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Diallyl trisulfide suppresses dextran sodium sulfate-induced mouse colitis: NF-κB and STAT3 as potential targets

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ABSTRACT

Diallyl trisulfide (DATS), one of the volatile constituents of garlic oil, has been reported to possess antioxidant, anti-inflammatory, and anti-carcinogenic properties. In this study, DATS (10 μmol) given orally for 7 days before and for another 7 days after starting administration of 2.5% dextran sulfate sodium (DSS) in drinking water protected against colitis induced by DSS in male ICR mice. DATS significantly inhibited the DSS-induced DNA binding of NF-κB, phosphorylation of IκBα and the expression of pro-inflammatory proteins, such as cyclooxygenase-2 and inducible nitric oxide synthase, which are major target proteins of NF-κB. The DSS-induced DNA binding and phosphorylation at the Tyr 705 residue of signal transducer and activator of transcription 3 (STAT3), and expression of its major target protein cyclin D1 in mouse colonic mucosa were also attenuated by DATS administration. Likewise, DSS-induced phosphorylation of extracellular signal-regulated kinase 1/2 was suppressed by DATS treatment. In conclusion, DATS ameliorates the DSS-induced mouse colitis presumably by blocking inflammatory signaling mediated by NF-κB and STAT3.

1. Introduction

Garlic (*Allium sativum*) has been known to have protective effects on cardiovascular disease, microbial and fungal infection, immune suppression, and carcinogenesis [1]. During the last few decades, both population-based and clinical investigations as well as laboratory studies have demonstrated anti-carcinogenic activities of garlic and some of its ingredients [2]. Several organosulfur compounds (OSCs) derived from garlic, especially diallyl sulfide, diallyl disulfide and diallyl trisulfide (DATS), have been considered to contribute to its chemopreventive and cytoprotective activities [3]. Of the three garlic-derived OSCs, DATS is thought to be most potent in terms of anti-carcinogenic activities [4]. Oral administration of DATS inhibited chemically-induced tumor formation [5,6]. Anti-carcinogenic activities of DATS are associated with induction of cancer cell apoptosis, inhibition of aberrant cell cycle progression, and induction of phase 2 carcinogen detoxifying enzymes [7]. DATS also inhibited capillary-like tube formation and migration of human umbilical vain endothelial cells via suppression of vascular endothelial growth factor secretion [8] and invasion of colon cancer cells by blocking expression of matrix metalloproteinase-2, -7, and -9 [9]. DATS appears to exert its chemopreventive effects through modulation of multiple cellular signal transduction pathways involved in multi-stage carcinogenesis.

Colorectal cancer is one of the major malignancies worldwide especially in western societies [10]. Multiple lines of evidence support a close association between inflammation and cancer [11,12]. For example, chronic inflammatory bowel disease, such as ulcerative colitis and Crohn's disease, promotes colorectal carcinogenesis [13]. Cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) are immediate early response gene products whose expression is transiently upregulated by inflammatory stimuli. Moreover, COX-2 expression is enhanced in up to 90% of sporadic colon carcinomas and 40% of colonic adenomas, but is not prominent in the normal colonic epithelium [14,15]. iNOS is also overexpressed in colon cancer of humans and experimental animals [16,17]. Although anticarcinogenic activities of garlic-derived OSCs have been observed in various colon carcinogenic models, their molecular mechanisms remain largely unresolved.

In the present study, we investigated the anti-inflammatory activity of DATS against dextran sodium sulfate (DSS)-induced colitis in mice and plausible underlying molecular mechanisms.

2. Materials and methods

2.1. Materials

DATS was obtained from LKT laboratories (Minneapolis, MN, USA). DSS was obtained from ICN Biomedicals, Inc. (Aurora, OH,

