Protection of Curcumin against Streptozocin-Induced Pancreatic Cell Destruction in T2D Rats

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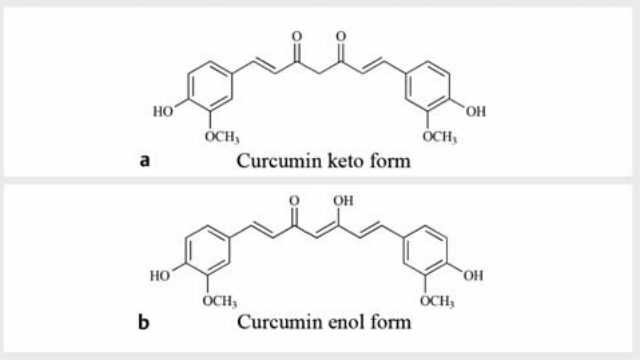
ABSTRACT

As a kind of traditional Chinese medicine extract, curcumin has been proven to be effective in inhibiting inflammation and apoptosis in pancreatic islet β cells in the streptozotocin-induced diabetes mellitus rat model, although the underlying mechanism has not yet been clarified. To examine the effect of curcumin on inflammation and apoptosis in pancreatic islet β cells, we established a type 2 diabetes rat model by feeding the animals a high-fat diet and intraperitoneally injecting streptozotocin. The curcumin was administered by intraperitoneal injection. The rat body weight, fasting blood glucose, intraperitoneal glucose tolerance tests, and insulin tolerance tests were recorded and analyzed. Hematoxylin and eosin staining was used for morphological analysis, and a TUNEL assay was performed to detect the apoptotic cells. The expression levels of proteins related to oxidative stress, inflammation and apoptosis were detected by Western blotting and ELISA. Curcumin administration significantly decreased fasting blood glucose and promoted recovery of pancreas function in type 2 diabetes rats. In curcumin-treated rats, the pancreatic tissue destruction and apoptosis index were reduced. The expression of IL-1β, IL-6, TNF-α, caspase-3, Bax, and malondialdehyde were significantly reduced, and Bcl-2, superoxide dismutase 2, and glutathione peroxidase were significantly increased. Curcumin inhibited the expression of phosphorylated JNK and NF-κB proteins to block the RAGE/JNK/NF-κB signaling pathway. In conclusion, these results indicate that curcumin blocks the phosphorylation of JNK and NF-κB protein to inhibit this signaling pathway, thereby further inhibiting inflammation and apoptosis in pancreatic islet β cells. Curcumin has potential value for the treatment of diabetes.

Introduction

Diabetes mellitus (DM) is one of the three major chronic noncommunicable diseases that threaten human health. With disease exacerbation, serious complications gradually appear and have a serious impact on the quality of life of patients. The International Diabetes Federation estimates that the global prevalence of diabetes will increase from 425 million in 2017 to 629 million by 2045 [1]. Insulin resistance (IR) and islet β cell dysfunction are the two main causes of type 2 diabetes (T2D) [2, 3]. The existing treatment methods mainly include promoting insulin secretion, improving insulin resistance, inhibiting glucose absorption, and inhibiting glycogen output, which can regulate blood sugar more effectively. However, as the disease progresses, the treatment cannot prevent the continuous destruction of islet β cells [2, 3]. Systematically elucidating the mechanism of islet β cell damage and exploring effective interventions are urgent problems that need to be solved.

Curcumin (Cur) is an acidic polyphenolic substance and is extracted from the traditional Chinese medicine turmeric. The main chain of curcumin contains unsaturated aliphatic and aromatic groups. It is a natural active substance with multiple effects and



▶ **Fig. 1** The structure of curcumin. **a** The structure of the curcumin keto form. **b** The structure of the curcumin enol form.

extremely low toxicity. Cur is used as a spice, food coloring, and traditional herbal medicine. Modern pharmacological studies have shown that Cur has antioxidant, antitumor, anti-inflammatory, hypolipidemic, and other pharmacological effects in different pathophysiological processes [4, 5]. Some scholars have conducted many basic studies on the function of Cur in diabetes, and the results showed that Cur can treat hyperglycemia, hyperlipidemia, obesity, and obesity-related metabolic diseases [6–8]. In the T2D rat model, Cur plays an important role in anti-inflammatory and antioxidative stress effects to improve glucose metabolism and protect islet β cells [9]. However, its targeting mechanism is not well understood, which affects its clinical application.

