Curcumin protects against acute renal injury by suppressing JAK2/STAT3 pathway in severe acute pancreatitis in rats

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Abstract. The aim of the present study was to investigate the effect of curcumin on acute renal injury in a rat model of severe acute pancreatitis (SAP). A SAP model with acute kidney injury was established in rats by retrograde injection of 5% sodium taurocholate into the pancreatic duct. The serum amylase, creatinine (Cr) and blood urea nitrogen (BUN) levels in rats were measured. Hematoxylin and eosin staining was used to assess pancreatic and renal histological changes. Serum tumor necrosis factor (TNF)-α and interleukin (IL)-6 levels were measured using ELISA kits. Renal protein levels of Janus kinase (JAK) 2/signal transducer and activator of transcription (STAT) 3 pathway components were determined by western blot assay. The results showed that curcumin significantly decreased serum amylase, Cr and BUN levels, and alleviated pancreatic and renal histological changes in SAP rats. Furthermore, curcumin markedly decreased serum TNF-α and IL-6 levels and downregulated renal protein levels of JAK2/STAT3 pathway components. These results proved that curcumin ameliorates acute renal injury in a rat model of SAP. The molecular mechanism of its effect may be associated with the suppression of the JAK2/STAT3 pathway to reduce TNF-α and IL-6 levels in SAP-induced acute renal injury. Therefore, the findings of the present study revealed the potential use of curcumin for the prevention and treatment of SAP and the associated renal injury.

Introduction

Severe acute pancreatitis (SAP), an acute inflammatory condition of the pancreas, is considered to be a paradigm of sterile inflammation leading to systemic multiple organ dysfunction syndrome (MODS) and death. Acute renal injury (ARI) is one of the main complications of SAP and significantly increases the mortality rate of patients with AP (66.6 vs. 14.5%) (1). However, the underlying mechanisms of ARI occurring in patients with SAP have remained to be clarified. Increasing evidence has indicated that pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α) and interleukin (IL)-6, have an important role in the pathological mechanisms of SAP and SAP-associated organ failure (2-4). Therefore, inhibiting the transcription and translation of mediators to reduce the secretion of pro-inflammatory factors may ameliorate inflammation and renal failure in SAP.

Signal transducers and activators of transcription (STATs), a protein family comprised of seven members (STAT1, -2, -3, -4, -5a, -5b and -6), generally transduce signals from activated receptors or intracellular kinases to the nucleus, thus activating and regulating gene transcription (5). The Janus kinase 2 (JAK2)/STAT3 pathway is well known to be involved in the immune response of numerous cytokines, including TNF-α and IL-6 (6). In addition, evidence derived from numerous clinical and experimental studies suggests the involvement of the JAK2/STAT3 pathway in pancreatitis (7-9) or renal diseases (10-12).

Curcumin (diferuloylmethane), the active phytochemical component of turmeric (a spice used mostly in Asia) has been isolated from the rhizome of the *Curcuma longa* plant. Curcumin has a myriad of pharmacological effects, including anti-inflammatory (13,14), anti-bacterial (15), anti-oxidative (16) and renal-protective activities (17,18). A previous study suggested that curcumin has a therapeutic role in a rat model of SAP (19). Another study has reported that curcumin inhibited renal inflammation in cisplatin-induced nephrotoxicity in mice (20) and suppressed JAK2/STAT3 signaling to ameliorate renal endothelial dysfunction in fructose-fed rats (21). All of the above suggests the potential use of curcumin in the treatment of acute renal failure following SAP. Thus, the present study investigated the effect of curcumin on acute renal failure arising from SAP and to explore the molecular mechanism.

