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The effect of high glucose-based peritoneal dialysis fluids on thioredoxin-interacting protein expression in human peritoneal mesothelial cells

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ABSTRACT

Background: It has been demonstrated that thioredoxin-interacting protein (TXNIP) interacted with NACHT, LRR and PYD domains-containing protein 3 (NLRP3) and participated in the NLRP3 inflammasome activation. Our previous study has demonstrated that in human peritoneal mesothelial cells (HPMCs), exposure to high glucose-based peritoneal dialysis (PD) solutions induced mitochondrial reactive oxygen species (ROS) production, activation of NLRP3 inflammasome and IL-1β expression. This study aimed to investigate the effect of high glucose-based PD fluids on the TXNIP expression and the underlying mechanisms by which TXNIP-NLRP3 interaction mediates the inflammatory injury to HPMCs in high glucose-based PD fluids conditions.

Methods: TXNIP gene and protein expression was detected by real-time polymerase chain reaction (RT-PCR) and immunoblot. Immunoprecipitation was used to evaluate the interaction between TRX1 and TXNIP, TXNIP and NLRP3. ROS production and IL-1β expression was examined by flow cytometry and immunoblot and enzyme-linked immunosorbent assay (ELISA) respectively.

Results: It was identified that high glucose-based PD solutions enhance the level of TXNIP gene and protein in cultured HPMCs and a rat-based PD model. We also found that ROS generation induced by high glucose-based PD solutions disrupts the TRX1-TXNIP association, while promoting the binding of TXNIP to NLRP3 in HPMCs. Furthermore, the application of a ROS inhibitor (APDC) to HPMCs blocked the high glucose-based PD solution-induced TXNIP-NLRP3 binding, in addition to ROS production and IL-1β expression.

Conclusion: The results of the present study revealed a novel mechanism underlying high glucose-containing PD-mediated peritoneal inflammatory injury, supporting the attenuation of ROS generation as a potential therapeutic strategy to alleviate such pathology.

1. Introduction

Peritoneal dialysis (PD) has been a primary treatment option for patients with end-stage renal disease for > 30 years. Accordingly, great interest has been aroused in the physiology and biology of peritoneal mesothelial cells (PMCs). It has been suggested that the bio-incompatible nature of conventional PD solutions, including non-physiological pH, elevated levels of glucose and lactate, high osmolality, and toxic glucose degradation products, may contribute to intraperitoneal inflammation in PMCs [1–3].

Inflammasomes are multimeric complexes of innate immune receptors and their formation leads to caspase-1 activation, which subsequently promotes the processing and secretion of inflammatory cytokines, including interleukin (IL)-1β and IL-18 [4]. There is growing evidence that the activation of the NACHT, LRR and PYD domains-containing protein 3 (NLRP3) inflammasome via sensing of cellular stress signals serves a direct role in the pathophysiology of a broad spectrum of autoinflammatory and autoimmune diseases [5,6]. Reactive oxygen species (ROS), the production of which is induced by a variety of NLRP3 inflammasome activators, was identified to be the second messenger mediating the assembly and activation of the NLRP3 inflammasome [7,8]. Notably, mitochondrial ROS are essential for activating the NLRP3 inflammasome [9]. Despite extensive studies supporting an important role of ROS in driving inflammasome activation, further investigation is required to determine whether the NLRP3 inflammasome senses redox alterations via a general mechanism or mechanisms varying between different cell types.

