Food and Chemical Toxicology 125 (2019) 354–360

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Diallyl disulfide (DADS) boosts TRAIL-Mediated apoptosis in colorectal cancer cells by inhibiting Bcl-2

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ARTICLE INFO

Keywords:
TRAIL-Resistance
Diallyl disulphide
Bcl-2
Death receptor 5

ABSTRACT

Ever since several targeted agents were introduced a decade ago, progress in new therapeutic strategies for colorectal cancer (CRC) has been much slower than that for other cancers. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is widely known to induce cellular apoptosis in numerous cancer cell types. However, many cancer cells are resistant to the effects of TRAIL, and thus, approaches are needed to overcome TRAIL resistance. We demonstrated that non-cytotoxic doses of diallyl disulfide (DADS) increased TRAIL-associated cell death in CRC cell lines. Additionally, synergistic effects between DADS and TRAIL were validated *in vivo* in nude mice. One process involved in these effects includes down-regulation of the anti-apoptotic protein Bcl-2, and the synergistic effect of DADS with TRAIL was attenuated in Bcl-2-over-expressing cells. Taken together, the results of this study give new insights into the role of DADS in TRAIL-related repression of CRC progression by inhibition of Bcl-2.

1. Introduction

The incidence rate of colorectal cancer (CRC) is approximately 10% of all prevalent cancers, and approximately 600,000 CRC deaths occur each year worldwide (Jemal et al., 2010). In cases of locally advanced, metastatic, or recurrent CRC, systemic chemotherapy is the first-line treatment. Despite the introduction of several targeted agents, including a vascular endothelial growth factor A inhibitor (bevacizumab), epidermal growth factor receptor inhibitor (cetuximab), and multi-kinase inhibitor (regorafenib), better therapies are urgently needed (Wolpin and Mayer, 2008).

Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is widely known to induce cellular apoptosis in numerous cancer cell types by binding to death receptor 4/5 (DR4/5) or decoy receptor 1/2 (Jin et al., 2004). TRAIL binding to DR4/5 induces the formation of downstream compounds such as Fas-associated protein with death domain, resulting in the activation of the caspase cascade to initiate cancer cell death signaling (Aggarwal, 2003; Bellail et al., 2010). TRAIL induces cellular apoptosis only in tumor cells, indicating its potential use as a novel therapeutic agent. However, many cancer cells are resistant to the effects of TRAIL (Jin et al., 2004; Kuijlen et al., 2010; Panner et al., 2009). The possible mechanisms of TRAIL resistance include down-regulation of DR4/5, overexpression of anti-apoptotic proteins including c-FLIP, Bcl-2, or Bcl-xL, and reduced expression of pro-apoptotic proteins including Bax, Bim, or PUMA (Kelly et al., 2002; Walczak et al., 2000; Zhang and Zhang, 2008). To overcome resistance to TRAIL, it is essential to identify a sensitizer or combined therapy strategy.

Diallyl disulfide (DADS) is one of the main components present in the distilled oil of garlic, along with diallyl trisulfide (DATS) and diallyl tetrasulfide. Garlic has been shown to have a preventive effect against stomach cancer (You et al., 1989) and CRC (Steinmetz et al., 1994); thus, garlic oils, particularly DADS and DATS, are promising novel anti-carcinogenic agents capable of inducing apoptosis (Bottone et al., 2002; Hosono et al., 2005). As with most herbal medications, the mechanism by which DADS induces apoptosis is not well-known. Although three *in*

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https://doi.org/10.1016/j.fct.2019.01.023
Received 2 October 2018; Received in revised form 14 January 2019; Accepted 21 January 2019
Available online 22 January 2019
0278-6915/

vitro studies demonstrated that DATS induces apoptosis by sensitizing TRAIL-mediated cell death (Hwang et al., 2017; Murai et al., 2012; Shankar et al., 2008), no studies reported in English have investigated the association between DADS and the TRAIL pathway.

Because it is important to overcome TRAIL resistance, and since the mechanism by which DADS induces apoptosis is scarcely clarified, we investigated whether DADS significantly increases TRAIL-mediated apoptosis in CRC cells. We also examined the mechanism by which DADS sensitizes CRC cells to TRAIL-induced cell death, using human CRC cells and an animal model.

