

Silencing of peroxiredoxin I expression ameliorates ulcerative colitis in a rat model

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Abstract

Background: Peroxiredoxin I (PRDXI), a protein with anti-inflammatory and anti-apoptotic properties, shows elevated expression in ulcerative colitis (UC). However, PRDXI's specific role in UC is poorly understood.

Methods: UC was induced in rats using dextran sulfate sodium (DSS). *In vivo* RNA interference was used to silence the PRDXI expression. PRDXI expression levels and the inflammatory cytokines tumor necrosis factor (TNF)- α , interleukin (IL)-1 β , IL-6, transforming growth factor (TGF)- β and interferon (IFN)- γ in tissues were assessed by real-time quantitative polymerase chain reaction and western blotting. Colonic injury was assessed by hematoxylin–eosin staining. ELISA was used to assess levels of the inflammatory cytokines TNF- α , IL-1 β and IL-6 in colon tissues. Apoptosis of intestinal epithelial cells was assessed by terminal deoxynucleotidyl transferase dUTP nick end labeling, and expression of the apoptotic proteins bcl-2, Bax, cleaved caspase-3 and caspase-3 was assessed by western blotting.

Results: PRDXI expression was significantly increased in rats with DSS-induced UC. Silencing of PRDXI expression improved colon injury in rats with DSS-induced UC. In addition, silencing of PRDXI expression inhibited inflammatory responses and apoptosis of intestinal epithelial cells in rats with DSS-induced UC.

Conclusions: Silencing of PRDXI expression can ameliorate colon injury in rats with DSS-induced UC.

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Keywords

Peroxiredoxin 1, ulcerative colitis, inflammation, apoptosis, RNA interference, dextran sodium sulfate

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Introduction

Ulcerative colitis (UC) is a chronic nonspecific inflammatory disease of the intestine mainly affecting the rectum and colon. UC is characterized by intermittent diarrhea, mucous pus and blood in the stool, and abdominal pain.¹ UC is difficult to cure and has a high recurrence rate, and can also lead to cancer. Clinical treatment of UC with glucocorticoids, immunosuppressants and amino salicylic acid was not effective.² Therefore, understanding the etiology and pathogenesis of UC and identification of new therapeutic targets has been the focus of research in recent years.

Peroxiredoxin 1 (PRDX1) is a member of the PRDX family that is predominantly found in the cytoplasmic matrix. PRDX1 is one of several antioxidants that are commonly expressed in the body.³ PRDX1 is mainly used to scavenge free radicals and avoid cell damage caused by free radicals. In addition, PRDX1 has anti-inflammatory and anti-apoptotic effects.^{4,5} PRDX1 reduces brain damage caused by cerebral hemorrhage by affecting the stability of inflammation- and apoptosis-associated mRNAs.⁶ During myocardial ischemia/reperfusion injury, PRDX1 alleviates inflammation and apoptosis by controlling MAPK pathway activation by reactive oxygen species.⁷ Recently, PRDX1 has been recognized as a novel damage-associated molecular pattern that contributes to the development of acute liver injury.⁸ PRDX1 knockout can significantly reduce apoptosis and inflammatory

responses in mouse models of cerebral ischemia-reperfusion injury, thus reducing tissue or cell damage.⁹ It has been reported that PRDX1 is differentially expressed in inactive and active UC, and that expression of PRDX1 in the mucosal crypt epithelial cells of patients with UC increases with increasing inflammation.^{10,11} Therefore, the expression of PRDX1 may reflect the severity of oxidative stress and colitis activity in UC patients. In addition, Zhang et al.¹² demonstrates that elevated PRDX1 levels in the serum and colonic mucosa may be closely related to the progression of irritable bowel syndrome and gastrointestinal symptoms. However, the specific role of PRDX1 in UC is poorly understood.

Using the GEO database, we found that PRDX1 (GSE36807) was significantly upregulated in patients with UC compared with normal controls. Therefore, we conducted *in vivo* experiments to assess the specific effects of PRDX1 on colonic injury in a rat model of UC.

