In turn, oxidative stress and inflammatory responses further erode telomeres and damage mitochondria [9], which eventually generates systemic inflammatory response syndrome (SIRS), leading to organ failure. Therefore, effective and selective clearance of damaged mitochondria is therefore essential to maintain to the current environment of the organism [10].

Mitophagy is the process by which dysfunctional mitochondria can be recognized by specific autophagic vesicles and then selectively transported to lysosomes to complete degradation [11]. Enhancement of mitophagy facilitates the clearance of dysfunctional mitochondria and prevents excessive cellular damage.Pink1/Parkin pathway is a classical pathway that regulates mitophagy. This pathway is involved in the development of several diseases. In septic mice, Pink1 and Parkin knockout resulted in more severe intracellular mitochondrial damage and higher levels of organ failure and mortality [12–15]. However, the role of Pink1/Parkin induced-mitophagy in pulmonary injury in EHS remains unclear. Mitochondrial damage and SIRS occur in EHS owing to its pathophysiological mechanism being similar to that of sepsis. In this study, we established an EHS rat model to observe the effect of Parkin overexpression on the lung tissue and explore the role of the Pink1/Parkin pathway in EHS induced-lung injury. Our results provide a theoretical basis for the treatment of acute lung injury by EHS.

Results

Effect of Parkin overexpression on the survival rate of EHS rats

As shown in Fig. 1A, the survival rate of rats in the EHS group was about 87% (13/15) at 1 h, 53% (8/15) at 3 h, and 33% (5/15) at 5 h after heat stroke. Compared with the EHS group, the survival rates of rats in the EHS + Parkin group were significantly higher ($P < 0.05$), except for the 5th-hour survival rate. there was no difference in the survival rates of rats between CON group and CON + Parkin group.

Effect of Parkin overexpression on lung images in EHS rats

As shown in Fig. 1B, Micro-CT of rat lungs showed patchy exudate and increased lung texture in the EHS group (shown by red arrows). There was the higher CT scores of lung injury in EHS rats than that in CON rats ($P < 0.05$, Fig. 1C). In the EHS + Parkin group, the patchy exudation of both lungs was significantly decreased and the texture was slightly increased compared to the EHS group. The CT scores of injury in EHS + Parkin rats was lower than that in EHS rats ($P < 0.05$, Fig. 1C). There were no significant differences observed between the CON and CON + Parkin groups.

Effect of Parkin overexpression on lung coefficient and pulmonary vascular permeability in EHS rats

Compared with CON, the lung coefficient and pulmonary vascular permeability were significantly higher in the EHS group, and the difference was statistically significant ($P < 0.05$, Fig. 1D and E). In contrast, the lung coefficient and pulmonary vascular permeability of the rats in the EHS + Parkin group decreased significantly compared with those in the EHS group, and the difference was statistically significant ($P < 0.05$, Fig. 1D and E). There was no significant difference in the lung coefficient and pulmonary vascular permeability between the CON group with the CON + Parkin group ($P > 0.05$).

Histological pathological changes of lung in EHS rats by Parkin overexpression

The lung tissue structures of the CON and CON + Parkin groups were clear, the alveolar wall was smooth, and no fluid exudation was observed in the alveolar cavity (Fig. 1F). In the EHS group, a large number of red blood

