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Omentin-1 attenuates inflammation and barrier damage in DSS-induced ulcerative colitis in mice by inhibiting endoplasmic reticulum stress

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Abstract. Ulcerative colitis (UC) is a diffuse inflammatory disease that occurs in the mucosa of the colon and rectum. Research illustrated that omentin-1 level was significantly lower in the serum of patients with UC. This study systematically examines the emerging roles of omentin-1 in UC and its related mechanisms. Omentin-1 level in dextran sulfate sodium (DSS)-induced mice was examined by Western blot and RT-PCR. The expressions of endoplasmic reticulum (ER) stress-related proteins were detected adopting Western blot with or without the addition of ER stress inducer tunicamycin (TM) in colitis mice. Subsequently, in DSS-induced UC mice, colonic damage was determined by H&E staining, body weight, colon length, and disease activity index (DAI). Inflammation and barrier damage were examined by ELISA and Western blot. Cell apoptosis in colon tissues was examined by TUNEL and Western blot. Omentin-1 expressed lowly in DSS-induced colon tissues of UC mice, and its overexpression inhibited ER stress. Additionally, overexpression of omentin-1 also inhibited DSS-induced colon damage, inflammation, barrier damage and cell apoptosis in UC mice; however, these changes were partly abolished by TM administration. In conclusion, omentin-1 attenuates DSS-induced inflammation and barrier damage in UC mice by inhibiting ER stress, suggesting omentin-1 may be a useful target for the treatment of UC.

Key words: Omentin-1 — Ulcerative colitis — Inflammation — Endoplasmic reticulum stress — Barrier damage

Introduction

Ulcerative colitis (UC) is a diffuse inflammatory disease that occurs in the mucosa of the colon and rectum, and the incidence of UC has risen over the past few decades throughout the world, particularly in developing countries (da Silva et al. 2014). The etiology and pathogenesis of UC remain rather complex, including genetic predisposition, intestinal barrier dysfunction, environment and dysregulated immune responses (Ordas et al. 2012; Feuerstein et al. 2019). Among them, endoplasmic reticulum (ER) stress may be a key factor in the pathogenesis of UC, due to the fact that dysregulation of ER stress may lead to UC by inducing epithelial cell death, impairing intestinal barrier function and activating intestinal inflammatory responses (Kaser and Blumberg 2009; Yin et al. 2021). Accordingly, regulation of disorganized ER stress is well regarded as a potential therapeutic option for the treatment of UC.

Omentin is a novel multipotent adipokine secreted mainly by visceral adipose tissue, endothelial cells, vascular smooth muscle, colon and small intestine (Genre et al. 2020). There is growing evidence that omental adipose tissue is actively involved in the pathogenesis of Crohn's disease, a type of inflammatory bowel disease (Paul et

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al. 2006). Additionally, omentin is encoded by 2 genes, omentin-1 and omentin-2, the former being the major circulating form. Decreased serum omentin-1 levels have been reported to be closely associated with the development of many diseases, including benign prostatic hyperplasia, polycystic ovary syndrome and coronary artery disease (Askin et al. 2020; Franik et al. 2020; He et al. 2020). In addition, serum omentin-1 levels have been also shown to be significantly lower in patients with UC (Yin et al. 2015), suggesting that serum omentin may be a potential marker of UC disease activity.

ER is a critical intracellular dynamic organelle that mediates the synthesis and export of proteins and glycoproteins (Senft and Ronai 2015). Just as aforementioned, aberrant ER stress is involved in the pathogenesis of UC by regulating inflammation, apoptosis, and intestinal barrier damage (Ren et al. 2019; Wang et al. 2021). Coincidently, it has been demonstrated that omentin-1 prevents high glucose-induced vascular endothelial dysfunction by inhibiting ER stress and oxidative stress (Liu et al. 2020), indicating a potential inhibitory effect of omentin-1 on ER stress. Therefore, it is deserved to explore whether omentin-1-mediated ER stress can participate into the regulation of UC development.

In this study, we first established an *in vivo* mice model of UC and observed the level of omentin-1 in colon tissues of mice. Subsequently, after overexpressing omentin-1, the effects of omentin-1 on ER stress, colon damage, apoptosis, inflammation and barrier damage were explored in dextran sulfate sodium (DSS)-induced UC mice, respectively. The investigation of the molecular mechanisms of omentin-1 brought new perspectives for the identification of more effective therapeutic strategies for UC.

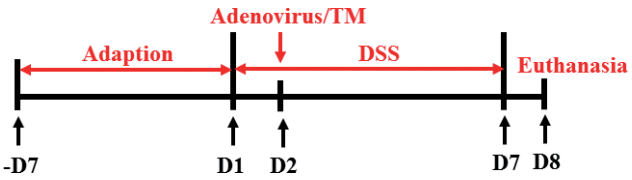


Figure 1. Schematic representation of the experimental procedures. After adaption for 1 week (−D7~D1), mice were administered with of 5% dextran sulfate sodium (DSS) dissolved in drinking water for 1 week (D1–D7) to induce ulcerative colitis (UC group). For the control group, mice were given regular drinking water. The day after administration of DSS (D2), mice were injected transrectally with adenovirus omentin-1 in UC+oe-omentin-1 group but injected with adenoviral β-galactosidase in UC+oe-NC group. Mice in TM+UC+oe-omentin-1 group received intraperitoneally 1 mg/kg tunicamycin (TM), as well as injection of adenovirus omentin-1 on D2. By the end of treatment (D8), all mice were sacrificed.