Thioredoxin-interacting protein (TXNIP) is an intracellular protein

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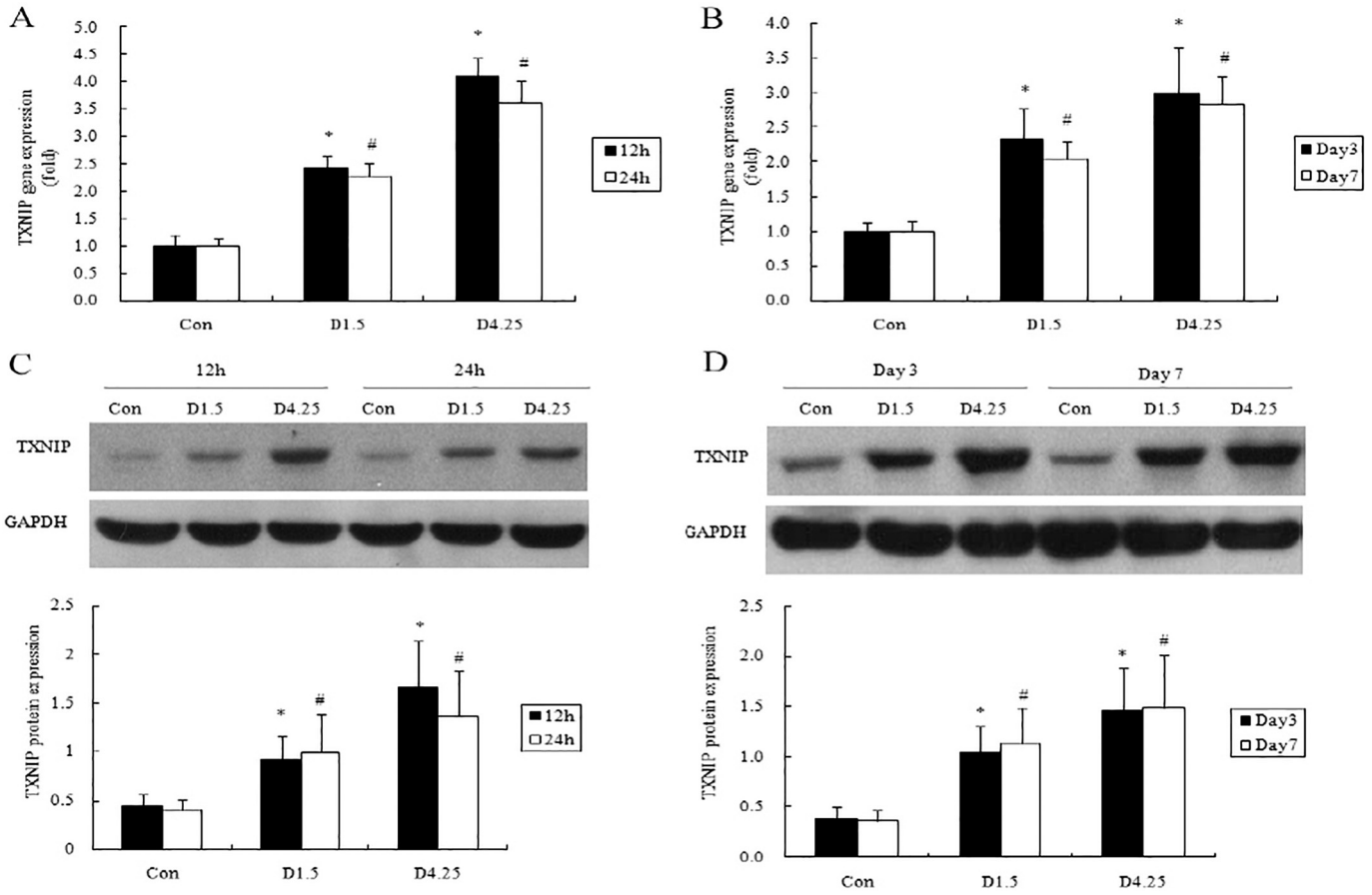

Fig. 1. High glucose-based PD fluids upregulate TXNIP gene and protein expression in HMrSV5 cells cultures and rat peritoneal tissues.
HMrSV5 cells were exposed to two Dianeal concentrations (1.5% and 4.25%, respectively) for 12 and 24 h, and the derived cell lysates were analyzed by RT-PCR and immunoblotting to determine the TXNIP gene (A) and protein expression (C) levels. A PD model was established in rats, and visceral peritoneal tissues (mesentery tissue) were collected on days 3 and 7 followed by RT-PCR and immunoblot analysis to determine the TXNIP gene (B) and protein expression (D) levels. β-Actin and GAPDH were used as a loading control. Results are representative of at least three independent experiments. *P < 0.05 vs. Con. PD, peritoneal dialysis; TXNIP, thioredoxin-interacting protein; D, Dianeal; Con, control.

which was originally identified to be an interactor of thioredoxin (TRX1) protein, regulating its antioxidant function [10]. However, TXNIP has been demonstrated to have a novel role in mediating cellular stress responses. Zhou et al. [11] demonstrated that a time-dependent release of TXNIP from the TRX1 association to form a complex with NLRP3 is an important step toward inflammasome formation, thus providing a novel mechanism for the oxidative stress-mediated activation of the inflammasome. The expression of TXNIP protein may be detected in cells of various origins, including skeletal myocytes, pancreatic β cells, endothelial cells, adipocytes and kidney cells [12,13]. An association between TXNIP and the cellular response to glucose exposure was initially suggested due to the finding that TXNIP expression was significantly upregulated by glucose in a microarray study of human pancreatic islets [14]. Additional studies have further demonstrated that high glucose-induced TXNIP upregulation occurs in mesangial and endothelial cells [15,16]. Previously, it was reported that human PMCs (HPMCs), when exposed to conventional high glucose-based PD fluids, exhibit a significant induction of mitochondrial ROS, along with the activation of the NLRP3 inflammasome and the enhanced production of mature IL-1β [17]. In the present study, the effects of high glucose-based PD fluids on the TXNIP gene and protein expression level in HPMCs were examined, in order to further determine whether the recruitment of TXNIP to NLRP3 underlies the activation of the inflammasome during the course of glucose-induced inflammatory injury to HPMCs.