Materials and methods

Animals

Sixty male Wistar rats (200–230 g) were purchased from Taizhou Second People's Hospital (Taizhou, China). All animals were housed for 1 week under sterile conditions and fed laboratory chow and water. All experimental procedures were performed in accordance with international guidelines for the care and use of laboratory

animals and were approved by the Ethics Committee of Taizhou Second People's Hospital. After 1 week of adaptive feeding, the animals were divided into a control group (n=10) and an UC model group (n=10). UC was induced in rat by administering 5% dextran sodium sulfate (DSS, MP Biomedicals, Shanghai, China) dissolved in drinking water for 7 days.¹³ The control group had access to distilled water. Expression of PRDX1 in colon tissue was assessed after successful induction of UC. Subsequently, to understand the role of PRDX1 in UC, rats were subdivided into the control group, the DSS model group, the DSS+negative control small interfering RNA (si-NC) group, and the DSS+PRDX1 small interfering RNA (si-PRDX1) group. After UC was successfully induced, the rats in the control group and DSS group were injected with 100 to 200 μ L of saline intravenously. Rats in the DSS+si-PRDX1 group received PRDX1 siRNA (15 nmol/20 g) by tail vein injection on day 8 and day 11 according to the manufacturer's instructions.¹⁴ On day 14, the rats were sacrificed and colon tissue was collected. The rats in the DSS+si-NC group received the same dose of si-NC with the same schedule. The rats were euthanized using anesthesia followed by cervical dislocation. Our study strictly followed the ARRIVE guidelines.

Real-time quantitative PCR (RT-qPCR)

Total RNA was extracted from colon tissues using the RNeasy Mini kit (Qiagen, Hilden, Germany) following the manufacturer's protocol. RNA samples were reverse transcribed using Quantiscript reverse transcriptase (Qiagen). Total RNA concentration and purity were assessed using a Thermo Fisher Scientific NanoDrop 2000C and the Pharmacia GeneQuant Pro RNA/DNA calculator. The SuperScript III Platinum SYBR Green One-Step qRT-PCR

Kit (Invitrogen, Carlsbad, CA, USA) was used according to the manufacturer's instructions. Forward and reverse primers used in RT-qPCR were as follows: PRDX1 forward 5'-TCCCAAGCGCACC ATTGCTCA-3' and reverse 5'-CACAGA GCGGCCAACGGGAA-3'; tumor necrosis factor (TNF)- α forward 5'-CTCGAGT GACAAGCCCGTAG-3' and reverse 5'-G GCAGCCTTGTCCCTTGAAG-3', interleukin (IL)-6 forward 5'-CCTTCCTACCC CAACTTCCA-3' and reverse 5'-GAGTTG GATGGTCTTGGTCC-3'; IL-1 β forward 5'-TGGAAAAGCGGTTTGTCT-3' and reverse 5'-ATAAATAGGTAAGTGTT GCC-3'; transforming growth factor (TGF)- β forward 5'-AACATGATCGTGC GCTCTGCAAGTGCAGC-3' and reverse 5'-AGGACGGACAGACGTGATAAGG AA-3'; interferon (IFN)- γ forward 5'-G CTGATTCAAATTCCGGTGGA-3' and reverse 5'-CAGGCAGGAGGACCATTA CG-3'; glyceraldehyde 3-phosphate dehydrogenase (GAPDH) forward 5'-TGCAC CACCAACTGCTTAGC-3' and reverse 5'-GGCATGGACTGTGGTCATGAG-3'.

Western blotting

Rat colon tissues were lysed using radioimmunoprecipitation buffer (Thermo Fisher Scientific, Waltham, MA, USA). Thereafter, total proteins were separated using 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis and then transferred onto polyvinylidene difluoride membranes. After blocking with 10% non-fat milk for 1 hour at room temperature, the membranes were incubated with primary antibodies overnight at 4°C. The next day, the membranes were incubated with corresponding secondary antibodies membranes at room temperature for 2 hours. The blots were visualized using enhanced chemiluminescence (Amersham Pharmacia, Piscataway, NJ, USA) and a semiquantitative analysis was conducted

using ImageJ software (NIH, Bethesda, MD, USA). The primary antibodies used were as follows (all from Abcam, Cambridge, UK): anti-PRDX1-1 (1:1000 dilution, ab15571), anti-Bcl-2 (1:1000 dilution, ab185002), anti-Bax (1:1000 dilution, ab32503), anti-cleaved caspase 3 (1:1000 dilution, ab2302), anti-caspase 3 (1:1000 dilution, ab13847), and anti-GAPDH (1:1000 dilution, ab181602).

Histopathological examination

A section of the lower colon was detached and fixed by immersion in 10% neutral buffered formalin solution (pH 7.4). The section was cut transversely, paraffin embedded, and 3- μ m-thick sections were stained with hematoxylin and eosin for microscopic assessment of colon injury. The tissues were examined under a microscope in random order.

