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Tetramethylpyrazine Showed Therapeutic Effects on Sepsis-Induced Acute Lung Injury in Rats by Inhibiting Endoplasmic Reticulum Stress Protein Kinase RNA-Like Endoplasmic Reticulum Kinase (PERK) Signaling-Induced Apoptosis of Pulmonary Microvascular Endothelial Cells

Authors' Contribution:
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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Acute lung injury (ALI) is a life-threatening complication of sepsis. Tetramethylpyrazine (TMP) has been used in the clinical treatment of vascular diseases. The aim of this study was to investigate the therapeutic effects and possible involved mechanisms on ALI.

Material/Methods: Cecal ligation and puncture (CLP) was used to establish a sepsis model in rats. TMP at various dosages were administrated to rats using a intragastric method. Animal survival rate was calculated. The lung functions were evaluated by lung weight/dry weight ratio (W/D), PaO_2, dynamic compliance (DC), and airway resistance index (ARI). Pulmonary microvascular endothelial cells (PMVECs) were isolated from lungs harvested from rats with sepsis. TUNEL assay was used to detect apoptosis. Protein expression and phosphorylation levels were assessed by western blotting.

Results: TMP administration increased the survival rate of septic rats. TMP also decreased W/D and DC, but increased PaO_2 and ARI in septic rats. Moreover, PMVECs apoptosis was inhibited in septic rats that received TMP treatment. The expression levels of GRP78, ATF4, caspase-12, active caspase-3, as well as the phosphorylation levels of PERK and eIF2α were suppressed in PMVECs isolated from TMP-treated septic rats.

Conclusions: TMP alleviated sepsis-induced ALI by suppressing PMVECs apoptosis via PERK/eIF2α/ATF4/CHOP apoptotic signaling in endoplasmic reticulum stress.

MeSH Keywords: Apoptosis • Capillary Permeability • Sepsis • Severe Acute Respiratory Syndrome

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Background

Caused by bacterial infection-induced activation of inflammatory cascade, sepsis is one of the most common reasons leading to death in the intensive care unit (ICU) [1]. According to previous reports, the mortality rate for severe sepsis is as high as approximately 20–30%. It is accepted that sepsis-induced acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are the underlining cause of the high mortality [2]. ALI and ARDS were identified in half of the cases and responsible for 30% of the total mortality of the patients with sepsis [3]. Respiratory failure is the characteristic clinical manifestation of ALI and ARDS, usually causing hypoxia and subsequent circulatory failure. Microcirculation includes certain small arteries and veins which are immediately adjacent to capillaries, forming the pre- and post-capillary units [4]. Microvascular endothelium takes up most of the area of the pulmonary vascular branch tree. Sepsis-associated microvascular endothelial integrity impairment increases the pulmonary vascular permeability which leads to both structural and functional dysfunctions and destructions [5]. Apoptosis of pulmonary microvascular endothelial cells (PMVECs) induces the dysfunction of microvascular endothelium which is associated with lung parenchyma and interstitial edema [6].

Endoplasmic reticulum (ER) is an important organelle, executing fundamental cellular functions such as protein folding, protein post-translational modification, protein maturation, calcium metabolism, and lipid synthesis. When ER is challenged by harmful stimuli, the unfolded protein response (UPR) is triggered. UPR is considered a protective mechanism which shuts down transcription of most functional proteins and initiates several responding proteins facilitating the processing and eliminating of unfolded and mis-folded portions [7]. However, if UPR is sustained and prolonged, the basic function of ER might not be restored, and ER stress (ERS) would resulted [8]. ERS is an established pro-apoptotic pathway leading to cell death. The apoptotic signaling is conducted by 3 ERS resident proteins such as protein kinase RNA (PKR)-like ER kinase (PERK) [9]. It has been reported that ERS is highly activated during sepsis [10]. Moreover, the association of ERS and ALI has also been reported [11]. However, the role of ERS-induced microvascular endothelial apoptosis in ALI has been rarely investigated in previous studies.

