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Requirement of T-lymphokine-activated killer cell-originated protein kinase for TRAIL resistance of human HeLa cervical cancer cells

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ABSTRACT

T-lymphokine-activated killer cell-originated protein kinase (TOPK) appears to be highly expressed in various cancer cells and to play an important role in maintaining proliferation of cancer cells. However, the underlying mechanism by which TOPK regulates growth of cancer cells remains elusive. Here we report that upregulated endogenous TOPK augments resistance of cancer cells to apoptosis induced by tumor necrosis factor-related apoptosis inducing ligand (TRAIL). Stable knocking down of TOPK markedly increased TRAIL-mediated apoptosis of human HeLa cervical cancer cells, as compared with control cells. Caspase 8 or caspase 3 activities in response to TRAIL were greatly incremented in TOPK-depleted cells. Ablation of TOPK negatively regulated TRAIL-mediated NF-κB activity. Furthermore, expression of NF-κB-dependent genes, FLICE-inhibitory protein (FLIP), inhibitor of apoptosis protein 1 (c-IAP1), or X-linked inhibitor of apoptosis protein (XIAP) was reduced in TOPK-depleted cells. Collectively, these findings demonstrated that TOPK contributed to TRAIL resistance of cancer cells via NF-κB activity, suggesting that TOPK might be a potential molecular target for successful cancer therapy using TRAIL.

Introduction

TRAIL (tumor necrosis factor-related apoptosis inducing ligand) is known to function as one of death receptor ligands of TNF superfamily, which selectively kill tumor cells [1]. Binding of TRAIL to the death receptors DR4/DR5 recruits the adaptor protein FADD and procaspase 8, forming complex called as death-inducing signaling complex (DISC), followed by activation of procaspase 8 and subsequent effector caspases 7, 9, and 3 [2]. Eventually, activated caspase 3 is translocated to nucleus, resulting in cleavage of target substrates such as PARP [3]. A variety of anti-apoptotic proteins including FLIP, Bcl-2 family, and IAPs are known to interfere with TRAIL-mediated apoptotic signal via regulation of caspases-activating cascades [4,5]. Although TRAIL specifically induces apoptosis in tumor cells, cancer cells still have resistance to the apoptotic TRAIL, restricting its possibility as one of potential drugs for cancer therapy [6].

It has been suggested that T-LAK cell-originated protein kinase (TOPK), a MAPKK-like protein kinase, is upregulated in many malignant tumors including leukemias, lymphomas, and myelomas [7,8]. TOPK has been proposed to act as a marker for amplifying neural progenitors in the adult subependymal zone (SEZ), implying the role of TOPK in proliferation of neuronal cell [9]. TOPK is composed of major two domains, kinase domain including the conserved dual specificity active site sequence (D-X-K-X-X-N) spanning amino acids 174–179, and a C-terminal ETDV motif that binds PDZ domains [8]. It has been reported that phosphorylated TOPK during mitosis formed complex with cdk1/cyclin B1 and PRC1, stimulating the cdk1/cyclin B1-driven phosphorylation of PRC1 and subsequent cytokinesis [7,10]. Recently, TOPK was shown to play a key role in phosphorylation of histone H3 at Ser10 *in vitro* and *in vivo*, and to function as molecular marker in breast cancer [11]. Furthermore, it has been suggested that TOPK is closely implicated in tumorigenesis of colon cancer cells or ras-induced cell transformation via regulation of stimuli-specific signaling pathways [12,13]. However, the underlying mechanism regarding TOPK-mediated regulation of proliferation of tumor cells still remains to be undiscovered.

Here we uncovered that TOPK conferred cancer cells resistance to TRAIL-induced apoptosis. We demonstrated that ablation of endogenous TOPK abolished TRAIL induction of NF-κB activity and sensitized cancer cells to the apoptotic TRAIL signaling. We also provided evidence showing that TOPK positively regulated expression of NF-κB-dependent anti-apoptotic genes via NF-κB activity.

