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ORIGINAL RESEARCH

USP15 alleviates the cerulein-induced cell apoptosis and inflammatory injury to AR42J cells through regulating TAB2/3/NF-κB pathway in acute pancreatitis

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Abstract

Acute pancreatitis, characterized by parenchymal cell death and inflammatory process of pancreas, is a lethal disease. USP15 (ubiquitin-specific peptidase 15) belongs to USP family and participates in the ubiquitination system. USP15 was implicated in inflammatory processes and involved in the tumor progression. However, the roles of USP15 in acute pancreatitis-associated inflammation and apoptosis have not been reported yet. Firstly, *in vitro* cell model of acute pancreatitis was established through incubation of AR42J with cerulein. Results showed that cerulein induced inflammatory response in AR42J with up-regulation of TNF-α, IL-6 and IL-1β. USP15 was up-regulated in cerulein-induced AR42J. Secondly, siRNA-mediated silence of USP15 reduced levels of TNF-α, IL-6 and IL-1β, and pcDNA-mediated over-expression of USP15 enhanced the levels of TNF-α, IL-6 and IL-1β. Moreover, cell apoptosis of cerulein-induced AR42J was suppressed by silence of USP15 with reduced cleaved caspase-3 and cleaved caspase-9, while promoted by USP15 over-expression. Lastly, silence of USP15 decreased protein expression of p65 phosphorylation and TAB (Transforming growth factor-β activated kinase-1 binding protein) 2/3 in cerulein-induced AR42J, while the protein expression was enhanced by USP15 over-expression. In conclusion, USP15 contributed to cerulein-induced AR42J inflammatory response and cells injury through regulation of TAB2/3/NF-κB pathway in acute pancreatitis.

Keywords

USP15; Cerulein; Apoptosis; Inflammatory; AR42J; TAB2/3/NF-κB; Acute pancreatitis

1. Introduction

Acute pancreatitis is a life-threatening disease with a high mortality rate and is one of the most common gastrointestinal disorders [1]. Acute pancreatitis is characterized by systemic inflammation and pancreatic necrosis/apoptosis [2]. Acute pancreatitis can develop into many severe diseases, such as acute respiratory distress syndrome, multi-organ dysfunction syndrome and systemic inflammatory response syndrome that increases the mortality rates of patients up to more than 50% [3]. Previous study has shown that pro-inflammatory cytokines, such as tumor necrosis factor TNF-α and interleukin (IL)-6, are associated with the severity of pancreatic injury in acute pancreatitis [4]. Therefore, it is of great clinical significance to explore the mechanism of inflammation and find out the potential therapeutic target for acute pancreatitis against the inflammatory response [5].

As deubiquitinating enzymes, ubiquitin-specific proteases (USPs) play an important role in various cellular processes, such as DNA repair, chromatin remodeling, protein degradation, cell cycle regulation, endocytosis and metastasis [6]. USP15 belongs to USPs family, and participates in the ubiquitination system to deubiquitinate vital target proteins [7]. USP15 is implicated in the immune and inflammatory response to autoimmune or infectious insults following tissue damages [8]. For example, USP15 mutation was resistant to neuroinflammation through inhibiting type I interferon responses [9]. Moreover, USP15 also regulated pathways involved in tumor onset and progression [8]. In addition, USP15 can inhibit anti-tumor T cell responses and tumor cell apoptosis [10]. USP15 was correlated with the expression transforming growth factor-β receptors in patients with pancreatic ductal adenocarcinoma and pathological N (pN) stage and the survival time of patients, suggesting its potential prognostic role [11]. However, the effects of USP15 on acute pancreatitis-associated inflammation and cell apoptosis have not been reported yet.

In this study, AR42J cell, an immortalized pancreatic adenocarcinoma cell, was treated with cerulein to establish the *in vitro* cell model of acute pancreatitis. Effects of USP15 on cell apoptosis and inflammatory response in AR42J cells induced by cerulein were then investigated. The USP15-mediated downstream signaling pathway involved in cerulein-induced inflammatory response and cell injury was also ex-

plored, which might provide a therapeutic target for treating acute pancreatitis.