Tetramethylpyrazine (TMP) is one of the bioactive alkaloid components extracted from the Chinese Medical herb *Ligusticum chuanxiong* which has been used in clinical treatment of vascular diseases and inflammatory diseases for decades in Traditional Chinese Medicine [12]. There is a wide spectrum of biological activities of TMP, such as anti-inflammatory, anti-apoptotic, and anti-oxidative effects [13]. Previous investigations have indicated that TMP is potent in inhibiting apoptosis by modulating multiple pathways [14]. However, very few studies investigated the effects of TMP on ERS-induced apoptosis. In the current study, the sepsis-induced ALI animal model was created by the cecal ligation and puncture (CLP) approach. Therapeutic effect of TMP on the ALI animals was investigated. Moreover, the involvement of ERS-induced microvascular endothelial apoptosis was studied. We believe that results from this study could not only deepen our understanding of sepsis-induced ALI, but also provide new information concerning the pharmacological mechanisms of TMP.

Material and Methods

Agents and antibodies

Agents and antibodies used in this study included: TMP (Sigma-Aldrich), RPMI1640 medium (Gibco), bovine serum (Gibco), L-glutamine (Sigma-Aldrich), heparin (Sigma-Aldrich), penicillin and streptomycin mix (Invitrogen), proteinase K (Sigma-Aldrich), TUNEL assay kit (Roche), DAPI (Invitrogen), Cell Lysis Buffer system (Santa Cruz), PMSF (Santa Cruz), Cytoplasmic Extraction kit (Beyotime), BCA kit (Pierce), GRP78 (Abcam), PERK (Cell Signaling Tech), phosphorylated PERK (p-PERK, Cell Signaling Tech), eIF2α (Cell Signaling Tech), phosphorylated eIF2α (p-eIF2α), ATF4 (Abcam), CHOP (Abcam), caspase-12 (Abcam), activated caspase-3 (Abcam), GAPDH (Cell Signaling Tech), HRP-conjugated secondary antibodies (Abcam, Cell Signaling Tech), and ECL kit (Pierce).

Animals and modeling

Sprague Dawley (SD) rats were purchased from School of Medicine, Zhejiang University. Animal experiments protocols were approved by Animal Ethics Committee of Zhejiang Cancer Hospital. All animal experiments were carried out according to Recommended Guideline for the Care and Use of Laboratory Animals issued by Chinese Council on Animal Research. Rats were raised in polypropylene cages in an artificial environment providing constant temperature at (25±3°C), humidity at 50% and a 12-hour light/dark circle. All rats had free access to distilled water and standard chow. The CLP procedure was performed in accordance with previous descriptions [3]. Briefly, rats were anesthetized by isoflurane inhalation (0.6 l/min). Operation area was sterilized, and a 3 cm abdominal incision was made to expose the cecum. Operating suture was used to make a ligation between the terminal and ileocecal valve. Then the central segment of the ligation was punctured by an 18-gauge needle. Cecal contents were squeezed out of the ligation through the punctured tissue. Then the cecum was restored in the abdominal cavity which was then closed. Animals received TMP via intragastric administration at various dosages (0, 20, 40 and 60 mg/kg bodyweight) after the

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CLP procedure, for 14 consecutive days. The survival rate was calculated 14 days after the CLP procedure. Rats were divided randomly and equally into 5 groups (15 rats were assigned to each group). Control rats received intragastric administration of physiological saline for 14 days without a CLP procedure. Septic rats received the CLP procedure and intragastric administration of physiological saline for 14 days. Treatment rats received the CLP procedure and intragastric administrations of TMP at dosages of 0, 20, 40, and 60 mg/kg bodyweight after CLP procedure for 14 consecutive days. Dosages of TMP were decided according to our pre-experiments and previous descriptions [15].

Lung function assessments

In this study, the lung functions were assessed by PaO_2, lung edema, and plethysmographic parameter. Fourteen days after the CLP procedure, rats were anesthetized by isoflurane inhalation. The trachea was exposed after a small neck incision was made. A cannula was inserted into the trachea and then connected to a ventilator (Physiosuite Physiological Monitoring System, Kent Scientific). The airway was challenged with aerosolized methacholine-PBS. Dynamic compliance (DC) and airway resistance index (RI) were measured by analyzing the flow wave curves. Arterial blood samples were harvested from the aorta. PaO_2 was measured by automatic blood gas analyzer (Cobas b 123, Roche). The right lung was harvested and weighed (wet weight). Then the dry weight was obtained after lung tissue was dried at 70°C for 48 hours. The wet/dry weight ratio (W/D) was calculated to evaluate the lung edema.

