RASSF1A Suppresses the c-Jun-NH₂-Kinase Pathway and Inhibits Cell Cycle Progression

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Abstract

Some oncogenes, such as activated Ras, cause the malignant transformation of lung cells. c-Jun-NH₂-kinase (JNK) activation is essential for the oncogenic function of these cells. In this study, we show that RASSF1A inhibits the growth of lung cancer cells by blocking the JNK pathway. The exogenous expression of RASSF1A suppressed JNK phosphorylation, and cells stably transfected with RASSF1A showed reduced JNK and c-Jun phosphorylation and Cyclin D1 down-regulation. An in vitro kinase assay showed that the exogenous expression of RASSF1A inhibited JNK activity and that JNK activity suppression due to ectopically expressed RASSF1A was revived by RASSF1A siRNA treatment. Based on our data, we suggest that RASSF1A exerts a tumor-suppressing effect by blocking oncogene-mediated JNK activation in lung cells. (Cancer Res 2005; 65(9): 3682-90)

Introduction

RASSF1A is a putative tumor suppressor gene. It is located on chromosome 3p21.3, a region that frequently shows loss of heterozygosity (LOH) in a wide range of tumors, including lung cancer (1, 2). In addition to LOH, epigenetic inactivation of RASSF1A has also been detected in a variety of human cancers (3–7). This aberrant promoter methylation has been detected in 100% of small cell lung cancers and in 63% of non–small cell lung cancers (3). The methylation of the CpG island in the RASSF1A promoter has also been observed in primary non–small cell lung cancers (30–40%; refs. 3, 5). RASSF1A was produced by the alternative mRNA splicing of human RASSF1A and was found to inhibit the growth of lung cancer cells in vitro and in vivo (5). The mechanism by which RASSF1A suppresses tumor cell growth was primarily elucidated by the Shivakumar et al. (8). They observed that the ectopic expression of RASSF1A in H1299 human lung carcinoma cells leads to a blockage of cell cycle progression at the G1 phase through the JNK pathway. The upstream mediator of JNK activation has been shown to be Ras in lung carcinoma cells (19). Oncogenic Ras induces JNK activation through Raf, which then up-regulates the transcription of c-Jun and activating transcription factor-2 (ATF-2; refs. 20, 21). Cyclin D1 is one of the major targets of several growth stimulatory signaling pathways and is directly linked to G1 cell cycle progression (22); in addition, Cyclin D1 can be induced by the ectopic expression of c-Jun (23).

The tumor suppressor RASSF1A is known to suppress tumor growth by arresting the cell cycle at the G1 phase in lung carcinoma cells (8). However, the precise mechanism by which RASSF1A inhibits growth has not been established. Because RASSF1A contains a Ras association domain and binds the Ras effector Nore 1, it was suggested to exert its function through a Ras-mediated signal transduction pathway (5). In this present study, we will show that RASSF1A blocks cell cycle arrest at the G1 phase through the JNK pathway.

Materials and Methods

Cell cultures and transfection. NCI-H1299, BEAS-2B, and SNU638 cells were obtained from the American Type Culture Collection (ATCC, Manassas, VA) and were cultured in RPMI 1640 containing 10% fetal bovine serum (FBS) and antibiotics (100 units/mL penicillin and 100 µg/mL streptomycin) at 37°C in a humidified 5% CO₂ atmosphere. HeLa and MCF-7 cells were cultured in DMEM and A549 cells were cultured in Ham's F-12 medium. MRC-5 cells were purchased from the ATCC and cultured in MEM (with Earle’s salts) containing 10% FBS and antibiotics (100 units/mL penicillin and 100 µg/mL streptomycin). The day before transfection, H1299, MRC-5, BEAS-2B, and MCF-7 cells (5 × 10⁵) were plated in 60 mm plates; the next day, the cells were transiently transfected with 1 µg DNA of RASSF1A using LipofectAMINE reagent (Invitrogen, Carlsbad, CA). At 48 hours after transfection, cells were harvested for cloning assay or Western blot analysis. To generate cells stably expressing RASSF1A, H1299 cells were transfected with 1 g DNA of RASSF1A using LipofectAMINE reagent and colonies were selected from culture by treating them with G418 (800 g/mL). Selected colonies were maintained in medium containing G418 (200 g/mL); only low-passage cells (P < 10) were used for the experiments.

Antibodies and kinase inhibitors. Anti-RASSF1A monoclonal antibody (eB114) was purchased from eBiosciences (Minneapolis, MN). Antibodies for JNK and JNK activator peptides, including eB114, were purchased from eBiosciences (Minneapolis, MN).
Figure 1. The exogenous expression of RASSF1A inhibits the JNK pathway. H1299 cells transiently transfected with RASSF1A or the empty vector were harvested after 48 hours and the expressions of the indicated proteins were determined by Western blot analysis. β-actin was used as an internal loading control. A, RASSF1A expression was analyzed by Western blotting. HeLa cell lysates were used for the positive control. B, the expressions of phospho-JNK, phospho-c-Jun, and Cyclin D1 were also analyzed by Western blotting. Vector, H1299 cells transiently transfected with the empty vector (pcDNA3.1); RASSF1A, H1299 cells transiently transfected with RASSF1A.