2. Materials and methods

2.1. Reagents and antibodies

APDC [(2*R*,4*R*)-4-aminopyrrolidine-2,4-dicarboxylate] and monosodium urate (MSU) crystals were obtained from Sigma-Aldrich (Merck KGaA, Darmstadt, Germany). Mitotracker deep red, Mitotracker green, and MitoSOX were purchased from Invitrogen (Thermo Fisher Scientific, Inc. Waltham, MA, USA). The antibodies used in the present study were from: Abcam (Cambridge, UK; anti-NLRP3 for immunoblot ab16097 and anti-TRX1 ab26320); Invitrogen (Thermo Fisher Scientific, Inc., Waltham, MA, USA; anti-TXNIP 40-3700); Cell Signaling Technology, Inc. (Danvers, MA, USA; anti-IL-1β or pro-IL-1β 12242); and Santa Cruz Biotechnology, Inc. (Dallas, TX, USA; anti-GAPDH: sc-32233, anti-rabbit: sc-2357 and anti-mouse: sc-2954 IgG antibody); IL-1β enzyme-linked immunosorbent assay (ELISA) kit was obtained from R&D Systems (R&D Systems, Inc. Minneapolis, Minnesota, USA).

2.2. Cell culture conditions and methods

The generation of an SV40-immortalized HPMC line, termed HMrSV5, was reported previously [17,18]. Cells were grown in type I collagen-coated dishes in Dulbecco's modified Eagle's medium (DMEM, Gibco, Thermo Fisher Scientific, Inc.) containing 10% Fetal Bovine Serum (FBS, Gibco, Thermo Fisher Scientific, Inc.) and incubated at