Materials and methods

Cells and reagents. Human HeLa cervical cancer cells were purchased from American Type Culture Collection (ATCC). Cells were

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cultured in DMEM supplemented with 10% fetal bovine serum (FBS), 2 mM L-glutamine, and 1% penicillin/streptomycin. Recombinant human TRAIL or BrdU cell proliferation assay kit was purchased from Sigma (St. Louis, MO) or Chemicon (Billerica, MA), respectively. M-MuLV reverse transcriptase, DeadEnd fluorometric TUNEL System, and luciferase assay system were from Promega (Madison, WI). Antibody against tubulin was purchased from Santa Cruz Biotechnology, Inc. (Santa Cruz, CA). Antibodies against TOPK and p-IκBα (Ser-32) were from Cell Signaling Technology, Inc. (Beverly, MA). Lipofectamine LTX was from Invitrogen (Carlsbad, CA). Caspase colorimetric activity assay kit was from Chemicon (Billerica, MA).

Construction of stable TOPK siRNA cells. The TOPK siRNA construct was generated by subcloning synthesized and annealed duplex hairpin siRNA oligonucleotides, sense strand, 5′-GATCCGA GGTTTGTCTCATTCTCCTTCA AGAGAGGAGAATGAGACAAACCTCTTT TTTGGAAA-3′ and antisense strand, 5′-AAAA AACCTTTTCGAGA GGTTTGTCTCATTCTCCTCTCTTGAAGGAGAATGAGACAAACCTCG-3′, into the BamHI/HindIII sites of pSilencer 3.1-H1 neo vector (Ambion, Austin, TX) and the insert was verified by sequencing. Transfection of each 5 μg of TOPK siRNA construct or negative control, pSilencer neo vector (Ambion) which expresses a hairpin siRNA with limited homology to any known sequences in the human, mouse, and rat genomes, into HeLa cells growing on 100 mm dish was performed using Lipofectamine LTX according to manufacturer's instructions. Forty-eight hours after transfection, cells were incubated with G418 (400 μg/ml) containing medium. After 2 weeks, desired single clones were selected and propagated.

Terminal deoxynucleotidyl transferase-mediated dUTP nick end-labeling (TUNEL) assay. TUNEL assay was done using DeadEnd fluorometric TUNEL system (Promega). Briefly, cells grown on cover glass were fixed with 1 ml freshly prepared 4% methanol-free formaldehyde solution in PBS (pH 7.4). After washing with PBS, cells were permeabilized with 0.2% Triton X-100 solution in PBS. DNA breaks were labeled with Terminal deoxynucleotidyltransferase and nucleotide mixture including fluorescein-dUTP. After 1 h incubation at 37 °C in humidified chamber, cells were washed three times and added with one drop of anti-fading agent, VECTASHIELD+DAPI (Invitrogen) to slide glass and mounted. Cells were analyzed under a fluorescence microscope.

Bromodeoxyuridine (BrdU) cell proliferation assay. BrdU cell proliferation assay was performed according to manufacturer's instruction. Cells were plated at 1×10^4 cells per well in 96 well culture plates. After 24 h, cells were treated with TRAIL for 24, 48, or 72 h. Six hours before harvest, cells was added with BrdU, fixed at room temperature for 30 min. After washing, cells were incubated with anti-BrdU antibody for 1 h, washed, and then incubated with secondary antibody conjugated with peroxidase for 30 min. After washing, TMB peroxidase substrate was added, and then the plate was read using spectrophotometer microplate reader at wavelength of 450 nm.

Immunoblot analysis. Immunoblotting was performed as described [13]. To investigate the level of each protein in TOPK siRNA or control siRNA cells in the absence or presence of TRAIL, immunoblotting was carried out using each respective antibody. Twenty micrograms of each total cellular lysates was separated by SDS–PAGE, transferred to nitrocellulose membrane (Biorad, Hercules, CA), and probed with antibodies. Detection was done using Super-Signal west pico chemiluminescent substrate (Pierce Biotechnology, Inc., Rockford, IL) and exposed to X-ray film.