Materials and methods

Chemicals and reagents. Curcumin and hematoxylin and eosin were purchased from Sigma-Aldrich (Merck KGaA, Darmstadt,

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Germany). ELISA kits for assaying TNF-α and IL-6 were obtained from R&D (Minneapolis, MN, USA). Assay kits for amylase (AMY), creatinine (Cr) and blood urea nitrogen (BUN) were purchased from Jiancheng Biotech (Nanjing, China). TRIzol reagent was obtained from Invitrogen (Thermo Fisher Scientific, Inc., Waltham, MA, USA) and Moloney murine leukemia virus (M-MLV) reverse transcriptase was from Promega, Corp. (Madison, WI, USA). Antibodies against JAK2 (cat no. 3230), phosphorylated (p)-JAK2 (cat no. 3776), STAT3 (cat no. 4904), p-STAT3 (cat no. 9145) and suppressor of cytokine signaling 3 (SOCS3; cat no. 2923) were purchased from Cell Signaling Technology, Inc. (Danvers, MA, USA) and horseradish peroxidase (HRP)-conjugated GAPDH antibody (cat no. sc-2577) was purchased from Santa Cruz Biotechnology (Dallas, TX, USA).

Animals. A total of 30 male Sprague-Dawley rats (age, 8-10 weeks; weight, 200-250 g) were obtained from Shanghai Laboratory Animals Co., Ltd. (Shanghai, China). All animals were housed under standardized conditions with a 12-h light/dark cycle with free access to standard laboratory chow and water. All protocols and procedures used in the study complied the US National Institute of Health Guidelines for the Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Utilization Committee of Fujian Medical University (Fuzhou, China).

Experimental models and groups. The rats were divided into three subgroups: Sham controls, SAP rats treated with saline and SAP rats treated with curcumin (100 mg/kg). Rats were fasted 12 h prior to the operation. The three groups were dived into 3, 12 and 24 h time-point groups (each sub-group contained 3 rats). After anesthesia with 10% chloraldurat (0.3 ml/100 g, Sigma Aldrich; Merck KGaA, Darmstadt, Germany), the SAP model was induced by a standard pressure-controlled infusion of a freshly prepared 5% sodium taurocholate (Sigma Aldrich; Merck KGaA) solution (0.1 ml/100 g) into the bile-pancreatic duct under laparotomy as previously described (22). Rats in the sham control group underwent the same operative procedure without the injection of 5% sodium taurocholate in the pancreatic duct. In the SAP + Cur group, rats were intraperitoneally injected with curcumin solution (100 mg/kg) 30 min prior to the establishment of the SAP model. After surgery, all animals were subcutaneously injected with saline (0.2 ml/kg) in order to replenish the missing fluid.

Blood and tissue preparation. The rats were sacrificed at designated time-points after the induction of pancreatitis. The blood samples were obtained via intracardiac puncture and then centrifuged to obtain the serum to be stored at -20°C until assay. Pancreas and kidney tissues were dissected quickly on ice, and parts of tissues were immediately fixed for hematoxylin and eosin staining analysis, while others were frozen in liquid nitrogen and stored at -80°C for later analysis.

Hematoxylin and eosin staining analysis. After blood collection, rat pancreas and kidney tissues were removed, immediately fixed and preserved in 70% ethanol. Subsequent to embedding in paraffin, specimens were cut in 4-μm-thick sections and mounted on 3-aminopropyltriethoxysilane-coated glass slides. The sections were de-paraffinized in xylene, re-hydrated in decreasing concentrations of ethanol in water and stained with hematoxylin and eosin reagent. Examination of sections was performed with a light microscope (Olympus Ltd., Tokyo, Japan).

Serum AMY, BUN and Cr assays. Serum levels of AMY and Cr as well as BUN were measured using standard diagnostic kits following the manufacturer's instructions.

Serum TNF-α and IL-6 levels. ELISA kits were used to detect serum TNF-α and IL-6 levels according to the manufacturer's instructions.