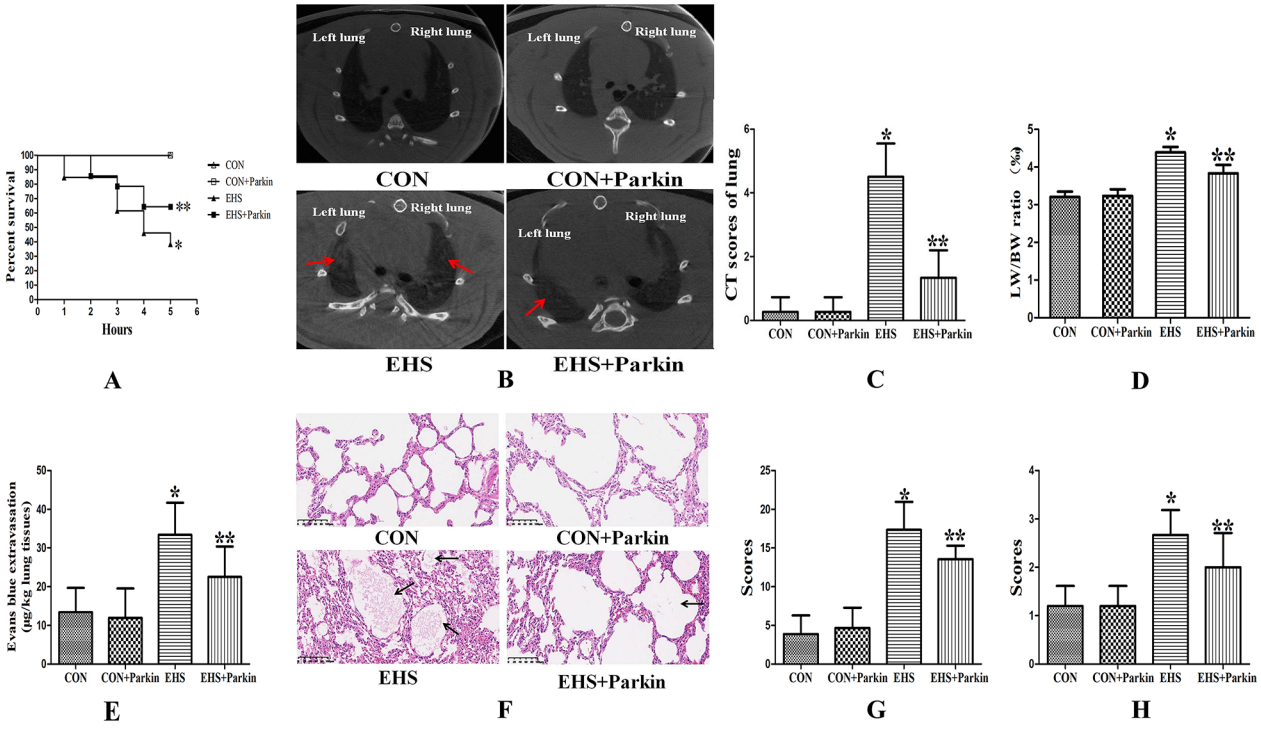

Fig. 1 The over-expression of Parkin increased the survival rate and alleviated the acute lung injury of EHS rats. **A**: The changes of the survival rate in each group. ($N=15$). **B**: Micro-CT images of rats in each group ($N=5$); Red arrow: patchy exudation. **C**: The CT scoring of rat's lung in each group ($N=5$). **D**: The changes of the lung coefficient in each group ($N=5$). **E**: The changes of the pulmonary vascular permeability of rats in each group ($N=5$). **F**: The Parkin over-expression rats resisted the HS-induced pathological changes of lung ($N=5$); Arrows indicate the exudation in the alveoli. **G**: The histologic scoring of lung injury ($N=5$). **H**: The histologic scoring of the pulmonary edema ($N=5$). *$P<0.05$ *vs.* Control group; **$P<0.05$ *vs.* EHS group

cells, inflammatory cells, and plasma-like substances were present in the alveolar cavity; and the pulmonary pathology and pulmonary edema scores increased significantly (Fig. 1F and G). Compared to the EHS group, alveolar collapse, inflammatory infiltration, pulmonary pathology score, and pulmonary edema score were significantly lower in the EHS+Parkin group (Fig. 1F and G).

Effect of Parkin overexpression on the levels of IL-6, IL-1β, TNF-α and ROS in lung tissues of rats with heat stroke

The levels of IL-6, IL-1β, TNF-α and ROS were significantly increased in the lung tissues of rats in the EHS group compared with the CON group ($P<0.05$, Fig. 2A~D), while the levels of all the above cytokines were significantly decreased in the lung tissues of rats in the EHS+Parkin group compared with the EHS group ($P<0.05$, Fig. 2A~D). There was no significant difference in the lung coefficient and pulmonary vascular permeability between the CON group with the CON+Parkin group.

Effect of Parkin overexpression on mitochondrial morphology in lung epithelial cells

The mitochondrial morphology in the lung type II epithelial cells of the CON (Fig. 3A)and CON+Parkin groups (Fig. 3B) was regular, and the mitochondrial cristae were tightly arranged and clearly visible. The mitochondria in the lung type II epithelial cells of the EHS group were swollen, the mitochondrial cristae were broken, and most of the mitochondria were vacuolated (Fig. 3C). In contrast, the mitochondria in the lung type II epithelial cells of EHS+Parkin rats were slightly enlarged, and the swelling of mitochondria was less than that in the EHS group, and the mitochondrial cristae were intact (Fig. 3D).

Effect of Parkin overexpression on apoptosis in lung tissues

Compared with the CON group, the number of apoptotic cells in the lung tissues of rats in the EHS group increased (Fig. 4A) and the apoptotic index was significantly higher ($P<0.05$, Fig. 4B). Compared with the EHS group, the apoptotic cells in the lung tissues of rats in the EHS+Parkin group were significantly reduced (Fig. 4A)and the apoptotic index was significantly lower ($P<0.05$, Fig. 4B). There was no significant difference in apoptosis between the CON group and CON+Parkin group (Fig. 4A and B).

Effect of Parkin overexpression on the mitophagy in lung tissues of EHS rats

As shown in Fig. 5A~D, the expression of Parkin protein in the lung tissues of both CON+Parkin and