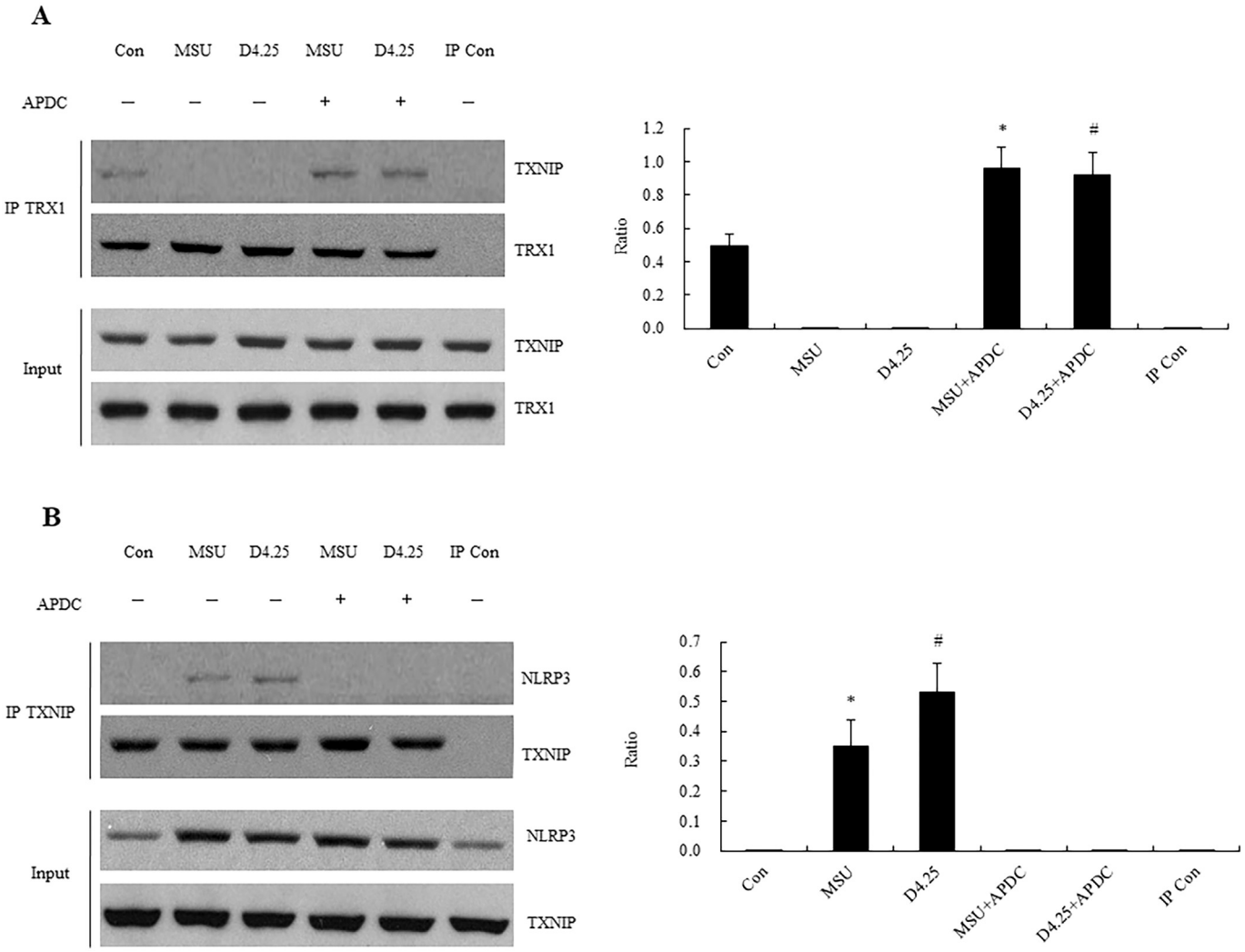

Fig. 2. ROS induced by high glucose-based PD solutions promotes the release of TXNIP from TRX1 to interact with NLRP3 in HMrSV5 cells.
HMrSV5 cells were incubated with or without the ROS inhibitor APDC (100 μM) for 30 min and subsequently left untreated, or treated for 4 h with MSU (150 μg/ml) or 4.25% Dianeal. The derived cell extracts were used for immunoprecipitation with antibodies against TRX1 or TXNIP (A. the interaction of TXNIP with TRX1; B. the interaction of TXNIP with NLRP3). The presence of the indicated proteins in the original cell lysates and immunoprecipitation samples was detected by immunoblot analysis. Input, original cell extracts. The results are representative of at least three independent experiments. The graph is the ratio of TXNIP expression in IP to input (A, *P < 0.05 vs. MSU. #P < 0.05 vs. D4.25) and NLRP3 expression in IP to input (B, *P < 0.05 vs. MSU + APDC. #P < 0.05 vs. D4.25 + APDC). ROS, reactive oxygen species; TXNIP, thioredoxin-interacting protein; TRX1, thioredoxin; Con, control; MSU, monosodium urate; D, Dianeal; IP, immunoprecipitation; NLRP3, NACHT, LRR and PYD domains-containing protein 3; APDC [(2*R*,4*R*)-4-aminopyrrolidine-2,4-dicarboxylate].

37 °C in a humidified 5% CO_2 atmosphere. All experiments with HMrSV5 cells were performed with early passage (passage 5 to 10) cells. Cell viability was evaluated via MTT reduction assay, as described previously [18]. Cells were seeded into tissue culture plate 6 (34.8 mm diameter) or 60-mm-diameter tissue culture plates. Near-confluent cells were incubated with serum-free medium for 24 h to synchronize cell growth and used in the following experiments.

2.3. Animal models of PD

Rat models of PD were established with 15 male Wistar rats (weight range, 300 ± 50 g, 8 weeks, Animal Research Center of Wuhan University) according to published experimental protocols [19]. The animals were kept in standard rat cages four per cage and maintained under housing conditions, including 12 h light-dark cycle, temperature (22 ± 2 °C), humidity (45–60%) and food and water was freely available. On day 1, under sterile conditions, the omentum was partially removed from anesthetized rats followed by implanting a peritoneal catheter into the peritoneal cavity, in the experimental and control groups. Following recovery, the rats were returned to their cages and subjected to dialysis twice daily for 1 week. For a typical daily dialysis procedure, 20 ml dialysis solution containing either 1.5% or 4.25% Dianeal (Baxter International, Inc., Deerfield, IL, USA) was administered once in the morning and once in the evening, without drainage until the next infusion, which allowed a gradual absorption of fluid from the peritoneal cavity. During the entire course of the study, the rats were allowed full mobility. All animal handling procedures received approval from the Animal Ethics Committee of Tongren Hospital affiliated to Wuhan University (Wuhan, China).

2.4. Real-time polymerase chain reaction

HMrSV5 cells (1×10^6) and visceral peritoneal tissues (mesentery tissue 50 mg) were washed with phosphate-buffered saline (PBS) and lysed in Trizol respectively. RNA was extracted accord to Chomczynski's method [20]. A total of one micrograms RNA was reverse transcribed to cDNA, using the PrimeScript™ 1st strand cDNA synthesis kit (Takara, Japan). The cDNA products for TXNIP were then subjected to