Reverse-transcription quantitative polymerase chain reaction (RT-qPCR) analysis. SOCS3 mRNA in the kidney tissue was detected by RT-qPCR analysis. In brief, total RNA was extracted from kidney tissues with TRIzol reagent according to the manufacturer's instructions, and was reverse-transcribed into complementary DNA using an oligo (dT) primer (SunShine Biotechnology, Nanjing, China) and M-MLV reverse transcriptase. The 20 μl PCR reaction mixture was prepared and contained 2-μl cDNA, 10 μl Power SYBR-Green PCR Supermix (Bio-Rad Laboratories, Inc., Hercules, CA, USA) and 1 μl of each primer and H2O-DEPC to 20 μl. RT-qPCR analysis were performed using SYBR-Green I dye (Bio-Rad Laboratories, Inc.) under the following reaction conditions: 1 min at 95°C followed by 40 cycles of 15 sec at 95°C, 1 min at 60°C. The following primers were used: SOCS3 forward, 5'-TTCGCC CTTAGCGTGAAGATGG-3' and reverse, 5'-TAGTGCTCC AGCAGCTCGAAGA-3'; GAPDH forward, 5'-CTTTGGTAT CGTGGAAGGACTC-3' and reverse, 5'-GTAGAGGCAGGGA TGATGTTCT-3'. The comparative Cq ($2^{-\Delta\Delta Cq}$) method was used to analyze the relative gene expression levels, as previously described (23). GAPDH was used as an internal positive control.

Western blot analysis. The expression of JAK2, STAT3 and SOCS3 protein as well as the levels of p-JAK2 and p-STAT3 in kidney tissues were measured by western blot analysis. Protein extracts were obtained by homogenizing samples in a cell lysis buffer (10 mM Tris-HCl, 1 mM EDTA and 250 mM sucrose, pH 7.4, containing 15 μg/ml aprotinin, 5 μg/ml leupeptin, 0.1 mM phenylmethanesulfonyl fluoride, 1 mM NaF and 1 mM Na_3VO_4), followed by centrifugation at 12,000 x g for 15 min. The protein concentration was determined using a bicinchoninic acid kit (Thermo Fisher Scientific, Inc.). A total of 30 μg protein per lane was separated by 10% SDS-PAGE, transferred onto polyvinylidene fluoride membranes (Millipore, Billerica, MA, USA), blocked with 5% skim milk and incubated with primary antibodies (p-JAK2: 1:1,000, JAK2: 1:1,000, p-STAT3, 1:1,000, SOCS3: 1:1,000, GAPDH: 1:500) at 4°C overnight. Then the blots were incubated with the corresponding secondary antibody (HRP-conjugated whole-goat anti-rabbit IgG, 1:10,000; cat no. 074-1506; Kirkegaard & Prerry Lab Inc., Gaithersburg, MD, USA) for 2 h at room temperature. Finally, immunoreactive bands were visualized via enhanced chemiluminescence (Cell Signaling Technology, Inc., Danvers, MA, USA) and the membranes were then immediately exposed to autoradiographic film (Eastman Kodak, Rochester, NY, USA).
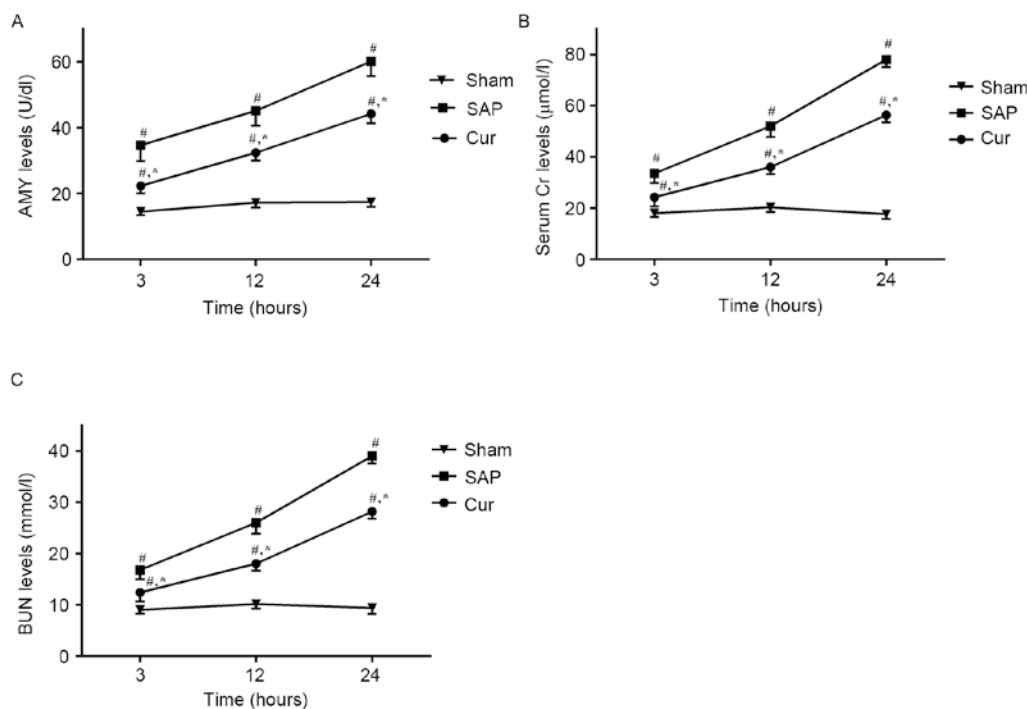
Figure 1. Effects of curcumin on the levels of serum (A) AMY and (B) Cr as well as (C) BUN in SAP rats. Values are expressed as the mean ± standard deviation (n=4). #P<0.05 vs. Sham group; *P<0.05 vs. SAP group. SAP, severe acute pancreatitis; Cur, SAP model rats pre-treated with curcumin; Cr, creatinine; BUN, blood urea nitrogen; AMY, amylase.