Materials and Methods

Model establishment

SPF-grade C57BL/6 mice (8–12 weeks old) were purchased from Beijing HFK Bioscience Co., Ltd (Beijing, China), and were housed in pathogen-free cages. The collection of animal tissues and experimental methods were approved in advance by the ethics committee of North China University of Science and Technology Affiliated Hospital. Mice were housed under standardized conditions at a temperature of 22–24°C, 20% humidity, and a 12-hour light/dark cycle. During this period, mice had free access to a standard diet and water. Mice were randomly assigned to groups ($n = 6$). To induce UC, 5% DSS (MP Biomedicals, Irvine, CA, USA) was administered to the drinking water of the mice for 1 week (UC group). Mice in the control group were given regular drinking water throughout the treatment period. The day after administration of DSS, mice were injected transrectally with 5×10^7 PFU of adenovirus omentin-1 to achieve omentin-1 overexpression (UC+oe-omentin-1 group). Mice injected with adenoviral β-galactosidase were regarded as negative control (UC+oe-NC group). Mice in TM+UC+oe-omentin-1 group received intraperitoneally 1 mg/kg tunicamycin (TM; Aladdin Chemistry Co. Ltd., Shanghai, China), as well as injection of adenovirus omentin-1, the day after administration of DSS. By the end of treatment, all mice were sacrificed (Fig. 1). The serum samples were collected and the colon was cleansed with saline, followed by the measurement of the colon length. A portion of the colonic tissue was subsequently fixed in 10% formalin for pathological examination, and the rest was stored at −80°C for subsequent testing.

Real-time quantitative polymerasechain reaction (RT-qPCR)

Total RNA isolation was undertaken by the use of TRIzol reagent (Thermo Fisher Scientific, Waltham, MA, USA) in keeping with the protocols put forward by the vendor. The reverse transcription into cDNA was carried out employing PrimerScript reverse kit (Takara, Dalian, Japan). The PCR reaction was conducted on the ABI Prism 7000 Sequence Detection System (ABI/Perkin Elmer, Foster City, CA, USA). The cycle conditions of PCR reaction were listed below: denaturation at 95°C for 20 s, 30 cycles of denaturation at 95°C for 30 s, annealing at 55°C for 30 s, and extension at 72°C for 30 s. The calculation of the mRNA expression of omentin-1 was verified by means of $2^{-\Delta\Delta CT}$ method. Each assay was performed in triplicate.

Western blot

The extraction of total protein was carried out from colon samples in ice-cold radioimmunoprecipitation assay

(RIPA) buffer with protease inhibitors. Following determining the concentration of protein with bicinchoninic acid (BCA) assay kit, 10% SDS-PAGE was applied for the separation of 50 μg protein extracted from each sample. Then, the nitrocellulose membranes were employed to carry the separated proteins, following by blocking with 5% non-fat milk for 2 h. The next incubation of membranes was done with primary antibodies against omentin-1 (R&D system, AF4254), ATF6 (Abcam, ab37149), p-eIF2α (Cell Signaling Technology, #9721), XBP1 (Abcam, ab37152), t-eIF2α (Cell Signaling Technology, #5324), Cox-2 (ABclonal, A1253), iNOS (Abcam, ab178945), occludin (Abcam, ab216327), ZO-1 (Abcam, ab216880), claudin-1 (Abcam, ab180158) at 4°C overnight. The Secondary antibody against either rabbit or mouse IgG (Cell Signaling Technology, #7071 and #7072) was applied for incubation with the membranes for 2 h at room temperature. The protein blots were visualized with the application of an enhanced chemiluminescence (ECL) kit and Bio-Rad ChemiDoc XRS (Bio-Rad, Hercules, CA, USA) was adopted to obtain the images.

Hematoxylin and eosin (H&E) staining

The collected colon segments were soaked in 10% formalin for 24 h. Subsequently, after paraffin embedding, these colon segments were cut into 5 μm sections. They were then stained with H&E staining (Solarbio Life Sciences, Beijing, China) for histopathological examination. The samples were placed under a 200× magnification for observation.

Detection of disease activity index (DAI)

Mice were observed daily for body weight, fecal traits and occult blood, and the scores for weight loss, fecal traits and occult blood were summed to obtain a DAI for each mouse to assess disease activity.

