Experimental Animals

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The sirtuin 1 activator SRT1720 alleviated endotoxin-induced fulminant hepatitis in mice

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Abstract: The metabolic sensor sirtuin 1 (SIRT1) also functions as a checkpoint in inflammation, and SRT1720 is a highly active and selective SIRT1 activator shown to alleviate inflammatory injury in several recent experimental studies. In the present study, the potential effects and underlying mechanisms of SRT1720 on lipopolysaccharide (LPS)-induced fulminant hepatitis in D-galactosamine (D-Gal)-sensitized mice were investigated. The results indicated that treatment with SRT1720 inhibited LPS/D-Gal-induced elevation of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), alleviated the histological abnormalities, suppressed the induction of tumor necrosis factor alpha (TNF-α) and IL-6, mitigated the phosphorylation of c-Jun N-terminal kinase (JNK), downregulated the activities of caspase 8, caspase 9 and caspase 3, decreased the level of cleaved caspase 3, reduced the TUNEL-positive cells, and improved the survival rate of the LPS/D-Gal-exposed mice. These data indicated that treatment with the SIRT1 activator SRT1720 alleviated LPS/D-Gal-induced fulminant hepatitis, which might be attributed to the suppressive effects of SRT1720 on TNF-α production and the subsequent activation of the apoptosis cascade.
Key words: apoptosis, endotoxin, fulminant hepatitis, sirtuin 1, SRT1720

Introduction

Fulminant hepatitis is a serious hepatic disorder with a high mortality rate [1]. It is characterized by the rapid development of an overwhelmed inflammatory response and massive hepatocyte death, which possibly induce sudden hepatic failure and even death [2, 3]. Although the signaling pathways regulating hepatic inflammation and hepatocyte apoptosis have been extensively investigated, effective pharmacological interventions for fulminant hepatitis are still limited, and fulminant hepatitis remains a life-threatening health problem worldwide [4, 5].

Recently, the close relationship between metabolic status and inflammatory injury has been highly concerning [6]. Cellular metabolism not only provides the energy supply and chemical substrates for inflammatory reactions but also actively modulates inflammatory signaling [7]. Silent information regulator 2 homolog 1 (sirtuin 1, SIRT1) is a crucial metabolic sensor that is

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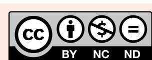
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activated by an increased cellular level of nicotinamide adenine dinucleotide (NAD^+), which functions as a deacetylase that modulates metabolic processes and signal transduction via removal of the acetyl group from histones and non-histone proteins [8, 9]. Accumulating evidence suggests that SIRT1 would be a metabolic checkpoint in inflammation and a promising target of interventions for inflammatory injury [10, 11].

Resveratrol, an active polyphenolic phytoalexin from grapes and berries, has been widely used as a SIRT1 activator in experimental studies, and treatment with resveratrol provides pharmacological benefits in various animal models [12]. SRT1720 is a synthesized selective SIRT1 activator, and the activity of SRT1720 is 1000-fold more potent than that of resveratrol [13]. It has been reported that treatment with SRT1720 improves glucose homeostasis and lifespan in mice [13, 14]. In addition, activation of SIRT1 by SRT1720 results in beneficial outcomes in experimental animals with ovalbumin-induced asthma, ischemia/reperfusion-induced acute kidney injury, and dextran sulfate sodium-induced colitis [15–17]. Therefore, SRT1720 has been considered a promising reagent for drug discovery [18].

Several recent studies have found that treatment with SRT1720 might provide protective effects in experimental animals with hepatic injury. In mice with high-fat diet-induced non-alcoholic fatty liver disease, chronic administration of SRT1720 suppressed the morphological abnormalities in the liver and the elevation of transaminase in serum [14, 19]. In addition, treatment with SRT1720 also suppressed cecal ligation and puncture-induced systemic inflammation and liver damage [20]. To further investigate the hepatic protective benefits of SRT1720, fulminant hepatitis was induced in mice by intraperitoneal injection of lipopolysaccharide (LPS) and D-galactosamine (D-Gal), which is widely used as an experimental animal model of fulminant hepatitis [21, 22]. LPS/D-Gal exposure quickly and selectively induces severe liver damage and usually results in lethal outcomes [23, 24]. In this study, the potential effects of SRT1720 on liver damage, inflammatory response, hepatocyte apoptosis, and animal survival were investigated in this experimental model.