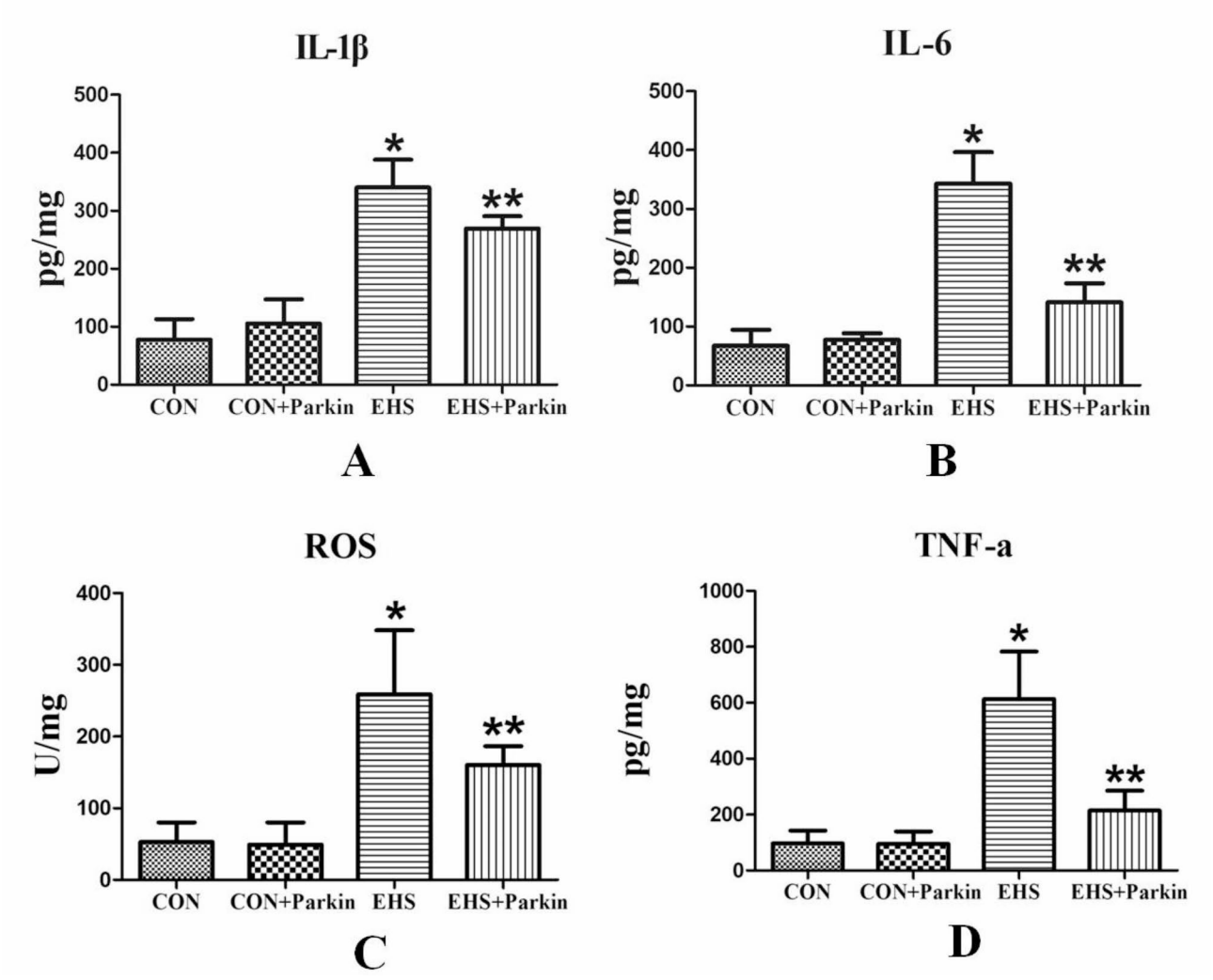

Fig. 2 The Parkin over-expression rats attenuated the levels of IL-1β、IL-6、TNF-α and ROS in the lung tissues of the EHS rats ($N=5$). **A**: IL-1β; **B**: IL-6; **C**: ROS; **D**: TNF-α. *$P<0.05$ *vs.* Control group; **$P<0.05$ *vs.* EHS group

EHS+Parkin groups rats was significantly increased after the injection of adeno-associated virus carrying Parkin gene by tail vein. Compared with the CON group, the expression of Parkin was increased in the lung tissues of the EHS group ($P<0.05$), the autophagy level marker LC3-II/LC3-I ratio was significantly lower ($P<0.05$), and the expression of P62 was increased ($P<0.05$). Compared with the EHS group, the LC3-II/LC3-I ratio was increased ($P<0.05$) and P62 expression was decreased ($P<0.05$) in the lung tissues of EHS+Parkin rats.

Immunofluorescence results (Fig. 5E) showed that the LC3 fluorescence intensity (green fluorescence) and the co-localization of LC3 with Tom20 (red fluorescence) in lung tissues of rats in the EHS group rats was reduced (orange fluorescence) compared with that in the CON group; the LC3 fluorescence intensity (green fluorescence) was significantly enhanced in lung tissues of rats in the EHS+Parkin group compared with that in the EHS group, and the co-localization of LC3 with Tom20 was also significantly enhanced. The LC3-II/LC3-I ratio was slightly increased in the lung tissues of the rats in the CON+Parkin group compared with the CON group, while the expression of P62 was not significantly different, and the LC3 fluorescence intensity (green fluorescence) and LC3 co-localization with Tom20 (orange fluorescence) were also enhanced in the lung tissues of the rats in the CON+Parkin group.