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USA). Rabbit polyclonal COX-2 antibody was the product of Cayman Chemical Co. (Ann Arbor, MI, USA). Primary antibody for iNOS was supplied from BD Bioscience (Franklin, NJ, USA). Antibodies against α-tubuline, extracelluar signal-regulated kinase 1/2 (ERK) and pERK were purchased from Santa Cruz Biotechnology (Santa Cruz, CA, USA). Anti-pIκBα, anti-cyclin D1, anti-signal transducer and activator of transcription 3 (STAT3) and anti-pSTAT3 were provided from Cell Signaling Technology (Danvers, MA, USA). Anti-actin was purchased from Sigma Aldrich (St. Louis, MO, USA). Anti-rabbit and anti-mouse horseradish peroxidase-conjugated secondary antibodies were products of Zymed Laboratories (San Francisco, CA, USA). An oligonucleotide probe containing the NF-κB consensus sequence (5′-AGT TGA GGG GAC TTT CCC AGG C-3′, 3′-TCA ACT CCC CTG AAA GGG TCC G-5′) located in the mouse COX-2 promoter region was obtained from Promega (Madison, WI, USA). An oligonucleotide probe containing the STAT3 consensus sequence (5′-GAT CCT TCT GGG AAT TCC TAG ATC-3′) was purchased from Santa Cruz Biotechnology. Polyvinylidine difluoride membranes were supplied from Gelman Laboratory (Ann Arbor, MI, USA). BCA reagent is a product of Pierce (Rockfold, IL, USA). The enhanced chemiluminescence (ECL) detection kit and [γ-^{32}P] ATP were purchased from Amersham Pharmacia Biotech (Buckinghamshire, UK). All other chemicals used were obtained in the purest form available at the commercial grades.

2.2. Animal treatment

Male Institute of Cancer Research (ICR) mice (5 weeks of age) were purchased from Sankyo Lab Service Corporation (SLC, Tokyo, Japan). The animals were housed in climate-controlled quarters (24 °C at 50% humidity) with a 12-h light/12-h dark cycle. Male ICR mice were divided into 4 groups [control mice, DSS-treated mice, DATS (5 μmol/mouse) + DSS-treated mice, DATS (10 μmol/mouse) + DSS-treated mice]. DATS suspended in 0.9% NaCl was given orally (5 μmol or 10 μmol) every other day for 7 days and then for another 7 days following administration of 2.5% DSS in drinking water. The body weight of mice and liquid consumption were checked every day, according to the institution protocol (SOP Education No. SNU-081020-1 of Seoul National University).

2.3. Assessment of clinical parameters and histopathological examinations

During the period of DSS administration, all mice were subjected to following examination on daily basis; weight, hemoccult test, gross blood and stool consistency. The disease activity index (DAI) was calculated by scoring changes described by Copper [18]. After treatment with DSS for 7 days, all mice were sacrificed by cervical dislocation and the length of colorectal parts was measured. Colorectal parts from different treatment groups were cut longitudinally and fixed with 10% formalin before embedded in paraffin. Each section (4 μm) was stained with hematoxylin and eosin (H&E).

2.4. Western blot analysis

Collected colon tissue was homogenized in ice–cold lysis buffer [150 mM NaCl, 0.5% Triton-X 100, 50 mM Tris–HCl (pH 7.4), 20 mM ethylene glycol tetraacetic acid (EGTA), 1mM dithiothreitol (DTT), 1 mM Na_3VO_4 and protease inhibitor cocktail tablet] and lysed for 30 min at 0 °C followed by centrifugation at 14,000 rpm for 15 min. Supernatant was collected, and the total protein concentration was measured by using the BCA protein assay kit. Cell lysates (30–50 μg protein) were boiled in sodium dodecyl sulfate (SDS) sample buffer for 5 min before electrophoresis on 8–12% SDS-polyacrylamide gel. After transfer to polyvinylidene difluoride (PVDF) membrane, the blots were blocked with 5% fat-free dry milk-PBST buffer [phosphate buffered saline (PBS) containing 0.1% Tween-20] for 1 h at room temperature and then washed with PBST. The membranes were incubated for 2 h at room temperature with 1:4000 dilutions of primary anti-actin, for 12 h at 4 °C with 1:1000 dilutions of primary anti-pERK, anti-pIκBα, anti-pSTAT3, anti-α-tubuline, anti-cyclin D1, anti-COX-2 and anti-iNOS. Blots were washed three times with PBST at 10 min intervals followed by incubation with 1:5000 dilution of respective horseradish peroxidase conjugated secondary antibodies (rabbit, goat or mouse) for 1 h and washed again three times with PBST. Immunoblots were visualized with an ECL detection kit according to the manufacturer's instructions.