2. Materials and methods

2.1 Cell culture and treatment

AR42J, the pancreatic acinar cell line, was purchased from ATCC (Rockville, MD, USA), and cultured in DEME containing 10% fetal bovine serum and 1% streptomycin/penicillin (Gibco BRL, Gaithersburg, MD, USA). Cells were incubated at 37 ℃ in a 5% CO_2 incubator. AR42J was divided into four groups: the control group was cultured in normal conditions, the cerulein groups were cultured in DMEM supplemented with 10 nmol/L cerulein (Sigma-Aldrich, St. Louis, MO, USA) for 4, 8 or 12 hours.

2.2 Cell transfection

siRNA targeting USP15 (si-USP15) and the negative control (si-NC) were provided by Genepharma (Shanghai, China). pcDNA-mediated over-expression of USP15 (pcDNA-USP15) and the empty vector (pcDNA) were provided by Genepharma. AR42J cells were seeded in a 96-well plate, and then transfected with si-NC, si-USP15, pcDNA, or pcDNA-USP15 with Lipofectamine 2000 (Invitrogen, Groningen NL, USA). Twenty-four hours later, the cells were cultured with DMEM containing 10 nmol/L cerulein for 8 hours before the functional analysis.

2.3 ELISA and flow cytometry

The culture supernatants of AR42J cells were harvested, and then assayed with commercial ELISA kits (Sigma-Aldrich) for the detection of TNF-α, IL-6, IL-1β, ROS, SOD and MDA. For cell apoptosis analysis, AR42J cells were harvested and resuspended in 1$\times$ binding buffer from annexin V/FITC kit (Beyotime, Shanghai, China). The mixed cell suspension was added with 5 μL annexin V/FITC for 5 minutes followed by 10 μL propidium iodide. The apoptotic activity of AR42J cells was analyzed by FACScan flow cytometer (Becton-Dickinson, Mountain View, CA, USA).

2.4 Western blot

AR42J cells were homogenized in RIPA buffer (Shanghai Biocolor BioScience & Technology Co., Shanghai, China), and the bicinchoninic acid protein quantitative kit (Pierce, Rockford, IL, USA) was used to determine the protein concentration. Each sample (40 μg) was separated by electrophoresis and then transferred onto polyvinylidene difluoride membranes. The membrane was blocked in Tris-buffered saline-0.1% Tween-20 buffer containing 5% non-fat dry milk. Specific antibodies, including USP15 (1:2000; Santa Cruz Biotechnology, Santa Cruz, CA, USA), cleaved caspase-3 and cleaved caspase-9 (1:2500; Santa Cruz Biotechnology), TAB2 and TAB3 (1:3000; Santa Cruz Biotechnology), p65 and p-p65(1:3500; Santa Cruz Biotechnology), GAPDH (1:4000; Santa Cruz Biotechnology). The membranes were first incubated with above mentioned specific antibodies, followed by incubation with horseradish peroxidase-conjugated secondary antibodies (1:5000; Kangcheng Inc., Shanghai, China). The enhanced chemiluminescence (Amersham Biosciences, Piscataway, NJ, USA) were used to detect the signals in the membrane under bio-image analysis system (Bio-Rad, Baltimore, MD, USA).

2.5 Statistical analysis

All data from at least triplicate experiments were presented as the means $\pm$ standard deviation. Comparison of the difference between two groups were analyzed by Student's t test under GraphPad Prism 7 (GraphPad Inc., San Diego, CA, USA), and one-way Analysis of Variance was used to analyzed the difference among multiple groups. $p < 0.05$ was considered as statistically significant difference.

3. Results

3.1 Elevated USP15 in cerulein-induced AR42J cells

To establish *in vitro* cell model of acute pancreatitis, AR42J cells were incubated with cerulein. Western blot analysis showed that USP15 was elevated in cerulein-treated AR42J cells compared with that in control (Fig. 1A). The expression of USP15 protein was higher in cells incubated with cerulein for 8 hours compared to cells incubated for 4 hours and 12 hours (Fig. 1A). Moreover, TNF-α, IL-6 and IL-1β expression was also up-regulated in cerulein-treated AR42J cells compared to control (Fig. 1B). Similarly, compared with cells with cerelein treatment for 4 hours and 12 hours, incubation with cerulein for 8 hours showed higher TNF-α, IL-6 and IL-1β levels (Fig. 1B). Therefore, cells were treated with cerulein for 8 hours in the following functional analysis.