Current studies suggest that advanced glycation end products (AGEs) and their receptors (receptors of AGEs, RAGE) play an important role in the development of diabetic complications, especially in islet β cell injury [10]. In animal and human diabetes specimens, studies have shown that activation of RAGE can increase the level of intracellular oxygen radicals and then further activate JNK/NF-κB, which plays a positive role in various physiological and pathological processes, such as apoptosis and the inflammatory response [11]. The activation of JNK/NF-κB signaling is involved in the destruction of pancreatic cells by promoting the secretion of inflammatory factors [12]. Therefore, finding natural and effective active drugs to block the JNK/NF-κB signaling pathway may be valuable strategies for the prevention and treatment of diabetes. Although the antihyperglycemia effect of Cur is known, its role in protecting pancreatic β cells has not yet been reported. The present study was conducted to study the protective effect of Cur on pancreatic β cell apoptosis in streptozotocin (STZ)-induced T2D rats and the underlying mechanism.

Results

The structure of curcumin is shown in ▶ **Fig. 1 a, b**. Curcumin is a tautomeric keto-enol mixture, and the enol form is predominant. As shown in ▶ **Table 1**, the body weights of the T2D, T2D + PBS, and T2D + Cur group rats were significantly lower than those of the control group. The fasting blood glucose (FBG) levels in the T2D, T2D + PBS, and T2D + Cur group rats were higher than those in the control group ($p < 0.05$), but the FBG levels in the T2D + Cur group ($p < 0.05$) were obviously decreased compared to those of the T2D and T2D + PBS groups. During the intraperitoneal glucose tolerance tests, shown in ▶ **Fig. 2**, all three groups of T2D rats showed hyperglycemia compared to that of control rats during the 120 min of observation after glucose injection. The glucose levels in the three groups of rats reached the highest levels at 30 min after glucose injection. The values recovered to the normal level in normal control rats, but T2D and T2D + PBS rats remained hyperglycemic at 120 min. The glucose levels in curcumin-treated rats also decreased to near normal levels. In the insulin tolerance tests, the blood glucose levels declined significantly in normal rats at 30, 60, 90, and 120 min after an intraperitoneal injection of insulin. Compared to the response of normal rats, the three T2D groups of rats lacked a response to insulin. Cur treatment increased the insulin sensitivity of T2D rats.

Compared with the control group (▶ **Fig. 3 a**), hematoxylin and eosin (H&E) staining of pancreatic tissue showed that compared with the control group (▶ **Fig. 3 a**), the pancreatic islet structure was destroyed and the number of islets was reduced in T2D (▶ **Fig. 3 b**), T2D + PBS (▶ **Fig. 3 c**), and T2D + Cur (▶ **Fig. 3 d**) group rats. TUNEL staining (▶ **Fig. 4**) showed that there was a small amount of residual islet in the three groups of T2D rats, and the apoptotic index of the T2D, T2D + PBS, and T2D + Cur groups was obviously enhanced compared to that of the control group. Curcumin treatment significantly decreased the apoptotic index in the T2D + Cur group rats ($p < 0.05$) (▶ **Fig. 4 e**).

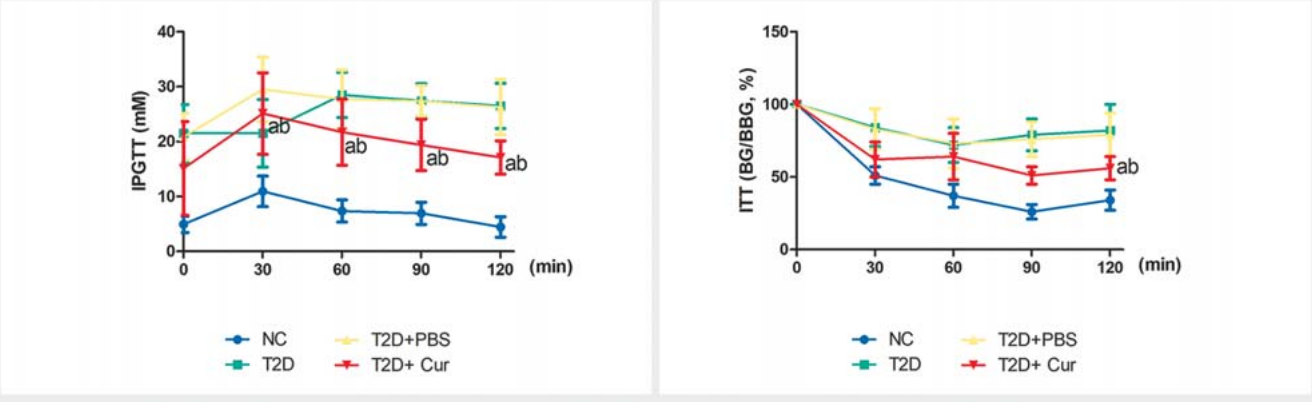
The expression of IL-1β (▶ **Fig. 5 a**), IL-6 (▶ **Fig. 5 b**), TNF-α (▶ **Fig. 5 c**), and malondialdehyde (▶ **Fig. 6 a**) in the pancreatic tissue was significantly increased in the T2D, T2D + PBS, and T2D + Cur groups compared to that of the control group. However, the expression of these substances was significantly decreased in the T2D + Cur group compared to that of the T2D and T2D + PBS groups. The antioxidant enzymes glutathione peroxidase (GSH-PX) (▶ **Fig. 6 b**) and superoxide dismutase (SOD2) (▶ **Fig. 6 c**) were significantly reduced in the T2D and T2D + PBS groups. However, GSH-PX and SOD2 levels in the T2D + Cur group were significantly enhanced compared to those of the control, T2D, and T2D + PBS groups.