2.5. Preparation of cytosolic and nuclear extracts from mouse colon

The nuclear extract from mouse colon was prepared as described previously [19]. In brief, collected colon of mice was homogenized in hypotonic buffer A [10 mM HEPES (pH 7.8), 10 mM KCl, 2 mM $MgCl_2$, 1 mM DTT, 0.1 mM EDTA and 0.1 mM phenylmethylsulfonylfluoride (PMSF)]. Ten percent Nonidet P-40 (NP-40) solution was added to the homogenate and the mixture was then centrifuged for 2 min at 14,000 rpm. The supernatant was collected as a cytosolic fraction. The precipitated pellets were washed twice with buffer A plus 10% NP-40, centrifuged, resuspended in buffer C [50 mM HEPES (pH 7.8), 50 mM KCl, 300 mM NaCl, 0.1 mM EDTA, 1 mM DTT, 0.1 mM PMSF, 20% glycerol] and centrifuged for 5 min at 14,000 rpm. The supernatant containing nuclear proteins was collected and stored at −70 °C after determination of the protein concentration.

2.6. Electrophoresis mobility shift assay (EMSA)

The EMSA for measuring DNA binding activities of NF-κB and STAT3 was performed using a DNA-protein binding detection kit, according to the manufacturer's protocol (Gibco BRL, Grand Island, NY, USA). Briefly, the NF-κB oligonucleotide probe 5′-GAG GGG ATT CCC TTA-3′ and the STAT3 oligonucleotide probe 5′-GAT CCT TCT GGG AAT TCC TAG ATC- 3′ were labeled with [γ-^{32}P] ATP by T4 polynucleotide kinase and purified on a Nick column (Amersham Pharmacia Biotech, Buckinghamshire, UK). The binding reaction was carried out in 25 μl of the mixture containing 5 μl of incubation buffer [10 mM Tris–HCl (pH 7.5), 100 mM NaCl, 1 mM DTT, 1 mm EDTA, 4% glycerol, and 0.1 mg/ml sonicated salmon sperm DNA], 10 μg of nuclear extracts, and 100,000 cpm of [γ-^{32}P] ATP-end labeled oligonucleotide. After 50-min incubation at room temperature, 2 μl of 0.1% bromophenol blue was added, and samples were electrophoresised through 6% non-denaturing polyacrylamide gel at 150 V in a cold room for 2 h. Finally, the gel was dried and exposed to X-ray film.

2.7. Statistical analyses

Values were expressed as the mean ± SD. The intensity of different Western blots was measured by using Gel-Pro analyzer. Statistical significance was determined by Student's *t*-test and $p < 0.05$ was considered to be statistically significant.

3. Results

3.1. DATS ameliorated pathological symptoms implicated in DSS-induced mouse colitis

Based on the severity of stool consistency and rectal bleeding, DSS-induced pathogenic conditions were scored from 0 to 4

according to the DAI system. Compared with the control group, DSS-administrated group exhibited loose stool and diarrhea as well as occult or gross rectal bleeding as revealed by markedly increased DAI (Fig. 1A). Oral administration of DATS (10 μmol) ameliorated the severity of diarrhea and rectal bleeding. We also undertook histological examination of the colonic sections to assess intestinal inflammatory status using H&E staining. Mice given DSS developed colitis as evidenced by the completely disrupted architecture of colonic mucosa, resulting in induced infiltration of inflammatory cells and thickening of lamina propria (Fig. 1B). Oral administration of DATS (10 μmol) dampened DSS-induced mucosal destruction, infiltration of inflammatory cells and expansion of lamina propria (Fig. 1B).

3.2. DATS inhibited DSS-induced DNA binding of NF-κB in mouse colon

NF-κB has been recognized as a tumor promoter in inflammation–associated carcinogenesis [20]. This ubiquitous eukaryotic transcription factor has been known to regulate expression of inflammatory proteins, such as COX-2 and iNOS [21]. One of the critical events for the activation of NF-κB is its dissociation from the inhibitory subunit IκBα, which requires phosphorylation of the IκBα. The phosphorylated IκB proteins are rapidly polyubiquitinated and degraded by proteasomes, releasing free NF-κB for translocation to the nucleus and subsequent regulation of transcription of target genes. We found that DATS (10 μmol) attenuated the DNA binding of NF-κB in the nuclear extract of DSS-treated colon (Fig. 2A). The phosphorylation of IκBα by DSS treatment was significantly inhibited by administration of DATS (10 μmol) (Fig. 2B). MAPKs, such as ERK, p38 and c-Jun N-terminal kinase (JNK)/stress-activated protein kinase, have been reported to be involved in activation of NF-κB [22,23]. We found that the ERK signaling was significantly activated via phosphorylation in mouse colon after administration of DSS. Oral administration of DATS (10 μmol) suppressed DSS-induced phosphorylation of ERK 1/2 in mouse colon (Fig. 2C).

