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Lipoxygenase inhibitor MK886 potentiates TRAIL-induced apoptosis through CHOP- and p38 MAPK-mediated up-regulation of death receptor 5 in malignant glioma

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ABSTRACT

Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) triggers specific apoptosis in tumor cells and is one of the most promising candidates for cancer gene therapy. However, resistance to TRAIL is one of the main impediments to use of TRAIL in cancer treatment. We showed previously that the lipoxygenase inhibitor MK886 in combination with TRAIL exhibits enhanced antitumor activities compared with each agent alone in human glioma cells. In this study, we elucidated the molecular mechanisms responsible for MK886-mediated sensitization to TRAIL-induced apoptosis. We found that MK886 sensitized glioma cells to TRAIL-induced apoptosis by upregulating the death receptor 5 (DR5) and that specific knockdown of DR5 attenuated cell death. The mechanisms underlying this sensitization involved activation of the MK886-induced p38 mitogen-activated protein kinase (MAPK) pathway and subsequent DR5 overexpression. However, treatment with a specific inhibitor or gene silencing of p38 MAPK abolished both the DR5 induction and the increase in apoptosis caused by TRAIL. Taken together, our findings indicate that the increased expression of DR5 in a p38 MAPK-dependent manner plays an important role in the sensitization of MK886 to TRAIL-induced apoptosis.

1. Introduction

Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a member of the tumor necrosis factor family, which exerts selective antitumor activity in a wide range of tumor cell types without damaging normal cells and tissues [1,2]. These actions make TRAIL one of the most promising candidates for cancer gene therapy. Because of the selectivity of TRAIL, both TRAIL and agonistic antibodies against its receptors are currently being studied in clinical trials [3]. However, many types of cancer, including gliomas, are resistant to TRAIL-induced apoptosis, and the highly invasive nature of glioma cells is the major obstacle to a cure [4].

Mesenchymal stem cells (MSCs) have been used recently as a cellular vehicle for the delivery of therapeutic genes because of their capacity for tracking tumors. Several studies including ours have reported the potential of MSC-based TRAIL delivery as a potent anticancer agent in experimental glioma models after overcoming some of the hurdles of conventional TRAIL-based treatments to provide continuous and highly concentrated local delivery of TRAIL by MSCs [5–10]. However, an additional issue with TRAIL-based therapy is that tumor cells can remain resistant to TRAIL. Thus, the identification of novel strategies that sensitize glioma cells to TRAIL-induced apoptosis is needed to overcome TRAIL resistance.

Many types of cancer cells, including most glioma cells, are resistant to TRAIL-induced apoptosis. TRAIL resistance appears to be mediated through the loss of TRAIL receptors, increased expression of caspase inhibitors such as cellular FLICE-inhibitory protein, X-linked inhibitor of apoptosis protein, cellular inhibitor of apoptosis protein, survivin, or alterations in expression of the Bcl-2 family proteins [11–13]. Recent reports have shown that chemotherapeutic agents or radiotherapy can increase the sensitivity to TRAIL by increasing the expression of TRAIL receptors or by downregulating antiapoptotic proteins in a range of tumors [14,15], suggesting that a synergistic antitumor effect may be achieved by using combination therapies to increase the apoptotic effects of TRAIL.

We reported previously that combined treatment using the 5-lipoxygenase (5-LOX) inhibitor MK886 and MSC-delivered TRAIL (MSC-TRAIL) increased apoptosis in glioma cells *in vitro* and tumor regression in a mouse xenograft model *in vivo* [16]. 5-LOX is a key enzyme involved in the metabolism of arachidonic acid to eicosa-

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noids [17]. MK886, a specific inhibitor of the 5-LOX–activating protein, induces antiproliferative effects and apoptosis in human myeloid leukemia, prostate cancer, breast cancer, and glioblastoma [18–21]. We also found that combined treatment with MK886 could overcome TRAIL resistance by increasing death receptor 5 (DR5)-mediated apoptosis, yet the mechanisms remained to be explored. Understanding the intracellular mechanisms is essential to overcoming of the resistance to TRAIL. In this study, we elucidated the molecular mechanisms mediated by DR5 upregulation of the enhanced antitumor effect of combined treatment with MK886 and MSC-TRAIL in glioma cells.

