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Protective Role of TNIP2 in Myocardial Injury Induced by Acute Pancreatitis and Its Mechanism

Authors' Contribution:
Study Design A
Data Collection B
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Literature Search F
Funds Collection G

ABCDEFG Hualei Xie*
BDEF Maoyong Yang*
BCDE Bo Zhang
CDEF Min Liu
ABCDEFG Shumei Han

Department of Emergency Medicine, The Second People's Hospital of Liaocheng affiliated to Taishan Medical College, Linqing, Shandong, P.R. China

* Equal contributors

Corresponding Author: Shumei Han, e-mail: hanshum2017@163.com

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Background: Aberrant regulation of nuclear factor-κB (NF-κB) and the signaling pathways that regulate its activity have been found to be involved in various pathologies, particularly cancers, as well as inflammatory and autoimmune diseases. Acute pancreatitis (AP) is a complex pathological process, depending on autodigestion caused by premature activation of zymogens. This study aimed to investigate the effect of high expression of TNIP2 gene on AP and AP-induced myocardial injury.

Material/Methods: To investigate the effect of TNIP2 on AP and AP-induced myocardial injury, we established an AP cell model and rat model. HE staining was applied for histological examination. ELISA was used to determine the level of pro-inflammatory cytokines (TNF-α and IL-6) and myocardial injury markers (LDH and CK-MB). QRT-PCR and Western blot analysis were performed to determine the mRNA and protein level of related genes, respectively.

Results: We found that the protein level of TNIP2 was relatively higher in the normal AR42J cells. At 4 h after stimulating with cerulein, the protein level of TNIP2 decreased, reached a minimum at 8 h, and then gradually increased. We also found that TNIP2 was correlated with the activation of NF-κB in cerulein-stimulated AR42J cells, and TNIP2 over-expression inhibited the inflammatory response caused by cerulein. Moreover, our results suggest that TNIP2 over-expression relieved the cerulein-triggered inflammatory response and AP-induced myocardial injury in mice.

Conclusions: TNIP2 was shown to exert a protective effect on AP and AP-induced myocardial injury.

MeSH Keywords: Heart Injuries • NF-kappa B • Pancreatitis

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Background

In recent years, acute pancreatitis (AP) was found to have a high incidence in many countries. Poland is one of the countries with a high incidence rate, which equals 79.7/100 000 [1]. Most cases of AP are mild, with recovery within 5–7 days by conservative treatment. Nonetheless, about 15%–20% of the patients have a severe, protracted course leading to death [2–4]. Numerous studies showed that pancreatic necrosis is crucial for the development of mild acute pancreatitis (MAP) to severe acute pancreatitis (SAP) [5–7].

MAP has a short course, and the pancreatic structure and function can be fully restored. However, in SAP, once acinar cells necrosis occurs, rupture of the acinar cell membrane releases a series of inflammatory factors, including TNF-α and IL-6, resulting in systemic inflammatory response syndrome, seriously damaging pancreatic structure and function [8]. Many clinical and experimental studies suggest that after AP, especially SAP, endocrine and exocrine function of the pancreas often suffer varying degrees of damage, even developing into permanent sequelae of pancreatic dysfunction [9–11]. Therefore, protecting acinar cells against necrosis in the early phase of AP could play an important role in the pathological processes of AP.

Recently, due to their vital roles in the occurrence and development of AP, signaling molecules and pathways are becoming a popular research topic [12]. As one of the most important signal molecules, nuclear factor-κB (NF-κB) was found to play critical roles in the AP process [13]. NF-κB is an important transcription factor involved in the regulation of proliferation, survival, apoptosis, immune, inflammatory reaction, and cancer metastasis [14–16]. Transcription factors of the NF-κB family are pivotal in controlling cellular responses to environmental stresses, and abnormal NF-κB activation is found in many autoimmune diseases and cancers [17,18]. Several components of the NF-κB signaling pathway have been reported to interact with protein TNIP2 (also known as ABIN2), and TNIP2 can both positively and negatively regulate NF-κB-dependent transcription of target genes [19].

