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Curcumin Attenuates Inflammation in a Severe Acute Pancreatitis Animal Model by Regulating TRAF1/ASK1 Signaling

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Inflammation plays an important role in initiation and development of severe acute pancreatitis (SAP). Curcumin exerts potent anti-inflammatory effects in many diseases, including acute pancreatitis. However, the specific molecular mechanisms are not clear.

Material/Methods: Intra-biliopancreatic duct injection of taurocholate was used to establish an animal model of SAP. Curcumin was administrated to animals as pre-treatments. Concentrations of cytokines in serum and ascites were measured by enzyme-linked immunosorbent assay (ELISA). A colorimetric method was used to determine the amylase activity. Western blotting was used to examine the expression levels and phosphorylation levels of proteins. Immunoprecipitation was used to assess the molecular association between apoptosis signal- regulating kinase 1 (ASK1) and thioredoxin (Trx).

Results: Pre-treatment with curcumin reduced the concentrations of interleukin (IL6) and tumor necrosis factor (TNFα) in serum and ascites, as well as the ascites volume and amylase activity in SAP rats. Pre-treatment with curcumin reduced the expression level of TNF receptor-associated factor 1 (TRAF1), IL6, and TNFα in pancreas in SAP rats. Moreover, the phosphorylation levels of mitogen-activated protein kinase (MAPK) kinase 4 (MKK4), MKK7, and c-Jun NH(2)-terminal protein kinase (JNK) were reduced by curcumin pre-treatment. The molecular association between ASK1 and Trx was recovered by curcumin pre-treatment. As a result, the nuclear translocation of nuclear factor kappa B (NF-κB) was suppressed in pancreases from SAP rats.

Conclusions: Activation of the TRAF1/ASK1/JNK/NF-κB signaling pathway is involved in the inflammation of SAP. Curcumin exerts anti-inflammatory effects by suppressing this proinflammatory pathway.

MeSH Keywords: Curcumin • Inflammation • Pancreatitis

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Background

Acute pancreatitis (AP) is a common abdominal emergency with a reported annual incidence rate of 13–45/100 000 [1]. Characterized by pancreatic edema, hemorrhage, autodigestion, and necrosis, approximately 30% of AP patients develop severe acute pancreatitis (SAP). SAP is a life-threatening situation caused by multiple organ dysfunctions (MODS), which is induced by inflammation cascade activation. The mortality rate associates with SAP is much higher than that of AP, which was reported at 15–30% [2]. The mechanisms of SAP are still not fully understood and no agent with satisfied efficacy has been developed. Among the therapeutic strategies of SAP treatment, inflammation inhibition was effective in suppressing SAP progression and reducing mortality [3]. In recent decades, bio-active agents extracted from Chinese medical herbs have attracted researchers' attention because of their potent anti-inflammatory activities.

Curcumin is a yellow pigment derived from the rhizome of turmeric (*Curcuma longa*), which has been applied in Traditional Chinese Medicine (TCM) in treatment of many chronic diseases from ancient times [4]. Modern pharmacological investigations have revealed the wide spectrum of curcumin's biological activities, such as anti-fibrosis, anti-cancer, anti-apoptosis, and anti-inflammation [5]. It is believed that curcumin can reducing levels of proinflammatory cytokines, including interleukins (IL) and tumor necrosis factors (TNF) in several inflammation disorders such as bacterial infection and autoimmune arthritis [6]. Moreover, several previous studies suggested the protective effects of curcumin in animal models of SAP [7]. However, these studies did not describe the specific molecular mechanisms involved. Moreover, very few studies have described the direct anti-inflammatory effects of curcumin on the pancreas.