2. Materials and methods

2.1. Cell lines and cell culture

Human bone marrow-derived MSCs were purchased from Lonza (Poietics® PT2501; Lonza Inc., Walkersville, MD, USA). The frozen stock was thawed, and the cells were maintained in MSC growth medium containing MSC growth supplements, L-glutamine, and GA-1000 (aqueous solution of gentamicin sulfate and amphotericin B), which were purchased from Lonza. Human glioma cell lines (U-87MG and U-373MG) were obtained from the American Type Culture Collection (Manassas, VA, USA) and maintained in DMEM (Invitrogen, Grand Island, NY, USA) supplemented with 100 U/mL penicillin, 100 μg/mL streptomycin, and 10% fetal bovine serum (Invitrogen). All cells were incubated at 37 °C in a humidified atmosphere containing 5% CO_2.

2.2. Production of TRAIL-secreting MSCs

The adenovirus carrying the secretable trimeric form of the TRAIL gene (Ad-TRAIL) engineered, as described previously [22], was kindly provided by Dong-A Pharmaceutical Co., Ltd. (Yongin, Korea). Cell-permeable peptide-mediated adenoviral transduction was performed as described previously [23]. TRAIL protein secreted into the culture supernatants was analyzed by ELISA, as described previously [5].

2.3. Transfection with siRNAs

DR5, C/EBP-homologous protein (CHOP), and p38 mitogen-activated protein kinase (MAPK) siRNAs were obtained from Santa Cruz Biotechnology (Santa Cruz, CA, USA), and extracellular signal-regulated kinase (ERK) was obtained from Cell Signaling Technology Inc. (Danvers, MA, USA). To transfect tumor cells with siRNA, cells (2×10^5 cells per well) were seeded into six-well plates, and transfection was performed using Lipofectamine 2000 (Invitrogen). Cells were exposed to a scrambled siRNA (Santa Cruz Biotechnology) and were used as controls.

2.4. Cell viability assay

Cell viability was measured using the MTT (3-(4,5-dimethylthiazol-2-yl)-diphenyltetrazolium bromide)-based cytotoxicity assay (Sigma, St. Louis, MO, USA). To measure TRAIL-induced cytotoxicity and MK886-mediated cell death, glioma cells (4×10^4) in 24-well plates were treated with MK886 (Calbiochem, La Jolla, CA, USA) and recombinant human TRAIL protein (R&D Systems, Minneapolis, MN, USA), MSC-TRAIL, or both reagents at appropriate concentrations and analyzed 48 h later. For coculture experiments, MSC-TRAILs (1×10^4) were plated in Transwell inserts with 0.4 μm pores (Corning Inc., Corning, NY, USA), glioma cells (4×10^4) were grown in the lower well of 24-well plates, and cells were analyzed 48 h after treatment. To evaluate the involvement of MAPK signaling or oxidative stress in the sensitizing effect of MK886 in TRAIL-induced apoptosis, cells were pretreated with the ERK inhibitor (PD98059), c-jun N-terminal kinase (JNK) inhibitor (SP600125), p38 MAPK inhibitor (SB203580), or antioxidant *N*-acetylcysteine (NAC) for 1 h and then incubated with MK886 in the absence or presence of TRAIL for 48 h. The MAPK inhibitors were purchased from Calbiochem, and NAC was purchased from Sigma. The plates were read using an absorbance plate reader at a wavelength of 570 nm (Molecular Devices Corporation, Sunnyvale, CA, USA).

2.5. Western blot analysis

Cells were lysed in 50 mM Tris–HCl, pH 8.0, with 150 mM sodium chloride, 1% IGEPAL CA-630 (NP-40), 0.5% sodium deoxycholate, and 0.1% sodium dodecyl sulfate (RIPA) buffer (Sigma) containing a protease inhibitor cocktail (Roche, Indianapolis, IN, USA). Proteins were transferred onto a nitrocellulose membrane (Invitrogen) and then incubated with primary antibodies against DR5 (R&D Systems), CHOP, caspase-3, caspase-8, caspase-9, p-ERK1/2, ERK1/2, p-JNK, JNK, p-p38 MAPK, p38 MAPK (Cell Signaling Technology Inc.), and β-actin (Sigma). The membranes were subsequently incubated with horseradish peroxidase-conjugated secondary antibodies (Santa Cruz Biotechnology), and the blots were detected using Amersham ECL detection reagents (GE Healthcare Life Sciences, Pittsburgh, PA, USA).