The TNIP2 gene encodes a protein identified as a suppressor of NF-κB activation. The encoded protein is also involved in the MAP/ERK signaling pathway in specific cell types and it may be involved in apoptosis of endothelial cells [20]. A previous study reported the link between TNIP2, cellular transport machinery, and RNA transcript processing [19]. However, the function of TNIP2 remains elusive and the cellular machinery associated with TNIP2 has not been systematically defined. The relationship between TNIP2 and NF-κB also remains largely unknown.

The present study investigated the effect of high expression of the TNIP2 gene on AP and AP-induced myocardial injury.

Material and Methods

Reagents

The AR42J acinar cell line was obtained from American Type Culture Collection (ATCC, Manassas, VA, USA); the DMEM medium, fetal bovine serum (FBS), and penicillin/streptomycin solution were purchased from Mediatech (Herndon, VA, USA) and Gibco (Grand Island, NY, USA), respectively; the cerulein (sigma, C9026) and ELISA kits were purchased from Excell (Shanghai, China); the Trizol reagent and ThermoScript RT-PCR system were obtained from Invitrogen (Grand Island, NY, USA); and the antibodies (TNIP2, p-p65, p65, and β-actin) were all purchased from Santa Cruz.

Cell culture and cell model of AP

AR42J acinar cells were grown in DMEM containing 10% FBS and 1% penicillin/streptomycin solution. Cells were incubated in a humidified incubator at 37°C with 5% CO_2. Cell culture medium was replaced every 2 days before being stimulated with cerulein. Cerulein is an analogue of cholecystokinin that can cause pancreatic exocrine and pancreatic cell inflammatory responses. Ten nmol/L of cerulein-induced pancreatic acinar cell inflammation is usually used as an *in vitro* model of AP. Cells were divided into 2 groups: an AP model group (10 nmol/L cerulein) and a blank control group (PBS). Then, the culture supernatant was collected at 0, 4, 8, 12, and 24 h after cerulein treatment and preserved at –80°C for further research.

TNIP2-plasmid transfection

Con-plasmid or TNIP2-plasmid was transfected into AR42J cells using Lipofectamine 2000 (Invitrogen) according to the manufacturer's instructions. At 24 h after cell transfection, cerulein was used to induce the AP cell model. The cells were then collected for PCR, Western blot, and ELISA analysis.

Animal model of AP

Female ICR mice, weighing 23–26 g, were obtained from Vital River Company (Beijing, China). Before the experiment, the animals were fed standard rodent chow and water, and were monitored in an environment with controlled temperature and a 12-h light/dark cycle for at least 1 week. The principles of Laboratory Animal Care (NIH publication number 85Y23, revised 1996) were followed, and the experimental protocol was approved by the Animal Care Committee, Taishan Medical College.

Mice were injected with cerulein (50 μg/kg) to build the AP model. Animals were randomly assigned to 4 groups (each group had 8 mice): Blank control; AP model; AP model + Con-plasmid; and AP model+TNIP2-plasmid. Mice in the blank control

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group were given saline (0.9% NaCl) solution intraperitoneally instead of the cerulein and plasmids. After cerulein treatment, blood was collected at 18 h for ELISA detection.

RNA preparation and qRT-PCR

Total RNA from AR42J cells was extracted by using Trizol reagent (Invitrogen, Grand Island, NY, USA) following the manufacturer's directions. cDNAs were synthesized by performing the reverse transcription experiment with the ThermoScript RT-PCR system (Invitrogen, Grand Island, NY, USA). The primer sequences used for RT-PCR were:
TNIP2:
Forward-5'-CTAAAGAGGCGGCAGGTCCCTC-3';
Reverse-5'-CAAGATGACCTTCCAGTGAC-3';
β-actin [21]:
Forward-5'-CTATCGGCAATGAGCGGTTC-3';
Reverse-5'-AGGAGCCAGGGCAGTAATCT-3'.