Compared to the expression in the control group, the expression of RAGE, JNK, p-JNK, NF-κB, and p-NF-κB was increased in the T2D, T2D + PBS, and T2D + Cur groups ($p < 0.05$) (▶ **Fig. 7**). However, curcumin treatment significantly decreased the expression of RAGE, JNK, p-JNK, NF-κB, and p-NF-κB in the T2D + Cur group (▶ **Fig. 7**). Similarly, compared to expression in the control group (▶ **Fig. 8**), expression of the apoptosis-related proteins caspase-3 and Bax was significantly enhanced in the T2D, T2D + PBS, and T2D + Cur groups. However, curcumin treatment significantly decreased the expression of caspase-3 and Bax in the T2D + Cur group. Expression of the apoptosis-related protein Bcl-2 (▶ **Fig. 8**) was significantly reduced in the T2D and T2D + PBS groups compared to that in the control group. However, curcumin treatment significantly increased the expression of Bcl-2 compared to those in the control, T2D, and T2D + PBS groups (▶ **Fig. 8**).

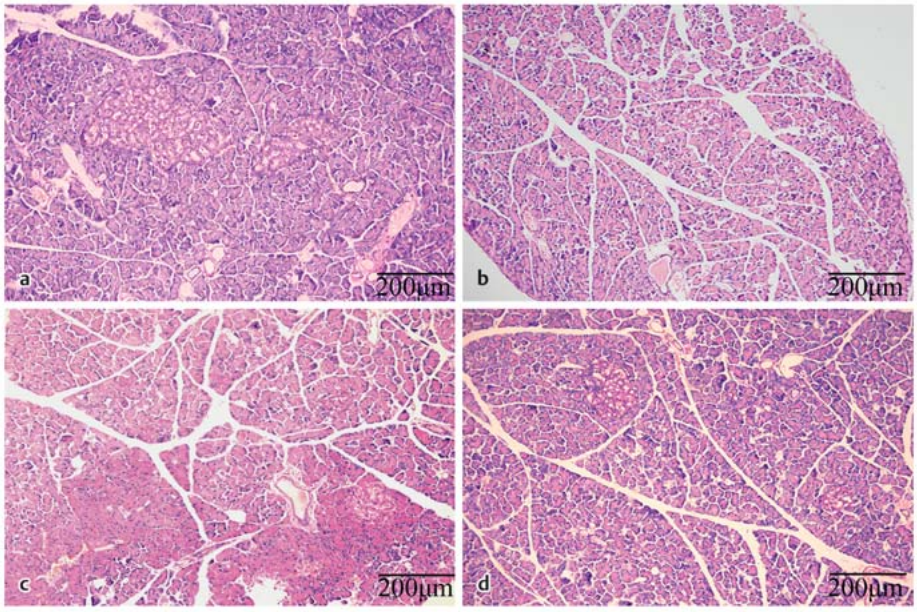
▶ **Table 1** Blood glucose metabolism and body weight.

Groups	NC	T2D	T2D + PBS	T2D + Cur
Body weight (g)	284.20 ± 17.59	222.60 ± 14.24[a]	236.15 ± 18.02[a]	241.60 ± 17.82[a]
FBG (mM)	4.84 ± 1.52	24.21 ± 4.54[a]	23.74 ± 5.14[a]	14.20 ± 3.45[a, b]