3.2 USP15 contributed to cerulein-induced inflammation in AR42J cells

To investigate effects of USP15 on cerulein-treated AR42J cells, AR42J cells transfected with si-USP15 or pcDNA-USP15 were incubated with cerulein for 8 hours. The transfection efficiency was verified in Fig. 2A. Cerulein-induced inflammation in AR42J cells was suppressed by silence of USP15 with reduced TNF-α, IL-6 and IL-1β expression (Fig. 2B), while over-expression of USP15 promoted the effect of USP15 (Fig. 2B). These results suggested that USP15 contributed to cerulein-induced inflammation in AR42J cells.

3.3 USP15 contributed to cerulein-induced oxidative stress in AR42J cells

Knockdown of USP15 reduced the level of ROS production in cerulein-treated AR42J cells (Fig. 3A), while ROS was up-regulated in cerulein-treated AR42J cells transfected with pcDNA-USP15 (Fig. 3A). Moreover, SOD expression was up-regulated and MDA expression was down-regulated by silence of USP15 (Fig. 3B). Over-expression of USP15 reduced SOD expression and enhanced MDA expression (Fig. 3B), indicating the pro-oxidative role of USP15 on cerulein-treated AR42J cells.

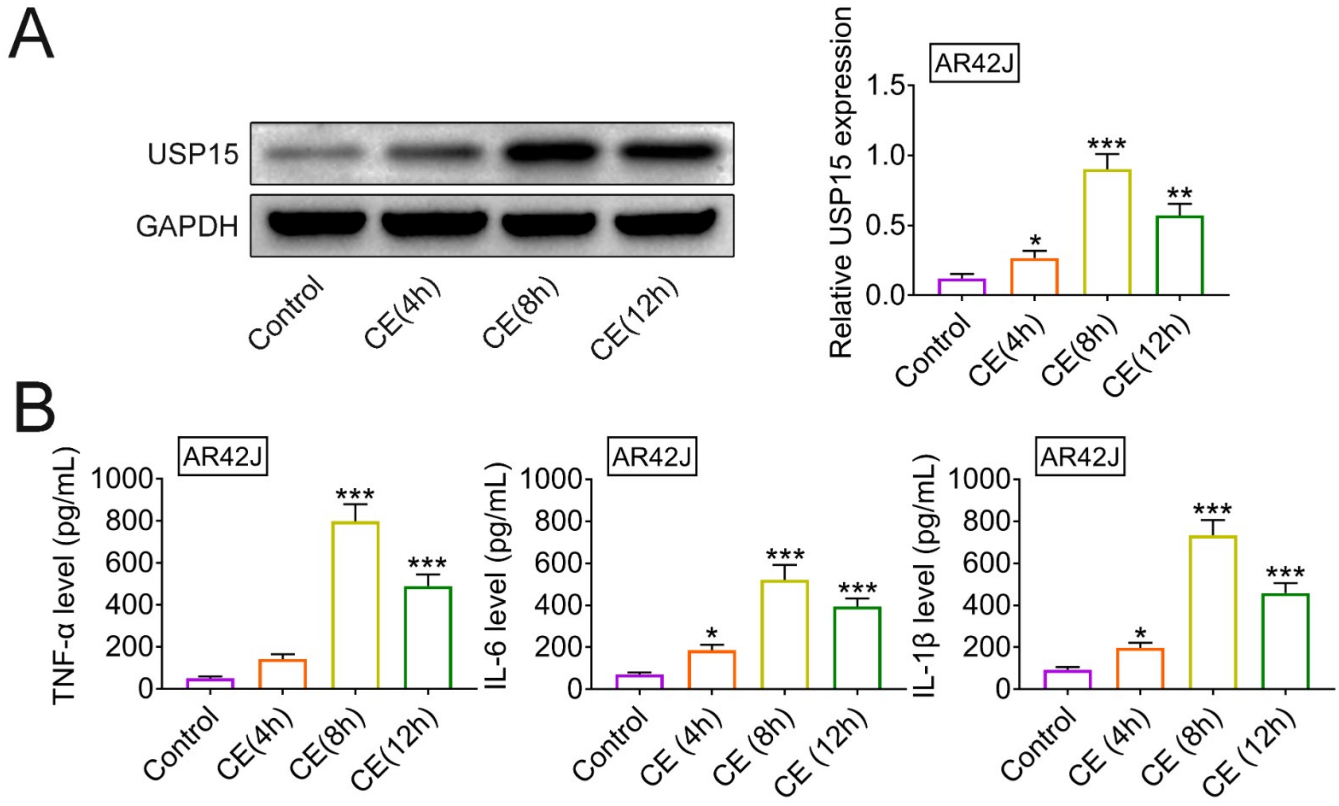

FIGURE 1. Elevated USP15 in cerulein-treated AR42J cells.
(A) Protein expression of USP15 in AR42J cells post cerulein treatment for 4, 8, or 12 hours.
(B) Expression of TNF-α, IL-6 and IL-1β in AR42J cells post cerulein Treatment for 4, 8, or 12 hours. *, **, *** vs. control, $p < 0.05$, $p < 0.01$, $p < 0.001$.

3.4 USP15 contributed to cerulein-induced apoptosis in AR42J cells

Knockdown of USP15 reduced cerulein-induced cell injury in AR42J cells through inhibition of cell apoptosis (Fig. 4A), and the cerulein-induced cell injury in AR42J was promoted by overexpressing USP15 (Fig. 4A). Moreover, protein expression of cleaved caspase-3 and cleaved caspase-9 were separately decreased and increased in cerulein-treated AR42J cells post si-USP15 and pcDNA-USP15 transfection (Fig. 4B), showing the pro-apoptotic role of USP15 in cerulein-treated AR42J cells.