Enzyme-linked immunosorbent assay (ELISA)

The levels of inflammatory cytokines tumor necrosis factor α (TNF-α), interleukin 1β (IL-1β) and IL-6 in serum samples of mice were detected with the use of a commer-

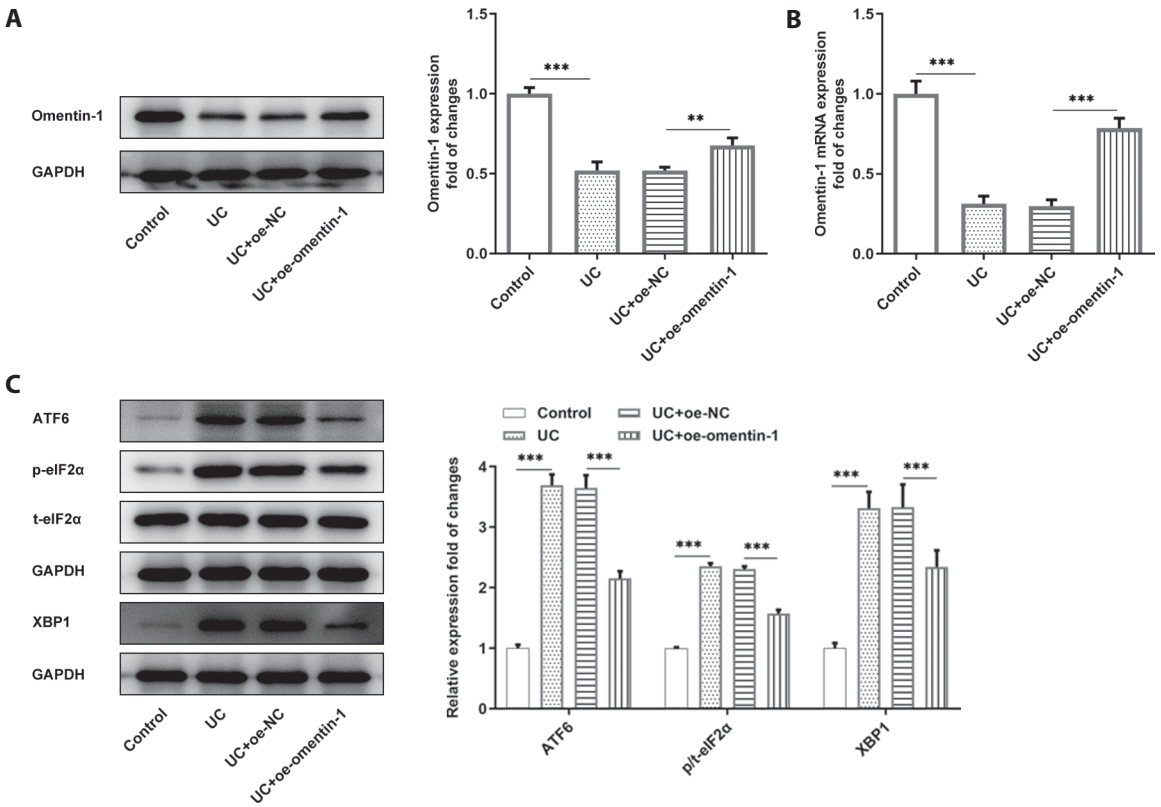
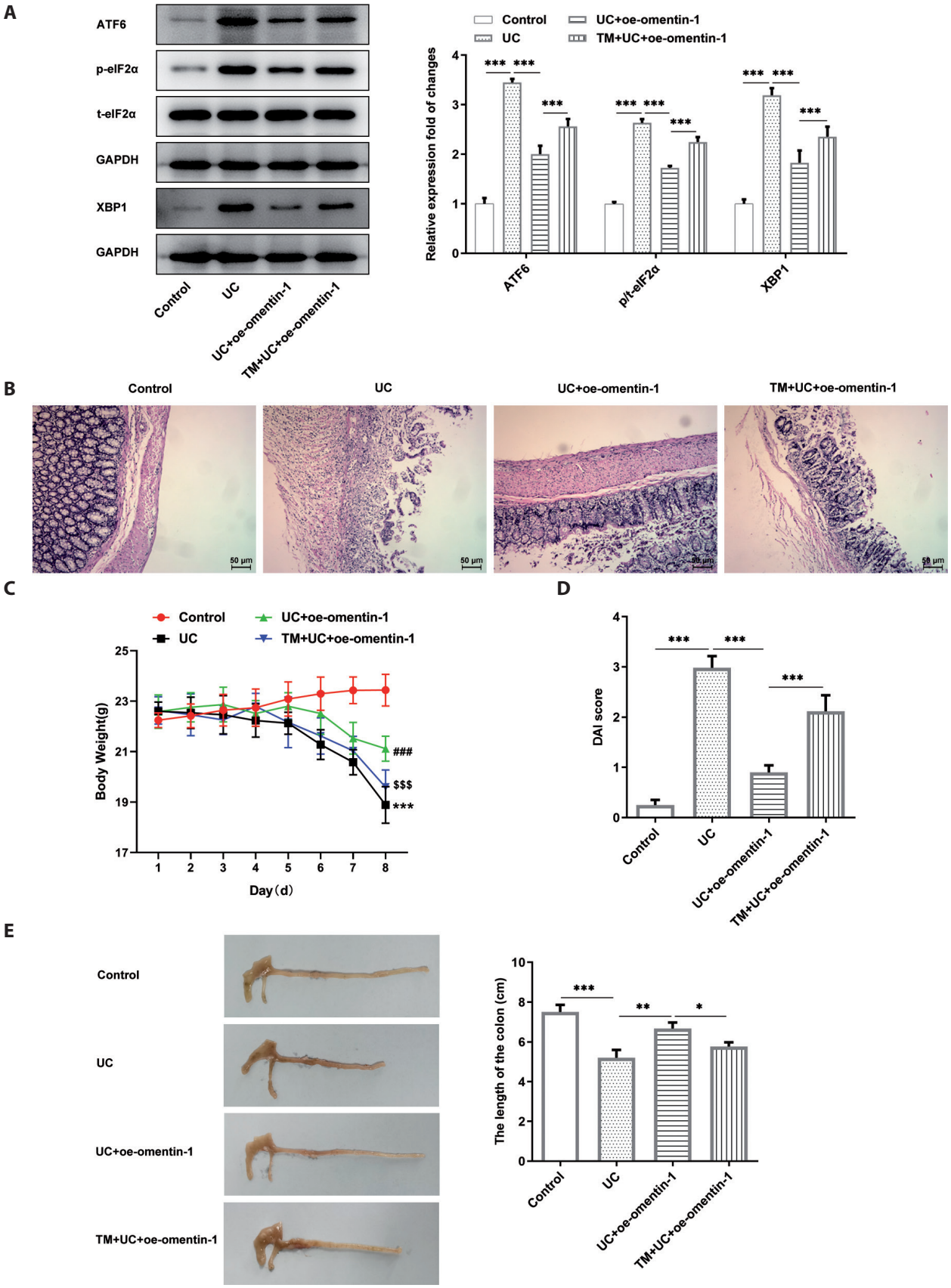