Measurement of caspase 3 and caspase 8 activities. Briefly, TRAIL-treated cells were resuspended with lysis buffer and incubated on ice for 10 min. After centrifugation for 10 min at 12,000 rpm, supernatant was subjected to caspase activity assay. Caspase 3 and caspase 8 activities were examined by caspase activity assay kit (Chemicon). The chromophore *p*-nitroaniline (pNA) produced from caspase substrate LEHD-pNA was quantified using spectrophotometer at 405 nm. Recombinant active caspase 3 and caspase 8 were used as standards of reference.

Reporter gene assays. For reporter gene assays, stable HeLa-TOPK siRNA or HeLa-control siRNA cells growing on six-well plates were transfected with each 1 μg of NF-κB promoter-driven luciferase reporter construct using each 2 μl of Lipofectamine LTX reagent. Twenty-four hours after transfection, cells were treated with TRAIL (Sigma) for 24 h. Cells were analyzed for luciferase activity. Co-transfection with 0.5 μg of the *pRL-SV40* gene for each transfection was done and *Renilla* luciferase activity was normalized for transfection efficiency.

Reverse transcription-PCR. Total RNAs were extracted from HeLa-control siRNA cells or HeLa-TOPK siRNA cells using the TRIzol reagent (Invitrogen). Reverse transcription and PCR amplification were performed using M-MuLV reverse transcriptase (Promega) and PCR master mix (Qiagen, Valencia, CA). PCR was performed for 1 cycle at 95 °C for 15 min, and 28 cycles at 95 °C for 30 s, 55 °C for 30 s, and 68 °C for 1 min. Sequences of each primer used are as follows. FLIP (forward), 5′-TCCAGAAGTACAAGCAGTCTGTTC -3′; FLIP (reverse), 5′-GAGTGAGTCTGATCCACA CCATAC-3′; c-IAP1 (forward), 5′-TCAAACTCTCCATCAAATCCTGTA-3′; c-IAP1 (reverse), 5′-GCATTTGACATCATCACTGTTACCC-3′; XIAP (forward), 5′-TATTCG AAG TGAATCTGATGCTGT-3′; XIAP (reverse), 5′-GTACCATAGGAT TTTGGAAGATGG-3′ GAPDH (forward), 5′-GTCGGAGTCAACGGAT T-3′; GAPDH (reverse), 5′-AAGCTTC CCGTTCTCAG-3′. The PCR products were analyzed on a 1.5% agarose gel and stained with ethidium bromide for visualization.

Statistical analysis. Results are shown as the means ± SD for at least three independent experiments in duplicates. Significant differences were evaluated by student's *t* test.

Results and discussion

Ablation of TOPK elevates TRAIL-induced apoptosis of HeLa cancer cells

TRAIL has been suggested to act as a potential activator of programmed cell death or apoptosis in tumor cells while sparing normal cells [1]. Although cancer cells were shown to have resistance to TRAIL-induced apoptosis, the underlying mechanism which cancer cells exhibit the resistance to TRAIL therapy remains elusive. It has been reported that TOPK was highly expressed in cancer cells and contributed to cell transformation and tumor growth, and to maintain survival of cancer cells in response to proapoptotic arsenite [13,14].

Therefore, we hypothesized that TOPK might confer cancer cells resistance in response to TRAIL. To investigate the role of TOPK in TRAIL-induced apoptosis, we first established stable human HeLa cervical cancer cell lines transfected with control siRNA or TOPK siRNA construct described in Materials and methods. Each level of endogenous TOPK in TOPK siRNA-stable cell lines was examined. As shown in Fig. 1A, most of selected single clones exhibited the least expression of endogenous TOPK, indicating that highly expressed endogenous TOPK in HeLa cells was successfully knocked down by introduction of TOPK siRNA construct. Among stable clones, we finally selected TOPK siRNA#1 clones and used for various analyses.