PMVECs isolation

The PMVECs were isolated from harvested lung tissue according to the protocol described previously [16]. Briefly, harvested lung was washed to remove blood. Lung tissue beneath the pleura was collected and minced into 1.5×1×1 mm small slices which were then cultured in gelatin-coated dishes. These slices were cultured with RPMI1640 medium containing 20% bovine serum, 4 mmol/L L-glutamine, 90 U/mL heparin, 100 U/ml penicillin and 0.1 mg/mL streptomycin in a cell incubator providing 95% fresh air and 5% CO_2 at 37°C for 60 hours. After that, the lung tissue slices were removed. The resulted adherent cells were considered PMVECs.

Cell apoptosis detection

The apoptosis of isolated PMVECs was detected by terminal transferase UTP nick end labeling (TUNEL) assay. PMVECs were treated with 20 μmol/L proteinase K. Cells were fixed by iced acetone. Then a TUNEL assay kit was applied to the cells according to the instruction of the manufacturer. After that, DAPI was used to tag the nuclei. Cells were then observed with an inverted fluorescence microscope. TUNEL-positive cells were tagged green fluorescence.

Western blotting

The PMVECs were subjected to Cell Lysis Buffer system supplemented with PMSF. Protein was extracted by using Cytoplasmic Extraction kit according to the manufacturer's instructions. The protein concentration was determined with a BCA kit. Protein samples were subjected to SDS-PAGE. The separated proteins were then transferred electronically to PVDF membranes. The unspecific bonding was eliminated by incubating the membranes with blocking buffer (Pierce). Primary antibodies against GRP78, PERK, phosphorylated PERK, eIF2α, phosphorylated eIF2α, ATF4, CHOP, caspase-12, activated caspase-3, and GAPDH were used to incubate the membranes at 4°C for 10 hours. After washing with TBST, the membranes were incubated with HRP-conjugated secondary antibodies. An ECL kit was used to develop the membranes. The images of immunoblots were acquired with Gene Genius (Syngene) and then analyzed by software ImageJ (version 1.28, NIH).

Statistics

Data in the current was expressed in a (mean ±SD) manner. Data was processed by using software SPSS (version 16.0, SPSS). Kaplan-Meier analysis along with log-rank tests was used to analyze the survival rates among groups. The differences between groups were analyzed by Student's *t*-tests and one-way ANOVA. The NSK tests were carried out as post-hoc tests. When $P<0.05$, the compared differences were considered statistically significant.

Results

TMP treatment significantly increased survival rate in rats with sepsis

The results are shown in Figure 1. The survival curves were plotted at the 14th day after the CLP procedure. The survival rate decreased significantly in rats that received the CLP procedure compared with the control group. However, the TMP treatment dramatically increased the survival rate of rats that received the CLP procedure.

TMP administration dramatically improved lung functions in rats with sepsis

The results are shown in Figure 2. Compared with the control group, the W/D and ARI increased while the DC and PaO_2 decreased significantly in rats that received CLP. However, the TMP treatment significantly improved the lung functions with

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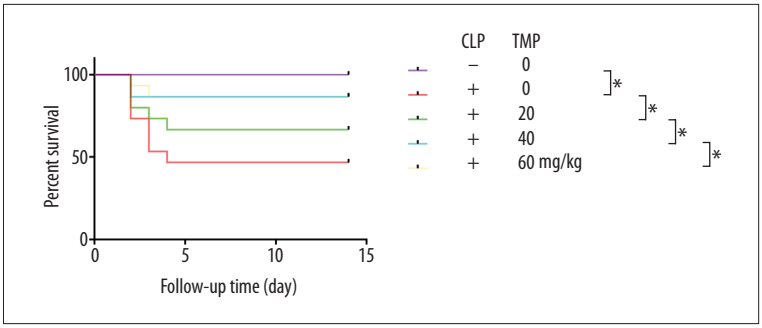

Figure 1. The chart shows the Kaplan-Meier survival curves of control and sepsis rats that received TMP at concentrations of 0, 20, 40, and 60 mg/kg. Log-rank test was carried out to analyze the differences between groups. * *P*<0.05 indicates differences significant between groups.