Figure 2. Omentin-1 is lowly expressed in the colon tissues of UC mice and overexpression of omentin-1 inhibits ER stress in DSS-induced UC mice. The protein (**A**) and mRNA (**B**) expressions of omentin-1 in the colon tissues of DSS-induced UC mice were examined by Western blot and RT-qPCR. **C.** The levels of reticulum stress-related proteins ATF6, p-eIF2α, XBP1 and t-eIF2α were examined utilizing Western blot in the colon tissues of DSS-induced UC mice after omentin-1 overexpression. ** $p < 0.01$, *** $p < 0.001$. For abbreviations of groups, see Fig. 1.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ATF6
p-eIF2α
t-eIF2α
GAPDH
XBP1
GAPDH
Control
UC
UC+oe-omentin-1
TM+UC+oe-omentin-1
Relative expression fold of changes
ATF6
p/t-eIF2α
XBP1
B
Control
UC
UC+oe-omentin-1
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50 μm
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Body Weight(g)
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D
DAI score
E
The length of the colon (cm)

cially corresponding ELISA kits (Elabscience, Wuhan, China).

Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay

One Step TUNEL Apoptosis Assay Kit (Beyotime, Shanghai, China) was applied for the detection of cell apoptosis in the colon tissues. Briefly, the sections of paraffin-embedded tissues were deparaffinized with xylene and rehydrated *via* graded ethanol. Afterwards, the sections were incubated with proteinase K for 30 min. Thereafter, the TUNEL assay solution was adopted to stain the sections at 37°C for 60 min. DAPI solution was used to stain the nuclei of cells with blue fluorescence. Finally, five areas of each section were randomly picked for testing using a fluorescence microscope (BX53; Olympus, Tokyo, Japan; magnification ×200), and the percentage of positive cells with green fluorescence was figured out.

Statistically analysis

Data were expressed in the form of mean ± SD and analyzed adopting GraphPad Prism (San Diego, CA, USA). Statistical comparisons among two groups were assessed with one-way analysis of variance (ANOVA), and Tukey's *post hoc* test was used for multiple comparison. The p-value <0.05 was taken as being statistically significant.

Results

Omentin-1 is lowly expressed in the colon tissues of UC mice and overexpression of omentin-1 inhibits ER stress in DSS-induced UC mice

To explore the role of omentin-1 in UC, we firstly assessed the expression of omentin-1 in DSS-induced mice, an *in vivo* UC mice model. The assays of RT-qPCR and Western blot in Figure 2 detected a marked decreased level of omentin-1 in UC group (*vs*. Control); however, an increased level of omentin-1 was found in UC+oe-omentin-1 group (*vs*. UC+oe-NC). Figure 2C illustrated that the levels of ER stress-related proteins ATF6, p-eIF2α and XBP1 were rapidly elevated in UC group (*vs*. Control), but successfully declined after omentin-1 overexpression (*vs*. UC+oe-NC). Considering the evidence, it indicated that DSS induced a low expression of omentin-1 and triggered ER stress in the colon tissues of UC mice, but overexpression of omentin-1 could inhibit DSS-induced ER stress in the colon tissues of UC mice.