ELISA

Levels of IL-6, IL-1 β and TNF- α in rat sera were assessed using an ELISA kit (Nanjing SenBeiJia Biological Technology Co., Nanjing, China) according to the manufacturer's protocol.

Assessment of myeloperoxidase (MPO) activity

The colon tissues were rinsed with cold phosphate-buffered saline, blotted dry and frozen immediately in liquid nitrogen. The tissues were finely minced in 0.5% hexadecyltrimethylammonium bromide dissolved in 50 mM potassium phosphate (pH 6.0), and then homogenized with an IKA-T10 basic homogenizer (Silmington, NC, USA) three times for 30 s each. The samples were always kept on ice. The solutions were centrifuged at 3000 \times g for 20 minutes at 4°C. The supernatant (5 μ L) was added to 200 μ L of 50 mM phosphate buffer (pH 6.0) mixed with 100 μ L of 0.68 mg/mL

o-dianisidine dihydrochloride and 0.1% hydrogen peroxide (Thermo Fisher Scientific). The change in absorbance at 460 nm was measured using a spectrophotometer (Molecular Devices, Sunnyvale, CA, USA).¹⁵

Evaluation of disease activity index (DAI)

The general condition of rats was observed and recorded daily. Rat body mass was measured and fecal characteristics and hematochezia were observed every day. Disease activity was assessed using a DAI score.¹⁶ Scoring was as follows: 0, no weight loss, no occult blood in the stools and normal stool consistency; 1, weight loss of 1% to 5%, no occult blood and normal stool consistency; 2, 5% to 10% weight loss, positive for fecal occult blood and loose stools; 3, 10% to 20% weight loss, positive for fecal occult blood and loose stools; and 4, greater than 20% weight loss, gross rectal bleeding and diarrhea.¹⁷

Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) staining

Apoptotic epithelial cells in colonic tissue were enumerated using the TUNEL assay (Beyotime, Nanjing, China) according to the manufacturer's instructions. TUNEL-positive nuclei were clearly identified via their green fluorescence, indicating DNA fragmentation resulting from apoptosis. TUNEL-positive cells were counted by observing randomly selected fields.

Statistical analyses

SPSS 18.0 (SPSS Inc., Chicago, IL, USA) was used to analyze results. All data were presented as means \pm standard deviations. Differences among multiple groups were assessed by single factor analysis of variance followed by Tukey's post hoc test. Differences between two groups were assessed using the *t* test. Values of

$p < 0.05$ were considered statistically significant.

Result

Silencing of PRDX1 expression improved colonic injury induced by DSS in a rat model of UC

Expression of PRDX1 in colon tissues was assessed by RT-qPCR and western blotting. Compared with the control group, expression of PRDX1 was significantly increased in the DSS group (Figure 1a and b). Expression of PRDX1 was silenced using RNA interference. RT-qPCR (Figure 2a) and western blotting (Figure 2b) showed that compared with the DSS + si-NC group, expression of PRDX1 in the DSS + si-PRDX1 group decreased. Measurements of colon length showed that compared with the control group, the rats in the DSS group had significantly shortened colons. Compared with the DSS + si-NC group, the colon lengths in the DSS + si-PRDX1 group were increased (Figure 2c and d). Moreover, compared with the control group, the UC DAI increased in the DSS group. Compared with the DSS + si-NC group, the UC DAI in the DSS + si-PRDX1 group was also decreased (Figure 2e). In addition,

hematoxylin and eosin staining showed that colon injury in the DSS group was more severe than in the control group. Compared with the DSS + si-NC group, the degree of colonic injury was decreased following silencing of PRDX1 (Figure 2f). These results showed that silencing of PRDX1 expression improved colonic injury induced by DSS in a rat model of UC.

Silencing of PRDX1 expression inhibited inflammation induced by DSS in a rat model of UC

Expression of inflammatory factors in colon tissue homogenates was assessed by RT-qPCR. Expression of TGF- β and IFN- γ were significantly increased in the DSS group compared with the control group. Expression of TGF- β and IFN- γ in the DSS + si-NC group were decreased following silencing of PRDX1 expression (Figure 3a). ELISA showed that TNF- α , IL-1 β and IL-6 levels were significantly increased in the DSS group compared with the control group. Levels of TNF- α , IL-1 β and IL-6 in the DSS + si-NC group were decreased following silencing of PRDX1 expression (Figure 3b). We assessed the activity of MPO, an important indicator of inflammatory cell infiltration in