2.6. Measurement of reactive oxygen species

To detect intracellular reactive oxygen species (ROS), cells (2×10^5) were seeded in a six-well plate. After 24 h, cells were incubated with MK886 at different doses for 1 h, stained with 10 μmol/L dichlorofluorescein diacetate (DCF-DA, Sigma) for 30 min, and then evaluated by flow cytometry (Moflo; Beckman Coulter Inc., Fullerton, CA, USA).

2.7. Statistical analysis

All data are expressed as mean ± SEM from at least three independent experiments. Significant differences between test conditions were identified using Student's *t* test. Probability values less than 0.05 were considered significant.

3. Results

3.1. MK886 sensitizes glioma cells to TRAIL-mediated apoptosis via upregulation of DR5

First, we measured the cytotoxicity of MSC-TRAIL combined with MK886 in human glioma cells. Because we have reported on the effective therapeutic potential for MSC-based TRAIL delivery [16], we used MSC-TRAIL in the present study. We found that MK886 induced significant cell death in the presence of MSC-TRAIL in both U-87MG and U-373MG cells (Fig. 1A), indicating that MK886 strongly sensitizes cells to TRAIL-induced cell death. Next, we examined whether treatment with MK886 affected DR5 and CHOP expression because several studies have shown that CHOP can induce the expression of death receptors [24]. Western blot analysis showed that DR5 expression increased markedly after treatment and that MK886 also induced CHOP expression in a dose-dependent manner in both U-87MG and U-373MG cells (Fig. 1B). These results indicate that MK886-induced DR5 upregulation is mediated by CHOP expression. To identify the role of DR5 in TRAIL-induced apoptosis, we used an siRNA specific to DR5. The effect of MK886 on TRAIL-induced apoptosis was abolished effectively in U-87MG cells transfected with DR5 siRNA

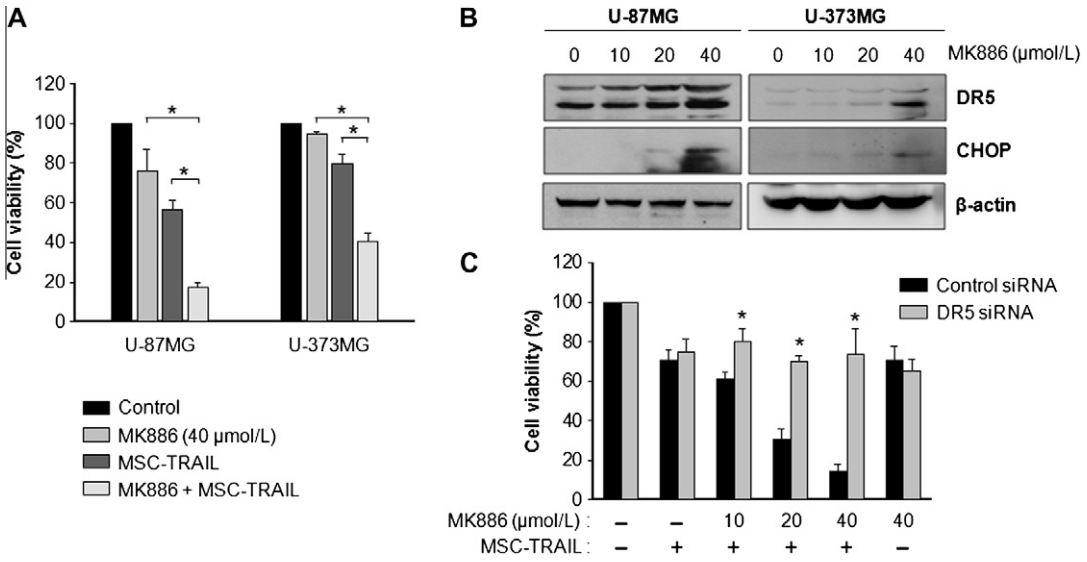

Fig. 1. Upregulation of DR5 is required for MK886-induced sensitization of TRAIL. (A) Cytotoxic effect of secreted TRAIL from MSC-TRAIL combined with MK886 (40 μmol/L) on U-87MG and U-373MG cells was analyzed by coculture using Transwell plates and the viability was determined at 48 h by MTT assay. Glioma cells (4×10^4) were in lower wells of 24-well plates and MSC-TRAIL (1×10^4) were in Transwell inserts (0.4 μm pores). *$P < 0.05$ as compared with treatment with MK886 or MSC-TRAIL alone, Student's t test. (B) Cells were treated with MK886 (0–40 μmol/L) for 24 h and then cell lysates were subjected to Western blot analysis using specific antibodies to DR5 and CHOP. (C) Effect of DR5 knockdown on the viability of U-87MG cells to the treatment of MK886 (0–40 μmol/L) and MSC-TRAIL was analyzed by coculture using Transwell plates and the viability was determined at 48 h by MTT assay. Scrambled-siRNA-treated cells were used as controls. *$P < 0.05$ in the comparison of DR5 siRNA-transfected cells with control siRNA-transfected cells after treatment, Student's t test.