Materials and Methods

Reagents

LPS (from *Escherichia coli*, 055:B5) and D-Gal were the purchased from Sigma (St. Louis, MO, USA). ELISA kits for detecting the mouse tumor necrosis factor alpha (TNF-α) and IL-6 were purchased from Neobioscience (Shenzhen, China). Assay kits for measuring alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were purchased from Nanjing Jiancheng Bioengineering Institute (Nanjing, China). A kit for extracting tissue proteins and assay kits for determining the activities of caspase 3, caspase 8 and caspase 9 were purchased from Beyotime Biotechnology Institute (Jiangsu, China). An in situ cell death assay kit for the determination of apoptotic cells was purchased from Roche (Indianapolis, IN, USA). Antibodies against cleaved caspase 3, c-Jun N-terminal kinase (JNK), phosphorylated JNK (p-JNK), and β-actin were purchased from Cell Signaling Technology (Danvers, MA, USA). A BCA Protein Assay Kit for determining the concentration of proteins, horseradish peroxidase-conjugated goat anti-rabbit antibody, and enhanced chemiluminescence (ECL) reagent were purchased from Pierce Biotechnology (Rockford, IL, USA).

Experimental animals

Male 6- to 8-week-old BALB/c mice with body weights of 18–20 g were provided by the Experimental Animal Center of Chongqing Medical University (Chongqing, China). The animals were given food and water ad libitum and kept at 20–25°C with a 12-h light/12-h dark schedule. All experiments involving animals were reviewed and approved by the Ethics Committee of Chongqing Medical University.

To induce fulminant hepatitis, LPS (10 μg/kg) and D-Gal (700 mg/kg), both resolved in normal solution, were administered by intraperitoneal injection. To investigate the potential effects of SRT1720, various doses (5–20 mg/kg) of SRT1720, dissolved in 10% DMSO and diluted with edible oil, were administered by intraperitoneal injection. Mice were sacrificed by cervical dislocation 1.5 h or 6 h after LPS/D-Gal treatment, and plasma and liver samples were collected.

Histological examination

Liver samples were fixed in 4% formaldehyde solution, embedded in paraffin, sectioned into 4 μm slices, stained with hematoxylin and eosin, and observed under a microscope (Olympus, Tokyo, Japan).

Survival analysis

The survival of the experimental animals was recorded every 6 h for 7 days, and the survival rate of the mice was analyzed by Kaplan-Meier curve.

Measurement of AST and ALT

ALT and AST activities were assessed with the assay kits according to the manufacturer's instructions (Nanjing Jiancheng Bioengineering Institute).

Measurement of TNF-α and IL-6

Plasma samples collected 1.5 h after LPS/D-Gal exposure were prepared for the measurement of TNF-α and IL-6 with the ELISA kits according to the manufacturer's instructions (NeoBioscience).

Measurement of caspase activity

Liver samples collected 6 h post LPS/D-Gal exposure were processed to prepare10% homogenates, and the homogenates were then centrifuged at 16,000 g under 4°C for 15 min. The supernatant was collected and used for the measurement of the activities of caspase 3, caspase 8, and caspase 9 with the assay kits according to the manufacturer's instructions (Beyotime Biotechnology Institute). To decrease the measurement error, the protein concentration of each sample was determined with the Bradford method, and the relative activities of caspase 3, caspase 8, and caspase 9 were normalized by the protein concentration of each sample.

Detection of apoptotic cells by TUNEL

Liver sections were subjected to a TUNEL assay to detect apoptotic cells according to the manufacturer's instructions (Roche). Briefly, dewaxed and hydrated slices were incubated with proteinase K at 37°C for 0.5 h, incubated with 0.1% Triston x-100 solution containing 0.1 g sodium citrate for 4 min at 4°C, incubated with freshly prepared 3% H_2O_2 methanol solution for 20 min at room temperature, incubated with TUNEL reaction solution at 37°C for 1 h, and incubated with POD for 30 min at 37°C. DAB solution was then added to develop color. The numbers of TUNEL-positive cells in 20 randomly selected high-power fields were counted under a microscope (Olympus).

Western blot

Total tissue protein was extracted from liver samples collected 6 h after LPS/D-Gal exposure. The protein samples were separated by SDS-polyacrylamide gel and transferred to a nitrocellulose membrane. Then the membrane was blocked with 5% defatted high-protein milk, incubated with the primary antibody overnight at 4°C, and incubated with the secondary antibody at room temperature for 2 h. The blot was then developed with the ECL reagent. The bands were visualized using a ChemiDoc Touch Imaging System (Bio-Rad, Hercules, CA, USA), and their intensities were semi-quantified using the ImageJ software (National Institutes of Health).