3.3. DATS inhibited DSS-induced activation of STAT3 and expression of its target protein in mouse colon

Like NF-κB, STAT3 is latent in the cytoplasm until being stimulated by inflammatory signals [24]. STAT3 is mainly activated via IL-6-gp130-JAK signaling leading to direct phosphorylation at Tyrosine 705 [24]. STAT3 has been reported to play a role in colitis-associated colorectal carcinogenesis [25]. ERK is also known to regulate the activation of STAT3 via phosphorylation of STAT3 at Tyrosine 705 [24]. DATS (10 μmol) exerted a significant inhibitory effect on DSS-induced DNA binding of STAT3 (Fig. 3A) and

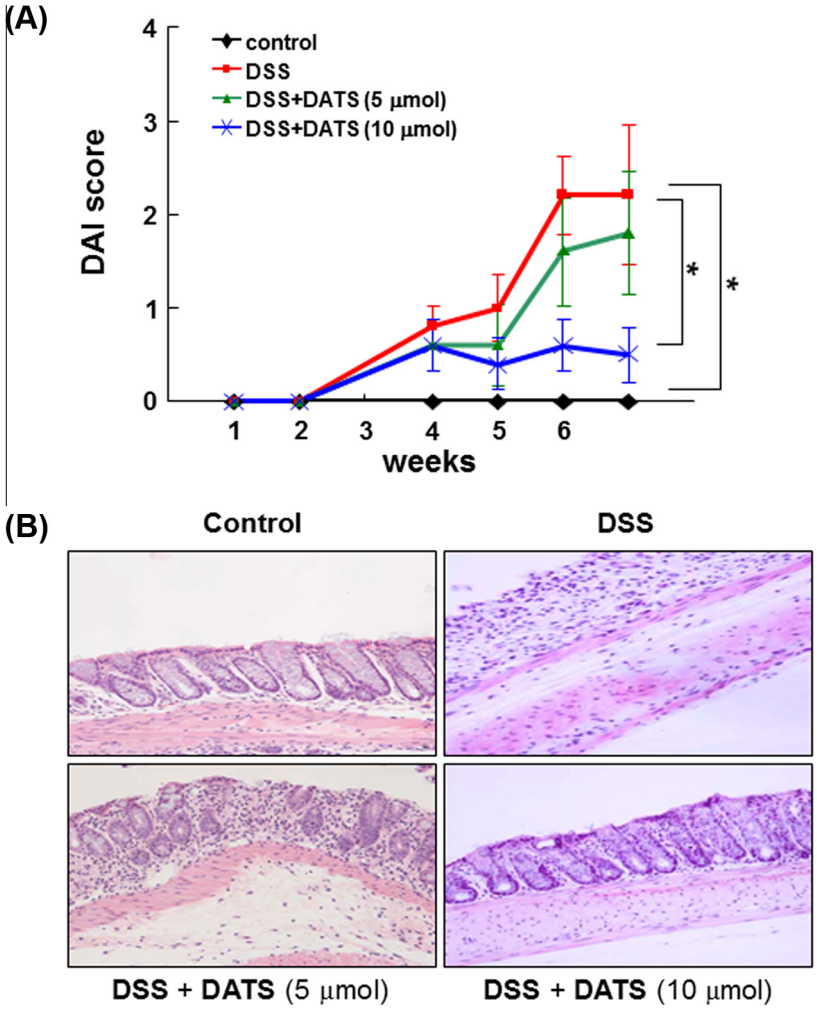

Fig. 1. DATS ameliorated pathological symptoms in a mouse DSS-induced colitis model. Male ICR mice (5 weeks of age) were treated with 2.5% DSS in drinking water for 7 days. DATS suspended in 0.9% NaCl was given orally (5 μmol or 10 μmol) every other day for 7 days before DSS treatment and 7 days together with 2.5% DSS. (A) DAI as the sum of stool consistency and rectal bleeding was scored from 0 to 4. *Significantly different between the groups compared ($p < 0.05$). (B) Representative distal colon sections stained with hematoxylin and eosin (H&E). Magnifications: ×200.