Parkin overexpression activated the Pink1/Parkin pathway in lung tissues of EHS rats

Western results (Fig. 6A~D) showed that the expression of Pink1, MFN2, and PTEN-L in the lung tissues of rats in the EHS group were significantly increased compared with the CON group. Compared with the EHS group, the expression of Pink1, MFN2 and PTEN-L in the EHS+Parkin group decreased ($P<0.05$). In contrast,

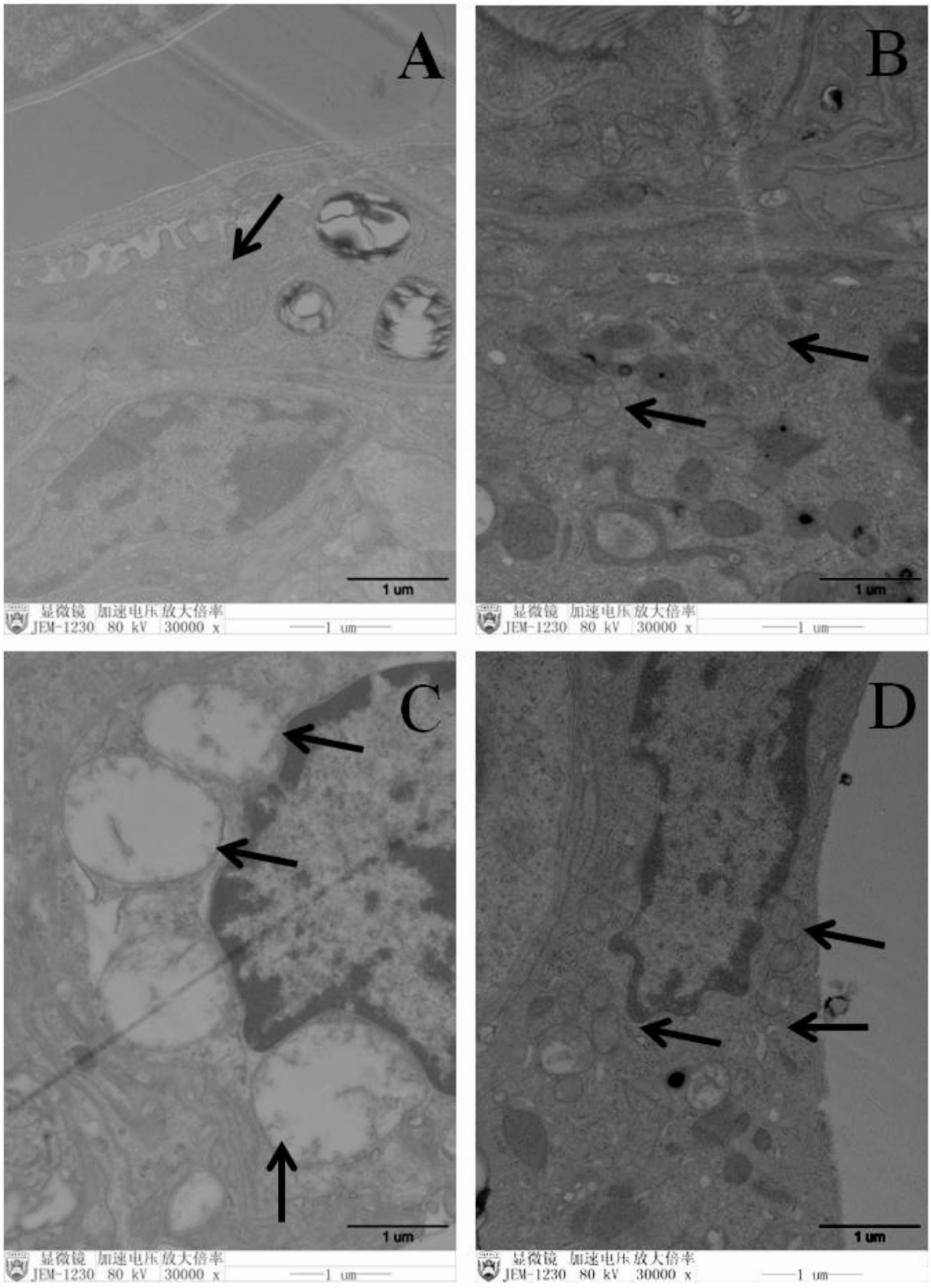

Fig. 3 Pulmonary mitochondrial injury was attenuated to a greater extent morphologically in the EHS + Parkin group rats. **A**: CON group; **B**: CON + Parkin group; **C**: EHS group; **D**: EHS + Parkin group. Arrows indicates the mitochondrion