2. Methods

2.1. Reagents and antibodies

DADS was obtained from Sigma. We obtained soluble recombinant TRAIL from Millipore (Millipore, Billerica, MA, USA). Anti-Bcl-2, anti-Bax, anti-DR4, and anti-DR5 were purchased from Santa Cruz Biotechnology (Dallas, TX, USA). Anti-XIAP, anti-cleaved caspase-3, anti-cleaved caspase-8, anti-cleaved caspase-9, anti-Survivin, anti-Bid, and anti-cleaved PARP-1 were purchased from Cell Signaling (Danvers, MA, USA). The secondary antibodies anti-mouse-IgG-horseradish peroxidase and anti-rabbit-IgG-horseradish peroxidase were purchased from Cell Signaling.

2.2. Cell culture

Human colon cancer cell lines, HCT116, DLD-1, HT29, and SW620 were obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA) and maintained according to the manufacturer's instructions. The human normal colon cell line (FHC) and corresponding growth medium (Eagle's Minimum Essential Medium) were purchased from ATCC. All cell lines were grown in RPMI 1640 or Dulbecco's Modified Eagle Medium supplemented with 10% fetal bovine serum and L-glutamine and grown in a 37 °C humidified chamber with 5% CO_2.

2.3. Cell viability

Cells were grown in tissue culture-coated 60-mm plates. For the trypan blue exclusion assay, trypsinized cells were pelleted and resuspended in 0.5 mL of phosphate-buffered saline and 0.5 mL of 0.4% trypan blue solution. Samples were mixed thoroughly, incubated at room temperature for 10 min, and examined under a light microscope. At least 500 cells were counted for each survival determination.

2.4. Small interfering RNA (siRNA)

Bcl-2 siRNA (Cat. No. SC-61899) and control siRNA (Cat. No. SC-37007) were obtained from Santa Cruz Biotechnology. Cells were transfected with siRNA oligonucleotides using Lipofectamine RNAi Max reagents (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's instructions. After 24 h of transfection, the cells were treated with TRAIL for further analysis.

2.5. Immunoblotting

Cells were lysed in RIPA buffer (50 mM Tris, 150 mM NaCl, 1% Triton X-100, 0.1% sodium dodecyl sulfate (SDS), and 1% Na-deoxycholate [pH 7.4]) with protease inhibitor and phosphatase inhibitor cocktails and were subjected to SDS-polyacrylamide gel electrophoresis (PAGE). The proteins were then transferred onto nitrocellulose membranes (GE Healthcare, Little Chalfont, UK), blocked with Tris-buffered saline containing 0.1% Tween 20 and 5% bovine serum albumin, incubated with the primary antibody, and then incubated with horseradish peroxidase-labeled secondary antibody. Immunoreactive proteins were visualized by chemiluminescence (ECL, Amersham plc, Amersham, UK).

2.6. Apoptosis assay (flow cytometry)

Untreated cells and cells treated with DADS, TRAIL, or a combination of the two agents were resuspended for 24 h in the binding buffer provided with the annexin V-fluorescein isothiocyanate Apoptosis Detection Kit (BioBud, Cat. LS-02-100). Cells were mixed with 2 μL annexin V-fluorescein isothiocyanate reagent and incubated for 15 min at room temperature in the dark. Staining was terminated, and the cells were immediately analyzed by flow cytometry.

2.7. Detection of DNA fragmentation

The quantity of cytoplasmic histone-associated DNA fragments (mononucleosome and oligonucleosomes) formed during apoptosis was measured using a Cell Death Detection ELISAPlus kit (Roche Molecular Biochemicals) according to the manufacturer's instructions.

2.8. Caspase-3/7 activity assay

Cells were plated in a 96-well black-walled plate at 3000 cells per well, in triplicate, followed by treatment with DADS, TRAIL, a combination of the two agents, or no treatment, and then resuspended for 24 h. One hour before the end of the experiment, Caspase-Glo 3/7 reagent (Promega) was added to each well according to the manufacturer's instructions. After 1 h of incubation in the dark, the caspase-3/7 activities of the samples were measured using a Fusion-α plate reader (PerkinElmer). Differences in caspase-3/7 activity in the drug-treated cells and untreated cells were expressed as fold-change in luminescence.

2.9. Transient transfection

Cells were transfected with human Bcl-2 tagged with Flag in the pCDNA3 vector or the corresponding empty vector (pCDNA).

2.10. Animal xenografts experiment

All animal procedures were carried out in accordance with the animal care guidelines approved by the Korea University Institutional Animal Care and Use Committee. Four-week-old BALB/c nude mice were purchased from Orient Bio (Seongnam, Kyonggi-Do, South Korea) and raised in a pathogen-free environment. The mice were allowed free access to food and water for one week for acclimation. SW620 cells (1×10^6) in 100 μL of culture medium were mixed with 100 μL of Matrigel and subcutaneously injected into 5-week-old BALB/c nude mice. The tumor size was measured every other day.