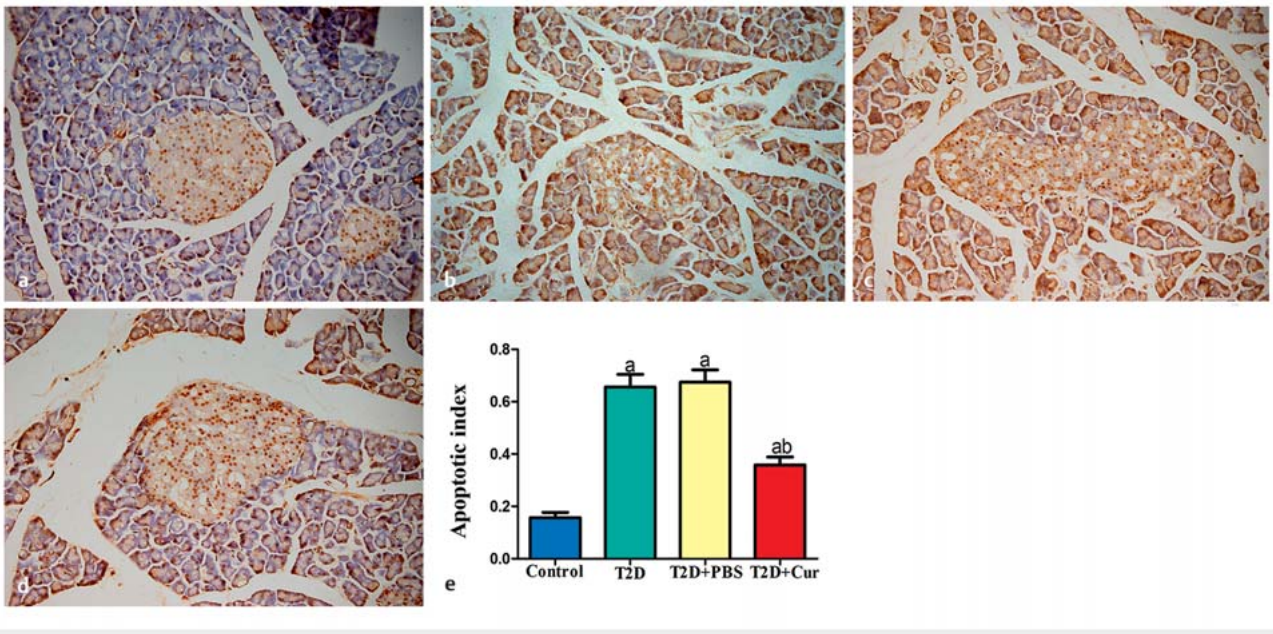
Data are presented as means ± SD (n = 6). NC = control rats; T2D = STZ-induced type 2 diabetic rats; T2D + PBS = T2D rats treated with PBS; T2D + Cur = T2D rats treated with curcumin. [a]Significant difference compared with the control group ($p < 0.05$). [b]Significant difference compared with the T2D and T2D + PBS groups ($p < 0.05$)



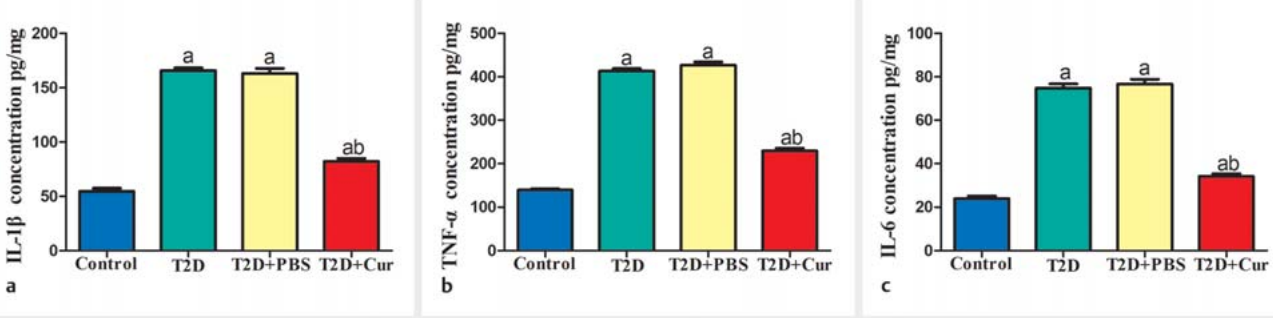
▶ **Fig. 2** Intraperitoneal glucose tolerance tests and insulin tolerance tests. NC = control rats; T2D = STZ-induced type 2 diabetic rats; T2D + PBS = T2D rats treated with PBS; T2D + Cur = T2D rats treated with curcumin. a Significant difference compared with the control group ($p < 0.05$, n = 6). b Significant difference compared with the T2D and T2D + PBS groups ($p < 0.05$, n = 6).



▶ **Fig. 3** Changes in pancreatic tissue histology. Compared with the control group (**a**), H&E staining of pancreatic tissue from the T2D (**b**), T2D + PBS (**c**), and T2D + Cur (**d**) groups revealed that the number of islets was reduced and the structure was destroyed. However, curcumin treatment improved the injury to pancreatic tissue.



▶ **Fig. 4** TUNEL assay of pancreatic tissue in the four experimental groups. **a–d** are representative TUNEL staining (200×) photomicrographs of the four experimental groups. **e** Changes in the apoptotic index in the four experimental groups. a Significant difference compared to the control group ($p < 0.05$, $n = 6$). b Significant difference compared to the T2D and T2D + PBS groups ($p < 0.05$, $n = 6$).