3.5 USP15 contributed to the activation of TAB2/3-NF-κB signaling in cerulein-treated AR42J cells

Over-expression of USP15 increased the expression of TAB2 and TAB3 protein in cerulein-treated AR42J cells (Fig. 5), while silence of USP15 reverse the results (Fig. 5). Although expression of p65 protein was neither affected by si-USP15 nor pcDNA-USP15 transfection in cerulein-treated AR42J cells (Fig. 5), phosphorylation of p65 was decreased by si-USP15 transfection while increased by pcDNA-USP15 transfection (Fig. 5). These results demonstrated that USP15promoted the activation of TAB2/3-NF-κB signaling in cerulein-treated AR42J cells.

4. Discussion

Ubiquitination system was reported to be involved in inflammatory injuries, such as autoimmune and toxic hepatitis, acute and chronic pancreatitis [12]. Ubiquitin-proteasome pathway-mediated IκBα degradation was inhibited, and NF-κB was then inactivated to attenuate acute pancreatitis and myocardial infarction [13]. Inhibitors targeting USPs enhanced ubiquitination and degradation of Beclin1, thus suppressing autophagy [14], and the inhibitors of autophagy are useful for cancers and acute pancreatitis treatment [15]. Therefore, USPs might be involved in the pathogenesis of acute pancreatitis. Previous study has shown that USP15 was implicated in the neuroinflammation and neurodegenerative diseases [8]. Therefore, the effects of USP15 on acute pancreatitis was investigated in this study.

Cerulein has been shown to induce pancreatic acinar cell inflammation, and lead to cell damages [16]. AR42J cells were widely used in the *in vitro* cell model of pancreatic inflammatory response and apoptosis [3]. Cerulein promoted cell apoptosis and inflammatory response in AR42J cells leading to cell injury in acute pancreatitis [3]. Here, it has been shown that incubation with cerulein up-regulated expression of pro-inflammatory cytokines including TNF-α, IL-6 and IL-1β, in AR42J cells, confirming successful establishment of *in vitro* cell model of acute pancreatitis.