Statistical analysis. Results were expressed as the mean ± standard deviation. Statistical analysis was performed using one-way analysis of variance followed by a post-hoc test (Fisher's least significant differences test) as appropriate with the statistical analysis system GraphPad Prism 6 (GraphPad Software, Inc., La Jolla, CA, USA). P<0.05 was considered to indicate a statistically significant difference.

Results

Curcumin attenuates SAP-induced increases in serum AMY, Cr and BUN. As shown in Fig. 1A, serum AMY levels were significantly increased in the SAP group at all time-points in comparison with those in the Sham group. However, in the Cur group, these increases in serum AMY levels were significantly inhibited. Moreover, the SAP group showed elevated levels of serum Cr (Fig. 1B) and BUN (Fig. 1C) compared with those in the Sham group. Treatment with curcumin obviously decreased the levels of serum Cr and BUN at the respective time-points.

Curcumin pre-treatment reduces histopathological changes in the pancreas and kidneys of SAP rats. Pancreatic and renal histological changes were assessed using hematoxylin and eosin staining. As shown in Fig. 2, obvious edema, inflammatory cell infiltration and necrosis were observed in the pancreases of SAP rats at 12 h (Fig. 2B). Compared to the SAP group, the pancreatic histological injuries were significantly ameliorated by pre-treatment with curcumin (Fig. 2C). Furthermore, Fig 3 shows that, SAP rats at 12 h demonstrated glomerular and tubular damage as well as inflammatory cell infiltration, suggesting renal injury (Fig. 3B). However, rats

pre-treated with curcumin demonstrated reduced histological features in the kidney in comparison with those in the SAP rats (Fig. 3C).

Curcumin reduces SAP-induced increases of serum TNF-α and IL-6 levels in SAP rats. The effect of curcumin on the serum levels of inflammatory cytokines, TNF-α and IL-6, were analyzed using ELISA kits. As shown in Fig. 4, a substantial increase in TNF-α and IL-6 levels was observed in the SAP group. However, pre-treatment with curcumin significantly decreased serum levels of TNF-α and IL-6 in this animal model.

Curcumin suppresses the JAK2/STAT3 signaling pathway in SAP rats. Elevated mRNA and protein levels of SOCS3 were observed in the kidneys of SAP rats. These alterations in SAP rats were attenuated by pre-treatment with curcumin at the mRNA and protein level (Fig. 5A and B). To further determine JAK and STAT3 signaling in the kidneys of rats at 12 h after induction of SAP, western blot analysis was applied. Compared to the Sham group, the SAP group showed elevated renal protein levels of p-JAK2 and p-STAT3. Curcumin distinctly inhibited the activation of JAK2 and STAT3 in this model (Fig. 5B).