Statistical analysis

The survival data were expressed with a Kaplan-Meier curve, and the other measurement data were expressed as the mean ± SD. The survival data were analyzed by the log-rank test; the other data were compared by one-way ANOVA, followed by the Tukey's test. $P<0.05$ was considered statistically significant.

Results

SRT1720 alleviated lethal liver injury

LPS/D-Gal-induced fulminant hepatitis was confirmed by significant elevation of ALT and AST, sensitive markers of hepatocytes damage used in clinical diagnosis and experimental studies [25], and treatment with SRT1720 dose-dependently suppressed the upregulation of ALT and AST in mice exposed to LPS/D-Gal (Fig. 1). Consistently, LPS/D-Gal-induced histological abnormalities, including extensive congestion, destruction of the hepatic lobule architecture, and hepatocytes necrosis, were alleviated by SRT1720 (Fig. 2). The overall outcome of the experimental animals was determined by monitoring the survival rate of the LPS/D-Gal-challenged mice, and the results indicated that treatment with SRT1720 sig-

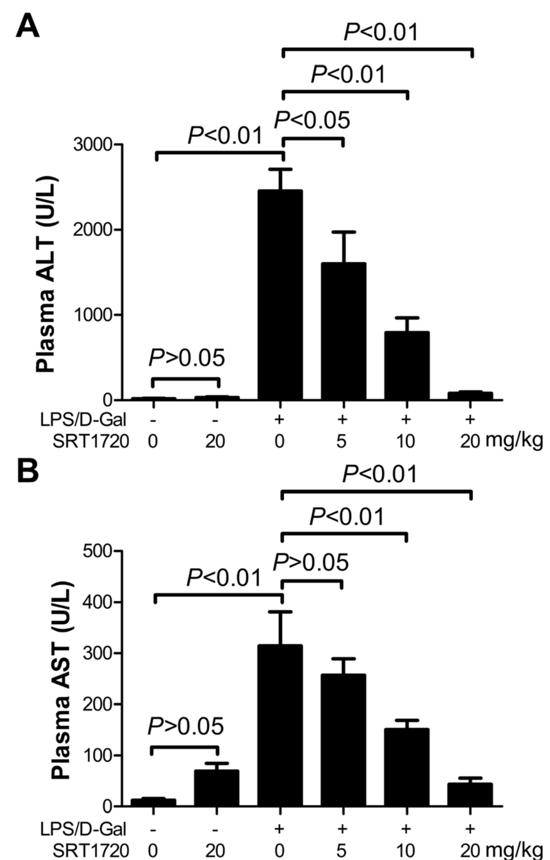

Fig. 1. SRT1720 suppressed the elevation of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). The levels of ALT (A) and AST (B) in the plasma samples collected 6 h after lipopolysaccharide (LPS)/D-Gal exposure were determined. Data are expressed as the mean ± SD, n=8.