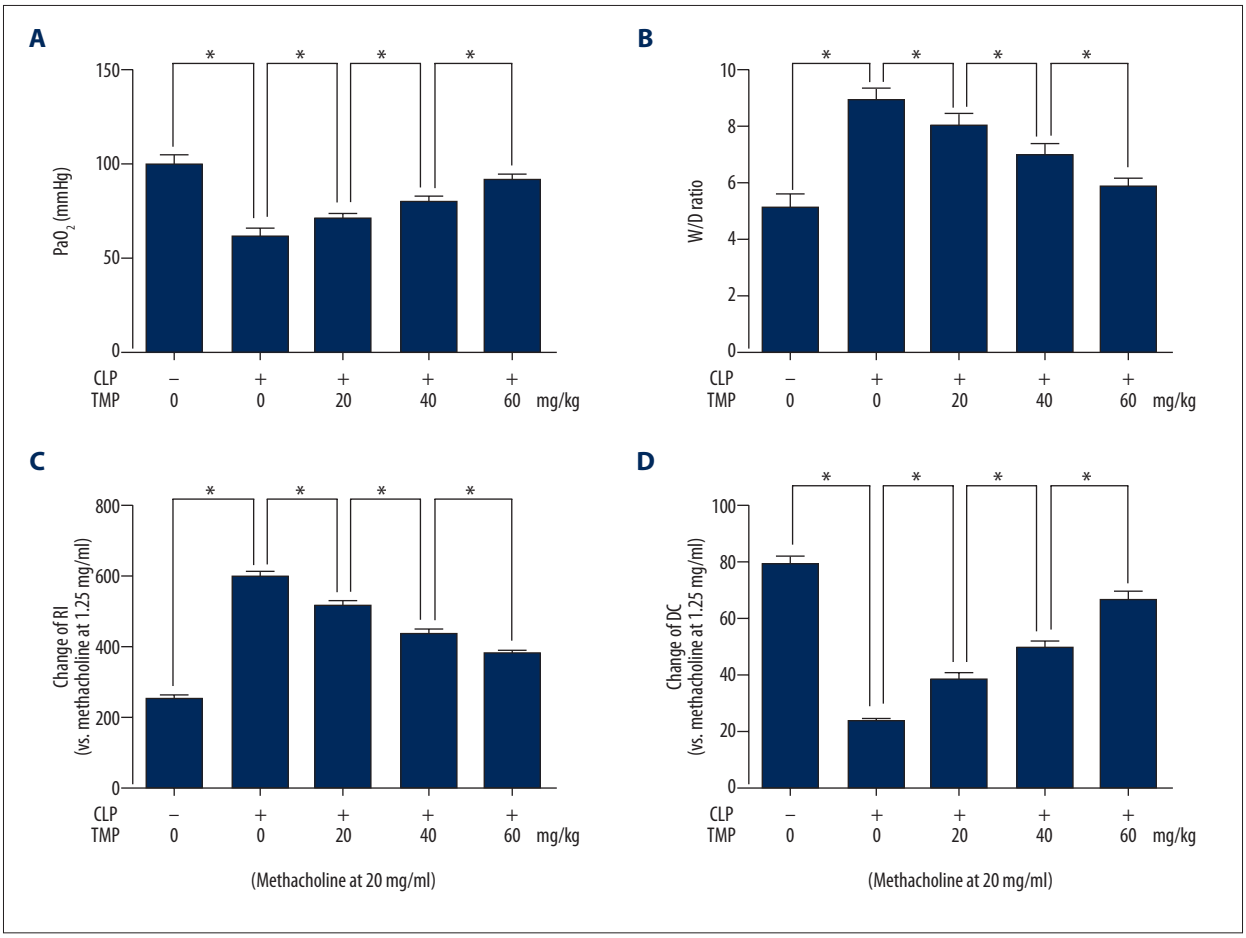

Figure 2. (**A**) Columns show the PaO_2 of blood sample collected from aorta in sepsis rats that received TMP at concentrations of 0, 20, 40 and 60 mg/kg. (**B**) Columns show the wet/dry weight ratio (W/D) of lung in sepsis rats that received TMP at concentrations of 0, 20, 40, and 60 mg/kg. (**C**) Columns show the change of airway resistance index (RI) in sepsis rats that received TMP at concentrations of 0, 20, 40, and 60 mg/kg. (**D**) Columns show the change of dynamic compliance (DC) in sepsis rats that received TMP at concentrations of 0, 20, 40, and 60 mg/kg. * *P*<0.05 indicates differences significant between groups.