(Fig. 1C). These results indicate that induction of DR5 is critical for the sensitization of glioma cells to the effect of MK886 on TRAIL-induced apoptosis.

3.2. Upregulation of DR5 induced by MK886 is regulated by p38 MAPK

Various studies have suggested that MAPK activation plays a role in TRAIL receptor induction [25,26]. Thus, we examined whether MK886 can activate ERK, JNK, and p38 MAPK in human glioma cell lines. MK886 induced a time-dependent phosphorylation of p38 MAPK in both cell lines (Fig. 2A). MK886 had no effect on the phosphorylation of ERK or JNK. Next, to investigate whether the activation of these MAPKs is involved in MK886-induced expression of DR5, we used the inhibitors of ERK (PD98059), JNK (SP600125), and p38 MAPK (SB203580). Pretreatment of U-87MG cells with the inhibitor of p38 MAPK suppressed MK886-induced DR5 and CHOP induction in a dose-dependent manner. By contrast, ERK and JNK inhibitors had no effect on MK886-induced DR5

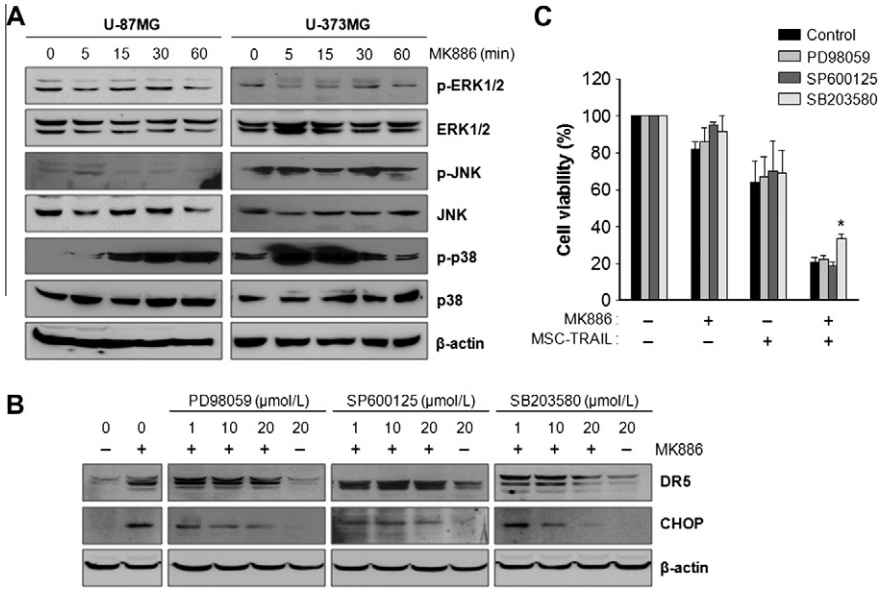

Fig. 2. MK886-induced activation of p38 MAPK is involved in TRAIL-induced apoptosis. (A) Cells were treated with MK886 (40 μmol/L) time-dependently and Western blotting was used to analyze for phosphorylated ERK, JNK, and p38 MAPK expression. (B) Cells were pretreated with various concentrations of PD98059, SP600125, and SB203580 for 1 h and then treated with MK886 (40 μmol/L) for 24 h. Cell extracts were analyzed by Western blotting using DR5 and CHOP antibodies. (C) Effect of MAPK inhibitors on cell death induced by MK886 plus MSC-TRAIL was evaluated by coculture using Transwell plates. U-87MG cells (4×10^4) in lower wells were pretreated with 20 μmol/L inhibitors against MAPKs for 1 h and treated with 40 μmol/L MK886 in the coculture of MSC-TRAIL (1×10^4) for 48 h. Cell viability was evaluated by MTT assay. *$P < 0.05$, Student's t test.