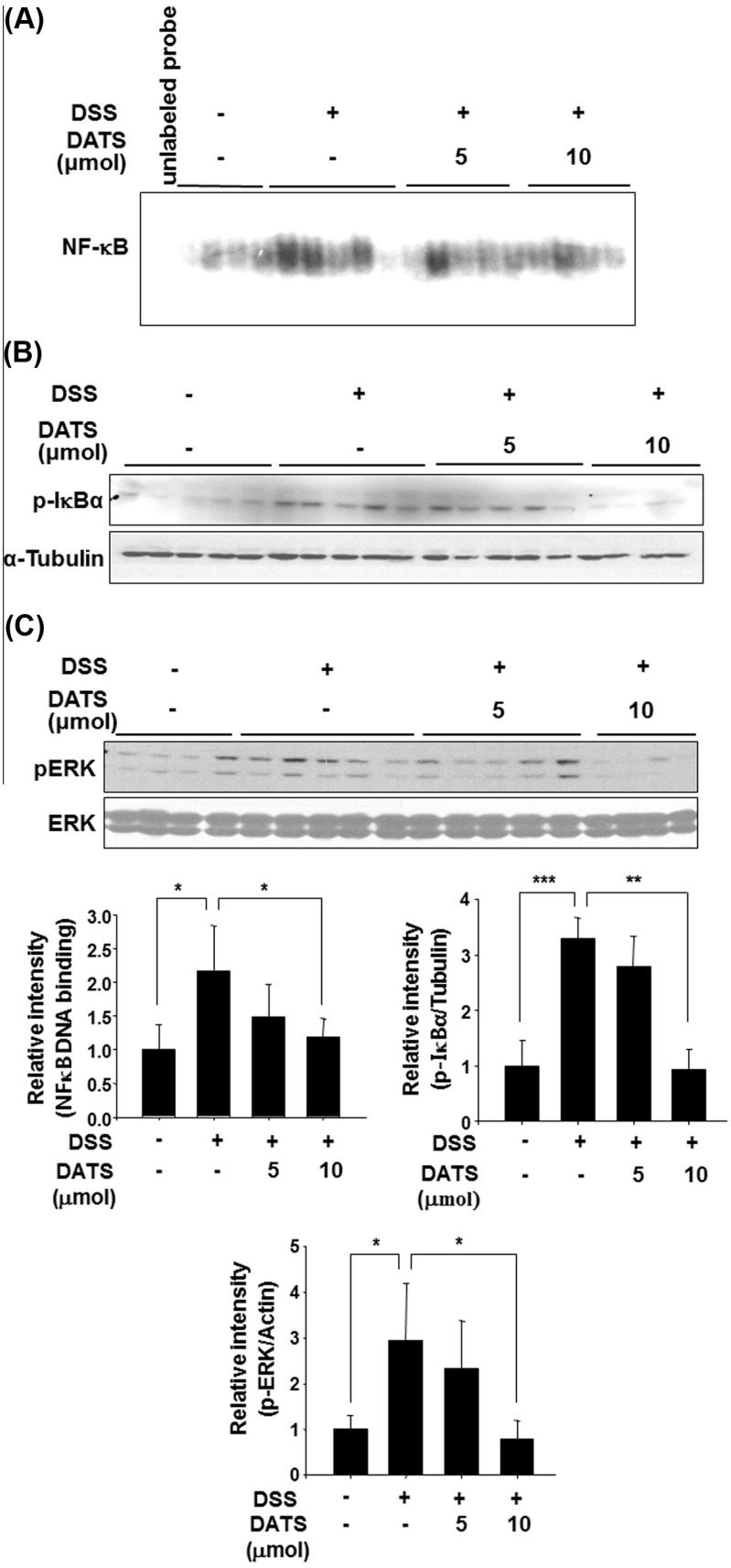

Fig. 2. DATS inhibited DSS-induced activation of NF-κB and phosphorylation of IκBα in mouse colon. (A) Nuclear extracts were prepared from colon of each treatment group. The effect of DATS on DNA binding of NF-κB was measured by EMSA as described in Section 2. (B) Phosphorylation of IκBα was measured by Western blot analysis of the cytosolic extract. (C) Phosphorylation of ERK1/2 and ERK was measured by Western blot analysis of whole tissue lysates prepared from colorectal parts of each treated mouse. Data are expressed as means ± SE. Significantly different between the groups compared ($^{*}p < 0.05$, $^{**}p < 0.01$ and $^{***}p < 0.001$).