the evidence that TMP decreased W/D and ARI while it increased DC and PaO_2 in rats that received CLP. Moreover, these protective effects were in a concentration-dependent manner.

TMP treatment significantly attenuated cell apoptosis of PMVECs isolated from rats with sepsis

Figure 3 demonstrates the results of the TUNEL assay. The apoptosis rate of PMVECs isolated from lungs harvested from rats that received CLP increased significantly. However, TMP

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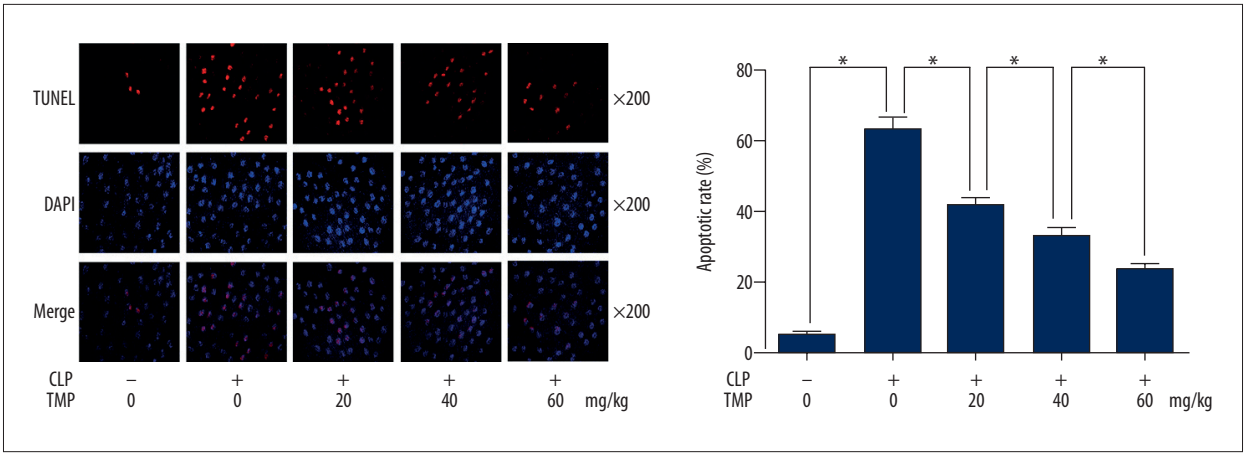

Figure 3. Upper portion shows the captured images of TUNEL, DAPI, and their merged images of PMVECs isolated from sepsis rats that received TMP at concentrations of 0, 20, 40, and 60 mg/kg. * *P*<0.05 indicates differences significant between groups.