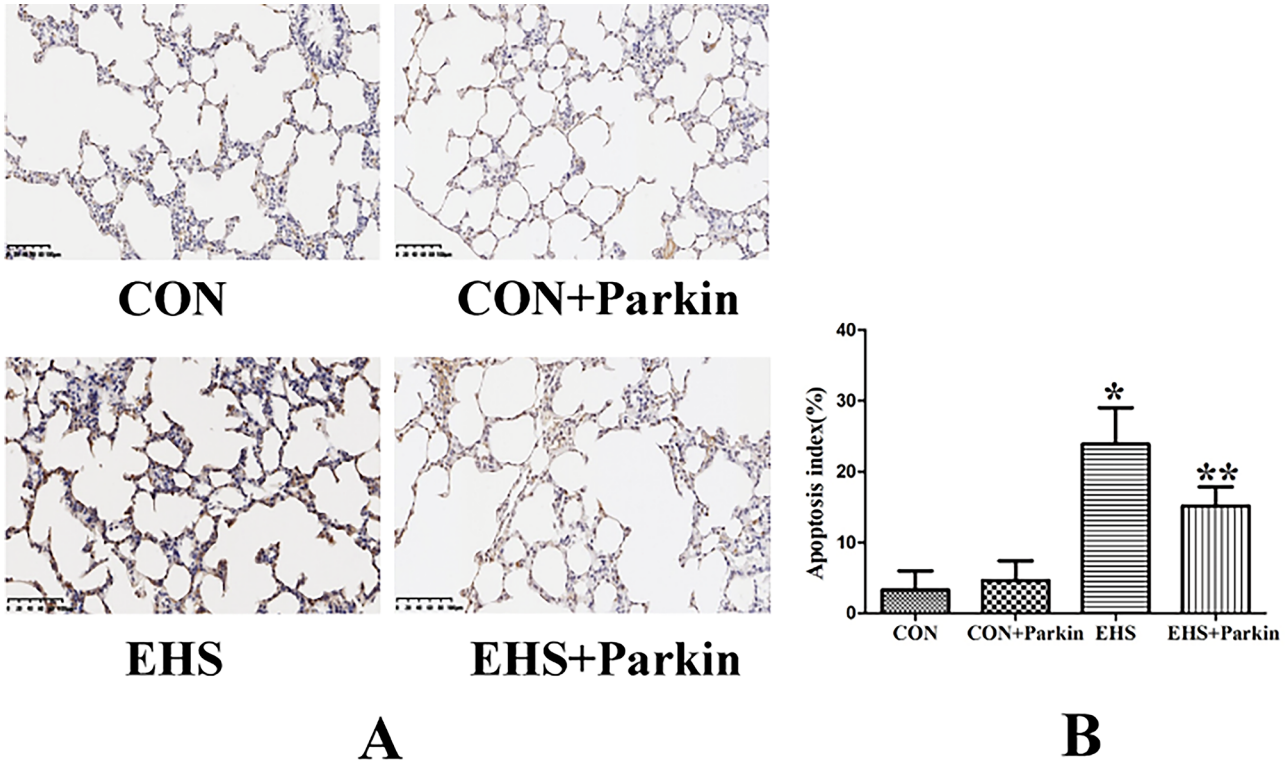

Fig. 4 Pulmonary apoptosis was attenuated to a greater extent in the EHS + Parkin group rats. ($N = 5$) **A**: The effect of Parkin overexpression on apoptosis in lung tissue. Apoptotic cells are stained brown, whereas normal cells are stained blue. **B**: Apoptosis index. *$P<0.05$ *vs.* Control group; **$P<0.05$ *vs.* EHS group

there was no difference in the expression of Pink1, MFN2 and PTEN-L in the CON+Parkin group compared with the CON group ($P>0.05$). There was also no significant difference in the expression of PTEN in the lung tissue of rats in each group ($P>0.05$)(Figure 6E).

Immunofluorescence results (Fig. 6F) showed that the intensity of Parkin fluorescence was significantly enhanced (red fluorescence) in the lung tissues of rats in both CON+Parkin and EHS+Parkin groups after tail vein injection of adeno-associated virus carrying Parkin gene. The intensity of Pink1 (green fluorescence) and Parkin (red fluorescence) co-localized in lung tissues of the EHS rats was reduced (orange fluorescence) compared with that in the CON group, whereas the intensity of Pink1 (green fluorescence) and Parkin (red fluorescence) co-localized in lung tissues of rats in the EHS+Parkin group was significantly enhanced compared with that in the EHS group. The intensity of Pink1 (green fluorescence) and Parkin (red fluorescence) co-localization fluorescence (orange fluorescence) in lung tissue of rats in the CON+Parkin group was slightly enhanced compared with the CON group.

Discussion

Exertional heat stroke is a fatal disease caused by thermal injury to the body which is characterized by multiple organ failure. ALI or ARDS are one of the common complications induced by EHS [16]. We established a rat model of EHS and found that the core body temperature of EHS rats increased sharply. Pulmonary pathological changes occurred in EHS rats, characterized by progressive interstitial vascular dilatation and hyperemia, massive alveolar hemorrhage, and blurred alveolar structure. Besides, there was an increase in the lung coefficient and pulmonary vascular permeability in EHS rats, as well as a large number of apoptotic cells. These results are consistent with those of the previous studies [5, 9, 17].