Overexpression of omentin-1 inhibits DSS-induced colon damage in UC mice by suppressing ER stress

Since ER stress was demonstrated to be triggered in UC, and omentin-1 exhibited an inhibitory effect on ER stress, we next evaluated whether omentin-1 could participate into the modulation of UC progression by inhibiting ER stress. Therefore, the ER stress inducer tunicamycin (TM) was administrated in omentin-1 overexpressing UC mice. Figure 3A showed that the levels of ER stress-related proteins ATF6, p-eIF2α and XBP1 decreased by overexpression of omentin-1 were now elevated again after addition of TM, verifying an activation of ER stress upon TM. Afterwards, we examined the histological changes of the colon of UC mice. As indicated in Figure 3B, the damage level of colon structure was increased markedly in UC group (*vs*. Control), decreased in the UC+oe-omentin-1 group (*vs*. UC+oe-NC), but rose again in TM+UC+oe-omentin-1 group. In addition, the body weight of mice in UC group exhibited a dramatical drop (*vs*. Control), but then gained a great increase in UC+oe-omentin-1 group (*vs*. UC), and this increase was weakened in TM+UC+oe-omentin-1 group (Fig. 3C). Furthermore, we documented the DAI of these UC mice in each group in Figure 3D, which presented that there was a dramatic elevation in the DAI of DSS-induced UC mice (*vs*. Control). While omentin-1 overexpression showed a sharply declined DAI in DSS-induced UC mice, but the addition of TM increased the DAI more than twice. More importantly, Figure 3E recorded the colon length of UC mice in each group and showed that the colon length was remarkably shorter in UC group than that in the control group, while the colon length became slightly longer after omentin-1 overexpression, and the colon length became shorter again in TM+UC+oe-omentin-1 group. Overall, these results support the notion that overexpression of omentin-1 ameliorates DSS-induced colon injury in UC mice by suppressing ER stress.

◀ **Figure 3.** Overexpression of omentin-1 inhibits DSS-induced colon damage in UC mice by suppressing ER stress. **A.** The levels of reticulum stress-related proteins ATF6, p-eIF2α, XBP1 and t-eIF2α were examined utilizing western blot in the colon tissues of DSS-induced UC mice after omentin-1 overexpression and addition of tunicamycin (TM). *** $p < 0.001$ **B.** Colon tissue damage was observed by H&E staining in DSS-induced UC mice. Magnification ×200. **C.** Body weight was measured and recorded every day in each group *** $p < 0.001$ *vs.* Control; ### $p < 0.001$ *vs.* UC; $$$ $p < 0.001$ *vs.* UC+oe-omentin-1. **D.** Disease Activity Index (DAI) in DSS-induced UC mice. **E.** Colon length of DSS-induced UC mice. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. For abbreviations of groups, see Fig. 1.

Overexpression of omentin-1 inhibits DSS-induced colon inflammation and barrier damage in UC mice by suppressing ER stress

In addition to histological changes, we also inspected the importance of ometin-1-mediated ER stress in terms of inflammation and barrier damage in UC. As shown in Figure 4A–C, there were increased levels of pro-inflammatory cytokines TNF-α, IL-1β and IL-6 in the serum of UC mice induced by DSS (*vs*. Control), which were brought down by omentin-1 overexpression. While the levels of TNF-α, IL-1β and IL-6 were obviously increased again in TM+UC+oe-omentin-1. From Figure 4D, we can see that the levels of inflammation-related proteins Cox-2 and iNOS were also