USP15 expression was found to be enhanced in cerulein-

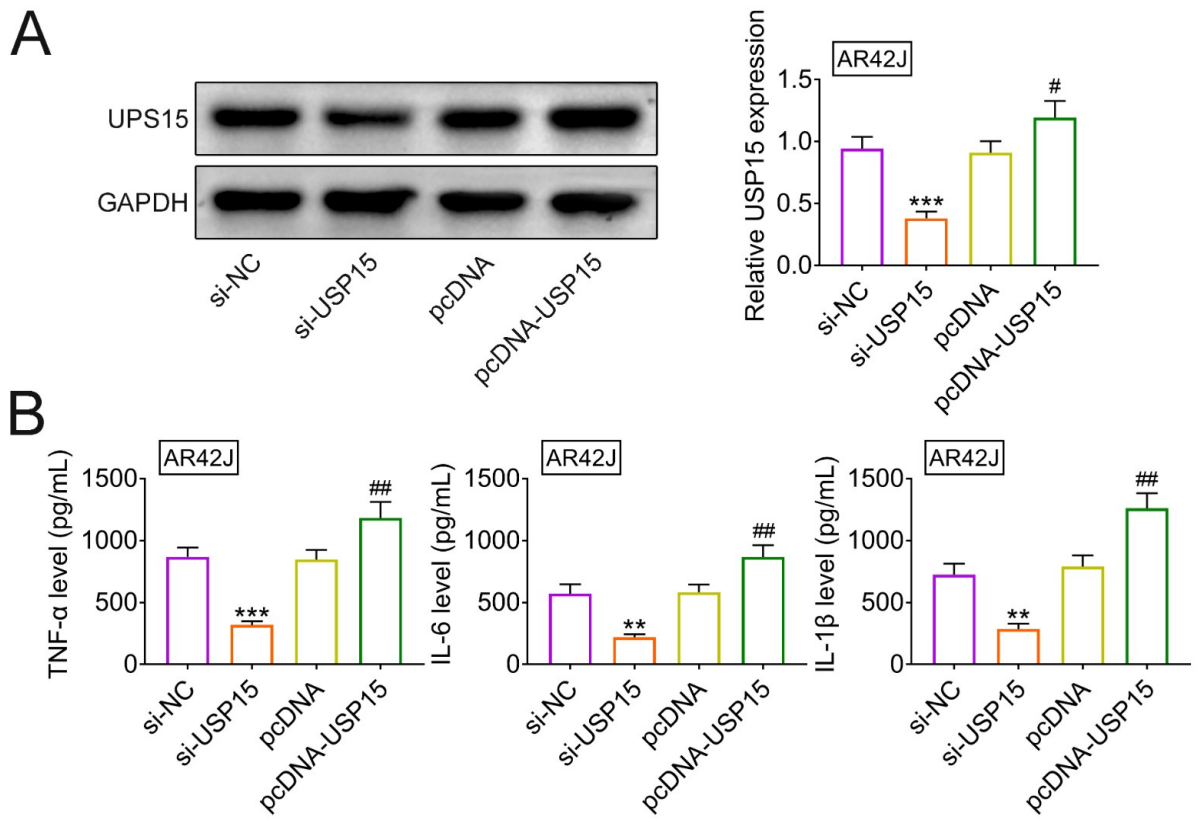

FIGURE 2. USP15 contributed to cerulein-induced inflammation in AR42J cells.
(A) Protein expression of USP15 in cerulein-treated AR42J cells transfected with si-USP15 or pcDNA-USP15.
(B) Silence of USP15 reduced TNF-α, IL-6 and IL-1β expression in cerulein-treated AR42J, while over-expression of USP15 enhanced the TNF-α, IL-6 and IL-1β production. **, *** vs. si-NC, $p < 0.01$, $p < 0.001$. #, ## vs. pcDNA, $p < 0.05$, $p < 0.01$.

treated AR42J cells. Over-expression of USP15 promoted expression of TNF-α, IL-6 and IL-1β, suggesting the pro-inflammatory role of USP15 in acute pancreatitis. However, knockdown of USP15 got an opposite result indicating decreasing USP15 inhibited cerulein-induced inflammation in AR42J cells. I, Tumor immunity has been reported to be inhibited by USP15 through deubiquitination of TET2 [17], and the virus-induced Type I interferon signaling was negatively regulated by USP15 [18]. Hence, the catalytic targets of USP15 involved in acute pancreatitis should be further investigated.

Oxidative stress was implicated in the pathogenesis of acute pancreatitis, and cerulein-induced oxidative stress in AR42J cells through increasing ROS and MDA production, down-regulating GSH and SOD expression [19]. Suppression of cerulein-induced oxidative stress attenuated the injury to pancreatic acinar cells [19]. USP15 has been shown to be involved in regulation of Nrf2-mediated anti-oxidative response [20], and inhibition of USP15 ameliorated glutamate-induced oxidative damage [21]. Silence of USP15 in this study decreased ROS and MDA production, while increased SOD expression, which attenuated cerulein-induced oxidative damage, suggesting the anti-oxidative effect of USP15 silence against acute pancreatitis.