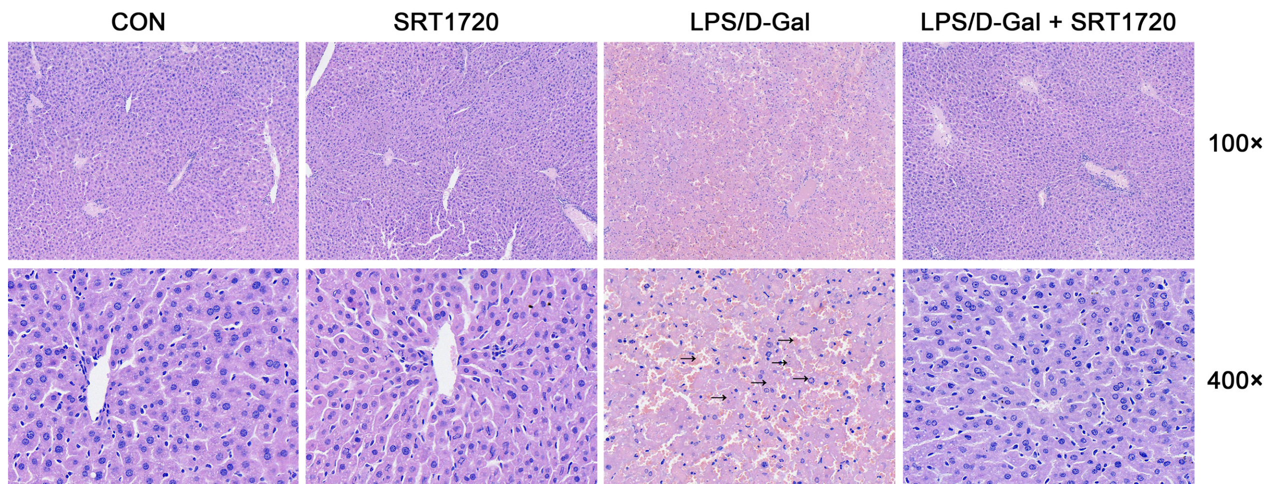

Fig. 2. SRT1720 alleviated liver damage. The liver sections were stained with hematoxylin and eosin for histological examination, and the representative sections are shown here. (original magnification 100× and 400×).

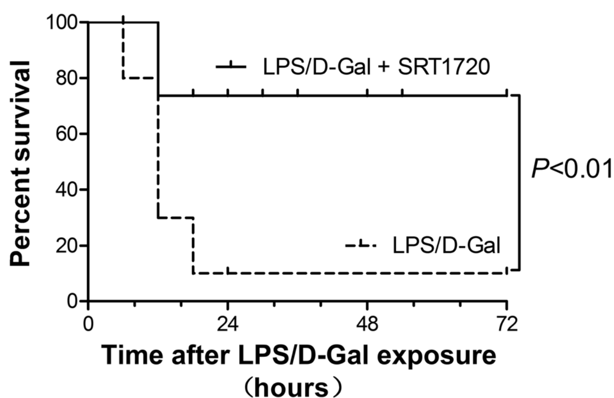

Fig. 3. SRT1720 improved the survival of lipopolysaccharide (LPS)/D-Gal-exposed mice. The mortality of the LPS/D-Gal-exposed mice was monitored every 6 h, and a cumulative survival curve was gernerated and expressed as a Kaplan-Meier survival curve (n=20).

nificantly improved the survival rate of the experimental animals (Fig. 3).

SRT1720 inhibited pro-inflammatory cytokine production

LPS/D-Gal-induced lethal liver injury largely depends on the overproduction of TNF-α, a crucial pro-inflammatory and pro-apoptotic cytokine [26]. To investigate the mechanisms underlying the protective effects of SRT1720, the level of TNF-α was determined by ELISA, and the results indicated that LPS/D-Gal-induced production of TNF-α was significantly suppressed by SRT1720 (Fig. 4A). To further confirm the suppressive effects of SIRT1720 on pro-inflammatory cytokine expression, the level of IL-6, another representative inflammatory mediator, was also determined, and the results indicated that treatment with SRT1720 also suppressed the induction of IL-6 in LPS/D-Gal-exposed mice (Fig. 4B).

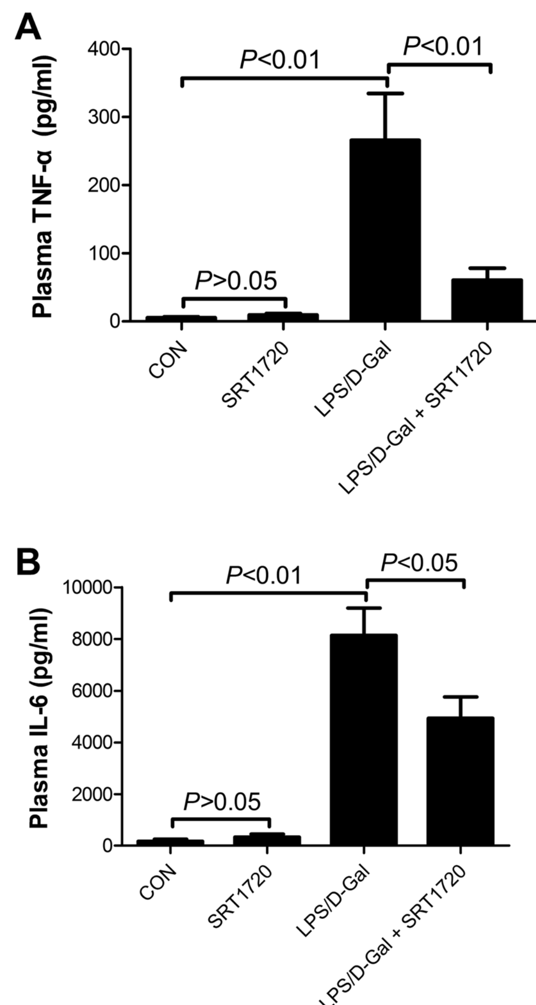

Fig. 4. SRT1720 downregulated the production of tumor necrosis factor alpha (TNF-α) and IL-6. The levels of TNF-α (A) and IL-6 (B) in the plasma samples collected 1.5 h after lipopolysaccharide (LPS)/D-Gal exposure were determined. Data are expressed as the mean ± SD (n=8).