Then, real-time PCR was applied in the following reaction conditions: 95°C for 5 min, 37 cycles at 95°C for 30 s, 55°C for 30 s, and 72°C for 30 s, then 72°C for 10 min. β-actin was used as an internal control.

Western blot analysis

After treatment with cerulein, the AR42J cells were washed with cold PBS and then lysed in RIPA buffer [50 mM Tris, pH 7.2; 150 mM NaCl; 0.1% SDS; 1% sodium deoxycholate; 10 mM NaF; 1% Triton-X 100; 1 mM Na_3VO_4; protease inhibitor cocktail (1: 1000)]. After sonication and centrifugation, protein concentration was detected using the BCA assay, and the bovine serum albumin was used as the standard. Protein samples were isolated on 10% SDS-polyacrylamide gel and then transferred to a polyvinylidene difluoride membrane. Membranes were blocked by incubating with PBS supplemented with 5% skim milk and 0.05% Tween 20, and then the membranes were incubated with a primary antibody (TNIP2, p-p65, p65, 1: 1000; β-actin, 1: 2000), followed by a secondary antibody. The Gel-Pro Analyzer densitometry software (Media Cybernetics) was used to quantify the band density.

Enzyme-linked immunosorbent assay (ELISA)

The cell culture supernatant and mice serum were harvested to determine the secretion of TNF-α, IL-6, LDH, and CK-MB by using an ELISA kit following the manufacturer's protocols. Every sample was detected at least 3 times by using a microplate reader (Bio-Rad).

Histological examination

Fresh specimens of mouse pancreas were fixed in 4% formaldehyde, embedded in paraffin blocks, stained with hematoxylin and eosin, and then examined with a light microscope. The histopathological scoring analysis of pancreas was performed blindly by 2 pathologists according to previously described methods.

Statistical analysis

The data are displayed as mean values ± standard deviation (mean ±SD). Comparison between 2 groups was performed by the *t* test. A level of $p<0.05$ was considered statistical significance.

Results

AR42J cell model of AP induced by cerulein

The AR42J cell model of AP is a mature cell model for studying intracellular mechanisms that participate in the AP process. The pro-inflammatory cytokines and cell injury marker (LDH) of the pancreatic cell were detected after cerulein stimulation. ELISA assay showed that the expression level of TNF-α, IL-6, and LDH in the cell model group had maximum enhancement at 8 h (Figure 1A–1C), then decreased. We also detected TNIP2 gene expression after cerulein treatment. Western blot results showed that the TNIP2 protein level reached its minimum at 8 h, and then gradually increased, and mRNA expression was similar to protein changes (Figure 1D, 1E). After cerulein stimulation, the expression level of TNIP2 was negatively correlated with the secretion of the pro-inflammatory cytokines, indicating that TNIP2 might be involved in the inflammatory response, which is critical in the development of AP.

Many studies have reported that NF-κB plays an important role in the AP process [22–24]. In the present study, the expression level of p65 and phosphorylated p65 in the AR42J cells at different time points after treatment with cerulein was detected. The results showed that the expression of phosphorylated p65 was correlated with the progression of AP and reached the highest level at 8 h, then slightly declined. Thus, we confirmed that cerulein stimulation notably improved the phosphorylation of p65, which indicates the activation of NF-κB, in AR42J cells (Figure 2).