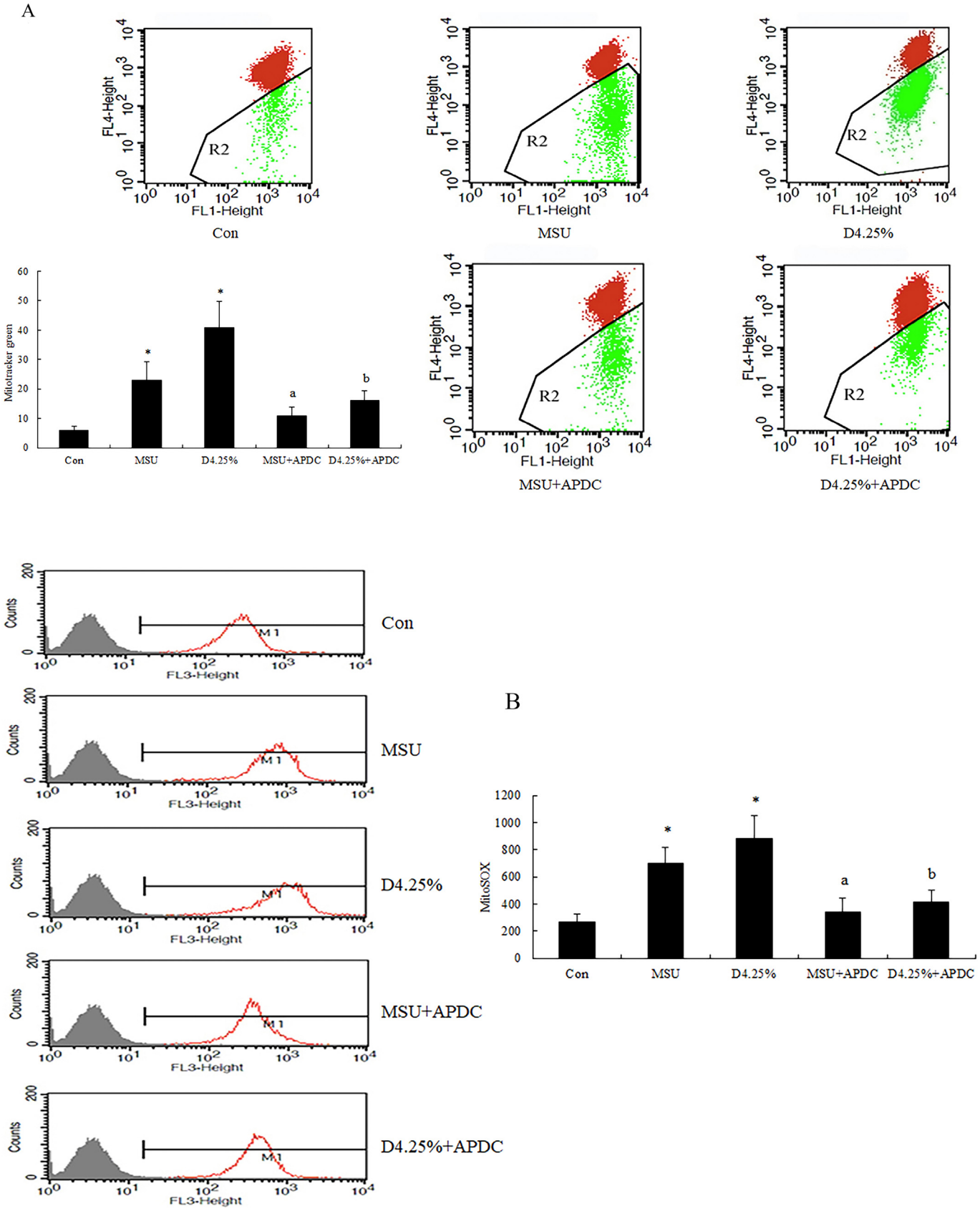

Fig. 3. The effect of ROS inhibitor on high glucose-based PD solution-induced mitochondrial ROS production.
HMrSV5 cells were incubated with or without the ROS inhibitor APDC (100 μM) for 30 min and subsequently left untreated, or treated for 4 h with MSU (150 μg/ml) or 4.25% Dianeal. The mitochondria-specific labels Mitotracker deep red and Mitotracker green (A) or MitoSOX (B) were used to stain cells respectively and analyzed by flow cytometry. The results are representative of at least three independent experiments. *P < 0.05 vs. Con. [a]P < 0.05 vs. MSU. [b]P < 0.05 vs. D4.25. Con, control; MSU, monosodium urate; D, Dianeal; APDC [(2*R*,4*R*)-4-aminopyrrolidine-2,4-dicarboxylate].