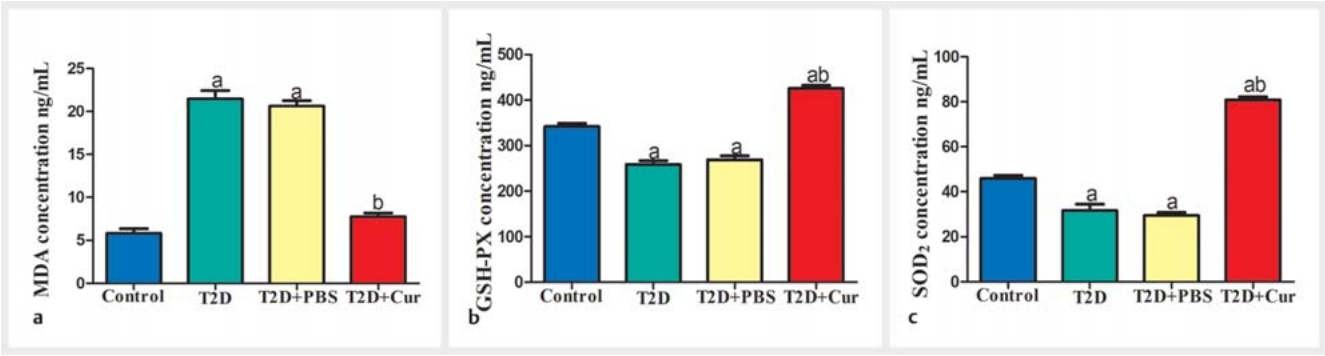


▶ **Fig. 5** Evaluation of changes in IL-1β, IL-6, and TNF-α in the pancreatic tissue using ELISA. (**a**) IL-1β expression, (**b**) IL-6 expression, and (**c**) TNF-α expression, n = 6. Data are expressed as the mean ± SD. a Significant difference compared to the control group ($p < 0.05$). b Significant difference compared to the T2D and T2D + PBS groups ($p < 0.05$).