2.11. Statistical analysis

Statistical analysis was conducted using GraphPad InStat 6 software (GraphPad Software, Inc., San Diego, CA, USA). Results with a p value < 0.05 were considered as statistically significant.

3. Results

3.1. Noncytotoxic doses of DADS effectively boost TRAIL-associated cell death in human CRC cells

To evaluate the efficacy of DADS as a sensitizer of CRC cells to TRAIL-associated apoptosis, we first assessed the sensitivity of several CRC cell lines including SW620, HT-29, HCT 116, and DLD-1 cells to TRAIL-induced cell death. Among the CRC cell line, SW620 cells were the most resistant to TRAIL over a range of concentrations, whereas

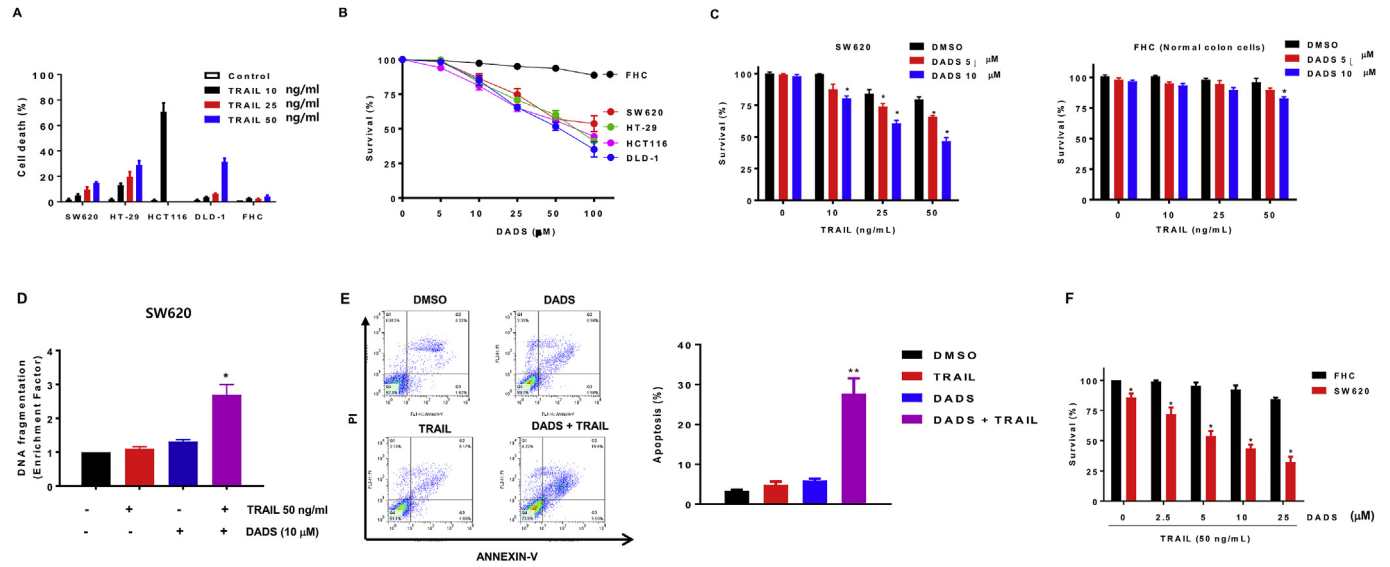

Fig. 1. Noncytotoxic doses of DADS boost TRAIL-related apoptosis in human CRC cells. (A) Several CRC cell lines including SW620, HT-29, HCT 116, and DLD-1 cells were treated or untreated with TRAIL at the indicated concentrations for 4 h. Each column represents the average of three individual experiments; bar indicates ± SD. (B) Normal colon cells and several CRC cell lines including SW620, HT-29, HCT 116, and DLD-1 cells were treated or untreated with DADS for 24 h at the indicated concentrations. Cell viability was analyzed by the Trypan blue assay. (C) Normal colon cells and SW620 cells were treated or untreated with DADS for 20 h at the indicated doses and additionally treated with TRAIL for 4 h at the indicated doses. Cell viability was analyzed by the Trypan blue assay. (D) Enrichment score obtained (E) The cells were stained with propidium iodide and annexin V. (F) Normal colon cells and SW620 cells were or were not treated with DADS for 20 h at the indicated doses and additionally treated with TRAIL at 50 ng/mL for 4 h. These findings are representative data obtained from at least three independent experiments. Statistical significance was determined by a Student's unpaired *t*-test. Asterisk (*) indicates significance at $p < 0.05$ and the double asterisk (**) indicates significance at $p < 0.01$ compared to control cells. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