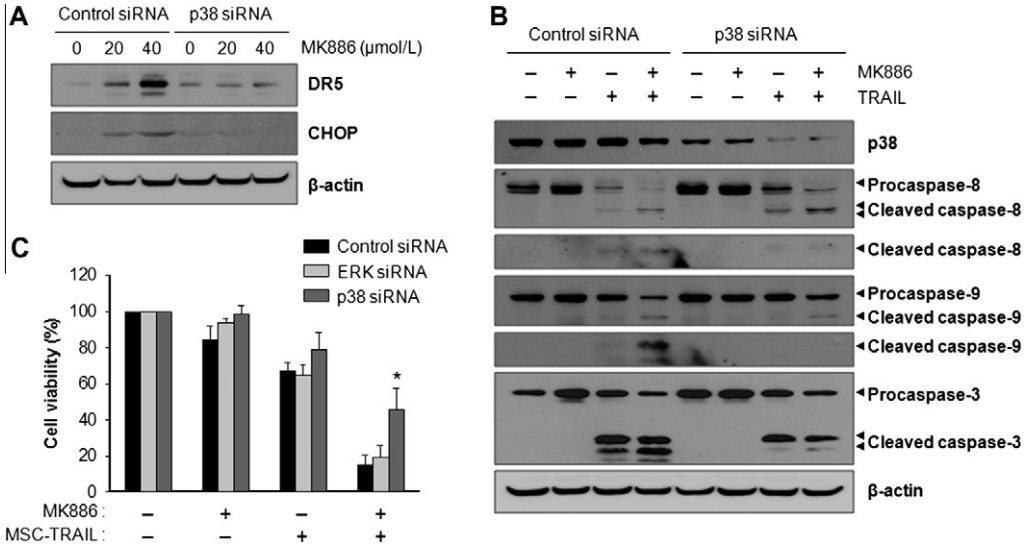

Fig. 3. Knockdown of p38 MAPK inhibits upregulation of DR5 and TRAIL-induced apoptosis. (A) U-87MG cells were transfected with either p38 MAPK siRNA or control siRNA. After 48 h, cells were treated with MK886 (0–40 μmol/L) for 24 h, and cell extracts were analyzed by Western blotting using DR5 and CHOP antibodies. (B) Western blotting analysis showed changes in apoptosis-related proteins (caspase-8, caspase-9, and caspase-3) in U-87MG cells treated with MK886 (40 μmol/L) and recombinant TRAIL (100 ng/mL) for 24 h. (C) Effect of p38 MAPK knockdown on cell death induced by MK886 plus MSC-TRAIL was evaluated by coculture using Transwell plates. U-87MG cells (4×10^4) were transfected with siRNA in lower wells treated with 40 μmol/L MK886 in the coculture of MSC-TRAIL (1×10^4) for 48 h. Cell viability was evaluated by MTT assay. $^*P < 0.05$, Student's t test.

expression. These results suggest that p38 MAPK plays a role in death receptor induction (Fig. 2B). We also found that pretreatment with the p38 MAPK inhibitor slightly, but significantly, reduced TRAIL-induced cell death during the combined treatment (Fig. 2C). This finding confirmed that MK886 sensitizes U-87MG cells to TRAIL through the involvement of p38 MAPK phosphorylation.

3.3. Knockdown of p38 MAPK blocks DR5 upregulation and TRAIL-induced apoptosis

We next examined whether silencing of p38 MAPK blocks DR5 upregulation and inhibits TRAIL-induced apoptosis. Western blot analysis showed that the reduction in the expression of p38 MAPK by gene silencing correlated with suppression of the MK886-induced upregulation of DR5 and with CHOP induction in a dose-dependent manner (Fig. 3A). Next, we investigated whether siRNA suppression of p38 MAPK expression inhibited the increase in TRAIL-induced apoptosis by MK886. As shown in Fig. 3B, knockdown of p38 MAPK significantly inhibited the increase in TRAIL-induced caspase activation compared with the treatment of control siRNA in U-87MG cells. Consistent with the Western blot analysis, cell death induced by MK886 combined with MSC-TRAIL was significantly inhibited in p38 MAPK siRNA-treated cells compared with control siRNA- or ERK siRNA-treated cells (Fig. 3C). These results suggest that CHOP-dependent DR5 upregulation contributes to the sensitizing effect of MK886 on TRAIL-induced apoptosis and confirm that MK886 sensitizes U-87MG cells to TRAIL through p38 MAPK activation.