The mechanism underlying lung injury caused by EHS remains unclear. At present, direct heat stress and secondary systemic inflammation are believed to be the pathophysiological bases of this disease [18]. Endotoxins and inflammatory cytokines have been detected during ARDS caused by HS. The inflammatory cell infiltration and alveolar macrophages increased simultaneously, indicating that there was an obvious inflammatory reaction in the lungs of patients with EHS [5]. Our study showed that the levels of IL-6, IL-1β, and TNF-α significantly increased in EHS rats, confirming that EHS

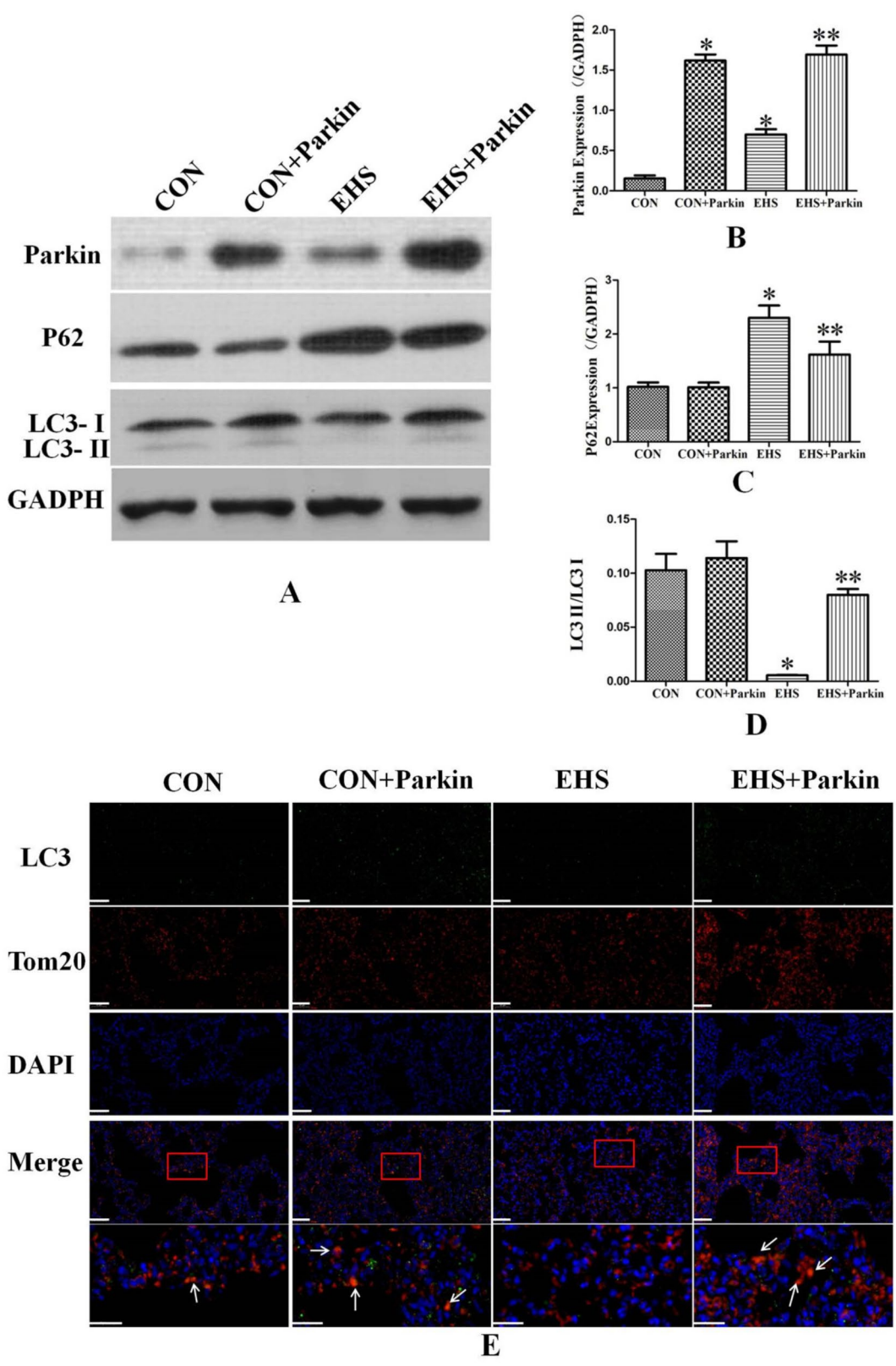

Fig. 5 Parkin over-expression exhibited the increasing mitophagy in lung tissues of EHS rats ($N=5$). **A**: The protein levels of Parkin、P62 and LC3 in lung tissues were performed by western-blot. **B~D**: The statistical analysis of Parkin、P62 expression and LC3-I/LC3-II ratio. *$P<0.05$ *vs.* Control group; **$P<0.05$ *vs.* EHS group. **E**: Immunofluorescence staining against LC3 and Tom 20 was performed and observed by fluorescent microscopy. LC3 (green), Tom20 (red), The colocalization (orange) of LC3 and Tom20 was showed by white arrow, bar = 50 μm