Elevated TNIP2 reduced acute pancreatitis

To further investigate the function of TNIP2, TNIP2-plasmids were transfected into AR42J cells, and the Con-plasmid was used as the control. At 24 h after transfection, the protein

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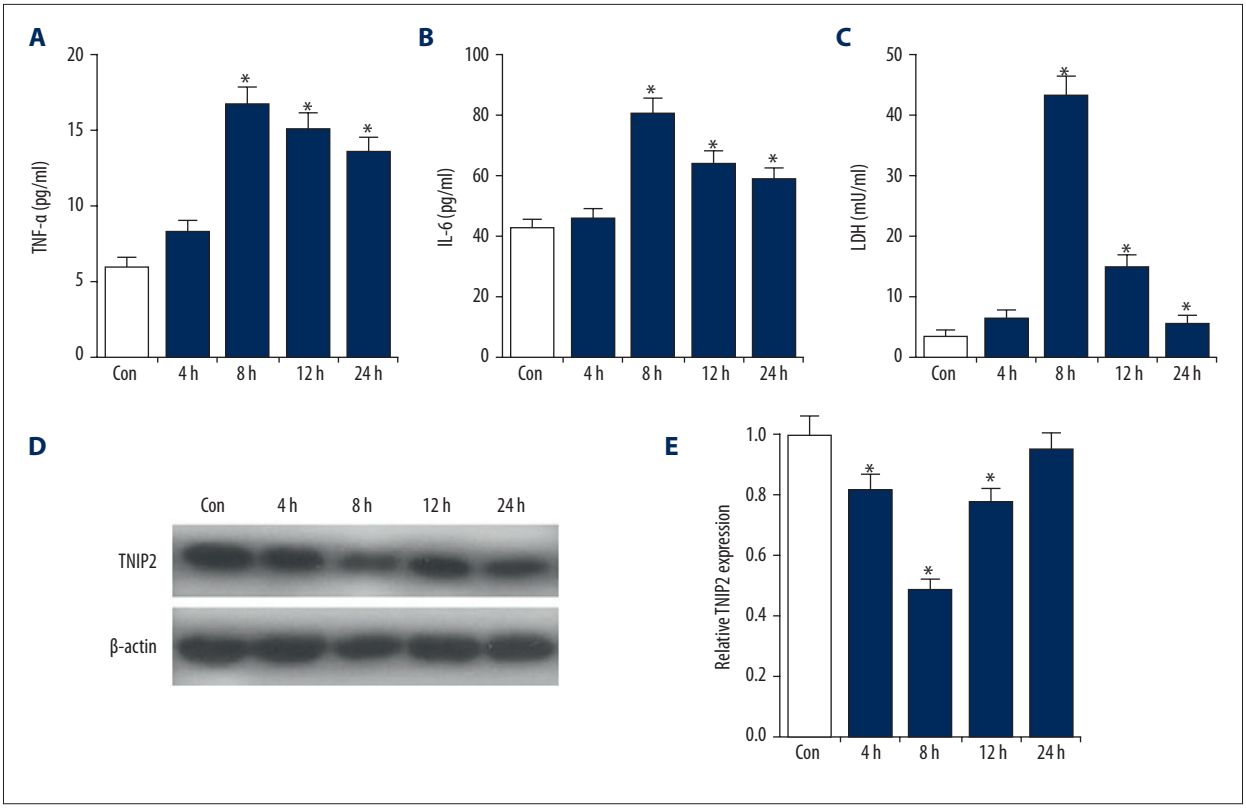

Figure 1. Cytokine production and TNIP2 expression in the AP cell model. AR42J cells were treated with 10 nM cerulein for up to 24 h. ELISA assay was performed for the detection of TNF-α (**A**), IL-6 (**B**) and LDH (**C**). Protein (**D**) and mRNA (**E**) level of TNIP2 were determined by Western blot and qRT-PCR, respectively. Con – blank control group; 4 h, 8 h, 12 h, and 24 h – cells treated with 10 nmol/L cerulein for 4 h, 8 h, 12 h, and 24 h, respectively. * p<0.05 *vs.* Con.