Discussion

The present study demonstrated that a) renal injury caused by SAP was significantly improved by pre-treatment with curcumin, b) curcumin greatly decreased the secretion of inflammatory cytokines and c) the mechanism by which curcumin ameliorates renal injury includes the reduction
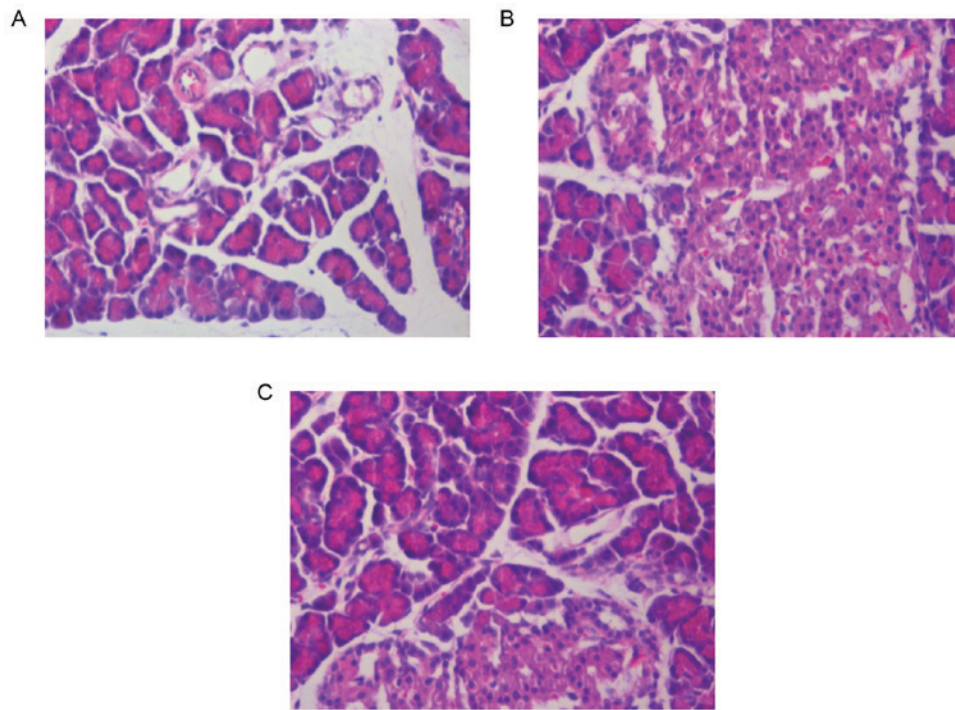
Figure 2. Effects of curcumin on morphological changes in the pancreas at 12 h following SAP in rats. Hematoxylin and eosin staining of pancreatic tissue of (A) Sham group, (B) SAP group and (C) curcumin-pre-treated SAP model rats (magnification, x200). SAP, severe acute pancreatitis.
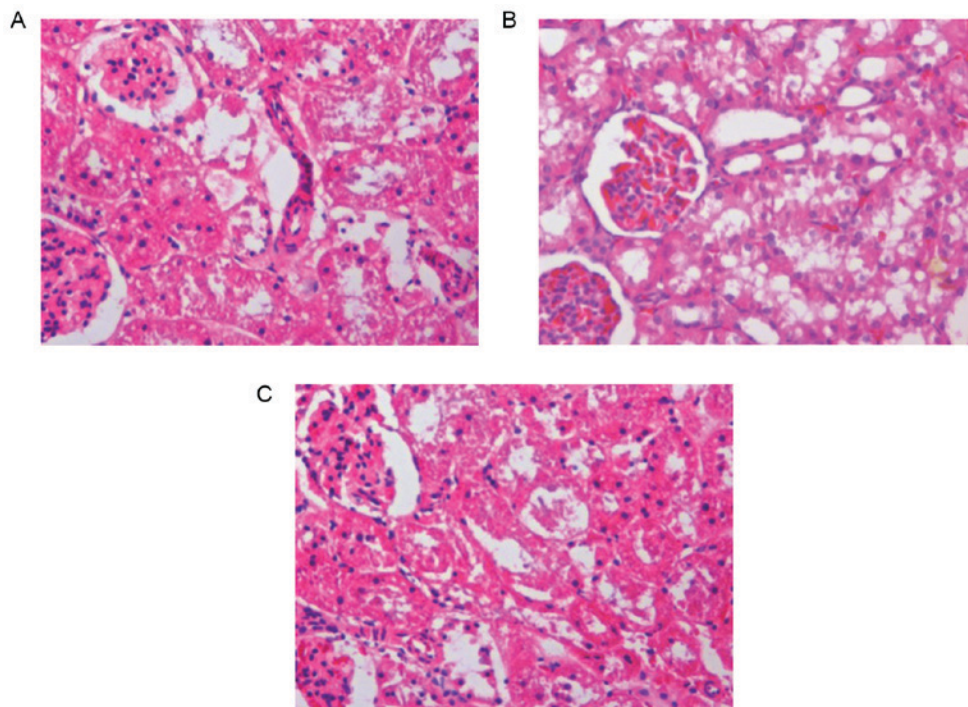