As a member of the tumor necrosis factor receptor (TNFR)- associated factor family, TRAF1 participates in facilitating inflammatory responses [8]. It was reported that the overexpression of TRAF1 can activate the ASK/JNK signaling pathway, which further facilitates activation of NF-κB [9]. It has been well-established that NF-κB mediates inflammation by initiating and increasing transcriptions of proinflammatory cytokines via translocating to nuclei [10]. Several previous descriptions of the association between curcumin and the ASK/JNK pathway [4,11] aroused our interests in investigating the mechanism of curcumin's therapeutic effect in SAP. In the present study, we investigated the suppressive effect of curcumin against pancreatic inflammation of an animal model of SAP. Moreover, we propose that the TRAF1/ASK/JNK signaling pathway is the underlying mechanism of curcumin's anti-inflammatory effect. We believe that results from this study not only add more information to our current understanding of curcumin's anti-inflammatory molecular mechanism, but also provide more solid evidence supporting the potential clinical application of curcumin or curcumin-containing compounds in treatment of SAP.

Material and Methods

Animals, SAP modeling, and treatments

A total of 100 male Sprague-Dawley (SD) rats (8 weeks old, 200±25 g) were provided by the Animal Experimental Center of Zhejiang University. Animals were raised in separate cages in a controlled environment providing room temperature at (25±3)°C, (50±5)% humidity, and an artificial 12-h light/dark circle. Rats had free access to standard chow and clean water. All animal experiments were carried out in accordance with Recommended Guideline for the Care and Use of Laboratory Animals issued by the Chinese Council on Animal Research. Specific animal experimental protocols were reviewed and approved by the Animal Ethics Committee of Medical School of Zhenjiang University.

After 1-week adaptive feeding, rats were subjected to SAP modeling according to previously described methods [12]. Water and food were withheld for 12 h prior to model induction. Rats were anesthetized by isoflurane inhalation. A midline laparotomy was performed to open the abdominal cavity. At the hepatic hilum level, a vascular clip was used to occlude the biliopancreatic duct, which was then cannulated transduodenally with a 24-gauge catheter. SAP was induced by slow injection of 1 ml/kg bodyweight injection of 5% sodium taurocholate (Sigma-Aldrich) into the biliopancreatic duct. The control animals received an equal-volume injection of sterile physiological saline in to biliopancreatic duct. Several rats received intraperitoneal injection of curcumin solution at concentrations of 0, 50, 100, and 150 mg/kg bodyweight 30 min prior to SAP model induction. At 24 h after model induction, the rats were sacrificed by CO_2 suffocation. Blood samples and pancreatic tissues were collected.

Ascites and blood sample collection

The abdomen was opened after the animals were sacrificed. With a syringe, the ascites was removed from the abdominal cavity and transferred to a cylinder used to measure the volume of ascites. Blood samples were collected from the abdominal aorta. The ascites and whole blood were centrifuged at 3000 rpm for 5 min at 4°C. The supernatants were collected and stored at –80°C for subsequent assays.

Enzyme-linked immunosorbent assay (ELISA)

ELISA assays were used to determine the concentrations of inflammatory cytokines, including IL6 and TNFα, in supernatants