In addition to the anti-inflammatory and antioxidative effects of USP15 silence on acute pancreatitis, silence of USP15 also exhibited an anti-apoptotic role on acute pancreatitis in this study. Silence of USP15 reduced expression of cleaved caspase-3 and cleaved caspase-9 protein in cerulein-treated AR42J cells, and repressed the cell apoptosis. Knockdown of USP15 induced deubiquitination and degradation of estrogen receptor α, and contributed to the proliferative inhibition of breast cancer cells [22]. Silence of USP15 reduced NF-κBp65 expression to promote the cell apoptosis of multiple myeloma [23]. Signaling pathways involved in USP15-mediated acute pancreatitis-associated inflammation and apoptosis were then investigated in the present study.

The expression of TAB2 and TAB3 protein were separately increased and decreased by over-expression of USP15 and silence of USP15 in cerulein-treated AR42J cells. TAB2/3 functions as an interacting protein of transforming growth factor-β activated kinase-1 to promote NF-κB activation [24]. TAB3 was up-regulated in cerulein-treated AR42J cells, and silence of TAB3 reduced the pro-inflammatory cytokines production, including TNF-α, IL-6 and LDH, through inactivation of NF-κB [25]. USP15 has been shown to enhance TAB2 stabilization through inhibition of lysosome-associated TAB2 degradation, and suppressed NBR1-mediated selective autophagic TAB3 degradation to promote NF-κB activation [26]. Protein expression of phosphorylated p65 was reduced by silence of USP15 in cerulein-treated AR42J cells, indicating that the suppressive effect of USP15 silence on acute pancreatitis-