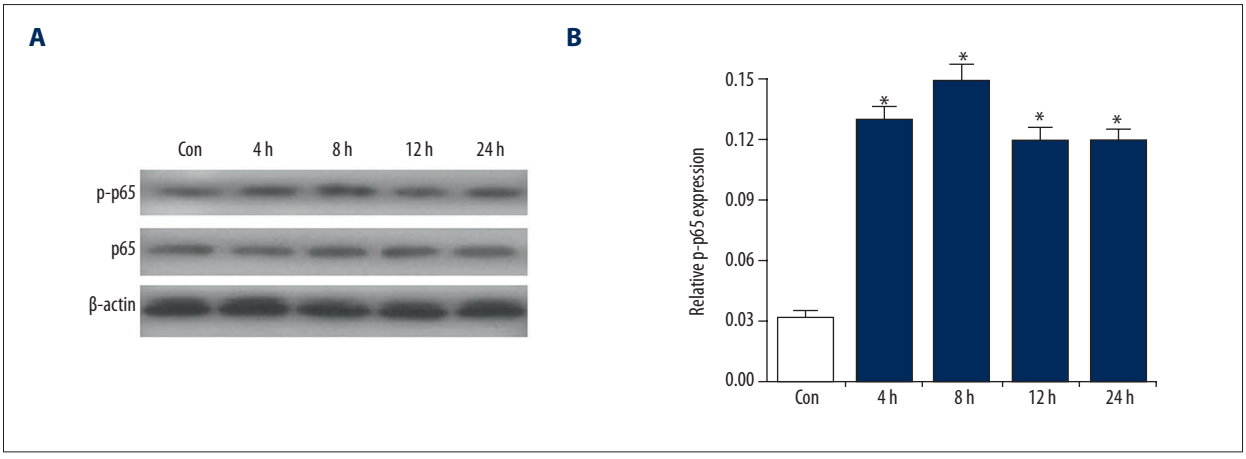

Figure 2. NF-κB activation in cerulein-stimulated AR42J cells. AR42J cells were treated with 10nM cerulein for up to 24 h. (**A**) The activating phosphorylation of p65 at different time points after cerulein treatment was detected by Western blot analysis; (B) relative quantitation data of p-p65 protein expression, β-actin was used as loading control. Con – blank control group; 4 h, 8 h, 12 h, and 24 h – cells treated with 10 nmol/L cerulein for 4 h, 8 h, 12 h, and 24 h, respectively. * p<0.05 *vs.* Con.

and mRNA levels of TNIP2 were significantly up-regulated (Figure 3A, 3B). Cerulein was then used to induce AP, and the expression level of TNF-α, IL-6, and LDH were detected by ELISA assay at 8 h after cerulein treatment. The results indicate that over-expression of TNIP2 reduced TNF-α, IL-6, and LDH expression (Figure 3D–3F), thereby relieving the inflammatory response.