Using the TOPK siRNA-stable cell lines, we examined whether knocking down of TOPK affected TRAIL-induced cell death. A DNA strand break assay using TUNEL showed that TRAIL-induced apoptosis proportion in HeLa-TOPK siRNA cells was increased about 34%, as compared to the proportion in HeLa-control siRNA cells (Fig. 1B). We next asked whether knocking down of TOPK also effected HeLa cell proliferation. Therefore, we investigated proliferation rate of HeLa-TOPK siRNA or control siRNA cells in response to TRAIL in time-dependent manner. TRAIL treatment of HeLa-control

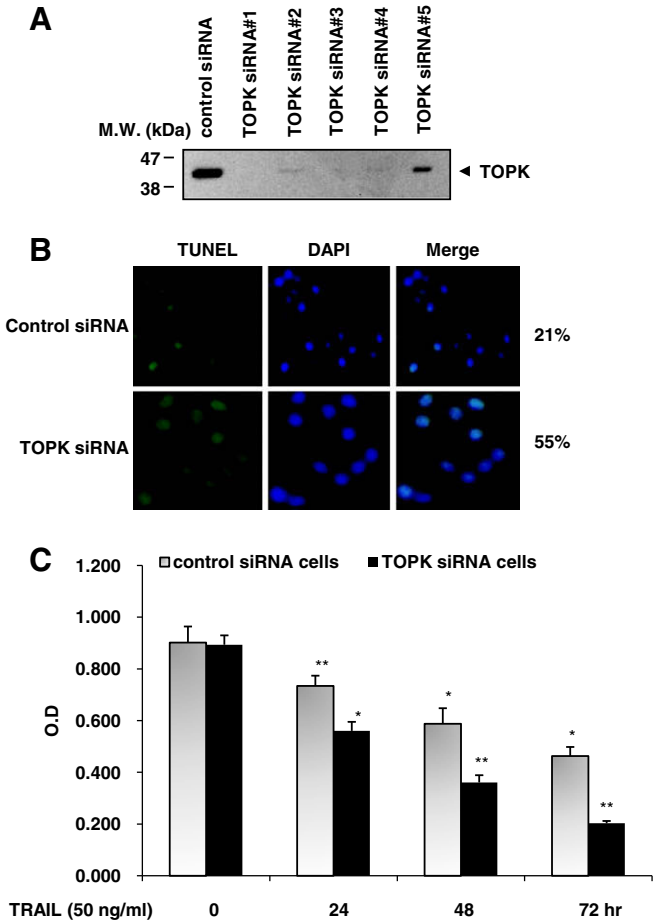

Fig. 1. Depletion of TOPK sensitizes HeLa cells to TRAIL-induced apoptosis. (A) HeLa cells were transfected with control siRNA or TOPK siRNA construct. At 48 h after transfection, cells were subjected to the selective medium containing G418.Among single clones stably transfected with TOPK siRNA, clone #1 was selected and used for further analysis. (B) Each stable transfectant (HeLa-TOPK siRNA or HeLa-control siRNA) grown on cover glass was treated with TRAIL (50 ng/ml) for 24 h. Apoptosis analysis was performed using TUNEL assay. The images were observed by immunofluorescence microscopy. The percentage of dead cells was calculated by counting dead cells and surviving cells (300 cells minimum) and shown. The nuclei were stained with DAPI and representative photos of at least three independent experiments are indicated. (C) HeLa-TOPK siRNA or HeLa-control siRNA cells were plated at 1×10^4 cells per well in 96 well culture plates and treated with TRAIL (50 ng/ml) for 24, 48, 72 h. BrdU incorporation assay was performed using BrdU antibody. $^{*}p < 0.01$, $^{**}p < 0.05$ compared with untreated control siRNA or TOPK siRNA cells.

siRNA cells for 24, 48, and 72 h resulted in 19%, 36%, and 49% decreases in cell proliferation rate, respectively. In case of HeLa-TOPK siRNA cells, 37%, 60%, and 78% decrease in response to TRAIL for 24, 48, and 72 h was shown, respectively (Fig. 1C). Taken together, these results demonstrate that ablation of endogenous TOPK sensitizes HeLa cancer cells to TRAIL-induced apoptosis, implying the importance of TOPK in maintenance of growth and proliferation in cancer cells. This is consistent with previous report that TOPK might function as a key survival factor for arsenite-induced apoptotic signal in cancer cells [14].