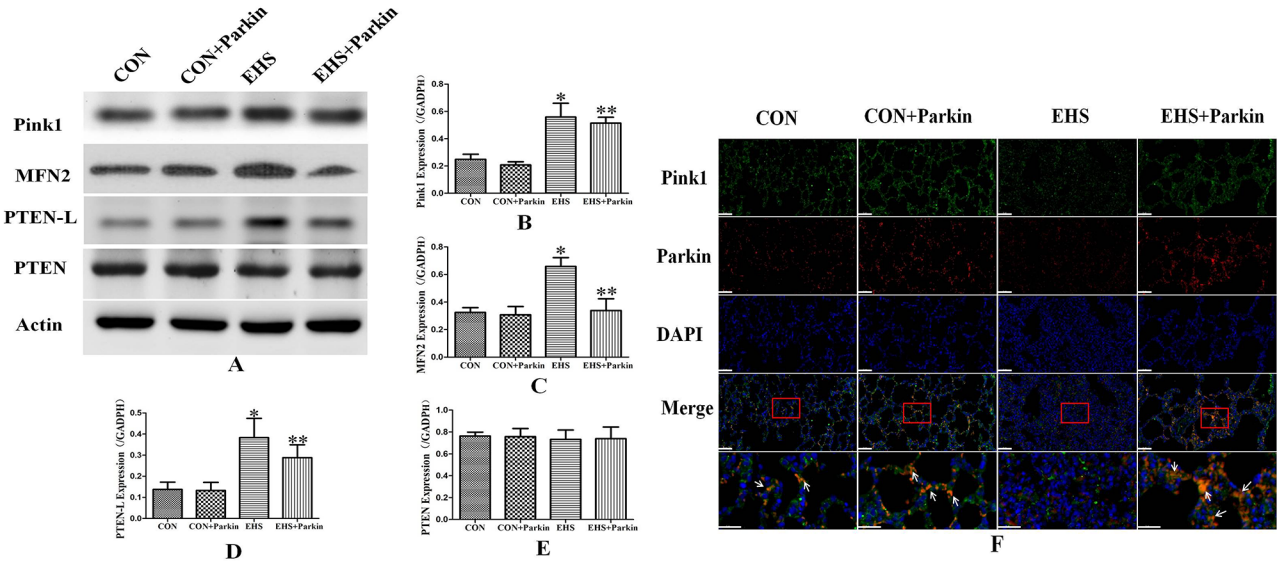

Fig. 6 Parkin over-expression activated the Pink1/Parkin pathway in lung tissues of EHS rats ($N=5$). **A**: The protein levels of Pink1、MFN2、PTEN-L and PTEN in lung tissues were performed by western-blot. **B~E**: The statistical analysis of Pink1、MFN2、PTEN-L and PTEN expression. *$P<0.05$ *vs.* Control group; **$P<0.05$ *vs.* EHS group. **F**: Immunofluorescence staining against Pink1 and Parkin was performed and observed by fluorescent microscopy. Pink (green), Parkin (red), The colocalization (orange) of Pink1 and Parkin was showed by white arrow, bar = 50 μm

cause activation of inflammatory response in lung tissue. Therefore, the cascade amplification of immune cells and inflammatory factors can induce an inflammatory storm, leading to more serious organ and tissue damage.

Oxidative stress plays an important role in the organ dysfunction induced by EHS. Our results suggest that the level of ROS in the lungs of EHS rats significantly increased, further verifing that EHS can lead to excessive activation of oxidative stress in lung tissue.

Mitochondrial dysfunction leads to increased intracellular oxidative stress and ROS expression [19]. Transmission electron microscopy revealed that the mitochondria in type II lung epithelial cells of EHS rats were swollen, the mitochondrial cristae were broken, and most of the mitochondria were vacuolated, confirming that the mitochondria in lung were seriously damaged by EHS. Mitochondrial damage triggers oxidative stress responses, and the enhancement of oxidative stress lead to the production of ROS, which in turn aggravates mitochondrial damage. This forms a vicious circle, causing a "waterfall" inflammatory reaction, apoptosis, and necrosis of cells, finally progressing to organ failure [20]. Therefore, the effectively removal of damaged mitochondria plays a vitial role in protecting organ function.

Mitophagy is an important regulatory mechanism that maintains the balance of mitochondrial quantity and quality and preserves the dynamic balance of the intracellular mitochondrial network [11]. Mutations in mitochondrial genes, high intracellular ROS levels, and the chemical factor antimycin may lead to mitochondrial damage and induce a mitophagy cascade response [21]. Enhanced mitophagy can clear up the damaged mitochondria, reduce ROS production, reduce oxidative stress response, and alleviate lung injury [20, 21]. Our study showed that a decrease in the ratio of LC3-II/LC3-I (a marker of autophagy), an increase in the expression of p62 and a reduction in LC3 binding to mitochondria in the lung tissues of EHS rats, suggesting that inhibition of mitophagy by EHS may be one of the mechanisms leading to an inflammatory response and cell injury in lung tissue.