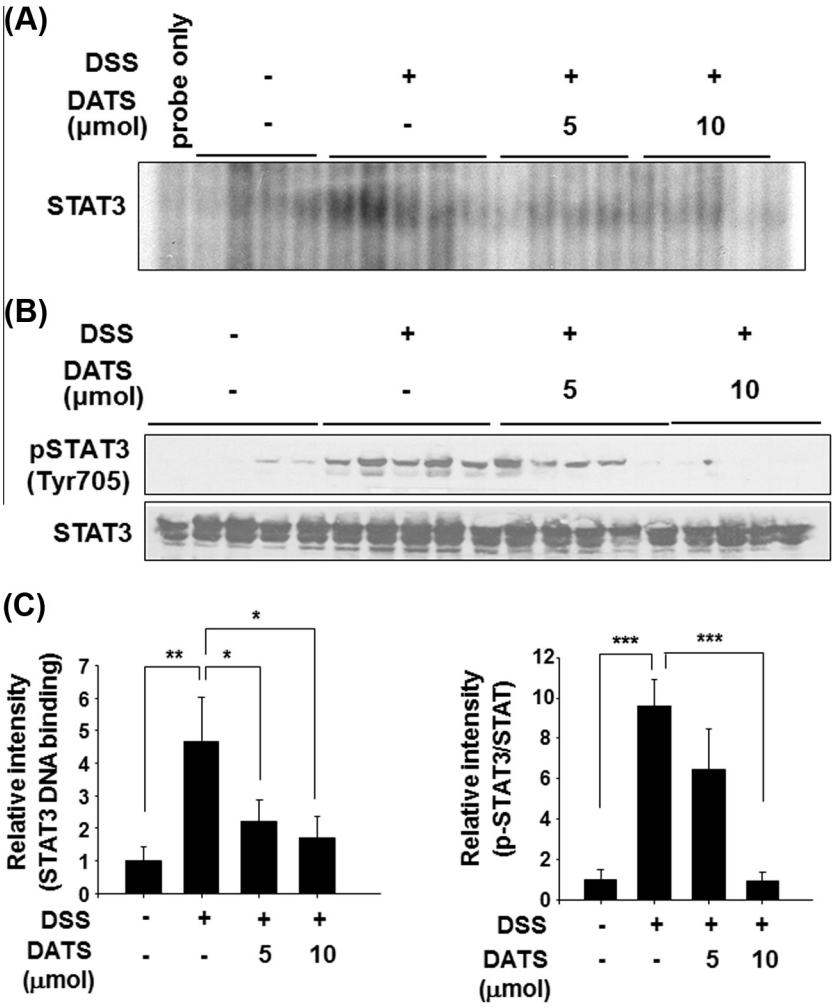

Fig. 3. DATS inhibited DSS-induced activation of STAT3 in mouse colon. (A) Nuclear extracts were prepared from the colon tissues of each treatment group. The effect of DATS on DNA binding of STAT3 was measured by EMSA as described in Section 2. (B) Phosphorylation of STAT3 was measured by Western blot analysis. Data are expressed as means ± SE. Significantly different between the groups compared (*$p < 0.05$, **$p < 0.01$ and ***$p < 0.001$).

phosphorylation of STAT3 at Tyr705 (Fig. 3B). It has been reported that stimulation of cell proliferation by STAT3 is mediated mainly by its target protein cyclin D1 [24]. DATS inhibited the expression of colonic cyclin D1 in mice challenged with DSS (Fig. 4A).

3.4. DATS attenuated DSS-induced expression of COX-2 and iNOS in mouse colon

COX-2 and iNOS have been known to play essential roles in mediating inflammation and are frequently overexpressed in colon cancer [14,16]. Compared with the control mice, those treated with DSS displayed significantly elevated levels of both enzymes in the colonic mucosa. DATS (10 μmol) given orally reduced the levels of both COX-2 and iNOS (Fig. 4A). DSS-induced COX-2 upregulation and its suppression by DATS were also verified by immunohistochemical analysis (Fig. 4B).