SRT1720 decreased JNK phosphorylation

Persistent JNK phosphorylation is a critical molecular event downstream in the pro-apoptotic activity of TNF-α [27]. To explore the signal pathway responsible for the alleviation of liver injury, the phosphorylation status of JNK was determined. The data indicated that LPS/D-Gal-induced phosphorylation of JNK was suppressed in the SRT1720-treated mice (Fig. 5).

SRT1720 suppressed activation of the caspase cascade and apoptosis

Apoptosis is the characteristic feature of LPS/D-Gal-induced lethal liver injury, and the activation of the caspase cascade is crucial for the induction of apoptosis [28]. In the present study, the activity of caspase 8, caspase 9, and caspase 3 and the apoptosis of hepatocytes were evaluated. The results showed that LPS/D-Gal induced significant upregulation of the activity of caspase 8, caspase 9, and caspase 3, but these activities were suppressed by SRT1720 (Fig. 6). Caspase 3 is the final executive caspase, and the cleavage of caspase 3 is indispensable for its activation [29]. The immunoblot analysis indicated that treatment with SRT1720 decreased the level of cleaved caspase 3, which also sug-

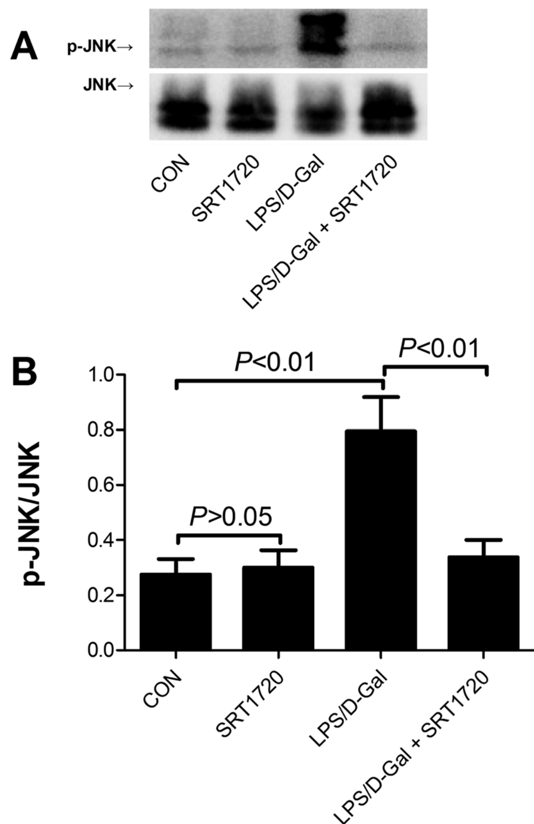

Fig. 5. SRT1720 suppressed the phosphorylation of c-Jun N-terminal kinase (JNK),. (A) The levels of phosphorylated JNK (p-JNK) and JNK in the liver samples collected 6 h after lipopolysaccharide (LPS)/D-Gal exposure were determined by Western blot. (B) The intensities of the protein bands were semi-quantified using the ImageJ software, and the ratio of p-JNK to JNK is expressed as the mean ± SD (n=4).