Endogenous TOPK alleviates TRAIL-induced caspase 8 and caspase 3 activities

Apoptosis of cancer cells in response to TRAIL is initiated by binding of the ligand to death receptor (DR) 4 and DR 5, followed by recruitment of caspase 8 via Fas-associated death domain protein (FADD) and activation of caspase 3. Also, TRAIL signaling indirectly activates the intrinsic mitochondria-mediated pathway via caspase 8-mediated Bid cleavage, which results in caspase 9 and caspase 3 activities, sequentially [15]. To whether TOPK expression affected TRAIL-mediated caspases activation, we next examined the rate of TRAIL-induced activation of caspase 8 or caspase 3 in HeLa-TOPK siRNA or HeLa-control siRNA cells, respectively. TRAIL treatment resulted in about twofold increase of caspase 8 or caspase 3 activities in HeLa-control siRNA cells. On the other hand, caspase 8 or caspase 3 activities were augmented about fourfold in TRAIL-treated HeLa-TOPK siRNA cells (Fig. 2). These results demonstrate that enhancement of caspase activities by TOPK depletion is responsible for sensitization of cancer cells to the TRAIL-induced apoptosis, because caspase activity is a direct indicator for apoptosis.

Depletion of TOPK attenuates TRAIL-induced NF-κB activity

Transcription factor NF-κB plays key roles in inflammation, immune response, and apoptosis. Particularly, it has been suggested that NF-κB is deeply implicated in cancer development and progression [16]. Therefore, blocking of NF-κB activity might be a promising therapeutic strategy for treatment of cancer. In unstimulated cells, NF-κB binds to IκBα in cytoplasm and its activity is restrained. IκBα is phosphorylated by stimuli-induced IκB kinase complex (IKK), followed by its ubiquitination and proteasomal degradation, thereby triggering NF-κB translocation into nucleus and subsequent induction of expression of NF-κB-target genes [17]. Several reports have suggested that NF-κB contributes to resistance of cancer cells to TRAIL-induced apoptosis [18–20]. In addition, it has been proposed that TRAIL activate NF-κB in a cell type-dependent manner [21,22].

We investigated whether knocking down of TOPK affected TRAIL-induced NF-κB activity. Expectedly, TRAIL treatment of HeLa-control siRNA cells resulted in increase of level of phosphorylated IκBα at 0.5 and 2 h after treatment. In contrast, no phosphorylated IκBα was observed in HeLa-TOPK siRNA cells (Fig. 3A). These results revealed that TOPK is closely implicated in TRAIL-induced NF-κB activity. We next examined the effect of endogenous TOPK on transcriptional activity of NF-κB promoter-driven luciferase reporter gene. In HeLa-control siRNA cells expressing endogenous TOPK, transcriptional activity of the luciferase gene in response to TRAIL was increased about threefold, whereas that of the luciferase gene was little augmented in TOPK-depleted HeLa cells (Fig. 3B). These findings demonstrated that TOPK might mediate TRAIL-in-

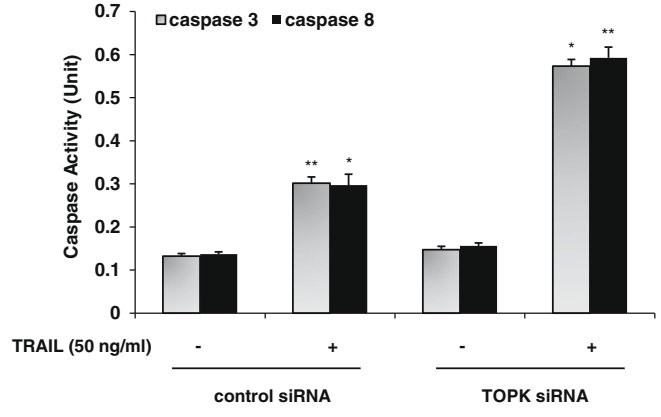

Fig. 2. TOPK diminishes TRAIL-mediated activation of caspase 8 and caspase 3. Each stable transfectant cell of control siRNA or TOPK siRNA was treated with TRAIL (50 ng/ml) for 24 h. Caspase 3 and caspase 8 activities was examined. Cells were lysed and incubated on ice for 10 min. After centrifugation, supernatants were used for measurement of caspase activity. $^{*}p < 0.01$, $^{**}p < 0.05$ compared with untreated control siRNA or TOPK siRNA cells.