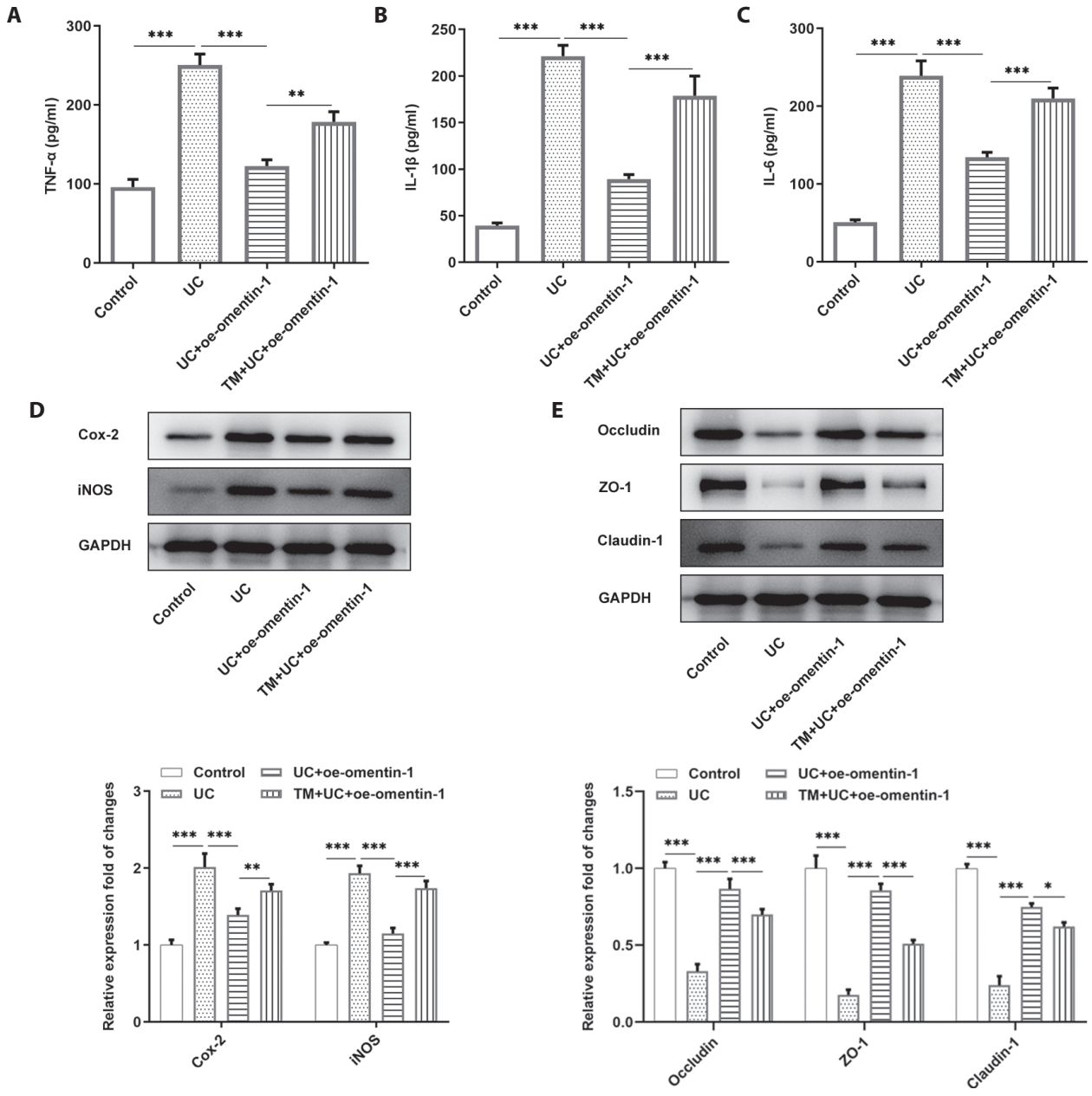

Figure 4. Overexpression of omentin-1 inhibits DSS-induced colon inflammation and barrier damage in UC mice by suppressing ER stress. Levels of inflammatory cytokines TNF-α (**A**), IL-1β (**B**) and IL-6 (**C**) in the serum of DSS-induced UC mice were examined by means of ELISA. ** $p < 0.01$, *** $p < 0.001$. **D.** The levels of inflammation-related proteins Cox-2 and iNOS were detected with the use of Western blot. **E.** The levels of tight junction proteins occludin, ZO-1 and claudin-1 in the colon tissues were examined by Western blot. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. For abbreviations of groups, see Fig. 1.

notably enhanced by the induction of DSS, but decreased by approximately half after overexpression of omentin-1, and the addition of TM brought their levels back up. UC also induced lower levels of tight junction proteins occludin, ZO-1 and claudin-1 in the tissues of UC mice, and oe-omentin-1 restored most of their levels rapidly, but these levels were reduced again with the addition of TM (Fig. 4E). In summary, these results outlined a critical role for omentin-1 that its overexpression could inhibit DSS-induced inflammation and barrier damage in UC mice by suppressing ER stress.

Overexpression of omentin-1 inhibits DSS-induced cell apoptosis of colon tissues in UC mice by suppressing ER stress

Eventually, we also assessed the critical role of omentin-1 during UC-induced apoptosis. As shown in Figure 5A, UC group showed more apoptotic cells (*vs.* Control). The apoptotic cells exhibited markedly less in the UC+oe-omentin-1 group than those in the UC group, but were re-increased in the TM+UC+oe-omentin-1 group. As indicated in Figure 5B, there was a drop in the expression of anti-apoptotic