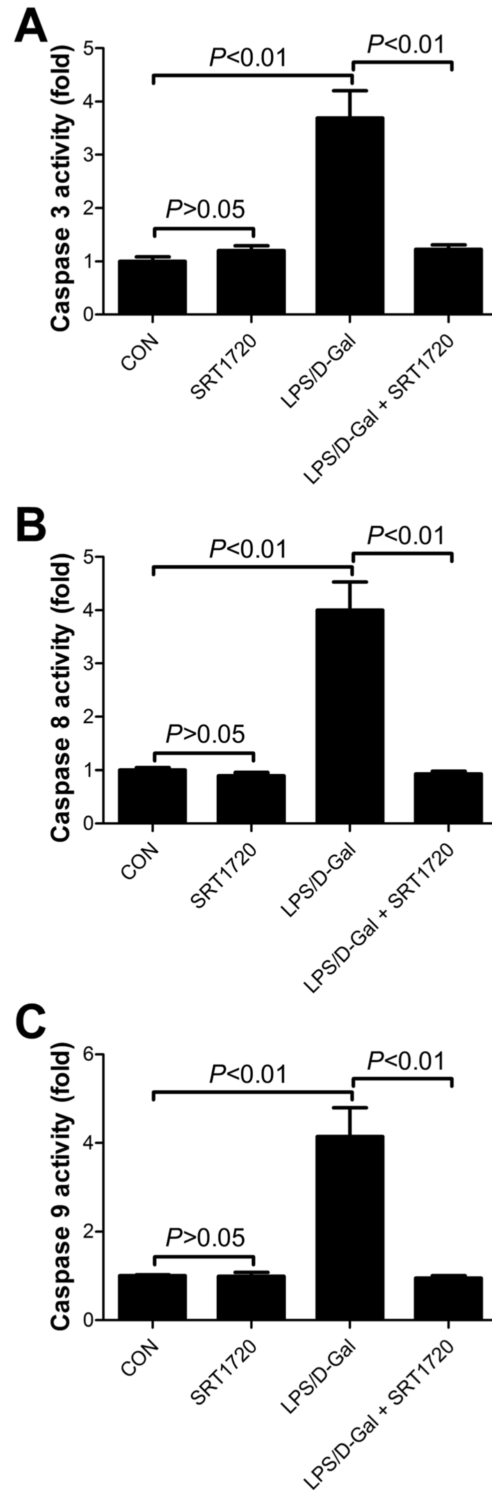

Fig. 6. SRT1720 inhibited the activation of caspase cascade. The activities of caspase 3 (A), caspase 8 (B), and caspase 9 (C) in the liver samples collected 6 h after lipopolysaccharide (LPS)/D-Gal exposure were measured. Data are expressed as the mean ± SD (n=8).

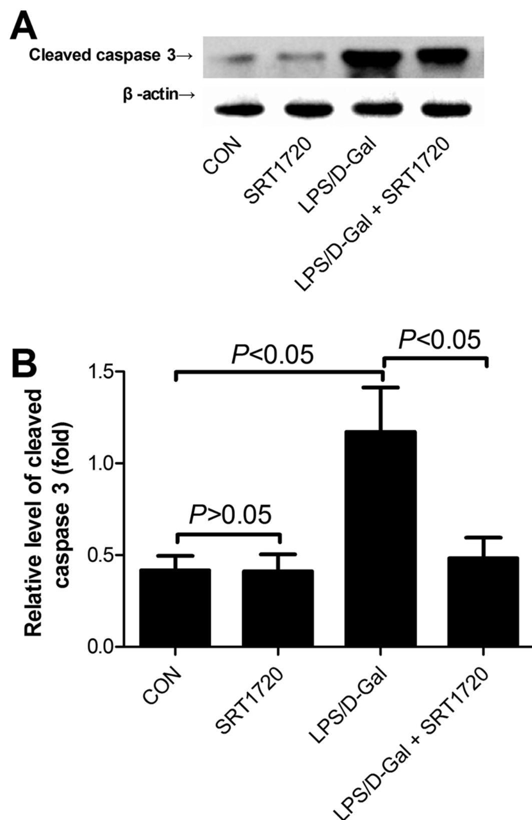

Fig. 7. SRT1720 decreased the level of cleaved caspase 3. The levels of cleaved caspase 3 (A) in the liver samples collected 6 h after lipopolysaccharide (LPS)/D-Gal exposure were determined by Western blot. (B) The intensities of the protein bands were semi-quantified using the ImageJ software, and the relative levels of cleaved caspase 3 are expressed as the mean ± SD (n=4).

gests that SRT1720 suppressed the activation of caspase 3 (Fig. 7). The apoptosis of hepatocytes was also evaluated by TUNEL assay, and the results indicated that SRT1720 reduced the abundance of TUNEL-positive cells in LPS/D-Gal-exposed mice (Figs. 8A and B).

Discussion

SRT1720 is a strong SIRT1 activator that has been used in a variety of experimental studies [30]. The anti-inflammatory and anti-apoptotic effects of SRT1720 have been observed both in vivo and in vitro [31, 32]. In the present study, we found that treatment with the SIRT1 activator SRT1720 significantly alleviated LPS/D-Gal-induced fulminant hepatitis and improved the survival rate of the experimental animals, suggesting that SRT1720 might have potential value for the control of fulminant hepatitis, a life-threatening condition.