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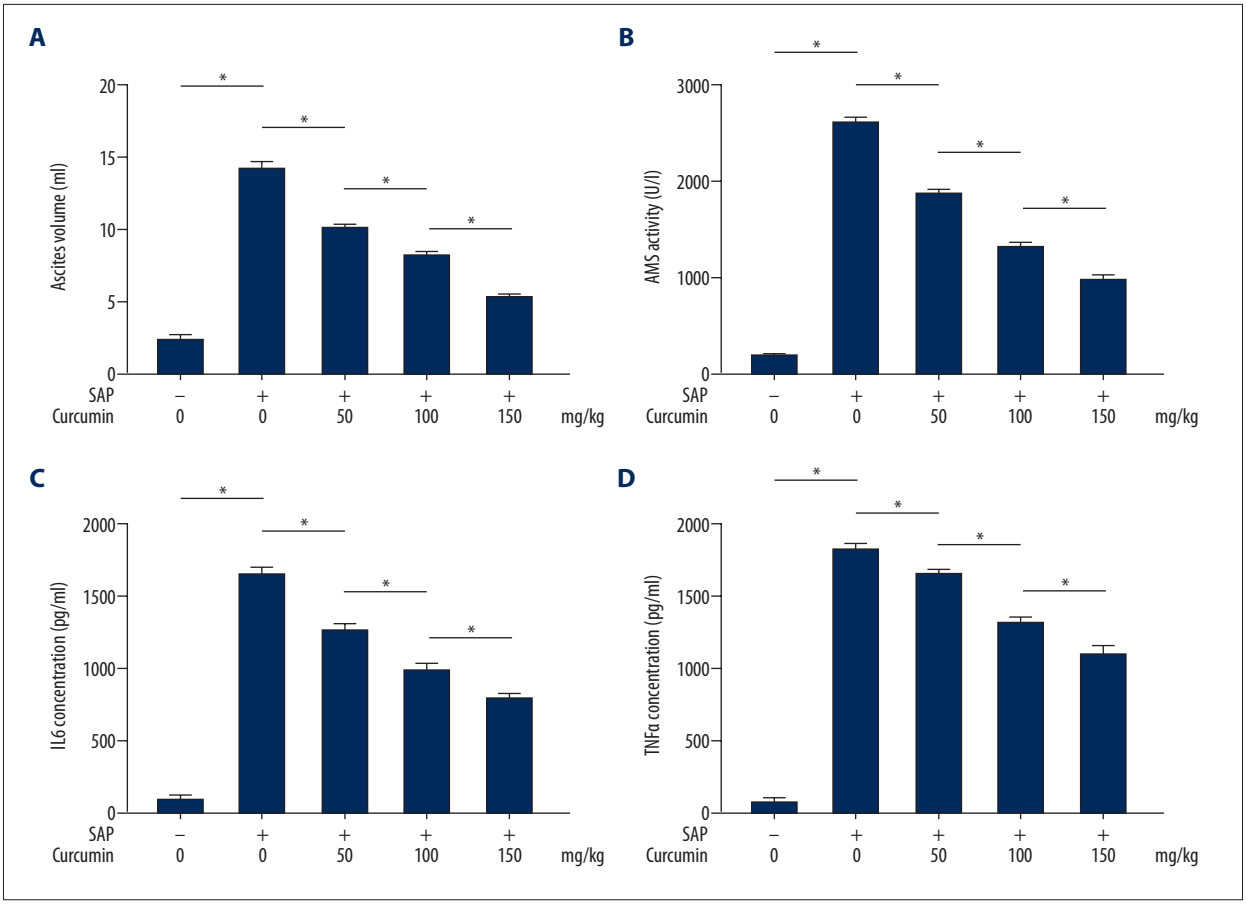

Figure 1. (**A**) Columns show volumes of ascites from SAP model animals that received curcumin at serial concentrations of 0, 50, 100, and 150 mg/kg. (**B**) Columns indicate the AMS activities detected in serum from SAP model animals that received curcumin at serial concentrations of 0, 50, 100, and 150 mg/kg. (**C, D**) Columns indicate the detected IL6 and TNFα concentrations in ascites from SAP model animals that received curcumin at serial concentrations of 0, 50, 100, and 150 mg/kg. [* differences were statistically significant].

of ascites and blood samples. Rat IL6 ELISA assay kit (R&D) and rat TNFα ELISA assay kit (R&D) were used to measure the concentrations of IL6 and TNFα, respectively. The protocol carried out following the instructions provided by the manufacturer.

Serum amylase activity

The activity of serum amylase activity was measured by a colorimetric method with an AMS activity assay kit (Leagene) and a plate reader (Bio-Rad). The protocol was carried out following the manufacturer's instructions.