Figure 3. Effects of curcumin on morphological changes in the kidney at 12 h following SAP in rats. Hematoxylin and eosin staining of the renal tissue of (A) Sham group, (B) SAP group, (C) curcumin-pre-treated SAP model rats (magnification, x200). SAP, severe acute pancreatitis.

of inflammation and suppression of JAK2/STAT3 pathway activation.

A previous study confirmed the protective effect of curcumin in a rat model of SAP (19). In the present study, hyperamylasemia and pancreatic pathological evidence were observed in the SAP model group, which were obviously improved by pre-treatment with curcumin. Moreover, the levels of BUN and serum creatinine were increased, alongside obvious pathological damage, which was indicative of renal injury in this SAP model. However, pre-treatment with curcumin significantly ameliorated the pathological changes in the kidneys of SAP rats and also decreased BUN
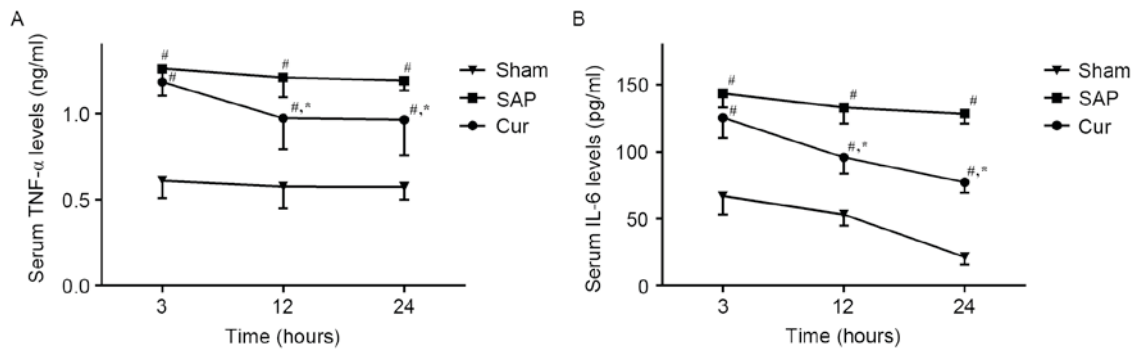
Figure 4. Effects of curcumin on serum (A) TNF-α and (B) IL-6 levels in SAP rats. Values are expressed as the mean ± standard deviation (n=4). #P<0.05 vs. Sham group; *P<0.05 vs. SAP group. SAP, severe acute pancreatitis; Cur, SAP model rats pre-treated with curcumin; TNF, tumor necrosis factor; IL, interleukin.
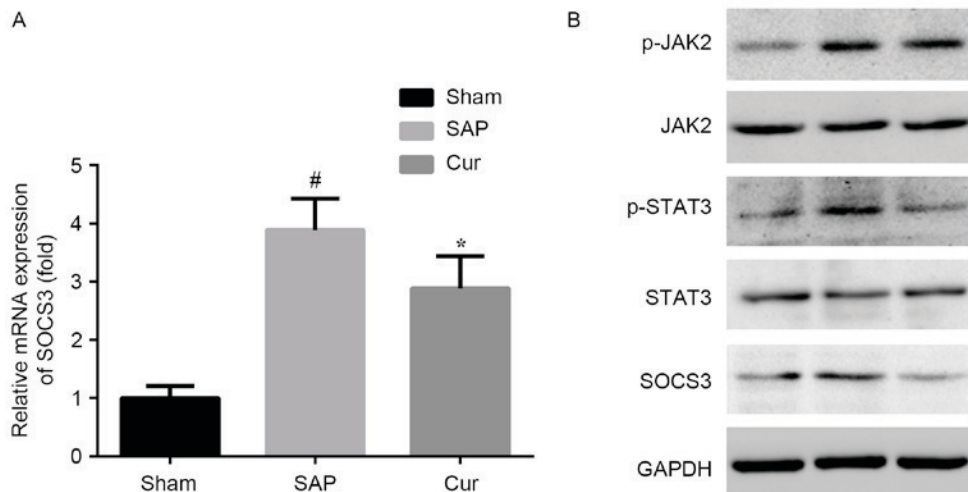