Pink1/Parkin pathway is a classical pathway of mitophagy. Under the stress of ROS, nutrient deficiency, cell aging and other effects, the mitochondria in cells will show depolarization of outer mitochondrial membrane (OMM). Pink1 accumulates specifically at the OMM of dysfunctional mitochondria, and recruit Parkin from the cytosol to damaged mitochondria [22]. Activated Parkin polyubiquitinates numerous substrates of OMM proteins, leading to the formation of autophagosomes including the Ub- and LC3-binding receptor SQSTM1/p62 [23]. Autophagosomes wrap the damaged mitochondria under the guidance of LC3 junction proteins, leading to mitophagy [24]. Our study showed that although EHS increased the expression of Pink1 and Parkin proteins in rat lung tissue, the binding degree between them decreased, suggesting that the inhibition of mitophagy by EHS was related to the blocking of interaction between Pink1 and Parkin. EHS inhibits the activation of the Pink1/Parkin pathway, resulting in a decrease in the production of mitochondrial autophagosomes in the lung tissue. The dysfunction of mitochondrial autophagy

further hinders the degradation of Pink1, Parkin, and MFN2 which accumulate in the lung tissue [25].

PTEN-L is a protein phosphatase that inhibits phosphorylation of ubiquitin Ser65-Ub by Pink1. Ser65-Ub phosphorylation is a key step in the Pink1-mediated translocation of Parkin to damaged mitochondria and the activation of Parkin E3 ubiquitin ligase. Increased expression of PTEN-L can prevent the translocation of Parkin to the mitochondria, inhibit the E3 ubiquitin ligase activity of Parkin, and prevent Parkin-induced mitophagy [26]. Our study found that the expression of PTEN-L in the lung tissue of rats with EHS was increased; however, PTEN levels did not change. As a negative regulator of the Pink1/Parkin pathway, upregulation of PTEN-L can weaken the interaction between Pink1 and Parkin, leading to inhibit the activation of mitophagy. This may explain why mitochondrial autophagy levels decreased, although EHS induced the increased expression of Pink1 and Parkin in lung tissues.

Studies have shown that activating the Pink1/Parkin pathway has a protective effect against lung, kidney, and liver injury caused by sepsis [13, 27, 28]. In our study, we found that the survival rate of EHS rats overexpressing Parkin significantly improved; the lung injury and the pulmonary vascular permeability were alleviated; the apoptosis significantly decreased. The levels of ROS and inflammatory factors (IL-6, IL-1β, and TNF-α)decreased significantly. The morphology of mitochondria was maintained. Immunohistochemistry and immunofluorescence showed that Parkin overexpression significantly enhanced the interaction between Pink1 and Parkin, increased the binding of LC3 to mitochondria and autophagy levels in lung tissues of EHS rats. These results suggest that Parkin overexpression can activate the Pink1/Parkin pathway, which partially counteract the EHS induced-inhibition of the Pink1/Parkin pathway by PTEN-L. Parkin overexpression in EHS rats' lung enhances mitophagy to clear up the damaged mitochondria and maintains the effectiveness of mitochondrial function and cell homeostasis to reduce inflammatory reactions and oxidative stress overactivation, reduces cell and acute lung injury, and improves the prognosis of EHS rats. In addition, Parkin overexpression reduced the excessive accumulation of Pink1 and MFN2 in the lung tissue by enhancing mitophagy. Therefore, the activation of the Pink1/Parkin pathway and enhancement of mitophagy have protective effects against lung injury caused by EHS.

A limitation of this study may be that the Pink1/Parkin pathway is only one of the pathway that affects mitophagy. Proteins on the mitochondrial membrane, such as NIP3-like protein X, can also be involved in Parkin-dependent mitophagy [29]. FUN14 domain-containing protein 1 receptor and Bcl-2-like protein 13 induce mitophagy in a Parkin-independent manner [15, 26]. Whether these mitochondrial pathways above are involved in the pathogenesis of lung injury during EHS requires further investigation.

In summary, this study demonstrated that Inhibition of mitophagy in the lung tissue is one of the mechanisms of EHS-induced lung injury. Parkin over-expression can alleviate the acute lung injury by activating Pink1/Parkin-mediated mitophagy.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-024-03222-3.

Supplementary Material 1

Supplementary Material 2

Author contributions

Guarantor of integrity of the entire study: Jiaxing Wang, Yuxiang Zhangstudy concepts: Ran Meng, Yan Gustudy design: Jiaxing Wang, Yuxiang Zhang, Ran Meng, Yan Gudefinition of intellectual content: Jiaxing Wang, Yuxiang Zhang, Zhengzhong Sun, Ran Mengexperimental studies: Jiaxing Wang, Yuxiang Zhang, Ran Meng, Zhengzhong Sun, Lyv Xuandata acquisition: Jiao Wangstatistical analysis: Jiaxing Wang, Zhengzhong Sun, Ran Mengmanuscript preparation: Jiaxing Wang, Zhengzhong Sun, Ran Mengmanuscript editing: Jiaxing Wang, Zhengzhong Sun, Ran Mengmanuscript review: Yuxiang Zhang, Yan GuAll authors have read and approved this article.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethical approval

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guides on the care and use of laboratory animals and has been approved by the Ethics Committee of the Eighth Medical Center of Chinese PLA General Hospital (approval number: 20208141030). This study is reported in accordance with ARRIVE guidelines.

Conflict of interest

None.

Competing interests

The authors declare no competing interests.

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