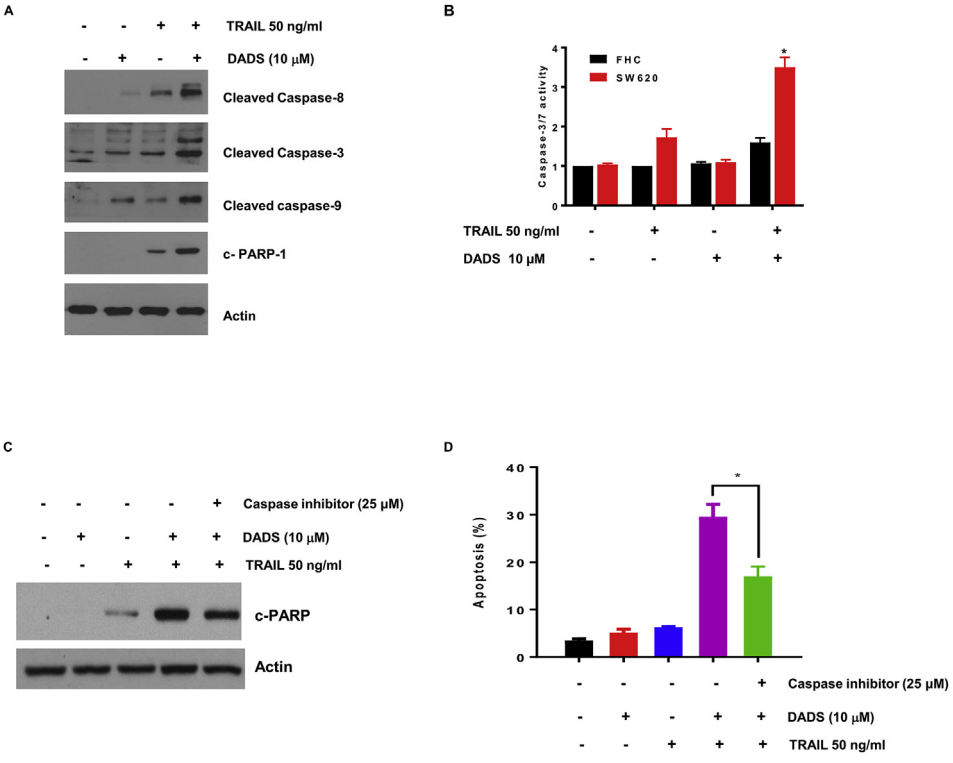

Fig. 2. DADS accelerates TRAIL-mediated apoptosis through caspase activation. (A) SW620 cells treated with 10 μM DADS alone, 50 ng/mL TRAIL alone, or DADS in combination with TRAIL; DADS for 20 h at the indicated doses and TRAIL for 4 h at the indicated doses. Equivalent amounts of protein (20 μg) from the lysates were separated by SDS-PAGE and immunoblotted with anti-caspase-8, anti-caspase-3, anti-caspase-9, or anti PARP-1 antibody. Actin was used to ensure equal amounts of protein in the lysates. (B) SW620 cells treated with 10 μM DADS alone, 50 ng/mL TRAIL alone, or DADS in combination with TRAIL; DADS for 20 h at the indicated doses and TRAIL for 4 h at the indicated doses. Relative caspase activities were analyzed according to the manufacturer's protocol. Error bars represent the mean ± SD from three independent experiments. Asterisk (*) indicates significance at $p < 0.05$ compared to untreated cells. (C) SW620 cells treated with 10 μM DADS alone, 50 ng/mL TRAIL alone, or DADS in combination with TRAIL; DADS for 20 h at the indicated doses and TRAIL for 4 h at the indicated doses. Equivalent amounts of protein (20 μg) from the lysates were separated by SDS-PAGE and immunoblotted with the anti PARP-1 antibody. SW620 cells were pre-treated with the pan-caspase inhibitor Z-VAD-FMK (25 μM) for 30 min and additionally treated with DADS in combination with TRAIL to determine the inhibitory effect of pan-caspase. (D) SW620 cells treated with 10 μM DADS alone, 50 ng/mL TRAIL alone, or DADS in combination with TRAIL; DADS for 20 h at the indicated doses and TRAIL for 4 h at the indicated doses. SW620 cells were pre-treated with the pan-caspase inhibitor Z-VAD-FMK (25 μM) for 30 min and additionally treated with DADS in combination with TRAIL. The results presented are representative of at least three independent experiments.