3.4. MK886-induced TRAIL sensitization is independent of ROS

Because several studies have reported that TRAIL receptor induction is regulated by ROS [27,28], we evaluated whether ROS also regulates MK886-mediated DR5 induction. To investigate the ability of MK886 to generate ROS, we used DCF-DA to measure the increase in ROS levels. As shown in Fig. 4A, MK886 did not induce ROS generation. We next examined whether ROS generation is needed for the activation of p38 MAPK and the induction of DR5 and CHOP expression. We found that pretreatment of U-87MG cells with the ROS scavenger NAC did not suppress MK886-induced upregulation of DR5 and CHOP expression as well as p38 MAPK activation (Fig. 4B). In addition, consistent with the Western blot analysis, pretreatment of NAC had no effect on the increase in TRAIL-induced caspase activation (Fig. 4C) or cell death (Fig. 4D) induced by MK886 combined with MSC-TRAIL compared with U-87MG cells that were not pretreated, suggesting that MK886-induced TRAIL sensitization is independent of ROS production.

4. Discussion

Although TRAIL is the only cytokine that can selectively induce apoptosis in tumor cells without affecting normal cells during treatment of cancer, the resistance of tumor cells to TRAIL-induced apoptosis is one of the major obstacles to development of this therapy. To overcome TRAIL resistance, novel strategies such as a combined use of sensitizers to TRAIL-mediated apoptosis are needed. In this study, we demonstrated that the 5-LOX inhibitor MK886 sensitized cells to TRAIL-induced apoptosis by upregulating DR5. The combined therapy of MK886 and MSC-TRAIL appears to be a more powerful modality compared with treatment using a single agent against glioma. We also found that MK886-induced upregulation of DR5 appears to be mediated through CHOP-dependent activation of the p38 MAPK pathway.

As in our previous report [16], we found that MK886 increased TRAIL-induced apoptosis in human glioma cells; however, in our previous report, we identified several possible means to increase TRAIL-induced apoptosis, but we did not identify the mechanism of sensitization. Identifying the intracellular signaling events responsible for MK886-mediated sensitization to TRAIL-induced apoptosis is of particular importance. One of the mechanisms of sensitization is the regulation of antiapoptotic proteins. We found previously that MK886 downregulates the expression of survivin, an antiapoptotic protein that has been linked to tumor cell resistance to TRAIL [29]. These results agree with those of several stud-