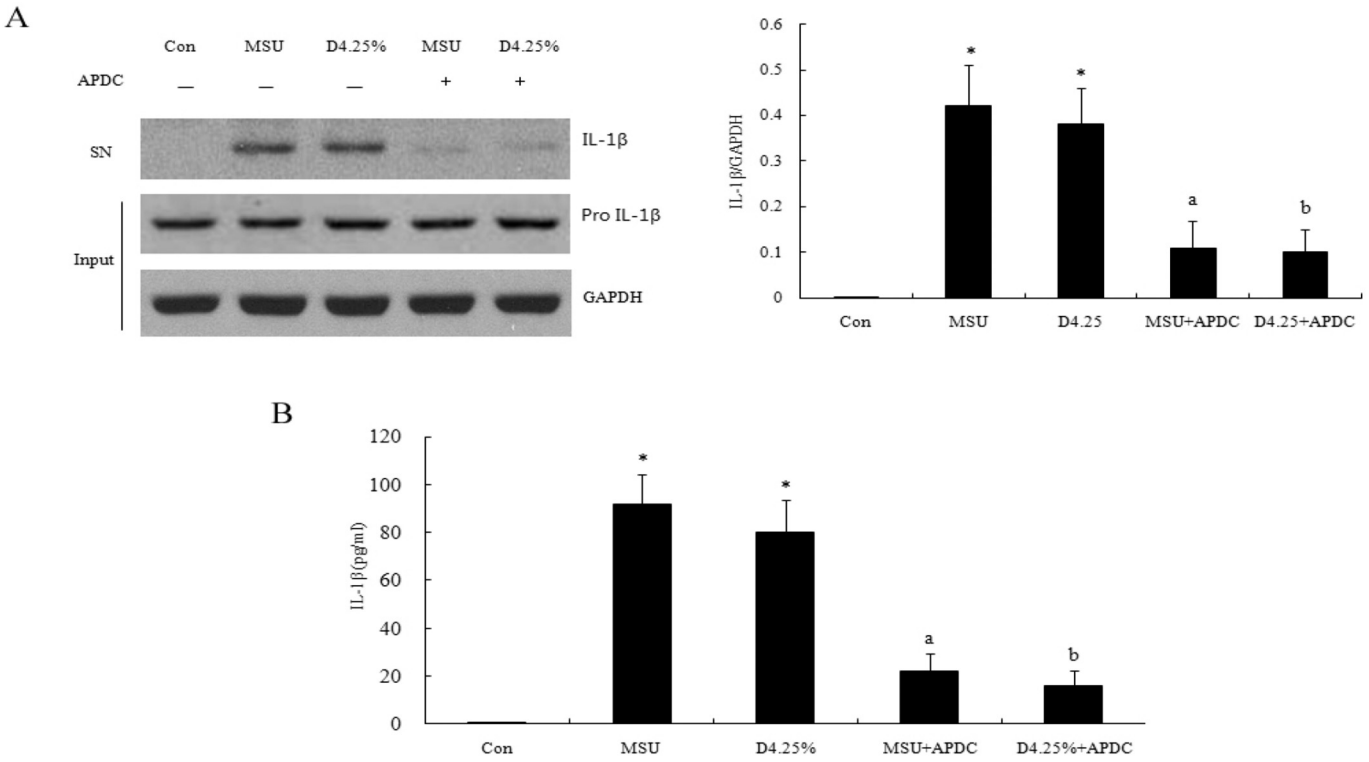

Fig. 4. Inhibition of ROS generation attenuates high glucose-based PD solution-induced IL-1β maturation.
HMrSV5 cells were pretreated with or without the ROS inhibitor APDC (100 μM) for 30 min, followed by 4 h incubation with either MSU (150 μg/ml) or 4.25% Dianeal. SN and cell extracts (input) were subjected to immunoblot analysis for the detection of the indicated proteins (A). Cell culture supernatants were subjected to ELISA for IL-1β (B). Results are representative of at least three independent experiments. *P < 0.05 vs. Con. [a]P < 0.05 vs. MSU. [b]P < 0.05 vs. D4.25. IL, interleukin; Con, control; SN, supernatant; MSU, monosodium urate; D, Dianeal; APDC [(2*R*,4*R*)-4-aminopyrrolidine-2,4-dicarboxylate].

quantitative polymerase chain reaction (qPCR) using an ABI 7900HT sequence detection system. The following sets of primers were used. CAGCCAACAGGTGAGAATGA (forward) and TTGAAGGATGTTCCCAG AGG (reverse) for human TXNIP, ACCATGGATGATGATATCGCC (forward) and GCCTTGCACATGCCGG (reverse) for human β-actin, CAAG TTCGGCTTTGAGCTTC (forward) and ACGATCGAGAAAAGCCTTCA (reverse) for rat TXNIP, GCAAATGCTTCTAGGCGGAC (forward) and AAGAAAGGGTGTAAAACGCAGC (reverse) for rat β-actin. Experiments were conducted in 96-well plates in triplicate, using SYBR Premix Ex Taq (Takara, Japan). The qPCR conditions were 95 °C for 30 s, followed by 40 cycles at 95 °C for 5 s and 55 °C for 31 s. Experimental data were analyzed with the $2^{-\Delta\Delta Ct}$ method.