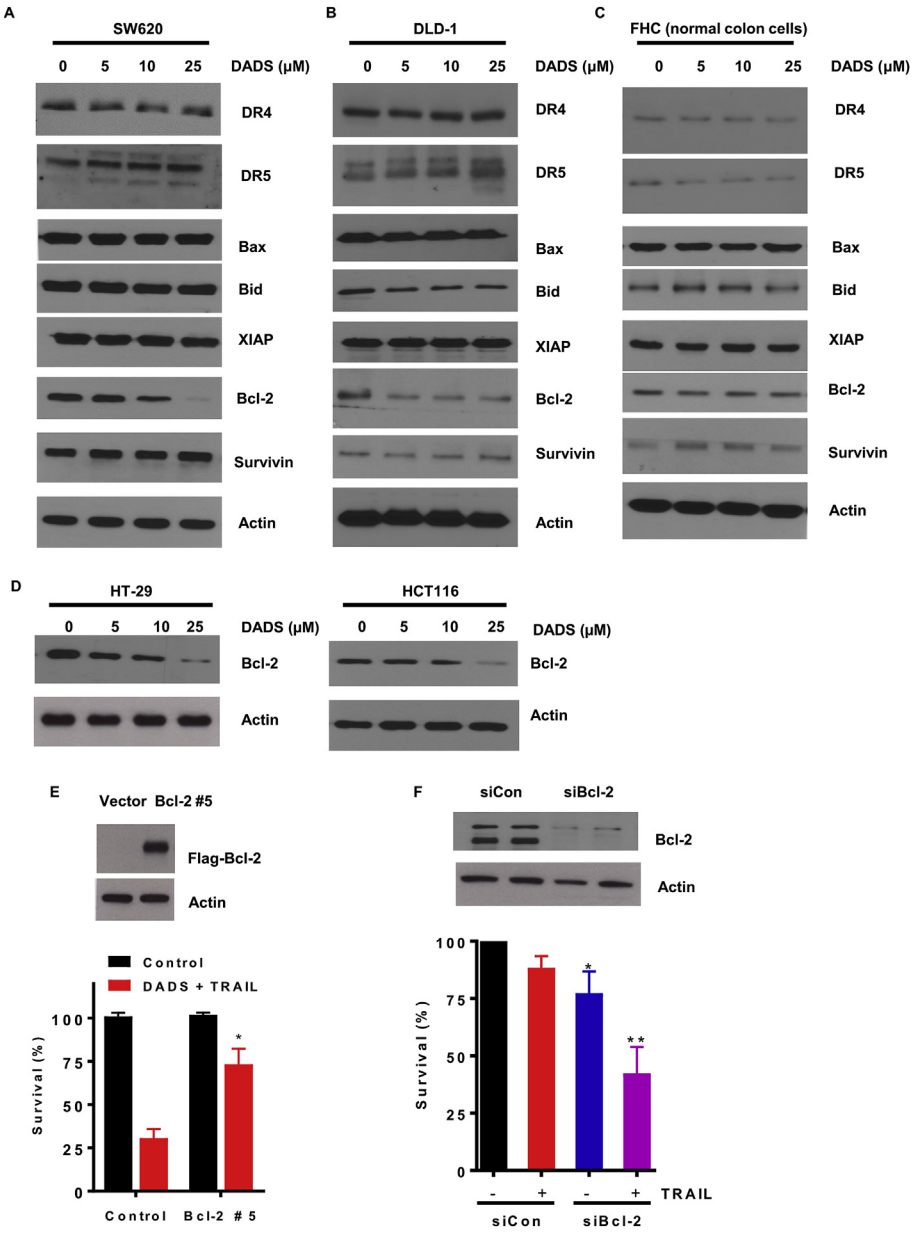

Fig. 3. DADS accelerates TRAIL-mediated apoptosis by down-regulating Bcl-2. Immunoblotting assays revealed the expression of DR4, DR5, Bax, Bid, XIAP, Bcl-2, and survivin in SW620 cells (A), DLD-1 cells (B), normal colon cells (C), HT-29 cells, and HCT116 cells (D) after treatment with different doses of DADS for 24 h. Immunoblotting assays are representative of at least three independent experiments. (E) SW620 cells were transfected with Bcl-2 #5 for Bcl-2 up-regulation or vector (control). Cell viability was analyzed by the Trypan blue assay. Significantly different survival following combined treatment of DADS + TRAIL between vector (control) and Bcl-2 #5-transfected cells. (F) SW620 cells were transfected with siBcl-2 or siCon (control). Asterisk (*) indicates significance at $p < 0.05$ and the double asterisk (**) indicates significance at $p < 0.01$ compared to control cells. The results presented are representative of at least three independent experiments. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