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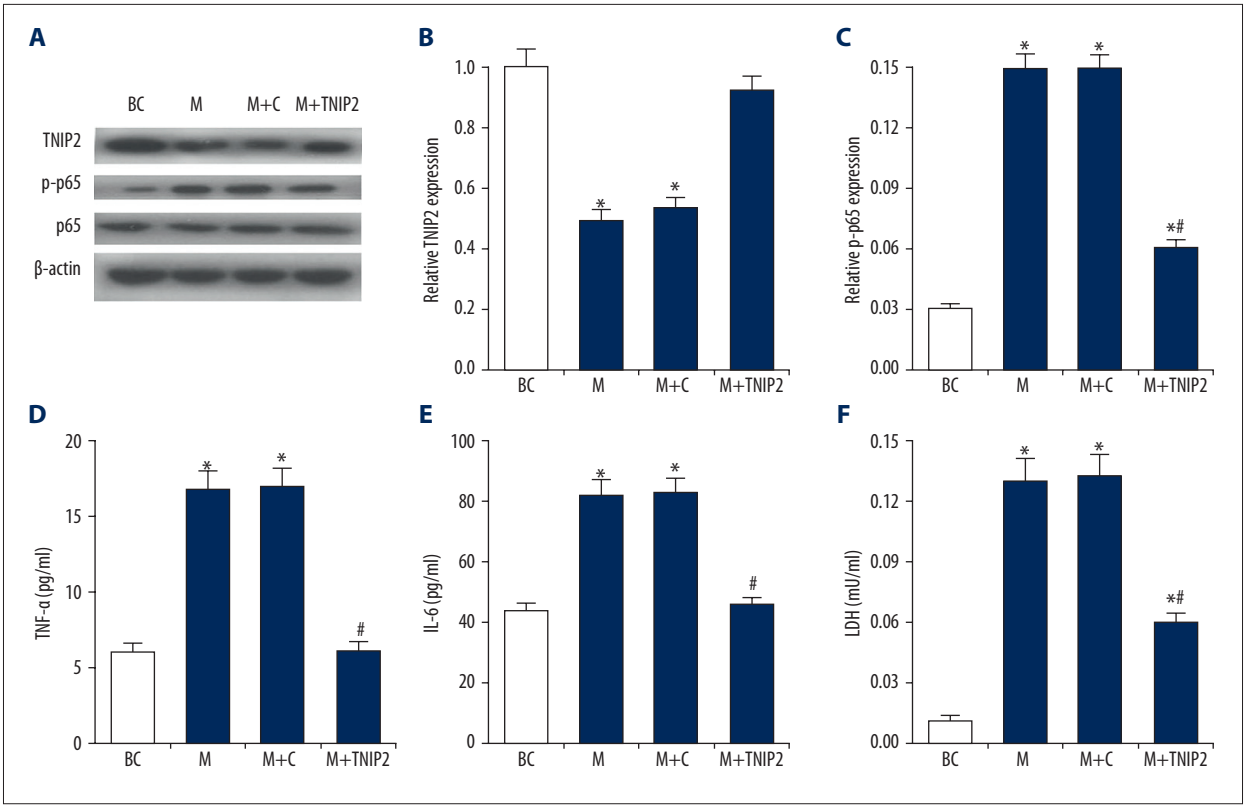

Figure 3. TNIP2 is associated with NF-κB activation in cerulein-stimulated AR42J cells. TNIP2 over-expression by TNIP2 plasmid alleviated cerulein-induced p65 activation and pro-inflammatory mediator production in AR42J cells. (**A, B**) protein and relative mRNA expression level of TNIP2 was detected by Western blot and qRT-PCR assay; (**A, C**) protein expression level of p-p65 was measured by Western blot analysis, and the relative quantitation data was calculated; (**D–F**) the levels of TNF-α (**D**), IL-6 (**E**), and LDH (**F**) in the culture supernatant were measured by ELISA. BC – blank control group; M – AP cell model group; M+C – cells transfected with Con-plasmid; M+TNIP2 – cells transfected with TNIP2-plasmid. * p<0.05 *vs.* BC; # p<0.05 *vs.* M.

TNIP2 inhibits inflammatory response by inhibiting NF-κB activation

The present study showed that TNIP2 might have roles in the inflammatory response in the pathological process of AP. To demonstrate the relationship between TNIP2 and NF-κB activation, p-p65 expression was determined after cell transfection. As expected, TNIP2 over-expression significantly inhibited p-p65 expression in AR42J cells (Figure 3A, 3C). Our data indicate that TNIP2 can inhibit NF-κB activation, thereby inhibiting the inflammatory response and reducing AP.

Establishment of acute pancreatitis mouse model

The murine model of AP induced by cerulein is widely accepted. In the present study, 18 h following treatment with 50 μg/kg cerulein, AP was observed according to the morphological characteristics and serum pro-inflammatory cytokines levels. In the AP group, the pancreatic tissue exhibited marked edema and was infiltrated by inflammatory cells. A mass of necrotic acinar cells and the disappearance of normal structure in the pancreatic lobes were also observed in the mice in this group (Figure 4A). As shown in Figure 4B–4E, in the AP group mice, a marked increase in the serum pro-inflammatory cytokines (TNF-α, IL-6) and myocardial injury marker (CK-MB\LDH) levels was noted after being induced for 18 h. The results indicate that inflammatory factors play important roles in the development of AP, and that myocardial injury was induced by AP.