LPS/D-Gal-induced fulminant hepatitis develops very quickly, and the experimental animals begin to die 6 h after LPS/D-Gal exposure [33]. The overproduction of the pro-inflammatory and pro-apoptotic cytokine TNF-α and the subsequent induction of hepatocyte apoptosis have been regarded as the major mechanisms underlying the development of LPS/D-Gal-induced liver injury [26]. In the present study, LPS/D-Gal-induced upregulation of TNF-α was significantly suppressed by SRT1720. The suppressive effects of SRT1720 on the induction of pro-inflammatory cytokines were further confirmed by deter-

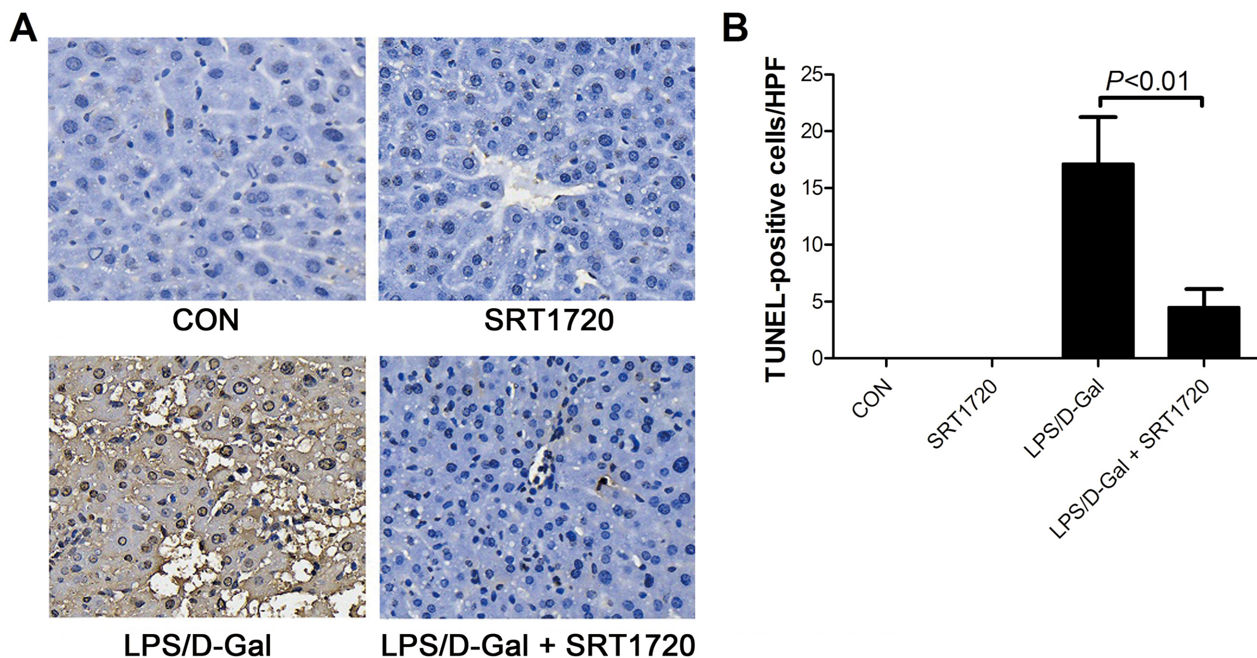

Fig. 8. SRT1720 reduced the count of apoptotic cells. (A) Liver samples were collected 6 h after lipopolysaccharide (LPS)/D-Gal exposure, and the apoptotic cells were detected by TUNEL assay. Representative liver sections are shown (original magnification 200×). (B) The numbers of TUNEL-positive cells in 20 randomly selected high-power fields were counted under a microscope. Data are expressed as the mean ± SD.

mination of the level of IL-6, another representative inflammatory mediator [34]. Therefore, suppression of the pro-apoptotic TNF-α as well as other detrimental inflammatory mediators might contribute greatly to the beneficial outcomes in SRT1720-treated experimental animals.