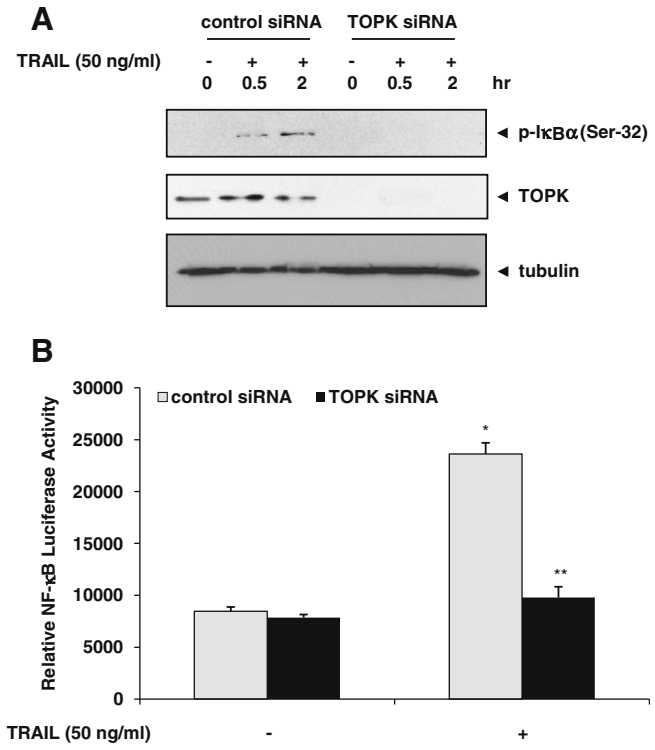

Fig. 3. TOPK mediates TRAIL-induced NF-κB activation. (A) HeLa-TOPK siRNA or HeLa-control siRNA cells were treated or not treated with TRAIL (50 ng/ml) and harvested 0.5 or 2 h later. Immunoblotting with anti-phospho-IκBα (Ser-32) antibody was done using each cell lysate. Tubulin level in each cell lysate was used for loading control (lower panel). (B) HeLa-TOPK siRNA or HeLa-control siRNA cells grown on six-well plates were transfected with 1 μg of NF-κB promoter-driven luciferase reporter gene together with 0.1 μg of *pRL-SV40* gene. At 24 h after transfection, cells were treated or not treated with TRAIL (50 ng/ml) and harvested 6 h later. Cell lysates were assessed for luciferase activity. The firefly luciferase activity was normalized against *Renilla* luciferase activity. $^{*}p < 0.01$, $^{**}p < 0.05$ compared with untreated control siRNA or TOPK siRNA cells.

duced NF-κB activation signaling pathways. Taken together, we found that highly expressed endogenous TOPK, at least in part, can prevent TRAIL-induced cancer cells apoptosis via NF-κB activity. Thus, TRAIL killing of cancer cells could be enhanced by knocking down of endogenous TOPK.

TOPK positively regulates the expression of NF-κB-responsive anti-apoptotic genes in response to TRAIL

NF-κB activation induces the expression of anti-apoptotic genes involving IAPs, FLIP, or Bcl-2 family, which can directly or indirectly inhibit apoptosis cascades. IAPs family is shown to inhibit apoptosis by direct binding to several caspases, particularly caspase 7 or caspase 3 [23]. FLIP is known to compete with caspase 8 for binding to FADD, thereby preventing apoptotic signaling [24].