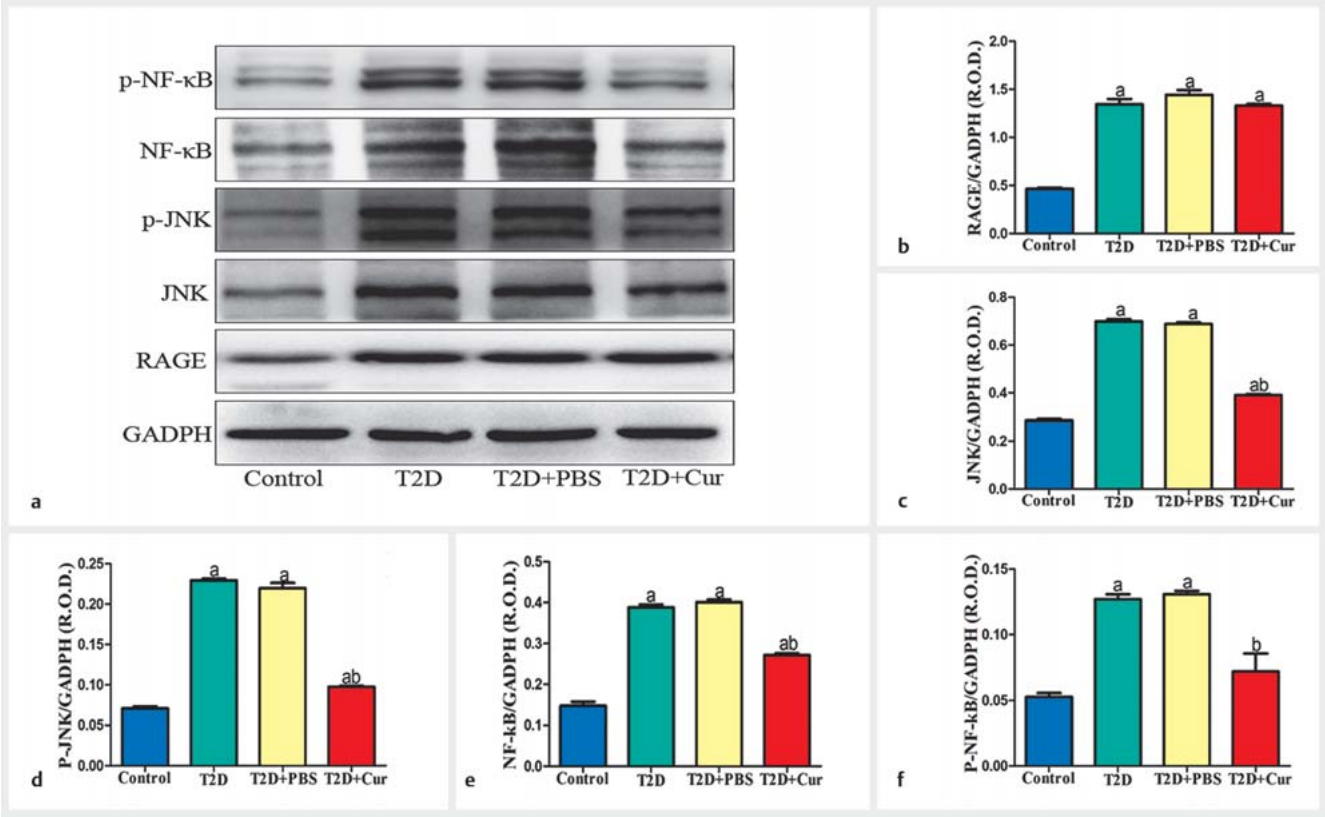
Discussion

There are two important processes in the development of T2D, namely, insulin resistance and islet β cell failure. In the early stage of T2D, insulin resistance in peripheral tissues is the main feature, and insulin secretion is relatively insufficient; as the disease progresses, insulin β cells fail, the number of cells decreases, and insulin secretion is absolutely insufficient. When the function of islet β cells fails, islet β runoff leads to a decrease in the number of cells, which makes T2D irreversible [13]. Therefore, studying the mechanism of islet β cell injury is particularly important for exploring how to protect islet β cells to prevent and control diabetes. Recent studies have shown that the imbalance in oxidative stress is responsible for causing inflammation and apoptosis of islets in pancreatic tissue in T2D [13, 14]. The strategy of improving the local microenvironment of the pancreatic tissue and regulating the inflammatory response and oxidative stress may be an effective way of treating diabetes.

Similar to previous reports, we found that STZ-induced diabetic rats had weight loss and a significant increase in serum FBS in this study [15, 16]. In addition, we found that the number of islets was reduced, and the islet structure was destroyed in the pancreatic tissue of diabetic rats. These findings suggest that islet β cell structure and function are disrupted. Previous studies have confirmed that tissue reactive oxygen species (ROS), reactive nitrogen species (RNS), lipid peroxide (MDA), and inflammatory fac-

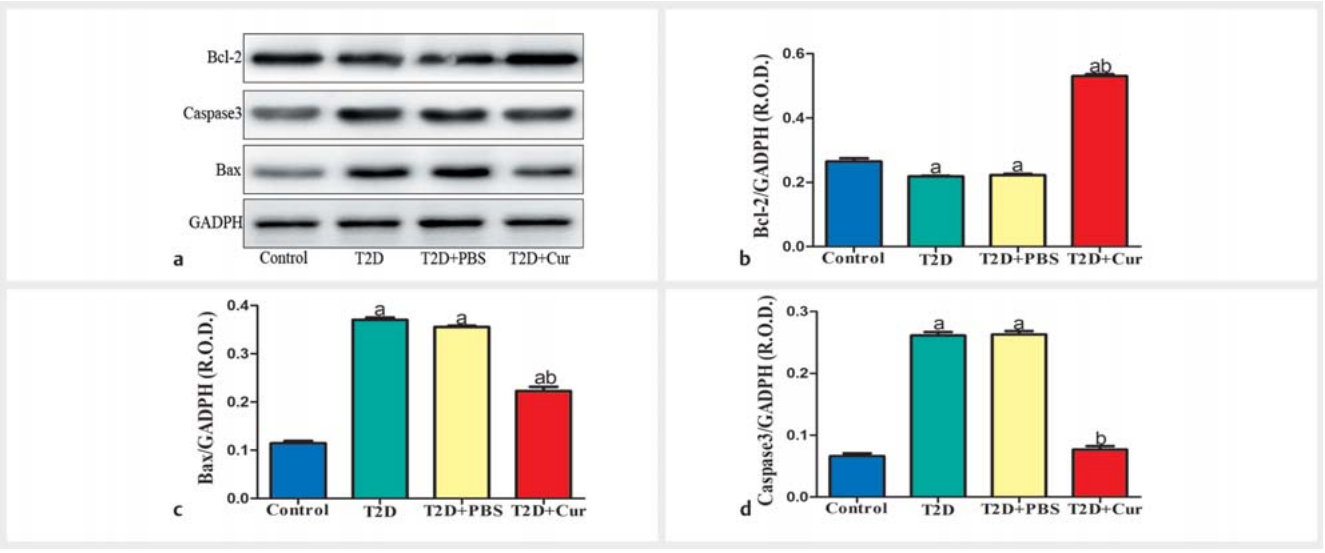


▶ **Fig. 6** Evaluation of changes in SOD2, MDA, and GSH-PX in the pancreatic tissue using ELISA. (**a**) MDA expression, (**b**) GSH-PX expression, and (**c**) SOD2 expression, n = 6. Data are expressed as the mean ± SD. a Significant difference compared to the control group ($p < 0.05$). b Significant difference compared to the T2D and T2D + PBS groups ($p < 0.05$).