4. Discussion

Chronic inflammation causes genomic instability, cell proliferation and evasion from apoptosis and ultimately contributes to carcinogenesis [21]. Therefore, targeting abnormally overactive inflammation signaling is considered to be an important chemopreventive strategy. Many chemopreventive agents have been found to modulate key molecules or events involved in inflammation-associated carcinogenic pathways. Numerous substances present in plant-based diet have been reported to modulate intracellular signal transduction pathways that become often awry during carcinogenesis. The US National Cancer Institute designated garlic as one of the most potential vegetables with pronounced cancer preventive properties. Epidemiological studies have suggested an inverse relation between garlic intake and the risk of certain types of cancer including distal colon cancer [26]. Thus, garlic inhibited formation of aberrant crypt foci in azoxymethane-treated rats [27]. Administration of DATS reduced the tumor volume and the weight compared to those in the control group in nude mice bearing colon cancer xenografts [9,28,29].

In this study, we found that DATS attenuated the DSS-induced colitis in mouse colon. DATS also inhibited overexpression of COX-2 and iNOS, which is attributable to its blockade of the nuclear transcription factor NF-κB signaling via suppression of phosphorylation of IκBα. The inhibitory effect of NF-κB activity by garlic derived OSCs has also been reported. Thiacremonone, a novel sulfur compound isolated from garlic, inhibited the tumor necrosis factor-alpha and 12-*O*-etradecanoylphorbol-13-acetate (TPA)-induced NF-κB transcriptional and DNA binding activities, which are associated with induction of apoptosis in colon cancer cells [30]. Thiacremonone also suppressed expression of COX-2 and iNOS as well as anti-apoptotic proteins such as Bcl-2, cIAP1/2,