Western blotting

The harvested pancreatic tissue was lysed on ice using a lysis buffer system (Santa Cruz) supplemented with PMSF (Santa Cruz). Total protein was extracted by using a Total Protein Extraction Kit (Beyotime). Nuclear protein was extracted by using a Nuclear Protein Extraction Kit (Beyotime). The protein concentration was measured with a BCA kit (Peirce). The protein was separated after being subjected to SDS-PAGE. Then, the separated proteins were transferred to PVDF membranes electronically. The membranes were then incubated with blocking buffer (Santa Cruz). Primary antibodies against TRAF1, MKK4, phosphorylated MKK4, MKK7, phosphorylated MKK7, JNK, phosphorylated JNK, NF-κB, IL6, TNFα, GAPDH, and Histone H3 were used to incubate the membranes at 4°C for 8 h. Then, the membranes were washed in TBST and further incubated with HRP-conjugated secondary antibodies for 2 h at room temperature. The immunoblots were developed by Lumi-Light substrate (Pierce) and visualized on X-ray films.

Immunoprecipitation (IP)

The association between ASK1 and thioredoxin (Trx) was evaluated by IP in this study according to methods described in previous studies [13]. Briefly, the whole-cell extract was precleared by incubating with normal rabbit serum plus protein

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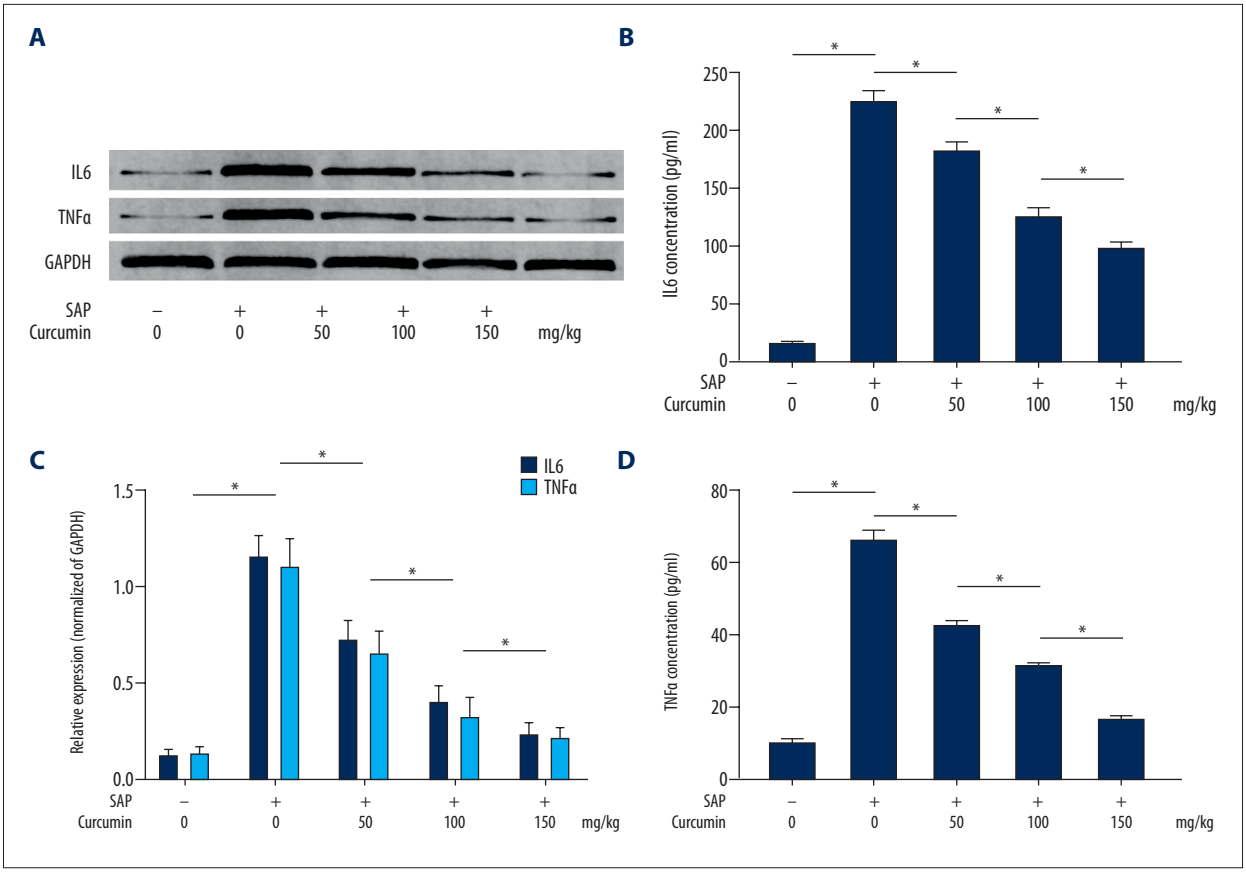