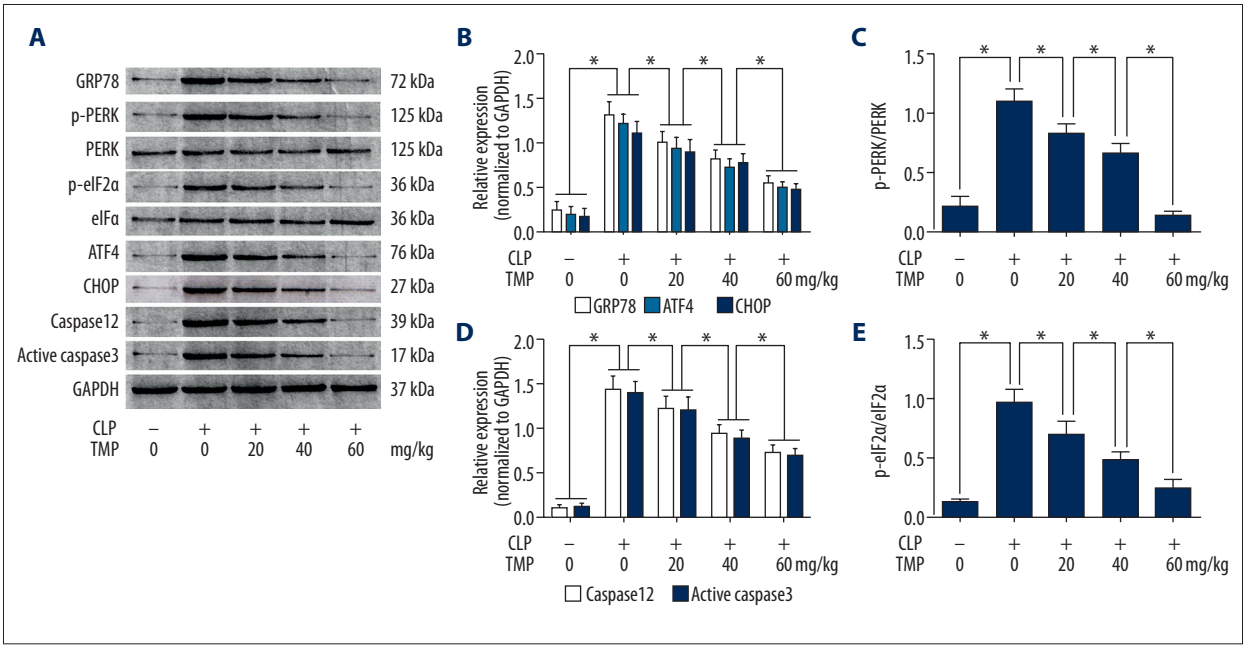

Figure 4. (**A**) Immunoblots of GRP78, p-PERK, PERK, p-eIF2α, eIF2α, ATF4, CHOP, caspase-12, active caspase-3, and GAPDH in PMVECs isolated from sepsis rats that received TMP at concentrations of 0, 20, 40, and 60 mg/kg. (**B**) Columns indicated the relative expression levels of GRP78 (white), ATF4 (blue), and CHOP (deep blue) in PMVECs isolated from sepsis rats that received TMP at concentrations of 0, 20, 40, and 60 mg/kg. (**C**) Columns show the phosphorylation level of PERK in PMVECs isolated from sepsis rats that received TMP at concentrations of 0, 20, 40, and 60 mg/kg. (**D**) Columns show the relative expression levels of caspase-12 (white) and active caspase-3 (deep blue) in PMVECs isolated from sepsis rats that received TMP at concentrations of 0, 20, 40, and 60 mg/kg. (**E**) Columns show the phosphorylation level of eIF2α in PMVECs isolated from sepsis rats that received TMP at concentrations of 0, 20, 40, and 60 mg/kg. * *P*<0.05 indicates differences significant between groups.

treatment significantly decreased the apoptosis rate of PMVECs isolated from lungs of rats that received CLP. This anti-apoptotic effect of TMP was in a concentration-dependent manner.

TMP administration significantly alleviated the activation of ERS and PERK apoptotic signaling in PMVECs isolated from rats with sepsis.

The results are shown in Figure 4. Expression levels of GRP78, eIF2α, CHOP, ATF4, caspase-12, activated caspase-3, as well as the phosphorylation level of PERK and eIF2α elevated significantly in PMVECs isolated from rats that received CLP. However, after TMP treatment, the expression levels of GRP78, CHOP, ATF4, caspase-12, activated caspase-3, as well as the

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phosphorylation level of PERK were obviously downregulated in PMVECs from rats that received CLP.