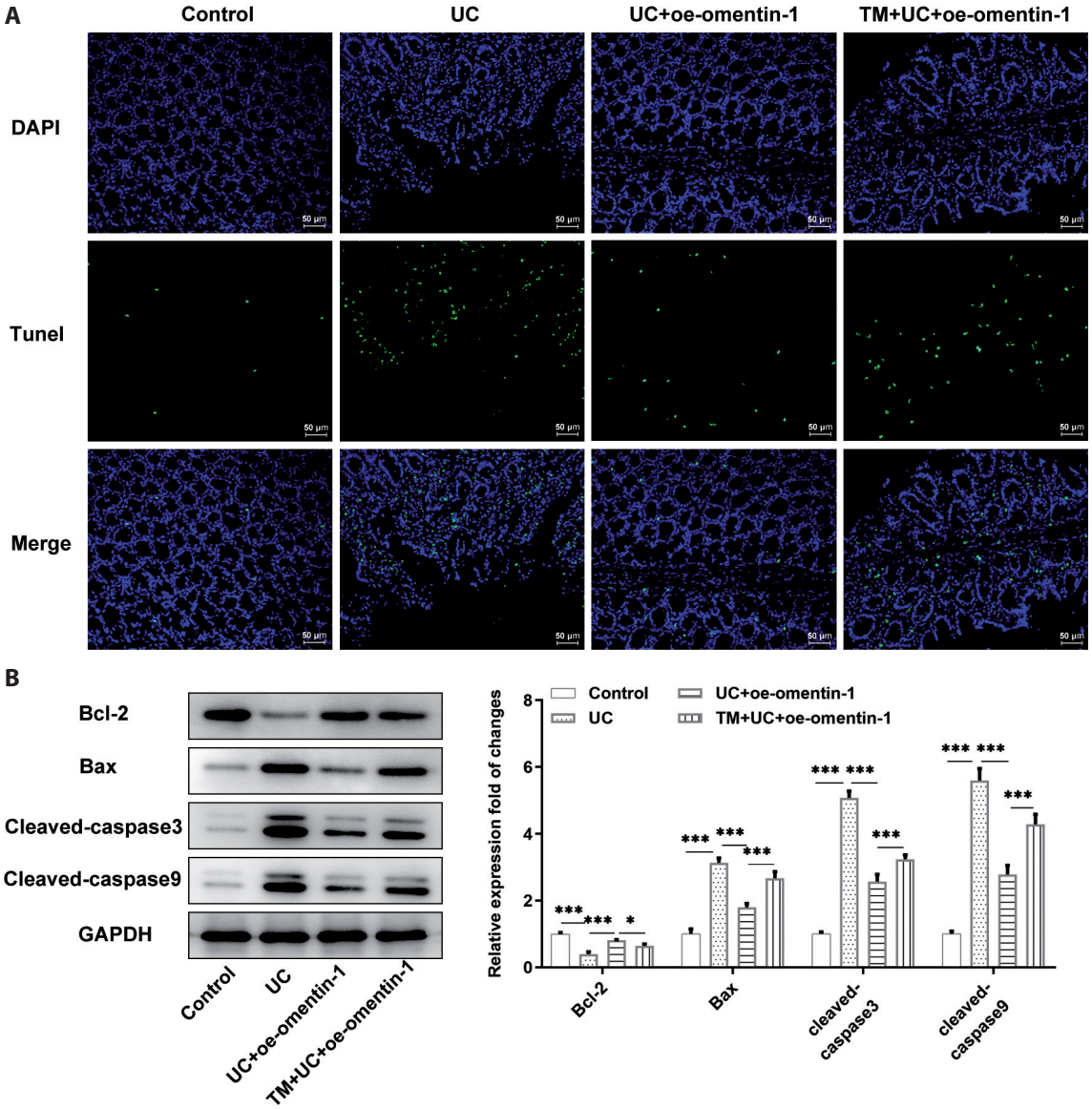

Figure 5. Overexpression of omentin-1 inhibits DSS-induced cell apoptosis of colon tissues in UC mice by suppressing ER stress. **A.** Cell apoptosis level was assessed by TUNEL staining in DSS-induced UC mice. Magnification ×200. **B.** The levels of apoptosis-related proteins Bcl-2, Bax, cleaved-caspase3, cleaved-caspase9 in tissues were assayed adopting Western blot in DSS-induced UC mice. * $p < 0.05$, *** $p < 0.001$. For abbreviations of groups, see Fig. 1.

protein Bcl-2 and an increase in the levels of pro-apoptotic proteins Bax, cleaved-caspase3 and cleaved-caspase9 in the UC group (*vs*. Control), as well as increased level of Bcl-2 and decreased levels of Bax, cleaved-caspase3 and cleaved-caspase9 in the UC+oe-omentin-1 group while TM weakened the regulatory effects of oe-omentin-1 on these proteins. The evidence showed in this section suggested that omentin-1 overexpression could exert inhibitory effects on DSS-induced cell apoptosis of colon tissues in UC mice by suppressing ER stress.

Discussion

UC is a chronic inflammatory disease of the intestine with lesions involving mainly the rectal and colonic mucosa (Christophi et al. 2016). It has been shown that an incompletely assembled molecule, the MUC2 precursor, accumulates in the endoplasmic reticulum of micro pharyngeal cells, leading to abnormal protein overload and causing an ER stress response (Heazlewood et al. 2008). ER stress may lead to a reduction in the mucus barrier, exposing the intestinal lining to more toxins and foreign substances and triggering local mucosal inflammation (Eugene et al. 2020). The release of inflammatory cytokines would damage the intestinal lining and exacerbate ER stress, thus establishing a cycle of intestinal damage and inflammation. Therefore, inhibition of ER stress is a key aspect in the treatment of UC. And some studies have indicated that low level of omentin-1 is associated with UC development. Therefore, this paper mainly looked at the role of omentin-1 in ER stress and its function in UC.