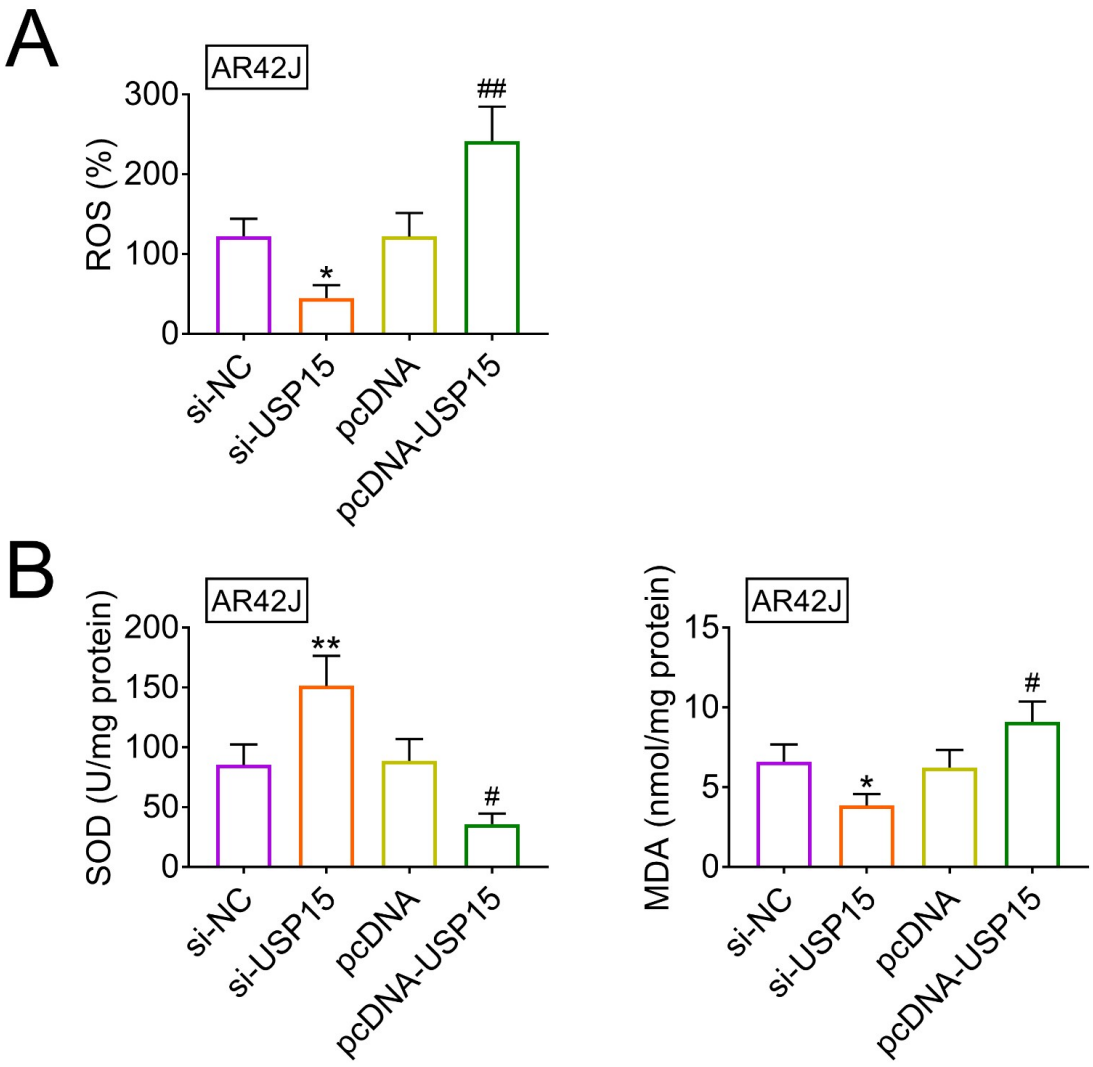

FIGURE 3. USP15 contributed to cerulein-induced oxidative stress in AR42J cells.
(A) Influence of silence and over-expression of USP15 on ROS production in cerulein-treated AR42J cells.
(B) Influence of silence and over-expression of USP15 on SOD and MDA expression in cerulein-treated AR42J cells. *, ** vs. si-NC, $p < 0.05$, $p < 0.01$. #, ## vs. pcDNA, $p < 0.05$, $p < 0.01$.

associated inflammation and apoptosis, which might be modulated by suppression of NF-κB activation.

5. Conclusions

In summary, this study provided an evidence that cerulein triggered inflammation and apoptosis in pancreatic acinar cells through activation of NF-κB. The silence of USP15 had an inhibitory effect on cerulein-induced inflammation, oxidative stress and apoptosis in AR42J cells. Moreover, knockdown of USP15 repressed TAB2/3-mediated NF-κB activation, suggesting USP15 is a potential therapeutic target for the treatment of acute pancreatitis. However, the effect of USP15 on an *in vivo* mice model of caerulein-induced acute pancreatitis should be investigated in the further research.