▶ **Fig. 7** Expression of proteins related to RAGE/JNK/NF-κB signaling in pancreatic tissue in the four experimental groups. **a** Representative expression of proteins related to RAGE/JNK/NF-κB signaling in the four experimental groups. **b–f** Changes in the expression of RAGE/JNK/NF-κB signaling-related proteins in the four experimental groups. a Significant difference compared with the control group ($p < 0.05$). b Significant difference compared with the T2D and T2D + PBS groups ($p < 0.05$).

tors are closely related to islet cell damage. Oxidative stress is an important factor leading to the decline of islet β cell function, which is associated with the loss of enzymes that protect against oxidative stress. Endogenous antioxidant kinases in the mitochondria, such as SOD, catalase (CAT), and GSH-PX, protect cells from free radical damage. ROS and RNS can directly damage β cells, especially by disrupting the cell mitochondrial structure to cause the loss of antioxidant-related enzymes and promote β cell apoptosis [17–19]. In addition, several studies have shown that in T2D patients and animal models, the expression of inflammatory cytokines (IL-1β, IL-6, and TNF-α) was upregulated, and inhibiting the expression of proinflammatory factors significantly reduces the



▶ **Fig. 8** Expression of apoptosis-related proteins in pancreatic tissue in the four experimental groups. **a** Representative expression of apoptosis signaling-related proteins in the four experimental groups. **b–d** Changes in the expression of apoptosis signaling-related proteins in the four experimental groups. a Significant difference compared to the control group ($p < 0.05$). b Significant difference compared to the T2D and T2D + PBS groups ($p < 0.05$).

apoptosis level of islet β cells and improves pancreatic function [20]. In this study, we found that the expression levels of inflammatory factors (IL-1β, IL-6, and TNF-α) and lipid peroxide (MDA) were significantly increased and that the antioxidant enzymes (GSH-PX and SOD2) were significantly reduced. In addition, we also found that the apoptotic index and apoptosis-related protein (caspase-3 and Bax) expression were obviously enhanced, and antiapoptotic protein (Bcl-2) expression was obviously reduced in the pancreatic tissue of T2D rats. These findings suggest that oxidative stress activation can induce inflammatory responses and apoptosis in pancreatic tissue. We used curcumin to treat T2D rat models and found that Cur treatment significantly decreased inflammatory factors (IL-1β, IL-6 and TNF-α), lipid peroxide (MDA), apoptotic index, and apoptosis-related proteins (caspase-3 and Bax) and enhanced antioxidant (GSH-PX and SOD2) and antiapoptotic protein (Bcl-2) expression in the T2D + Cur group. These results indicate that curcumin exerts anti-inflammatory and antiapoptotic effects in T2D pancreatic cells and may be the key to protecting pancreatic islet β cells from damage.

Recent studies suggest that RAGE signaling can cause damage to tissues and organs through inflammation and oxidative stress pathways. Blocking RAGE regulatory pathways in brain injury, diabetic heart disease, diabetic nephropathy, and other diseases can effectively exert anti-inflammatory, antioxidative, and antiapoptotic effects and protect tissues and organs [21,22]. Similarly, the increased expression and activation of RAGE are responsible for pancreatic β cell inflammation, toxicity, and apoptosis [23]. RAGE-related pathway activation may promote the overexpression of inflammatory factors and peroxides through JNK/NF-κB signaling, which participates in organ damage. In this process, the phosphorylation of JNK protein is a key link in signal pathway activation [24–26]. In the present study, we found that expression of RAGE, JNK, p-JNK, NF-κB, and p-NF-κB was increased in STZ-induced diabetic rats, suggesting that RAGE activation can activate JNK/NF-κB signaling through the phosphorylation pathway to participate in the apoptotic destruction of pancreatic tissue. The phosphorylated JNK and NF-κB proteins, p-JNK, and p-NF-κB expression levels were significantly increased in all three groups of T2D rat pancreas islet β cells and was partly inhibited in T2D + Cur rats. These data suggest that Cur may inhibit the RAGE/JNK/NF-κB signaling pathway by blocking the phosphorylation of JNK and NF-κB, thereby blocking the apoptotic destruction of pancreatic tissue. Combined with our research, we hypothesize that curcumin may be responsible for protecting pancreatic tissue against inflammatory damage, and the underlying mechanism involves the inhibition of the RAGE/JNK/NF-κB signaling pathway.

Based on this, we can conclude that curcumin protects the pancreatic islet and improves recovery of pancreatic function in diabetic rats by blocking the RAGE/JNK/NF-κB signaling pathway to inhibit inflammation and apoptosis. Curcumin is an effective treatment for diabetes.