We investigated whether TOPK affected expression of NF-κB-responsive anti-apoptotic genes such as FLIP, XIAP, or c-IAP1 in response to TRAIL. We observed that knocking down of TOPK caused decrease of endogenous FLIP, XIAP, or c-IAP1 mRNA level, implying that TOPK is closely implicated in regulation of NF-κB activity. Moreover, TRAIL treatment of HeLa-control siRNA cells markedly elevated the mRNA level of FLIP, XIAP, or c-IAP1 genes (Fig. 4A). Similarly, mRNA level of the genes in HeLa-TOPK siRNA cells was also increased by treatment of TRAIL. However, transcription of the anti-apoptotic genes is highly upregulated in TRAIL-treated control cells, as compared with TOPK-depleted cells (Fig. 4A, *compare lane 2 with lane 4*). These results demonstrated that highly expressed TOPK in cancer cells positively regulated expression of the

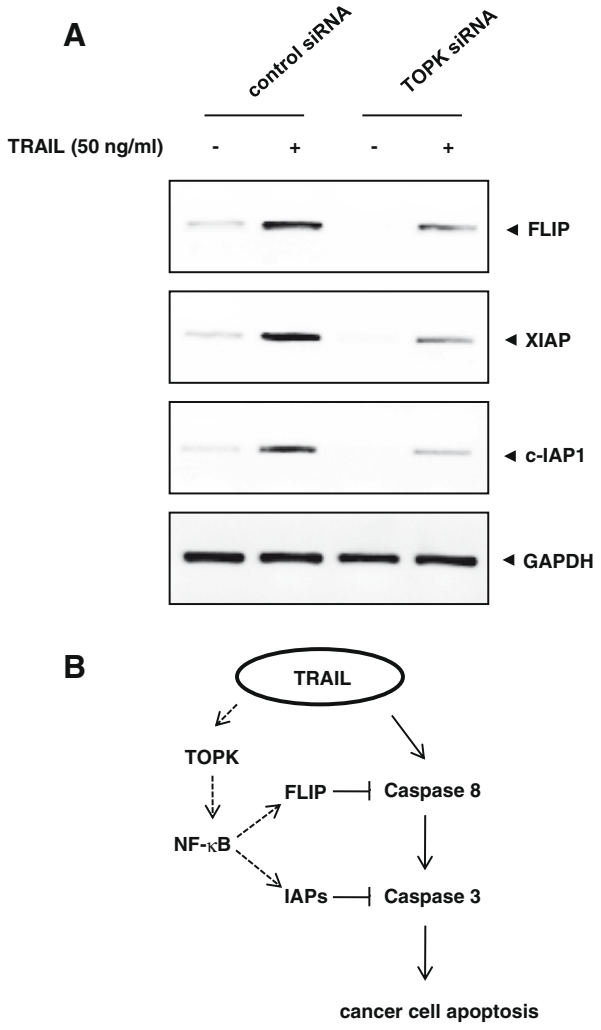

Fig. 4. Ablation of TOPK negatively regulates the expression of NF-κB-responsive anti-apoptotic target genes in response to TRAIL. (A) Total RNAs were extracted from HeLa-TOPK siRNA or HeLa-control siRNA cells untreated or treated with TRAIL (50 ng/ml), and then cDNAs was synthesized using M-MuLV reverse transcriptase from 2 μg of each total RNAs. Subsequent PCR was performed using each primer for FLIP, XIAP, c-IAP-1, or GAPDH genes, respectively. The PCR products were separated on a 1.5% agarose gel and analyzed using GelDoc (Biorad). (B) Schematic diagram for role of TOPK in TRAIL-induced apoptotic signaling. TOPK can contribute to TRAIL resistance of HeLa cells through mediating NF-κB activation leading to subsequent induction of NF-κB target genes, which blocks the apoptotic signaling.

anti-apoptotic genes in response to TRAIL. These findings suggest that reduced expression of the anti-apoptotic genes by TOPK depletion is responsible for enhanced sensitivity of cancer cells to TRAIL-induced apoptosis, which might be mediated via direct or indirect modulation of NF-κB activity by TOPK. Collectively, we revealed the evidence that endogenous expression of TOPK can provide TRAIL resistance to cancer cells. Thus, TOPK might be a promising molecular target for killing of cancer cells, particularly for TRAIL therapy against cancer.

Conclusions

Ablation of TOPK sensitizes cancer cells to TRAIL killing, and diminishes cancer cell proliferation. Also, TOPK positively regulates NF-κB activity in TRAIL signaling, leading to induction of anti-apoptotic genes. Therefore, we conclude that TOPK contributes to TRAIL resistance of cancer cells via induction of NF-κB and its responsive anti-apoptotic genes.

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