AUTHOR CONTRIBUTIONS

YZ and WM designed the study, supervised the data collection, CM and XR analyzed the data, interpreted the data, YW and ZF prepare the manuscript for publication and reviewed the draft of the manuscript. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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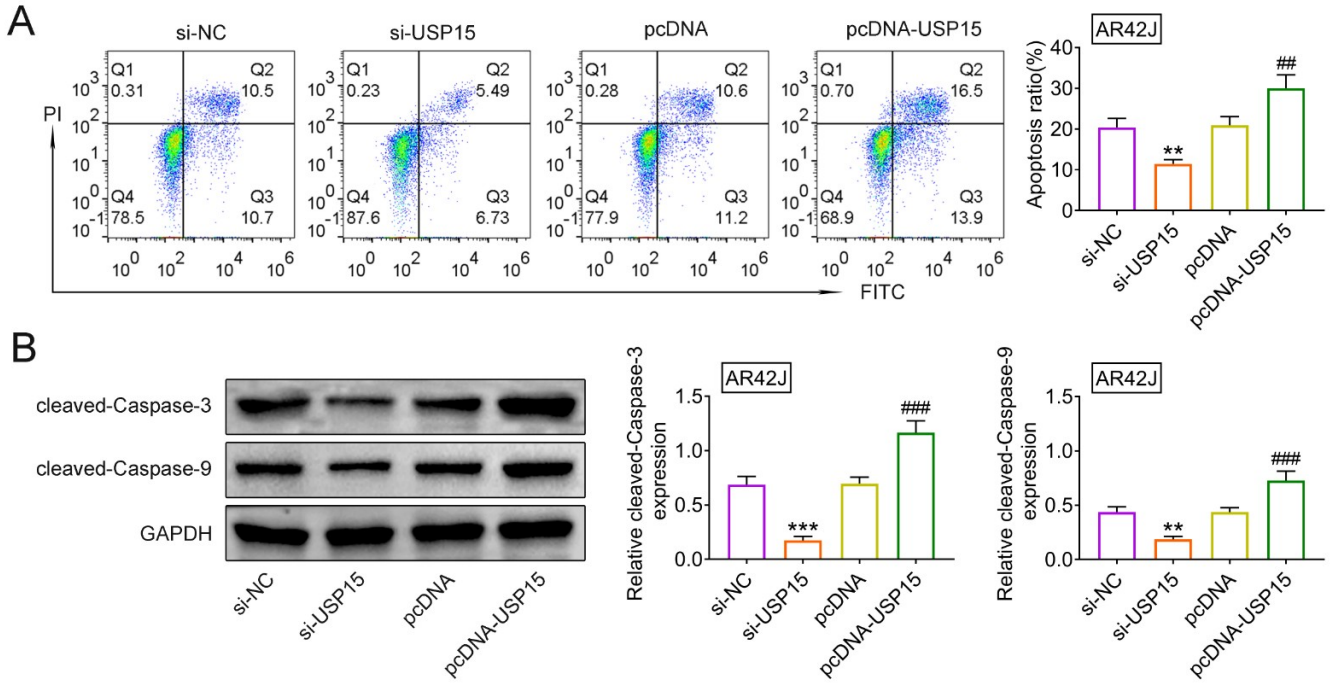

FIGURE 4. USP15 contributed to cerulein-induced apoptosis in AR42J cells.
(A) Cell apoptosis of cerulein-treated AR42J cells with silence and over-expression of USP15.
(B) The expression of cleaved caspase-3 and cleaved caspase-9 in cerulein-treated AR42J cells with silence and over-expression of USP15. **, *** vs. si-NC, $p < 0.01$, $p < 0.001$. ##, ### vs. pcDNA, $p < 0.01$, $p < 0.001$.

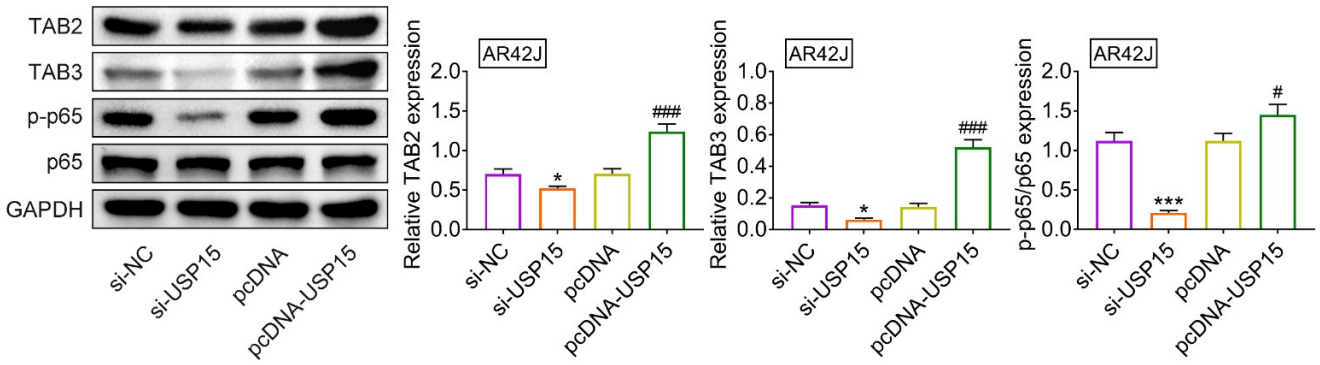

FIGURE 5. USP15 contributed activation of TAB2/3-NF-κB in cerulein-treated AR42J cells.
The expression of TAB2, TAB3, p-p65 in cerulein-treated AR42J cells with silence and over-expression of USP15. *, *** vs. si-NC, $p < 0.05$, $p < 0.001$. #, ### vs. pcDNA, $p < 0.05$, $p < 0.001$.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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