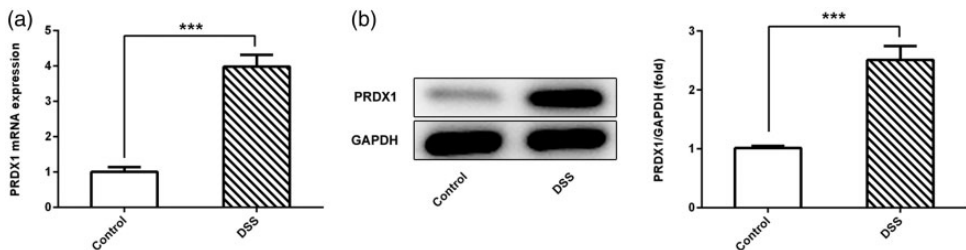


Figure 1. Expression of periredoxin I (PRDX1) in a rat model of dextran sodium sulfate (DSS)-induced ulcerative colitis. (a) Real-time quantitative polymerase chain reaction was used to assess the expression of PRDX1 in colon tissues of control or DSS-treated mice. (b) Western blotting was used to assess the expression of PRDX1 in colon tissues. Expression was normalized to that of glyceraldehyde 3-phosphate dehydrogenase (GAPDH). *** $p < 0.001$.

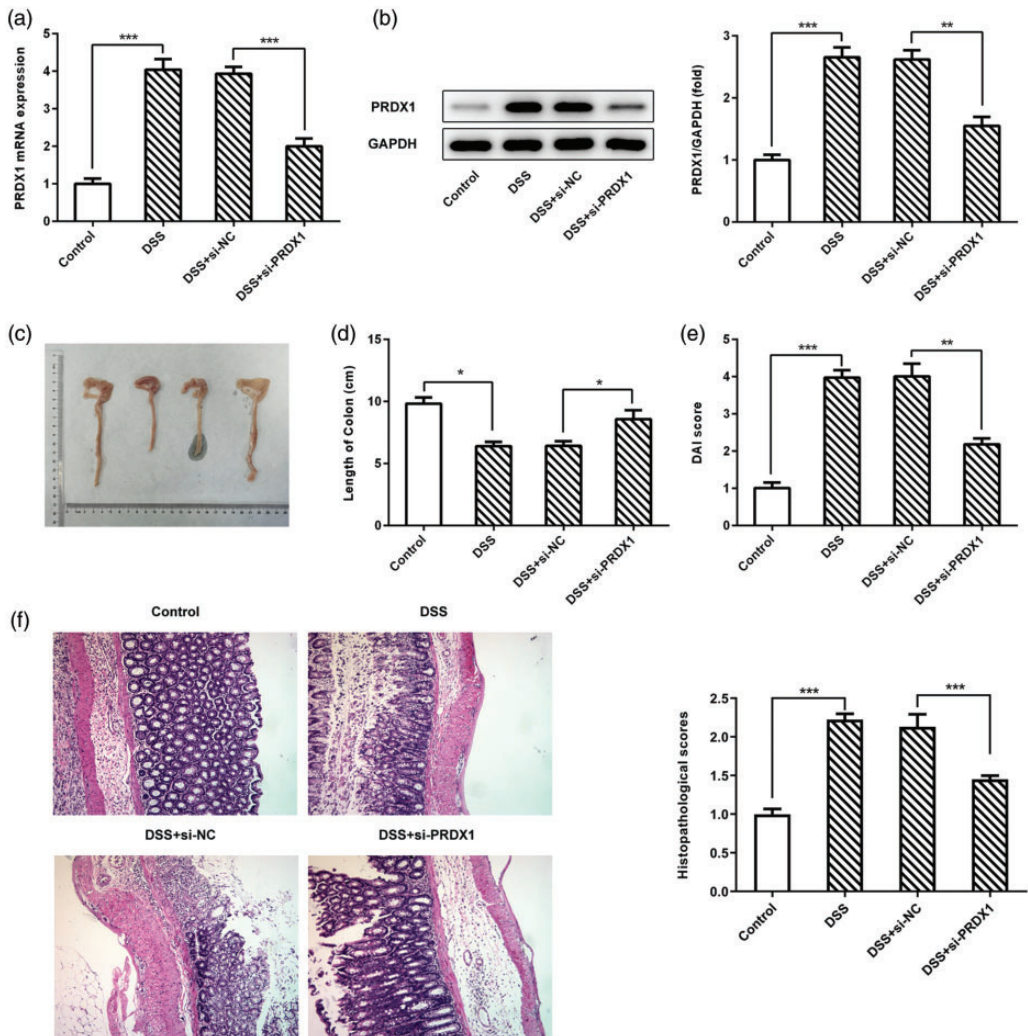


Figure 2. Silencing of periredoxin I (PRDX1) expression improved colonic injury in a rat model of dextran sodium sulfate (DSS)-induced ulcerative colitis. (a) Real-time quantitative polymerase chain reaction was used to assess the expression of PRDX1 in colon tissues. (b) Western blotting was used to assess the expression of PRDX1 in colon tissues. Expression was normalized to that of glyceraldehyde 3-phosphate dehydrogenase (GAPDH). (c) Colon photos. (d) Statistical analysis of colon length. (e) Statistical analysis of ulcerative colitis disease activity index. (f) Hematoxylin and eosin staining was used to assess the degree of colonic tissue damage. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

colitis, and found that this was consistent with the expression of TNF- α and other inflammatory factors (Figure 3c). These results showed that silencing of PRDX1 expression inhibited inflammation induced by DSS in a rat model of UC.