Effect of TNIP2 on AP and AP-induced myocardial injury in mice

In the previous experiments, AP mouse models were successfully constructed using cerulein induction. We found that over-expression of TNIP2 inhibited the inflammatory response and reduced AP in the cell model. To further confirm the role of the TNIP2 gene in the process of AP in mice, TNIP2-plasmid was used. The results showed that TNIP2-plasmid significantly down-regulated the serum CK-MB\LDH, TNF-α, and IL-6 expression (Figure 4), thereby reducing the inflammatory response

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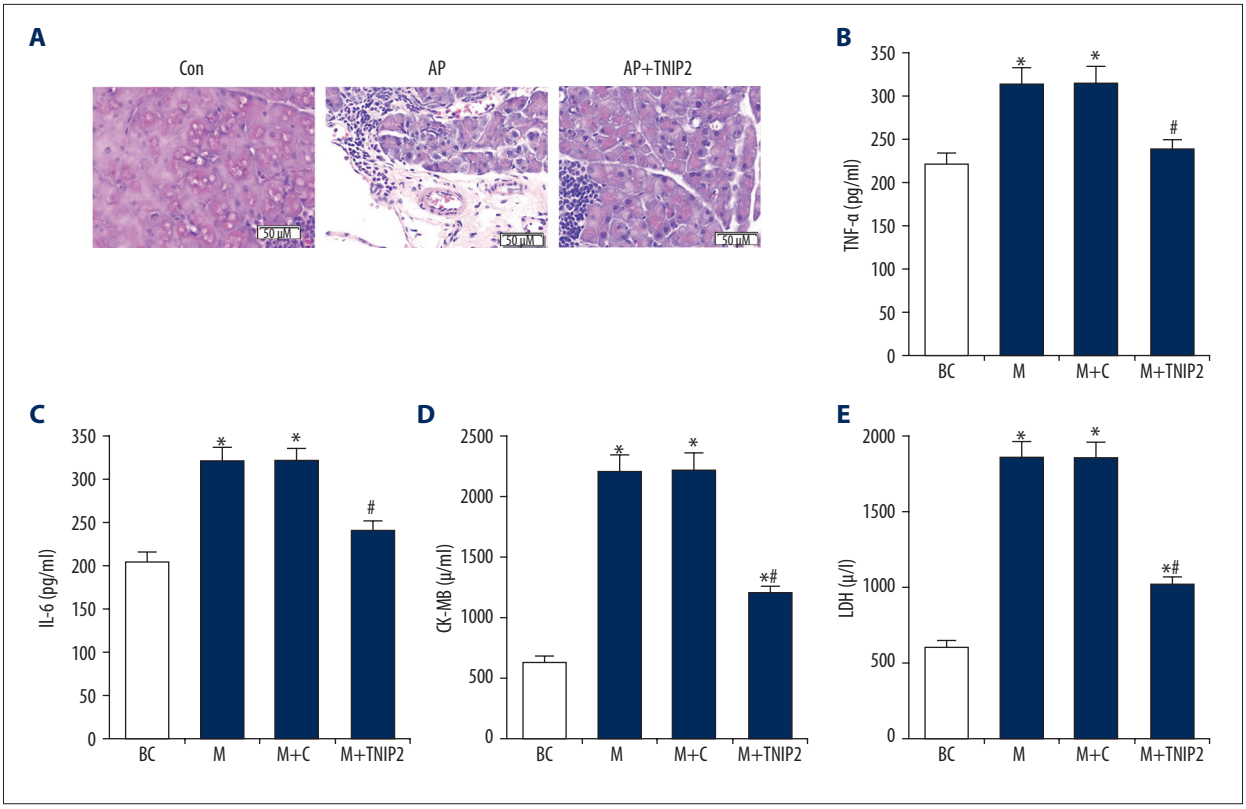