Discussion

Caused by trauma, shock, and infection, sepsis is one of the life-threatening situations leading to multiple organ dysfunctions and failure. ALI is one of the typical organ injuries caused by sepsis, which is characterized by lung edema and intractable hypoxemia [17]. The molecular mechanisms of ALI are still unclear. The damage of pulmonary microvascular barrier would lead to gas exchange and vascular permeability dysfunctions. Natural products attracted researchers' attention in recent decades due to their therapeutic activities. In the current study, the CLP-induced rat sepsis model was employed. We investigated the therapeutic effect of TMP and involved molecular mechanism in treatment of sepsis-induced ALI.

TMP ($C_8H_{12}N_2$), also known as ligustrazine, is one of the major bio-active components extracted from a Chinese medical herb chuanxiongqin which has been applied clinically in traditional Chinese medicine since ancient times [18]. TMP was artificially synthesized in 1970s and has been used in the clinical treatment of cardiovascular and cerebrovascular diseases such as myocardial infarction, stroke, and pulmonary embolism [15]. In this study, TMP was administrated to rats with sepsis. The result showed that TMP administration significantly increased the survival rate of sepsis rats. Moreover, we found that TMP treatment significantly decreased W/D, indicating that TMP alleviated the lung edema in sepsis rats. TMP increased air way compliance and decreased air flow resistance in sepsis rats. As a result, the PaO_2 was dramatically increased. These results suggested that TMP treatment could improve the poor prognosis of sepsis by attenuating ALI/ARDS.

Recently, accumulating evidences have suggested that the pulmonary microvascular dysfunction was associated with the hyper-permeability which played a critical role in the occurrence and development of ALI/ARDS [19]. The pulmonary microvascular endothelium is consisted by a continuous monolayer of PMVECs which form the internal wall of microvessels; the integrity maintains the gas exchange and homeostasis. In the current study, we employed a heparin conditioning cell culturing to isolate the PMVECs from lungs harvested from septic rats. This method is helpful in avoiding chemical and mechanical injuries on isolated PMVECs. We found that the apoptosis of PMVECs isolated from septic rats increased significantly compared with normal control. The TMP administration, however, dramatically attenuated the apoptosis of PMVECs in a concentration-dependent manner.

ERS-induced cell death is one of the major pathways conducting apoptotic signaling [20]. When encountering harmful stimuli, misfolded or unfolded protein accumulates in ER lumen. ERS would be induced when ER is not capable of handling these proteins, which is also called UPR. Under these circumstances, the sensor protein PERK would be activated by auto-phosphorylation [21]. Activated PERK would further phosphorylates the α-subunit of its downstream protein eIF2α which eliminates the translation inhibition of ATF4. Dependent on ATF4, the expression of CHOP would also be increased during ERS [21]. CHOP is a typical pro-apoptotic factor which induces the expression caspase-12 (caspase-4 in human) to trigger caspase cascade activation [22]. In this study, we found that the expression level of GRP78, the molecular marker of ERS, increased significantly in PMVECs isolated from septic rats. However, TMP treatment suppressed the expression of GRP78 in PMVECs, indicating TMP exerted inhibitory effect on ERS in microvascular endothelium in septic rats. Furthermore, evidenced by elevated phosphorylation levels of PERK and eIF2α, as well as the expression levels of ATF4, CHOP, and caspase-12/3, the PERK apoptotic signaling was activated in PMVECs isolated from septic rats. TMP administration, however, dramatically inhibited the activation of PERK/eIF2α/ATF4/CHOP apoptotic signaling pathway.

Conclusions

We conclude from this study that: 1) microvascular endothelial apoptosis was involved in sepsis- induced ALI; 2) PERK/eIF2α/ATF4/CHOP signaling pathway was activated to induce apoptosis in PMVECs; and 3) TMP showed therapeutic effects on sepsis-induced ALI by attenuating ERS mediated PMVECs apoptosis via inhibiting PERK/eIF2α/ATF4/CHOP signaling pathway. We believe that the results from this study provide evidence for treating ALI as a new clinical indication of TMP.

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