2.5. Immunoblot analyses

Immunoblot analyses were performed following a published protocol [18]. HMrSV5 cells (1×10^6) and visceral peritoneal tissues (mesentery tissue 50 mg) were collected. The protein concentrations of cell or tissue lysates were measured using a Pierce bicinchoninic acid kit (Thermo Fisher Scientific, Inc.). A total of 20 μg protein per sample was resolved by denaturing electrophoresis on a 10% SDS-polyacrylamide minigel. Following electro-transfer of the gel to a nitrocellulose membrane, the membrane was blocked with 5% non-fat milk for 60 min at room temperature, followed by overnight incubation at 4 °C with the indicated primary antibodies (TXNIP 1:1000, NLRP3 1:1000, TRX1 1:1000, IL-1β or pro-IL-1β 1:1000, GAPDH 1:1000). The following day, the membrane was rinsed with 1× TBS-Tween 20 and subjected to a 60-min incubation with diluted secondary antibodies (1:2000 diluted anti-rabbit or anti-mouse IgG antibody) at room temperature, following by detection using an enhanced chemiluminescence system (Pierce; Thermo Fisher Scientific, Inc.).

2.6. Immunoprecipitation

HMrSV5 cells were incubated with or without 100 μM ROS inhibitor APDC for 30 min, and subsequently either treated with MSU (150 μg/ml) or 4.25% Dianeal for 4 h, or left untreated. Approximately 2.5×10^6 cells were collected and resuspended in lysis buffer (10× Cell Lysis Buffer, ab152163, Abcam. Dilute in sterile water to achieve 1× Cell Lysis Buffer, add phenylmethylsulfonyl fluoride (PMSF) to a final concentration of 1 mM) and incubated on ice for 20 min and the resulting extracts were subjected to immunoprecipitation with either TRX1 antibody (ab26320, Abcam) or TXNIP antibody (40-3700, Invitrogen).

2.7. Flow cytometric analyses

HMrSV5 cells were subjected to the indicated treatments described in the immunoprecipitation subsection. Approximately 1×10^6 cells were collected, then the mitochondria-specific labels Mitotracker deep red (50 nM), Mitotracker green (50 nM) or MitoSOX (2.5 mM) were used to stain cells (5×10^5) for 30 min at 37 °C respectively. Then the cells were rinsed with PBS and resuspended in cold PBS containing 1% FBS for flow cytometric analyses.

2.8. Enzyme-linked immunosorbent assay

HMrSV5 cells were subjected to the indicated treatments described in the above section. Cell culture supernatants were collected. The assays of human IL-1β were performed according to the manufacturer's instructions. Triplicate samples were analyzed and compared to the standard curve.

2.9. Statistical analysis

Values were from three independent experiments and are expressed as mean ± standard deviation. The data were first assessed by one-way analysis of variance for determining statistical differences among groups, followed by analyses using the Bonferroni test for continuous variables with normal distribution. For all assessments, $P < 0.05$ was considered to indicate a statistically significant difference. The statistical calculations were performed using the statistical package SPSS for Windows 15.0 (SPSS, Inc., Chicago, IL, USA).

3. Results

3.1. High glucose-based PD fluids upregulate TXNIP gene and protein expression in HMrSV5 cells cultures and rat peritoneal tissues

Treatment with high glucose-based PD fluids led to upregulation of TXNIP gene and protein expression in HMrSV5 cells (Fig. 1A and C). This effect was further investigated in rat PD models. As illustrated in Fig. 1B and D, TXNIP expression was elevated on days 3 and 7, particularly in the 4.25% Dianeal treatment group.

3.2. ROS induced by high glucose-based PD solutions promotes the release of TXNIP from TRX1 to interact with NLRP3 in HMrSV5 cells

A previous study demonstrated that HMrSV5 cells, when exposed to high glucose-based PD fluids, exhibited elevated levels of mitochondrial ROS [17]. It was demonstrated in human THP-1 cells that ROS production triggers TXNIP release from TRX1-binding to interact with NLRP3, thus facilitating the formation and activation of the NLRP3 inflammasome [11]. Consequently, the present study investigated whether, in HMrSV5 cells, high glucose-based PD solutions may induce a protein interaction switch of TXNIP from TRX1 to NLRP3 via the production of ROS. The immunoprecipitation experiments detected the interaction between TXNIP and TRX1 in mock-treated cells (lane 1, Fig. 2A). By contrast, exposure to 4.25% Dianeal or MSU, a well-known ROS-generating NLRP3 activator, disrupted the TXNIP-TRX1 association (lanes 2 and 3, Fig. 2A); the effect was reversed by pre-treatment with the ROS inhibitor APDC (lanes 4 and 5, Fig. 2A). Conversely, exposure to 4.25% Dianeal or MSU promoted the ROS-dependent recruitment of TXNIP to NLRP3 (Fig. 2B).