Figure 2. (**A**) The upper panel demonstrates the immunoblots of IL6, TNFα, and GAPDH of serum protein from SAP model animals that received curcumin at serial concentrations of 0, 50, 100, and 150 mg/kg. Columns on the lower panel indicate the relative expression levels of IL6 and TNFα. (**B, C**) Columns indicate the detected IL6 and TNFα concentrations in serum from SAP model animals that received curcumin at serial concentrations of 0, 50, 100, and 150 mg/kg. [* differences were statistically significant].

A/G-agarose beads for 10 h at 4°C and were then incubated with first-protein (Trx)-specific antiserum for 2 h. After each IP, the immune complexes were collected by centrifugation at 14 000×g for 10 min. After washing in lysis buffer, the immune complexes were subjected to SDS-PAGE, which was then detected by immunoblot (Immobilon P, Millipore) with the antibody against second-protein ASK1.

Statistics

Data are presented as mean ±SD. Differences between groups were analyzed by one-way ANOVA and *t* tests. The NSK test was performed as a post hoc test. SPSS software (version16.0, SPSS) was used to perform the analysis. At P<0.05, the compared differences were considered to be statistically significant.

Results

Curcumin reduced ascites volume, serum amylase activity, and inflammation in SAP rats.

The results are demonstrated in Figure 1. The volume and inflammatory cytokines concentrations in ascites, as well as the serum amylase activity from SAP rats, increased significantly compared with control rats. The pre-treatment with curcumin decreased the serum amylase activity, volume of ascites, and the concentration of IL6 and TNFα in a concentration-dependent manner.

Curcumin suppressed the concentration and expression levels of inflammatory cytokines in serum in SAP rats.

Figure 2 shows that the concentration and expression levels of IL6 and TNFα in serum harvested from SAP rats increased significantly. The curcumin pre-treatment dramatically reduced both concentration and expression levels of IL6 and TNFα in a concentration- dependent manner.