Figure 4. Effect of TNIP2 on AP and AP-induced myocardial injury in the rat model. The AP rat model was induced by intraperitoneal injections of cerulein (50 μg/kg) in rats. (**A**) H&E staining of the pancreatic sections in the AP rat model. (n=8 per group; bar: 50 um); (**B–E**) the levels of TNF-α (**B**), IL-6 (**C**), CK-MB (**D**), and LDH (**E**) in the serum of rats were measured by ELISA. BC – blank control group; M – AP cell model group; M+C – cells transfected with Con-plasmid; M+TNIP2 – cells transfected with TNIP2-plasmid. * p<0.05 *vs.* BC; # p<0.05 *vs.* M.

of mice, reducing AP, and relieving the myocardial injury induced by AP.

Discussion

AP begins with the local inflammation in the pancreas, and causes systemic inflammatory reaction and complications [25]. The underlying mechanisms of this complex disease are still largely unclear [25]. Following exposure to several stimulants, a series of the downstream molecules of NF-κB are activated, such as TNF-α, IL-10, IL-6, IL-1b, and iNOS. Studies have reported that cerulein induces NF-κB activation, thereby causing AP *in vitro* and *in vivo* [27–29]. In the present study, we found that cerulein stimulation promoted the phosphorylation of p65 and thus caused the activation of NF-κB in AR42J cells.

To investigate the potential function of TNIP2 in the AP process, an AP cell model was established by stimulating with cerulein. We found that in the control group, the level of TNF-α, IL-6, and LDH was relatively lower after cerulein stimulation, and the expression of pro-inflammatory cytokines increased significantly, reached a peak at 8 h, and then gradually decreased. However, the expression level of TNIP2 was negatively correlated with the pro-inflammatory cytokines, indicating that TNIP2 might be involved in the inflammatory response in the pathological process of AP.

NF-κB activation plays a key role in the induction of several pro-inflammatory mediators. The nuclear translocation of the NF-κB transcription factor is the hallmark of the signal pathway activation. To identify the inflammatory pathways involved in the role of TNIP2 in the pathogenesis of AP, we examined the expression level of NF-κB p65 and p-p65 after TNIP2 was overexpressed in AR42J acinar cells. We found that TNIP2 inhibited NF-κB activation. We conclude that TNIP2 reduces the expression level of TNF-α and IL-6 through inhibiting the NF-κB signaling pathway, thereby reducing the symptoms of pancreatitis.

Most AP involves peripancreatic tissues and other distant organs, and then develops into serious secondary local and systemic complications, such as infected pancreatic necrosis (IPN), acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), sepsis, and myocardial injury (MI). In the present

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study, we established an AP mouse model, studied the effect of TNIP2 on AP and AP-induced myocardial injury, and we determined the level of pro-inflammatory cytokines (TNF-α and IL-6) and myocardial injury markers (LDH and CK-MB). We found that the serum levels of pro-inflammatory cytokines (TNF-α and IL-6) and myocardial injury markers (LDH and CK-MB) were significantly increased in the AP mouse model, and the pancreatic tissue exhibited marked edema and was infiltrated by inflammatory cells. We found that over-expression of TNIP2 reduced the expression of myocardial injury markers (LDH and CK-MB) and the pro-inflammatory cytokines (TNF-α and IL-6), which is consistent with the results of the cell model, indicating that TNIP2 inhibits the development of pancreatitis and reduces the myocardial injury caused by AP.

Conclusions

In conclusion, TNIP2 can alleviate the symptoms of AP and relieve AP-induced myocardial injury by regulating the NF-κB signaling pathway. This study provides a new target for the future treatment of pancreatitis.

Our data suggest that TNIP2 can relieve acute AP and AP-induced myocardial injury though regulating the NF-κB signaling pathway. TNIP2 is a potential target for AP treatment.

Conflict of interest

None.

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