Silencing of PRDX1 expression inhibited apoptosis of intestinal epithelial cells induced by DSS in a rat model of UC

The TUNEL assay was used to assess apoptosis of intestinal epithelial cells in the

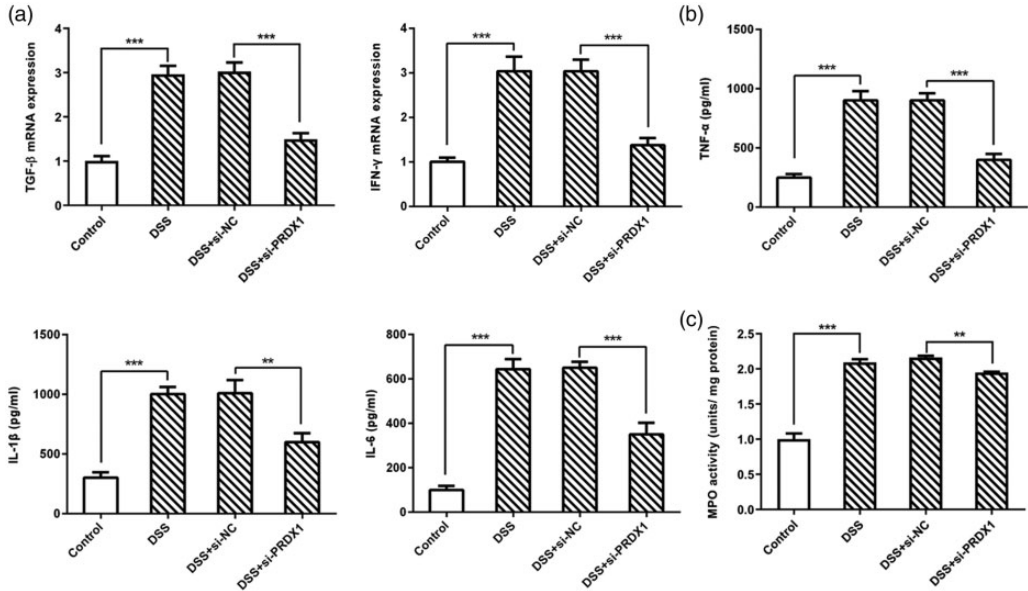


Figure 3. Silencing of periredoxin 1 (PRDX1) expression inhibited inflammation in a rat model of dextran sodium sulfate (DSS)-induced ulcerative colitis. (a) Real-time quantitative polymerase chain reaction was used to assess the expression of transforming growth factor (TGF)- β and interferon (IFN)- γ . (b) ELISA was used to assess the expression of tumor necrosis factor (TNF)- α , interleukin (IL)-1 β and IL-6. (c) The activity of myeloperoxidase (MPO) was assessed in colon tissues. *** $p < 0.01$, ** $p < 0.001$.

colon. Compared with the control group, apoptosis of intestinal epithelial cells was increased (Figure 4a). Increased apoptosis was accompanied by upregulated expression of Bax and cleaved caspase-3 and downregulated expression of Bcl-2 (Figure 4b). Compared with the DSS + si-NC group, apoptosis of intestinal epithelial cells in the DSS + si-PRDX1 group decreased following silencing of PRDX1 expression. Concurrently, the expression of Bax and cleaved caspase-3 decreased, while the expression of Bcl-2 increased. These results showed that silencing of PRDX1 expression inhibited apoptosis of intestinal epithelial cells induced by DSS in a rat model of UC.