DLD-1 cells were relatively sensitive to TRAIL (Fig. 1A). DADS alone caused slow CRC cell deaths (< 20%) at doses of 10 μM or less, and thus, we used these subtoxic concentrations of DADS in subsequent experiments of combined treatment with TRAIL (Fig. 1B). The survival of SW620 cells was significantly decreased following co-treatment of TRAIL at a fixed dose and DADS at varying doses or conversely with DADS at a fixed dose and TRAIL at varying doses (Fig. 1C). Annexin V and propidium iodide staining assays and the DNA fragmentation assay showed similar results. SW620 cells cotreated with a combination of TRAIL and DADS exhibited a characteristic ladder pattern of inter-nucleosomal fragmentation and significantly high accumulation of sub-G1-phase cells (Fig. 1E). In contrast, normal colon cells were resistant to combined treatment with DADS and TRAIL, as well as to treatment with each agent alone (Fig. 1F), suggesting that this combination regimen is selectively toxic to CRC cells. Together, these results indicate that DADS accelerates TRAIL-associated cellular apoptosis, particularly in CRC cells rather than in normal colon cells.

3.2. DADS accelerates TRAIL-mediated apoptosis through caspase activation

Next, we examined the cleavage of PARP and activation of caspases following co-treatment with DADS and TRAIL, because caspase activation is an essential process in TRAIL-mediated cell death (Baliga and Kumar, 2003). Combination treatment with DADS and TRAIL enhanced the activation of caspase-3, caspase-8, and caspase-9 in SW620 cells (Fig. 2A). Additionally, relative caspase activity assays revealed that caspase activity was upregulated in SW620 cells treated simultaneously with DADS and TRAIL (Fig. 2B). The pan-caspase inhibitor significantly weakened the sensitizing effect of DADS to TRAIL-mediated apoptosis in SW620 cells, and a low rate of cell death was detected in SW620 cells treated with DADS or TRAIL alone (Fig. 2C).

3.3. DADS boosts TRAIL-mediated apoptosis by down-regulating Bcl-2

To examine how DADS induces TRAIL-related cell death, we investigated the expression of death receptors, pro-apoptotic proteins, and anti-apoptotic proteins in CRC cell lines and normal colon cells at