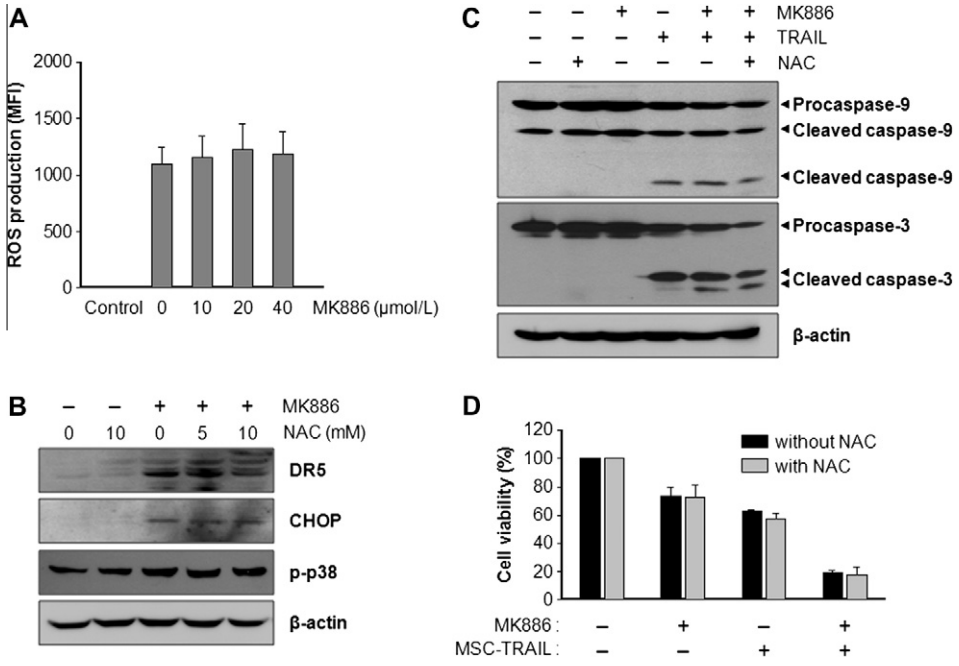

Fig. 4. MK886-induced TRAIL sensitization is not mediated with ROS production. (A) U-87MG cells were treated with the indicated dose of MK886 for 3 h, incubated with DCF-DA for 30 min, and then examined for ROS production by flow cytometry. Mean fluorescence intensity (MFI) was shown. (B) U-87MG Cells were pretreated with various concentrations of NAC for 1 h, treated with 40 μmol/L MK886 for 24 h (for DR5 and CHOP) or 30 min (for p-p38), and then Western blot analysis was carried out using DR5, CHOP, and phosphor-p38 antibodies. (C) Western blotting analysis showed changes in apoptosis-related proteins (caspase-9 and caspase-3) in U-87MG cells treated with MK886 (40 μmol/L) and recombinant TRAIL (100 ng/mL) in the presence or absence of NAC pretreatment (10 mM). (D) Effect of NAC pretreatment (10 mM) on cell death induced by MK886 plus MSC-TRAIL was evaluated by coculture using Transwell plates. U-87MG cells (4×10^4) in lower wells treated with 40 μmol/L MK886 in the coculture of MSC-TRAIL (1×10^4) for 48 h. Cell viability was evaluated by MTT assay.

ies showing that survivin downregulation increases TRAIL-induced apoptosis in glioma cells [30].

In this study, we found that in addition to downregulating anti-apoptotic proteins, MK886 induced DR5 expression in glioma cells. We found that gene silencing of DR5 abolished TRAIL-induced apoptosis, suggesting that DR5 upregulation is critical for the sensitization of glioma cells to TRAIL. Numerous mechanisms have been proposed to explain the induction of the death receptor, including p53 induction, peroxisome proliferator-activated receptor-γ activation, and MAPK activation [31,32]. Various studies have suggested that MAPK activation plays a role in TRAIL receptor induction [25,26]. Thus, we investigated whether MAPK plays a role in MK886-induced DR5 induction. We found that MK886-mediated DR5 induction was related to p38 MAPK activation. We confirmed that inhibition of p38 MAPK using the specific inhibitor or gene silencing of p38 MAPK led to suppression of MK886-induced DR5 expression and thus suppression of the MK886-mediated increase in TRAIL-induced cell death.

We also found that DR5 upregulation is mediated through CHOP induction. We showed previously that MK886 induced CHOP expression and that the gene silencing of CHOP by siRNA blocked the effect of MK886 on the induction of DR5 and on TRAIL-induced apoptosis [16]. Although p53 induction has also been linked to DR5 induction [31], we found that the MK886-induced upregulation of DR5 was independent of p53. In this study, we also found that inhibition of p38 MAPK using the specific inhibitor or gene silencing of p38 MAPK suppressed both MK886-induced DR5 and CHOP expression, and thus TRAIL-induced apoptosis or activation of caspases. Taken together, these results suggest that CHOP-dependent DR5 upregulation contributes to the sensitizing effect of MK886 on TRAIL-induced apoptosis through involvement of p38 MAPK activation.

Several studies have reported the involvement of ROS generation and/or MAPK signaling pathways in the sensitization of cancer cells to TRAIL-induced apoptosis [26–28]. The ROS generation induced by chemicals acting as TRAIL sensitizers is considered important for the activation of MAPKs and the upregulation of DR5 leading to apoptosis [33,34]. However, in this study, we found that MK886 did not induce the production of ROS, which might be an upstream signal linked to the activation of MAPKs and the upregulation of DR5. The scavenging of ROS by NAC also had no effect on the activation of p38 MAPK and CHOP-mediated DR5 upregulation and subsequent MK886-mediated potentiation of TRAIL-induced apoptosis and caspase activation. Further studies are needed to elucidate the signal pathway involved in the upregulation of DR5 induction by MK886 treatment, especially the upstream signal(s) leading to the activation of MAPKs.

In summary, we conclude that CHOP-dependent DR5 upregulation contributes to the sensitizing effect of MK886 on TRAIL-induced apoptosis and that MK886 sensitizes glioma cells to TRAIL through involvement of the p38 MAPK pathway. These results demonstrate that the combination of MSC-TRAIL with MK886 is a potent therapeutic approach to overcoming resistance to TRAIL in malignant gliomas.

Acknowledgments

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