Omentin-1 is a key adipokine secreted by visceral adipose tissue (Greulich et al. 2013). It has been shown that omentin-1 level was significantly decreased in the serum of patients with inflammatory bowel disease (Genre et al. 2020). The expression of omentin is also downregulated in the colonic tissue of patients with active Crohn's disease and UC (Yin et al. 2015). Our experimental report also disclosed low level of omentin-1 in colon tissue of UC mice model, which was in accordance with previous reports. In addition, we found that the reduced level of colonic injury in UC mice, the lengthened colon length and the reduced DAI score in the UC+oe-omentin-1 group showed the ameliorative effect of omentin-1 overexpression on colonic tissue injury in UC mice. Whereas, the ameliorative effect was reversed by TM, indicating that overexpression of omentin-1 ameliorated colonic tissue injury by suppressing ER stress.

Emerging findings suggest that ER stress takes part in the onset and development of UC (Kaser and Blumberg 2009). In UC, the reduced number of functional phagocytes and mucus secretion leads to the accumulation of unfolded MUC2 precursor protein in secretory phagocytes, and such accumulation leads to abnormal ER stress by activating the unfolded protein response (Heazlewood et al. 2008; Das et al. 2013; Hasnain et al. 2013). In addition, there are three proximal effectors in the ER that sense unfolded protein, including inositol-requiring transmembrane kinase/endonuclease 1 (IRE1), pancreatic ER kinase (PERK), and activating transcription factor 6 (ATF6) (Shastri et al. 2020). Among them, PERK is able to inhibit eukaryotic translation initiation factor 2α (eIF2α), leading to the arrest of translation (Lebeau et al. 2018). XBP1 is a transcription target of ATF6f and is easily affected by ER stress (Todd et al. 2008). To look into the effect of omentin-1 on ER stress, we examined the expressions of ER stress-related proteins and found that overexpression of omentin-1 significantly reduced the expressions of ER stress-related proteins ATF6, p-eIF2α, XBP1. Likewise, the addition of TM increased the expressions of these protein related to ER stress, further indicating that omentin-1 significantly inhibited ER stress in UC.

A growing number of studies have found that ER stress is a major factor involved in triggering inflammation (Kaser et al. 2008). This is because ER stress activates IRE1α to recruit TRAF2 to the ER membrane and initiate inflammatory responses *via* the NF-κB pathway (Keestra-Gounder et al. 2016). Additionally, omentin-1 belongs to the omentin family and has anti-inflammatory effects. An investigation has confirmed that omentin could inhibit TNF-induced vascular inflammation in human endothelial cells (Yamawaki et al. 2011). Omentin-1 prevented inflammation-induced osteoporosis by the downregulation of the pro-inflammatory cytokines (Rao et al. 2018). Omental adipose tissue is also involved in the transmural and intraperitoneal inflammatory processes observed in Crohn's disease (Schaffler et al. 2007). Our experiments further validated the fact that overexpression of omentin-1 suppressed serum levels of inflammatory factors and expression of inflammation-associated proteins Cox-2 and iNOS, all of which were reversed upon TM addition, suggesting that the inflammatory inhibition of UC by omentin-1 is mediated through inhibition of ER stress. Additionally, previous studies have shown that ER stress and damage to the intestinal mucosa are closely related (Huang et al. 2018). The changes in the expressions and localization of tight junction proteins occludin, zonula occludens (ZO)-1 and claudin-1 would result in dysfunction of the paracellular barrier in the intestinal epithelium (Turner 2009). It was found in our experiments that omentin-1 overexpression increased the levels of occludin, ZO-1 and claudin-1, which brought down by TM. This result demonstrated that omentin-1 overexpression also reduced barrier damage by suppressing ER stress.

On the other hand, excessive ER stress activates many apoptotic signaling pathways rather than restoring the balance of ER protein fold (Cao 2015). One study pointed out that omentin-1 could stimulate angiogenesis in HUVECs by inhibiting apoptosis (Yin et al. 2017). In view of this, we

examined the apoptosis level and related protein expression in the colonic tissue of DSS-induced UC mice. There was a reduced level of apoptotic cells, an elevated level of anti-apoptotic protein Bcl-2, and the decreased levels of pro-apoptotic proteins Bax, cleaved-caspase3, cleaved-caspase9 in colon tissue of UC mice after omentin-1 overexpression while additional treatment of TM weakened the regulatory effects of omentin-1 on these proteins in UC mice. It indicated that omentin-1 overexpression also inhibited apoptosis by suppressing ER stress.

In view of all that has been discussed so far, we identified omentin-1 as a key factor in UC development that ameliorated DSS-induced inflammation and barrier damage in colon tissues of UC mice by inhibiting ER stress. Even though more comprehensive studies are needed to discovery more in-depth mechanism underlying the protective role of omentin-1 in UC, this study provides a possible foundation for omentin-1 as a biological target of UC prognosis and treatment in clinical.

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Conflicts of interest. No potential conflict of interest was reported by the authors.

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