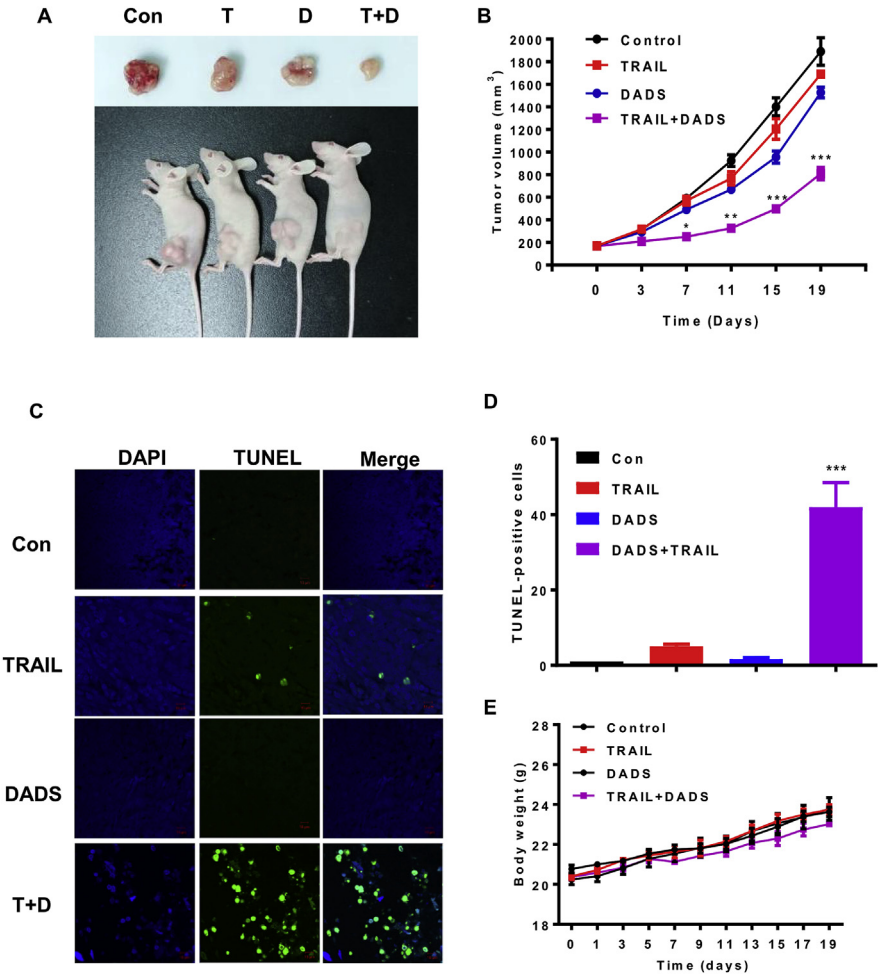

Fig. 4. SW620 cells were subcutaneously injected into BALB/c nude mice. As the tumor volume approached 150 mm^3, we randomized the mice into four groups including a control group, DADS alone group, TRAIL alone group, and DADS plus TRAIL group. (A) Representative tumor volume in xenograft mice. (B) We measured tumor dimensions every 4 days. (C, D) TUNEL assay was performed to assess apoptosis. DAPI assay was performed to visualize the nucleus. The ratio of TUNEL-positive cells was detected and shown as a histogram. (E) Combination regimen did not reduce the body weight of mice.

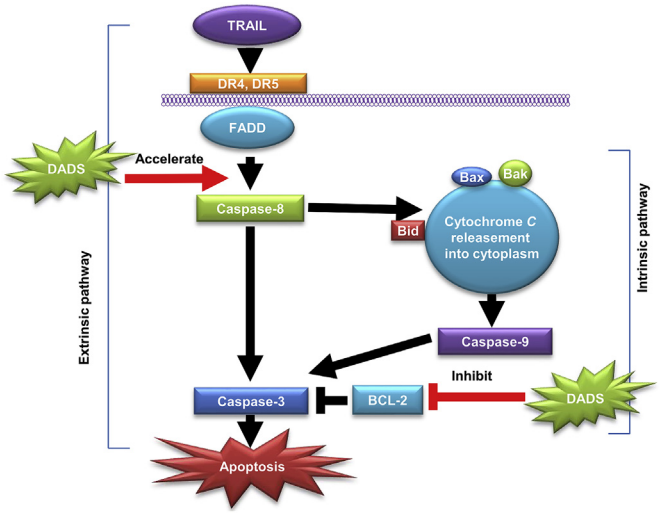

Fig. 5. Schematic of mechanism model of DADS increasing TRAIL-related apoptosis. DADS caused CRC cell apoptosis by modulating TRAIL-induced caspase activation. Repression of Bcl-2 by DADS was demonstrated to be an essential step in this process.

different concentrations of DADS. DR4 or DR5 expression was not altered by DADS, in contrast to the results observed for DATS (Hwang et al., 2017) (Fig. 3A and B). DADS treatment did not alter the expression of pro-apoptotic proteins, including BAX and BID, or anti-apoptotic proteins, including XIAP and survivin. The only protein down-regulated by DADS in CRC cell lines was Bcl-2 (Fig. 3A, B, and 3D), whereas Bcl-2 was not affected by treatment with DADS in normal colon cells (Fig. 3C). To confirm the role of Bcl-2 in the sensitizing efficacy of DADS on the TRAIL pathway, we up-regulated Bcl-2 by transfection with specific Flag-Bcl-2 in SW620 cells. Next, we demonstrated that the cell death rates induced by combined treatment with DADS and TRAIL were significantly decreased in cells transfected with Flag-Bcl-2 compared to those in control cells (Fig. 3E). Additionally, we demonstrated that silencing of Bcl-2 significantly enhanced TRAIL-induced cell death in SW620 cells (Fig. 3F). Together, these results indicate that Bcl-2 down-regulation by DADS plays a crucial role in the sensitizing efficacy of DADS to the TRAIL pathway.

3.4. Combined treatment with DADS and TRAIL has synergistic effects in vivo

We confirmed the synergistic effect between DADS and TRAIL through *in vivo* studies. We injected SW620 cells subcutaneously into BALB/c nude mice. As the tumor volume approached 150 mm^3, we randomized the mice into four groups: control group, DADS alone

group, TRAIL alone group, and DADS plus TRAIL group. Combined treatment with DADS and TRAIL effectively inhibited tumorigenicity compared to either single-treatment group and the control group (Fig. 4A and B). However, this combination regimen did not reduce the body weight of mice, suggesting the safety of this regimen (Fig. 4E). Additionally, a TUNEL assay was performed to assess apoptosis. Tumors treated with the combination regimen showed significantly high apoptosis rates compared to tumors in the single-treatment groups and control group (Fig. 4C and D). These *in vivo* results indicate that combined treatment enhances CRC cell apoptosis and has tolerable safety, which is consistent with the *in vitro* results.