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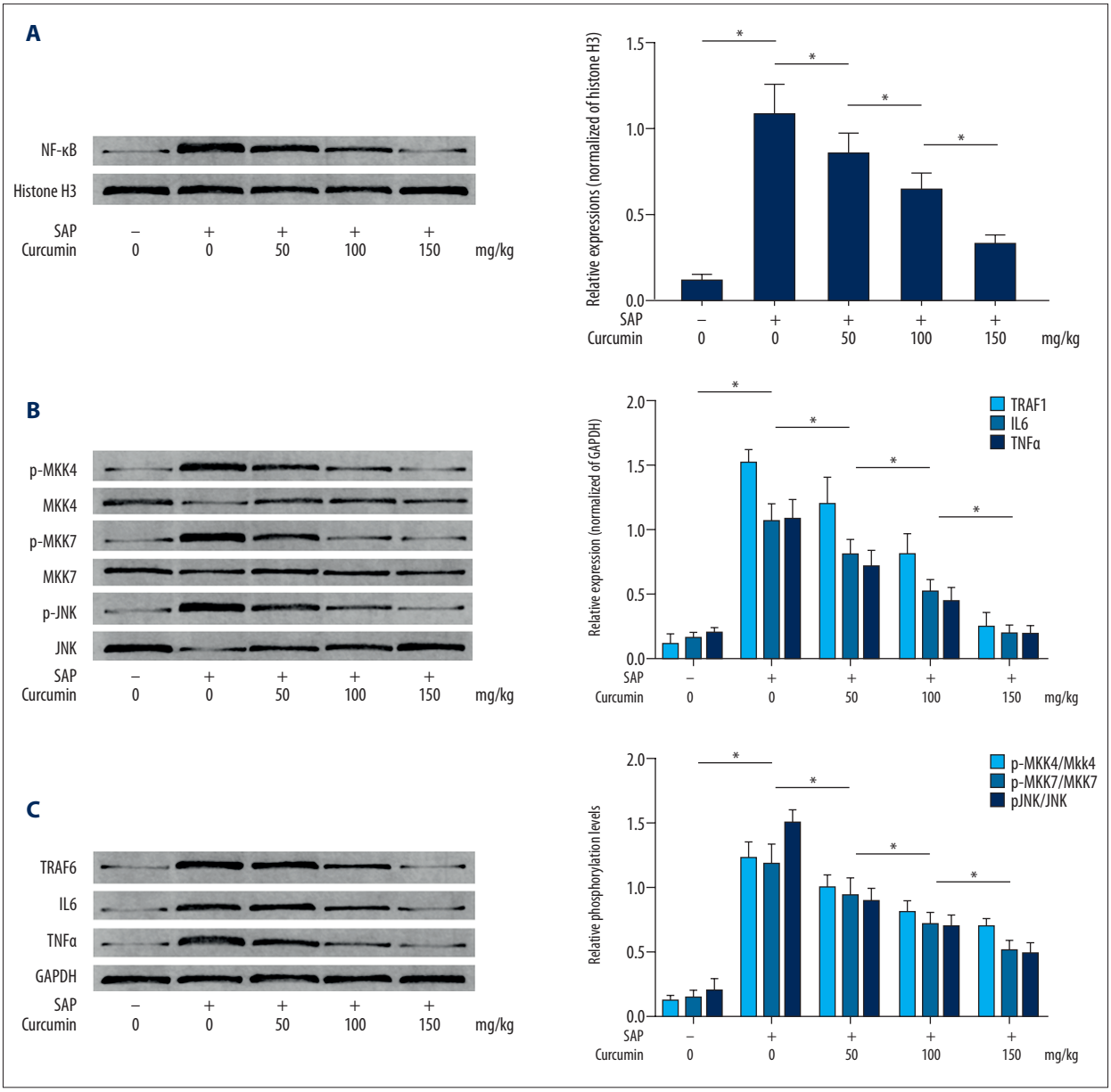

Figure 3. (**A**) The upper panel demonstrates the immunoblots of NF-κB and histone H3 in unclear protein extracted from rat pancreases. Columns on the lower panel indicate the relative expression levels of NF-κB in pancreases from SAP model animals that received curcumin at serial concentrations of 0, 50, 100, and 150 mg/kg. (**B**) The upper panel demonstrates the immunoblots of p-MKK4, MKK4, p-MKK7, MKK7, p-JNK, and JNK. Columns on the lower panel indicate the relative phosphorylation levels of MKK4, MKK7, and JNK in pancreases from SAP model animals that received curcumin at serial concentrations of 0, 50, 100, and 150 mg/kg. (**C**) The upper panel demonstrates the immunoblots of TRAF6, IL6, TNFα, and GAPDH. Columns on the lower panel indicate the relative expression levels of TRAF6, IL6, and TNFα from SAP model animals that received curcumin at serial concentrations of 0, 50, 100, and 150 mg/kg. [* differences were statistically significant].

Curcumin suppressed the MKKs/JNK/NF-κB signaling mediated inflammation in pancreatic tissue of SAP rats.