Methods

Animals

Sprague-Dawley rats were purchased from the animal laboratory of Chongqing Traditional Chinese Medicine Hospital. This study was approved by the Research Council and Animal Care and Use Committee of Chongqing Traditional Chinese Medicine Hospital. All animal procedures used here were approved by the Institutional Animal Care and Use Committee of Hubei University of Science and Technology (Approval no. SYLD2012015 and approval date April 12, 2012).

Type 2 diabetes mellitus induction and treatment

The type 2 DM rat model was established as previously described [27, 28]. Briefly, Sprague-Dawley rats (190–210 g) were randomly divided into four groups: control group (n = 12), T2D group (n = 12), T2D + PBS group (n = 12), and T2D + Cur group (n = 12). The T2D, T2D + PBS, and T2D + Cur rats were fed a high-fat diet (consisting of 22 % fat, 48 % carbohydrate, and 20 % protein with a total calorific value of 44.3 kJ/kg), while the control group was fed a common feed. After feeding with a high-fat diet for 4 weeks, T2D rats were injected intraperitoneally with STZ (35 mg/kg/week, ≥ 98 % (HPLC; Sigma-Aldrich) twice, with a 1-week internal between doses. Three days after STZ injection, rats with FBG > 16.7 mM were confirmed to be T2D rats. Treatment was initiated 3 days after STZ injection, which was considered the first day of treatment. Curcumin (200 mg/kg, ≥ 98 %, HPLC; Sigma) dissolved in 1 mL PBS was intraperitoneally injected into the T2D + Cur group once a day for 4 weeks. The dose of curcumin was based on previous studies [16, 29]. One milliliter of PBS was intraperitoneally injected into the T2D + PBS group once a day for 4 weeks. After 4 weeks, the pancreatic tissue was harvested for experiments.

Intraperitoneal glucose tolerance test and insulin tolerance test

After successful modeling, the body weights and FBG levels of the rats were measured after 4 weeks. After a 12-h overnight fast, the rats were intraperitoneally injected with 40 % glucose (2 g/kg body weight). Blood samples were collected from the tail veins at 0, 30, 60, 90, and 120 min to measure the glucose levels. Insulin (0.75 IU/kg) was injected intraperitoneally, and blood samples were collected from tail veins at 0, 30, 60, 90, and 120 min for the measurement of plasma glucose levels. Values are presented as the percentage of the initial plasma glucose level [28, 29].

Measurement of IL-1β, IL-6, IL-8, malondialdehyde, superoxide dismutase, and glutathione by ELISA

Pancreatic tissue from the four groups of animals was collected for ELISA analysis. The levels of IL-1β, IL-6, TNF-α (Westtang, Inc.), SOD2, MDA, and GSH-PX (Hushang, Inc.) were measured according to the manufacturer's assay instructions and measured at 450 nm with an ultraviolet microplate reader (Thermo Scientific Corporation).

Histology and TUNEL assay

The pancreatic tissues (n = 6) were stained with hematoxylin and eosin and TUNEL as previously described [28, 29]. DNA cleavage was detected using an *in situ* cell death detection kit (Roche Diagnostics) and examined under a microscope (Olympus). For each pancreatic islet in the TUNEL-positive section, the highest number of high-power fields (400×) of five positive cells (with brown-yellow particles in the nucleus) were selected, and the percentage of positive cells in all acinar cells was calculated.

Western blot analysis

As previously reported [30], Western blotting was used for protein expression detection (n = 6). The following primary rabbit polyclonal antibodies were used: anti-JNK (1 : 2000; CST), anti-NF-κB (1 : 3000; Abcam), anti-p-NF-κB (1 : 1000; CST), anti-p-JNK antibody (1 : 1000; CST), anti-IL-1β (1 : 1000; Santa Cruz Biotechnology), anti-Bax (1 : 600; Santa Cruz Biotechnology), anti-caspase-3 (1 : 800; Santa Cruz Biotechnology), anti-Bcl2 (1 : 500; Santa Cruz Biotechnology), and anti-SOD2 (1 : 600; Santa Cruz Biotechnology). The primary mouse polyclonal antibodies used were anti-GAPDH (1 : 800; Santa Cruz Biotechnology) and anti-RAGE (1 : 1000; Santa Cruz Biotechnology). The secondary antibodies were as follows: goat anti-rabbit IgG (1 : 2000; Zhongshan, Inc.) and horseradish peroxidase-conjugated goat anti-mouse IgG (1 : 2500; Zhongshan, Inc.). A ChemiDoc XRS+ Image System (Bio-Rad Laboratories) was used to analyze the protein band images.

Statistical analysis

All values are presented as means ± SD. Statistical analysis was performed using SPSS software (version 19.0). One-way ANOVA was applied for group differences. A p value < 0.05 was considered statistically significant.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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