3.3. The effect of ROS inhibitor on high glucose-based PD solution-induced mitochondrial ROS production

As shown in Fig. 3A and B, treatment with 4.25% Dianeal and MSU increased the total (Mitotracker green), and ROS-generating mitochondria (MitoSOX) when compared with control group. In contrast, pretreatment with the ROS inhibitor APDC obviously attenuated this effect.

3.4. Inhibition of ROS generation attenuates high glucose-based PD solution-induced IL-1β maturation

The present study sought to determine whether ROS generation is required for high glucose-based PD solution-induced inflammasome activation by examining a major downstream event: IL-1β processing. As presented in Fig. 4A, treatment with 4.25% Dianeal and MSU induced the processing of IL-1β from its initial form (pro IL-1β), which was not observed in control cells; pretreatment with the ROS inhibitor APDC significantly attenuated this inducing effect. In addition, as shown in Fig. 4B, the IL-1β expression in the supernatants was obviously increased in 4.25% Dianeal and MSU groups; pretreatment with APDC significantly decreased the production of IL-1β.

4. Discussion

PMCs constitute the largest population of cells residing in the peritoneal cavity. Long-term subjection of PMCs to bio-incompatible conventional PD fluids has been considered to be directly associated with a compromised local peritoneal host defense and intraperitoneal inflammation in patients [21,22]. A previous study reported that HPMCs, upon treatment with conventional glucose-based PD solutions, exhibited decreased levels of Toll-like receptors 2 and 4, and attenuated inflammatory response to pathogen-associated molecular patterns, including Pam3CSK4 or lipopolysaccharide. This previous finding provided a mechanistic explanation for the increased risk of peritoneal infection frequently observed in patients receiving continuous PD with conventional glucose-containing PD solutions [18].

In the present study, the analyses of HPMC cultures and rat peritoneal tissues demonstrated that treatment with high glucose-based PD solutions resulted in increased TXNIP gene and protein expression compared with the mock control. Parikh et al. [23] reported that the TXNIP expression level was increased in cultured cells upon elevation of medium glucose concentration, which was consistent with further observation that patients with diabetes exhibited marked upregulation of TXNIP expression. Koenen et al. [24] demonstrated that hyperglycemic ob/ob mice exhibited increased levels of TXNIP protein compared with a wild-type group, while long-term exposure to high glucose stimulated the production of TXNIP in human adipose tissues. The present results, together with the above reports, suggested that TXNIP upregulation may be a general cellular response to high glucose concentrations.

Previous studies have revealed that TXNIP serves an essential role in the formation and activation of the NLRP3 inflammasome [11,25–28]. The original study performed by Zhou et al. [11] demonstrated that, in unstressed cells, TXNIP is associated with TRX1 and its interaction with NLRP3 is absent, thus rendering the NLRP3 inflammasome inactive. However, in cells under oxidative stress, ROS production triggers TRX1-TXNIP dissociation and promotes the interaction between TXNIP and NLRP3, which facilitates the formation and activation of the NLRP3 inflammasome. This ROS-mediated TXNIP-NLRP3 association provides a mechanism for the ROS-dependency of inflammasome activation [11,25]. The present study therefore investigated whether the same mechanism applied to PMCs during the course of exposure to high glucose-based PD solutions. The results of the present study demonstrated that treatment with 4.25% Dianeal induced the recruitment of TXNIP to NLRP3 at the expense of its binding to TRX1 in HMrSV5 cells, supporting a general function of TXNIP in ROS-induced NLRP3 inflammasome activation.

It was previously demonstrated that high glucose-based PD solutions stimulate the production of mitochondrial ROS, cause to increased maturation and secretion of IL-1β primarily via activation of the NLRP3 inflammasome in HMrSV5 cells [17]. The results of the present study demonstrated that treatment with 4.25% Dianeal and MSU upregulated the production of ROS and IL-1β in HMrSV5 cells; treatment with a ROS inhibitor significantly attenuated this enhancing effect. These results further support the initial hypothesis that the ROS-inflammsome-IL-1β axis is an integral part of the cellular response to high glucose concentrations.

5. Conclusion

The present study provided the first evidence, to the best of our knowledge, that high glucose-based PD solutions upregulate TXNIP gene and protein expression in HPMCs and rat peritoneal tissues. It was further demonstrated that long-term exposure of HPMCs to high glucose-based PD solutions has profound effects on TXNIP functioning through ROS generation, modifying TXNIP from a TRX1 interacting protein to a facilitator of NLRP3 inflammasome activation by directly binding to NLRP3. Therefore, the present results revealed novel insights into the mechanisms underlying peritoneal inflammatory injury caused

by long-term high glucose-containing PD, specifically highlighting the attenuation of ROS generation as a potential therapeutic strategy.

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Conflicts of interest

None.

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