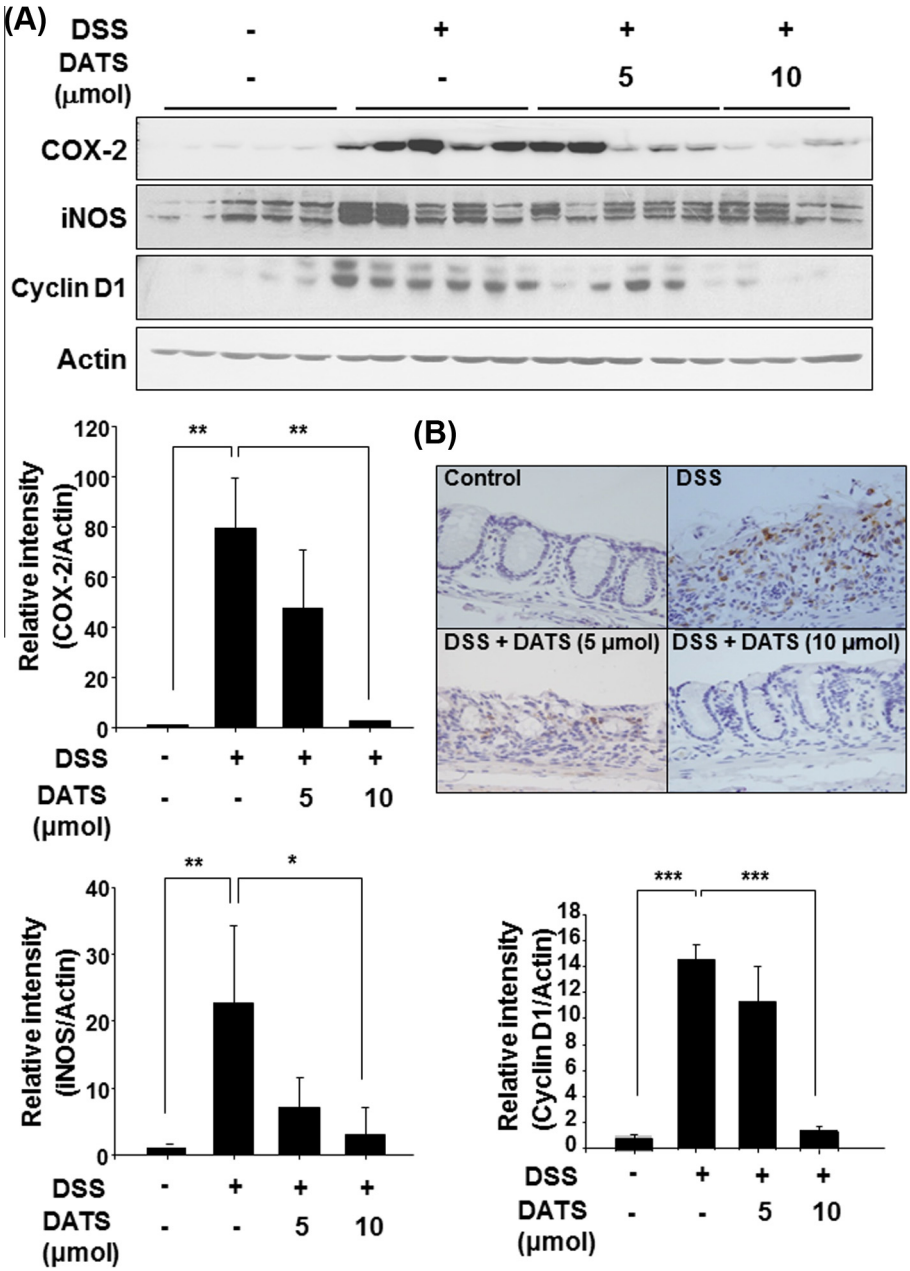

Fig. 4. DATS inhibited the expression of COX-2, iNOS, and cyclin D1 in DSS-treated mouse colon. (A) Colon tissue lysates from different treatment groups were separated by 12% SDS-polyacrylamide gel electrophoresis and immunoblotted by using specific antibodies. Data are expressed as means ± SE. Significantly different between the groups compared ($^{*}p < 0.05$, $^{**}p < 0.01$ and $^{***}p < 0.001$). (B) Immunohistochemical detection of COX-2 in mouse colon. Magnifications: ×400.

and XIAP, which are downstream target proteins of NF-κB [30]. In addition, oral administration of thiacremonone augmented docetaxel-induced inhibition of tumor growth which was associated with suppression of NF-κB activity and NF-κB target gene expression [31]. DATS was reported to inhibit lipopolysaccharide-induced nitric oxide production and iNOS expression as well as NF-κB activity in Raw 264.7 macrophages [32]. In our previous study, topical application of DATS significantly suppressed activator protein-1 and expression of COX-2 by targeting JNK in TPA-treated mouse skin [6]. DATS treatment also reduced the incidence and the multiplicity of papillomas formed in 7,12-dimethylbenz(*a*)anthracene-initiated and TPA-promoted mouse skin carcinogenesis [6].

Beside NF-κB, STAT3 is also known to be involved in colonic inflammation and activated by variety of cytokines and growth factors [24]. STAT3 is activated through phosphorylation of Tyr705 at the COOH terminus. Upon activation, STAT3 translocates to the nucleus, where it regulates genes involved in apoptosis (e.g., Bcl-X_l), cell cycle progression (e.g., cyclin D1), migration, and survival depending on the cell type [33]. Cyclin D1 is known to link ulcerative colitis-related inflammation and neoplasia [34]. We observed that DATS suppressed the DNA binding activity and phosphorylation of STAT3 at Tyr 705 and expression of its target protein cyclin D1. In line with our findings, Chandra-Kuntal and Singh also reported that DATS inhibited the nuclear translocation of phosphorylated STAT3 and STAT3 dimerization in interleukin 6-treated prostate cancer cells, which contribute to induction of apoptosis [35]. Furthermore, oral administration of DATS also reduced levels of pSTAT3 in the transgenic adenocarcinoma of mouse prostate (TRAMP) model [35]. Molecular mechanisms underlying suppressive effects of DATS on NF-κB and STAT3 remain unknown. It was reported that DATS containing an alkenyl functional moiety is likely to react with sulfhydryl groups present in critical cysteine

residues of cellular proteins [36]. DATS- induced cell cycle arrest is speculated to be associated with rapid microtubule disassembly through oxidative modification of specific cysteine residue present in the β-tubulin [29,36]. Cysteine residues present in STAT3 have been considered as critical sites for therapeutic development [37,38]. In addition, NF-κB is activated via phosphorylation-dependent degradation of IκBα, which is catalyzed by upstream kinases such as IκB kinase (IKK) β [39]. Cysteine-179 of IKKβ has been known to be essential for its activation by facilitating phosphorylation of activation loop serine [40]. Based on above findings, we have speculated that the inhibitory effect of DATS on NF-κB and STAT3 signaling is associated with its direct modification of cysteine residue present in both transcription factors.

In summary, the present study shows that DATS protects against DSS-induced colitis and suppresses activation of NF-κB and STAT3 transcription factors and expression of their target proteins COX-2, iNOS, and cyclin D1. These effects may account for chemopreventive potential of DATS in inflammation-associated colon carcinogenesis.

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