Figure 3 shows that, in pancreatic tissue from SAP rats, the phosphorylation of MKK4, MKK7, and JNK increased significantly in pancreatic tissues of SAP rats. Moreover, the nuclear translocation of NF-κB also increased dramatically in pancreatic tissues of SAP rats. The pre-treatment with curcumin significantly reduced the phosphorylation of MKK4, MKK7, and JNK, as well as the nuclear translocation of NF-κB, in pancreatic tissue of SAP rats in a concentration-dependent manner.

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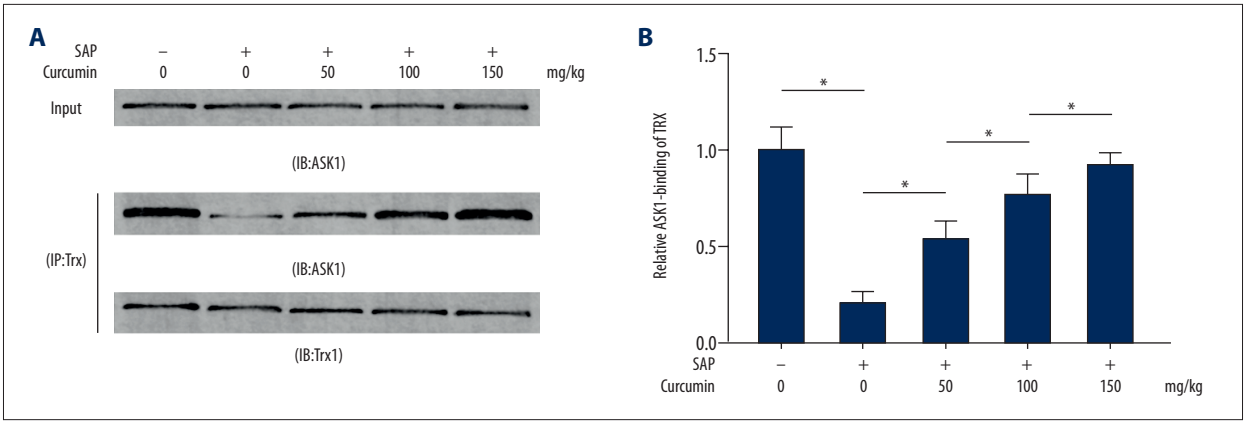

Figure 4. (**A**) Results of IP, which evaluated the association between ASK1 and Trx. Cell extract was immunoprecipitated with antibodies against Trx. Relative Trx-bound ASK1 was quantified by comparing pulldown ASK1/input ASK1. (**B**) Columns indicate the relative ASK1-Trx binding levels from SAP model animals that received curcumin at serial concentrations of 0, 50, 100, and 150 mg/kg. [* differences were statistically significant].

Curcumin inhibited activation of the TRAF1/ASK1 pathway in pancreatic tissues of SAP rats.

Figure 4 shows that the expression level of TRAF1 increased significantly in pancreatic tissues in SAP rats. The curcumin pre-treatment dramatically reduced the TRAF1 expression level. Furthermore, the association between ASK1 and Trx was significantly impaired in pancreatic tissues of SAP rats. The curcumin pre-treatment facilitated the association between ASK1 and Trx in pancreatic tissues from SAP rats.

Discussion

When AP develops into SAP, it is a life-threatening condition with severe complications and high mortality [14]. Inflammatory responses and cascade activation contribute to the high mortality of SAP by inducing systematic inflammatory response syndrome (SIRS) and MODS [15]. Thus, limitation of inflammation would be an effective strategy in SAP treatment. However, the mechanisms involved in the inflammation of SAP are complicated and still not completely understood. The pharmacological therapeutic remedies used to treat SAP are currently very limited. Therefore, more in-depth investigations concerning the pathogenic mechanisms of SAP are urgently required to identify more effective treatment strategies for SAP. In the present study, the SAP animal model was established by intra-biliopancreatic duct injection of 3% sodium taurocholate. We investigated the molecular mechanisms involved in inflammation of SAP by using this animal model.