In agreement with our findings, mice with high-fat diet-induced non-alcoholic fatty liver disease that were treatment with SRT1720 showed suppressed the expression of TNF-α and IL-6, reduced serum levels of ALT and AST, and attenuation of histological abnormalities [19]. Treatment with SRT1720 also suppressed cecal ligation and puncture-induced upregulation of IL-1β and IL-6, which was associated with alleviation of liver injury [20]. In addition, treatment SRT1720 ameliorated cisplatin-induced renal expression of TNF-α and IL-6 and attenuated histopathological alterations in the kidney [35]. Treatment with SRT1720 also resulted in decreased inflammatory cytokine levels, lower disease activity index, and alleviation of histological abnormalities in mice with DSS-induced colitis [31]. Therefore, the anti-inflammatory properties of SRT1720 might be responsible for its therapeutic benefits in hepatic disorders as well as other inflammation-based diseases.

The target of SRT1720 is the protein deacetylase SIRT1, which modulates the acetylation of a variety of proteins and thus alters their activities [36, 37]. Several inflammation regulators, such as nuclear factor kappa B (NF-κB) and activator protein 1 (AP-1), are regarded as the major downstream factors of SIRT1 [36, 37]. Deacetylation of NF-κB and AP-1 might result in suppressed transcriptional activities and reduced production of pro-inflammatory mediators [11]. NF-κB and AP-1 are the most important transcription factors driving the expression of various inflammatory mediators, including TNF-α and IL-6 [38]. Therefore, it is possible that SRT1720 might inhibit the expression of pro-inflammatory cytokines via suppression of the acetylation of inflammation-related transcription factors.

The potent pro-apoptotic activity of TNF-α is mainly mediated by TNFR1 [39]. After TNF-α binding, the death domain of TNFR1 recruits several adapter molecules, which further recruit the pro-form of caspase 8 [40]. Aggregation of pro-caspase 8 leads to its auto-activation and subsequent activation of caspase 3, which leads to cell apoptosis by digestion of its target proteins [41]. Additionally, strong and prolonged activation of JNK induced by TNF-α plays crucial roles in the activation of the mitochondrial apoptotic pathway and the promotion of TNF-α-induced apoptosis in hepatocytes [42]. Activated JNK has been shown to phosphorylate anti-apoptotic Bcl-2 and the pro-apoptotic Bim, which leads to the formation of the mitochondrial membrane pore, the release of cytochrome c, and the activation of caspase 9, which in turn activates the executive caspase 3 [42]. In the present study, LPS/D-Gal-stimulated pro-apoptotic signals, including the phosphorylation of JNK and activation of the caspase cascade, and hepatocyte apoptosis were suppressed by SRT1720, suggesting that SRT1720 might alleviate LPS/D-Gal-induced fulminant hepatitis via targeting of the TNF-α-activated pro-apoptotic signal pathway.

SIRT1 also plays crucial roles in the direct regulation of cellular fate. In pheochromocytoma cells, silencing of SIRT1 enhanced oxygen and glucose deprivation/reperfusion-induced apoptosis, while overexpression of SIRT1 suppressed apoptosis [43]. Genetic knockdown of SIRT1 also activated apoptosis in lung cancer cells [44]. Several studies have found that SRT1720 suppresses apoptosis in intestinal epithelial cells [31] and cardiomyocytes [45]. Therefore, SIRT1 might function as an anti-apoptotic factor under certain circumstance, and modulation of the acetylation of p53 has been suggested as a major mechanism underlying its anti-apoptotic activity [46].

On the other hand, overexpression of SIRT1 significantly augmented apoptosis in HeLa cells, but deletion of SIRT1 by siRNA transfection attenuated MPP^+-induced apoptosis in dopaminergic cells [47, 48]. In hepatocytes, a recent study found that conditionally inactivated SIRT1 in hepatocytes prevented TNF-α-induced apoptosis via the promotion of acetylation of NF-κB, a critical transcription factor controlling the transcription of a large number of anti-apoptotic genes [49]. These experimental data suggest that SIRT1 also has pro-apoptotic properties and might promote TNF-α-induced apoptosis in hepatocytes. Therefore, the anti-inflammatory activities, but not the apoptosis modulatory effects, of SRT1720 might be responsible for its hepatoprotective benefits in the present study.

Taken together, the present study found that treatment with the SIRT1 activator SRT1720 alleviated LPS/D-Gal-induced lethal liver injury, and the protective benefits might be attributed to the suppressive effects of SRT1720 on TNF-α production and its downstream pro-apoptotic pathway. Although the detailed mechanisms underlying the beneficial effects of SRT1720 require further investigation, the present study suggests that SRT1720 might have potential value for the pharmacological control of fulminant hepatitis.

Conflict of Interests

The authors declare that they have no conflicts of interest concerning this article.

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