4. Discussion

Ever since agents targeting vascular endothelial growth factor-A and epidermal growth factor receptor were introduced a decade ago, progress in therapeutic strategies for CRC has been slow compared to those for other cancers (Wolpin and Mayer, 2008). Because new treatments are needed for CRC and TRAIL resistance should be overcome, we investigated the synergistic effect of DADS with TRAIL by using comparatively TRAIL-resistant CRC cells. In this study, we demonstrated that non-cytotoxic doses of DADS increased the rate of TRAIL-associated cell death in CRC cell lines. We demonstrated that treatment with DADS combined with TRAIL caused DNA fragmentation, and caspase activation resulted in cleavage of PARP, an essential process in TRAIL-mediated cell death. This chain of processes includes down-regulation of the anti-apoptotic protein Bcl-2 and the synergistic effect of DADS with TRAIL was attenuated in Bcl-2 up-regulated cells. These findings suggest that suppression of Bcl-2 is essential to induce the sensitizing effect of DADS on the TRAIL pathway (Fig. 5).

Apoptosis, the process of programmed cell death in mammalian cells, is initiated through two principal pathways: extrinsic and intrinsic (Li and Yuan, 2008). Both pathways lead to the same endpoint of caspase activation, while the extrinsic pathway is induced through the activation of DRs by binding to members of the tumor necrosis factor superfamily, which includes TRAIL (Aggarwal, 2003; Bellail et al., 2010). The intrinsic pathway is initiated by activation of intra-cellular caspases under the control of mitochondria (Sprick and Walczak, 2004). A key molecule in the latter pathway is the apoptosome, a caspase-9-activating complex, which is formed after the release of cytochrome c from the mitochondria and induces activation of caspase-9, resulting in increased activity of executioner caspases (Baliga and Kumar, 2003). These events, including the release of cytochrome *c* and other pro-apoptotic proteins, are associated with the integrity of the mitochondrial membrane (Marsden and Strasser, 2003), which is controlled by the Bcl-2 family (Borner, 2003). Bcl-2 family proteins consist of three groups: pro-apoptotic proteins, BH3-only proteins, and anti-apoptotic proteins (Sprick and Walczak, 2004). Activation of a BH3-only protein, BID, triggers activation of pro-apoptotic proteins, including BAK and BAX, to increase mitochondrial membrane permeability (Kandasamy et al., 2003). Crosstalk between the extrinsic and intrinsic pathways of apoptosis depends on caspase-8, which is recruited by Fas-associated protein with death domain and mediates the cleavage of BID (Aggarwal et al., 2004). Therefore, overexpression of the anti-apoptotic proteins Bcl-2 or Bcl-XL may play a crucial role in TRAIL resistance by preserving mitochondrial integrity (Fulda et al., 2002). Previous studies have analyzed the repression of Bcl-2 to overcome TRAIL resistance (Hao et al., 2004; Sinicrope et al., 2004) (Fig. 5).

DADS has been reported to be beneficial for treating coronary artery diseases because of its preventive effect on plaque formation and cholesterol synthesis (Gupta and Porter, 2001; Omkumar et al., 1993) and was shown to suppress the proliferation of cancer cells including human colon, skin, lung, and breast cancer cells (Hong et al., 2000; Kwon et al., 2002; Sundaram and Milner, 1996). Several studies have demonstrated that DADS promotes apoptosis in cancer cells, and a few studies suggested that apoptosis induced by DADS depends on a mitochondrial pathway related to Bcl-2. Because Bcl-2 is one of the main obstacles in the TRAIL pathway and no studies have demonstrated an association between the TRAIL pathway and DADS, we used DADS as a potential sensitizer of TRAIL-induced apoptosis in TRAIL-resistant cell lines.

5. Conclusion

In this study, through *in vitro* and *in vivo* studies, we found that treatment with DADS at subtoxic concentrations effectively sensitized TRAIL-related cell death in CRC cell lines. We determined the molecular mechanism of this novel action of DADS, which was not observed in normal colon cell lines. DADS caused CRC cell apoptosis by modulating TRAIL-induced caspase activation. Repression of Bcl-2 by DADS was demonstrated to be an essential step in this process.

Conflicts of interest

The authors state no conflict of interest.

Acknowledgements

This work was supported by a National Research Foundation of Korea grant funded by the Korean government (MSIP) [2018R1A6A1A03023584] and supported by the Business for Cooperative R & D between Industry, Avicenna Research Institute funded Korea Small and Medium Business Administration in 20 (C0566291) and a Korea University Grant.

Transparency document

Transparency document related to this article can be found online at https://doi.org/10.1016/j.fct.2019.01.023.

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