Discussion

In recent years, with the application of genetic, immunological and molecular

biological tools, our understanding of UC has deepened. Studies have shown that the pathogenesis of UC is closely related to genes, the environment, increased production of inflammatory mediators, and other factors. However, the specific pathogenesis of UC remains unclear.

In this study, DSS was used to induce UC in rats. This is a widely used experimental model of the pathogenesis of UC.¹⁸ In the model group, the DAI and inflammation-related factors increased significantly, and severe colon injuries occurred in rats of the DSS group.

Using the GEO database, we found that the expression of PRDX1 was significantly upregulated in the tissues of UC patients compared with normal controls. Subsequently, we found that the expression of PRDX1 was also significantly increased in the sera of rats with DSS-induced UC. PRDX1 can clear hydrogen peroxide and

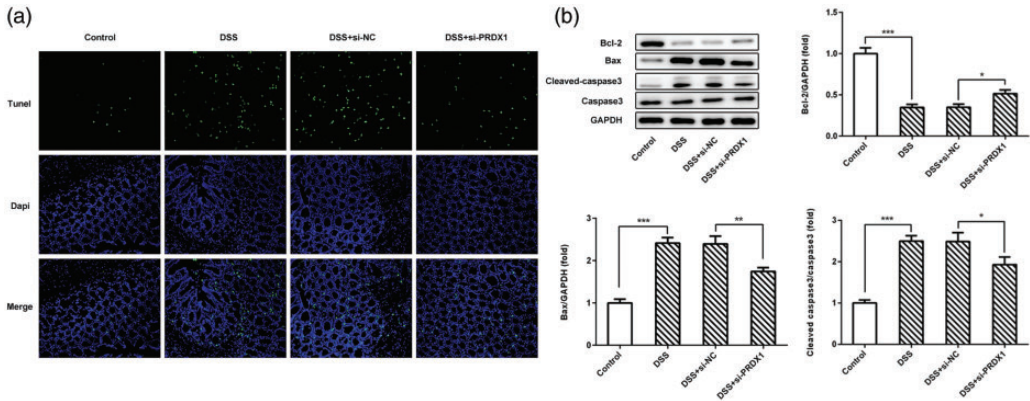


Figure 4. Silencing of periredoxin I (PRDX1) expression inhibited apoptosis of intestinal epithelial cells in a rat model of dextran sodium sulfate (DSS)-induced ulcerative colitis. (a) Terminal deoxynucleotidyl transferase dUTP nick end labeling was used to assess apoptosis of intestinal epithelial cells. (b) Western blotting was used to assess expression of apoptosis-related proteins. Expression was normalized to that of glyceraldehyde 3-phosphate dehydrogenase (GAPDH). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

lipid peroxide from the body, maintain normal redox balance, provide an effective defense mechanism for the body, and reduce oxidative stress damage.¹⁹ In addition, a study showed that the expression of PRDX1 was abnormally increased in colorectal cancer, and that PRDX1 can promote the expression of inflammatory factors such as TNF- α and IL-6.²⁰ In addition, Horie et al.¹⁰ found in clinical studies that PRDX1 expression was significantly increased in active UC tissues.

PRDX1 is a novel damage-related molecular pattern that exacerbates acute liver injury by promoting inflammation.⁸ In acute lung injury models, expression of PRDX1 was significantly increased, and overexpression of PRDX1 increased the expression of the pro-inflammatory cytokines IL-6, IL-8, and TNF- α .²¹ This finding showed that PRDX1 plays an important role in tissue injury. In addition, inflammatory reactions are involved in the development of UC and can damage the intestinal mucosa.²² TNF- α has long been considered a key mediator of inflammation in the

colon, and increased TNF- α expression reflects increased local or systemic inflammation, both of which are associated with the severity of UC.²³ Our results confirmed that PRDX1 silencing could inhibit colonic injury in UC rats, inhibit the expression of the inflammation-related factors TNF- α , IL-1 β and IL-6 in colonic tissues, and inhibit the apoptosis of colonic epithelial cells.

Conclusion

We examined the effects of PRDX1 on colonic injury, inflammatory responses, and epithelial apoptosis levels in a rat model of UC. We demonstrated that silencing of PRDX1 expression can improve DSS-induced UC in rats. Our study provides a theoretical basis for targeted therapy of UC.

Ethics approval

The study protocol was approved by Taizhou Second People's Hospital. All animal experiments complied with the ethical requirements of the animal council.

Availability of data and materials

The analyzed data sets generated during the present study are available from the corresponding author on reasonable request.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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