Figure 5. Effects of curcumin on (A) SOCS3 mRNA and (B) protein levels of JAK2/STAT3 pathway components in SAP rats. Values are expressed as the mean ± standard deviation (n=4). #P<0.05 vs. Sham group; *P<0.05 vs. SAP group. SAP, severe acute pancreatitis; Cur, SAP model rats pre-treated with curcumin; p-JAK2, phosphorylated Janus kinase 2; STAT3, signal transducer and activator of transcription 3; SOCS3, suppressor of cytokine signaling 3.

and serum Cr levels in rats with renal injury associated with SAP.

At present, the pathogenesis of SAP-induced renal injury remains elusive. It has been generally recognized that the excess release of cytokines and inflammatory mediators has a pivotal role in SAP and SAP-associated renal injury (24). Cytokines such as IL-6 and TNF-α exert a major effect on the outcome of SAP, particularly by triggering the systemic inflammatory response and multisystem organ failure, which is mostly responsible for the associated mortality (25). In the present study, increased serum levels of IL-6 and TNF-α were observed in the SAP group, which were greatly decreased by treatment with curcumin. These results combined with the histological and biochemical changes in the kidneys of SAP rats indicated that curcumin attenuated renal injury in SAP rats, at least in part via the inhibition of inflammatory cytokines.

The JAK/STAT pathway is a pleiotropic cascade essential to cytokine and growth hormone receptor signaling (26). An increasing body of evidence has suggested the involvement of the JAK/STAT pathway in renal disease (27-29). A previous study indicated that the activation of JAK/STAT3 signaling induces the expression of IL-1β in cerulean-stimulated pancreatic acinar cells (30). Of note, studies have shown that curcumin, as an inhibitor of the JAK2/STAT3 pathway, exerts marked effects in several experimental models and human diseases (21,31). The present study found that the phosphorylation of JAK2 and STAT3 was significantly increased in the kidneys of SAP rats, which was inhibited by pre-treatment with curcumin, suggesting that the inflammatory response triggered by SAP was effectively inhibited by curcumin via interfering with JAK2/STAT3 pathway activation. However, few studies have investigated the role of JAK2/STAT3 signaling in renal injury following SAP. The present study provided in vivo evidence that the JAK2/STAT3 pathway is activated in renal injury following SAP, and that the reno-protective effect of curcumin in SAP is associated with the inhibition of this activation.

In conclusion, the present study demonstrated the reno-protective effect of curcumin in a rat model of SAP. The underlying mechanism of its effect is in part the inhibition of JAK2/STAT3 pathway activation to reduce the inflammation cascade and inflammatory cytokine secretion. Therefore, the findings of the present study revealed the potential use of

curcumin for the prevention and treatment of SAP and the associated renal injury.

Acknowledgements

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