Activation of NF-κB plays a vital role in mediating inflammatory responses [16]. It was reported that activated NF-κB translocates to nuclei to initiate its targeted down-stream genes encoding proinflammatory cytokines, including interleukins (IL) and tumor necrosis factors (TNF) [17]. In the present study, we found that the nuclear translocation of NF-κB was dramatically up-regulated in SAP pancreases, which is consistent with the observations reported by previous studies [14,18]. MAPKs are important protein kinases that play roles in responding to harmful pathological stress [19]. As a member of the MAPK family, JNK is well-known as a stress-activated protein kinase and acts as an activator of the NF-κB pathway [20]. In the present study, our results showed the elevated phosphorylation level of JNK, resulting in significantly elevated levels of typical proinflammatory cytokines – IL6 and TNFα – in the pancreas, ascites, and serum. These results indicate the inflammatory response is mediated by activation of the JNK/NF-κB pathway in SAP rats.

MAPKs are activated by phosphorylation and activate their down-stream effectors such as NF-κB, which further regulate its targeted genes [21]. The activation of MAPKs is modulated by their up-stream kinases MKKs [22]. Specifically, the phosphorylation of JNK is regulated by MKK4 and MKK7 [23]. In the present study, our results showed that the phosphorylation of MKK4 and MKK7 was significantly elevated in pancreases harvested from SAP rats. The activation of MKKs is mediated by ASK1. Under normal static conditions, ASK1 is combined with its intrinsic inhibitor, Trx, and its activation is blocked [24]. However, when challenged by harmful stimuli, the molecular association between Trx and ASK1 is impaired [25]. Previous studies pointed out that the association of ASK1-Trx complex is regulated by TRAF protein families and form the TRAF/ASK signaling pathway [26,27]. In the present study, our data show that the expression level of TRAF1 was dramatically increased in pancreases from SAP animals. As a result, as evidenced by IP, the molecular association between ASK1 and Trx was impaired. Taken together, our present results show a possible mechanism of inflammation activation. During SAP, up-regulated TARF1 impaired the association between Trx and ASK1,

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which facilitated the phosphorylation of MKK4 and MKK7. Activated MKK4/7 further activated JNK by phosphorylation, which eventually triggered NF-κB-mediated inflammation.

We also observed the therapeutic effects of curcumin against inflammation in the SAP animal model. Consistent with several previous descriptions, the treatment with curcumin dramatically inhibited the nuclear translocation of NF-κB and thus suppressed expression levels of IL6 and TNFα. We further investigated the possible mechanisms involved. We found that the curcumin pre-treatment dramatically decreased the expression level of TRAF1 in pancreases from SAP rats. As a result, the association between Trx and ASK1 was recovered and the phosphorylations of MKK4/7 were thus down-regulated. Thus, the activation of JNK was also inhibited, leading to impaired NF-κB inflammatory signaling suppression.

There are several limitations to this study. Firstly, the animals were sacrificed 24 h after model induction. Although the anti-inflammatory effect of curcumin in the SAP model was observed, it would be more persuasive if more time points were investigated. Secondly, our study investigated the involvement of the JNK pathway, which is a member of the MAPKs family. It would be more meaningful to study the role of other MAPKs, including p38 and ERK, in further studies.

Conclusions

Results from our study indicate that activation of the TRAF1/ASK1/JNK/NF-κB signaling pathway is involved in inflammation of SAP. Curcumin pre-treatment effectively reduced inflammatory cytokine levels by blocking the activation of the TRAF1/ASK1/JNK/NF-κB signaling pathway. We believe that our study not only adds new information on the pathological molecular mechanisms of inflammation in SAP, but also provides more solid evidence for application of curcumin as a part of the therapeutic strategy for SAP.

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