Figure 2. The ectopic expression of RASSF1A induces cell cycle arrest at the G1 phase and inhibits the JNK pathway. A, RASSF1A expression was analyzed by Western blotting. HeLa cell lysates were used for the positive control. B, for the colony formation assay, cells stably transfected with RASSF1A or empty vector were cultured for 2 weeks and the colonies were then counted as described in Materials and Methods. C, the cell cycle distributions of cells stably transfected with RASSF1A or empty vector were measured by propidium iodide staining. D, the expressions of phospho-JNK, phospho-c-Jun, phospho-ATF-2, and Cyclin D1 were analyzed by Western blot analysis in H1299 cells stably transfected with RASSF1A or empty vector. β-actin was used as an internal loading control. RASSF1A, H1299 cells stably transfected with RASSF1A.
against JNK, c-Jun, ATF-2, phospho-JNK (Thr183/Tyr185), phospho-c-Jun (Ser63), and phospho-ATF-2 were purchased from Cell Signaling Technology (Beverly, MA). Antibodies against p53 and Cyclin D1 were purchased from DAKO Corp. (Carpinteria, CA) and Santa Cruz Biotechnology, Inc. (Santa Cruz, CA), respectively. SP600125, PD98059, and rapamycin were purchased from Calbiochem (San Diego, CA).

**Growth studies.** MRC-5, BEAS-2B, and MCF-7 cells (5 × 10⁵) were plated in 60 mm plates. The next day, the cells were transiently transfected with 1 μg DNA of **RASSF1A** using LipofectAMINE (Invitrogen). H1299 cells were transiently transfected with 1 μg DNA of **RASSF1A**, JNKDD, wild-type p53, or the empty pcDNA 3.1 plasmid using LipofectAMINE (Invitrogen). At 48 hours after transfection, the cells were harvested and seeded in six-well plates for growth curves at 2 × 10⁴ cells/well. At 24, 48, and 72 hours after seeding, trypan blue–negative surviving cells were counted under a microscope. For the MCF-7 stable transfectant cells, MCF-7 cells were transfected with **RASSF1A** and treated with G418 to eliminate untransfected cells. After drug selection, the clones were pooled and seeded in six-well plates with 2 × 10⁴ cells/well for viability assay. At 24, 48, and 72 hours after seeding, trypan blue–negative surviving cells were counted under a microscope.

**Clonogenic assay.** Colonies were isolated after G418 selection and **RASSF1A** expression was confirmed by reverse transcription-PCR (RT-PCR).

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**Figure 3.** **RASSF1A** inhibits the JNK pathway in various cell lines. 
A, MRC-5, BEAS-2B, and MCF-7 cells transiently transfected with **RASSF1A** or the empty vector were harvested after 48 hours and analyzed for the expressions of the indicated proteins by Western blotting. B, for growth curves, cells were transiently transfected with **RASSF1A** or empty vector, harvested, and seeded in six-well plates. Cell numbers were determined by trypan blue exclusion at 24, 48, and 72 hours. C, the expressions of **RASSF1A** and phospho-JNK were analyzed by Western blotting in MCF-7 cells stably transfected with **RASSF1A** or empty vector. β-actin was used as an internal loading control. D, MCF-7 cells stably transfected with **RASSF1A** or empty vector were seeded in a six-well plate at 2 × 10⁴ cells/well. Cell numbers were determined by trypan blue exclusion at 24, 48, and 72 hours.
Cells stably expressing RASSF1A were seeded at 1,000 cells/60 mm plate. After G418 (800 μg/mL) selection, as colonies became visible, they were fixed with methanol for 15 minutes and then washed in PBS. The colonies were then stained with 0.1% crystal violet for 1 hour, rinsed with water, and finally counted using a Gel Doc colony counter image analyzer (Bio-Rad, Hercules, CA).

Reverse transcription-PCR assay. Total cellular RNA was isolated using TriReagent-RNA isolation reagent (Life Technologies, Inc., Gaithersburg, MD) according to the manufacturer's instructions. Aliquots of total RNA (1 μg) were used to produce cDNA using Moloney murine leukemia virus reverse transcriptase (Life Technologies) and Oligo-(dT)$_15$ primer (Roche, Indianapolis, IN) in a final volume of 20 μL. The cDNA products (1 μL) so obtained were used for the PCR amplification of RASSF1A and β-actin. The sense and antisense primers used for RASSF1A were 5'-TCT GGG GCG TGC GCA AA-3' and 5'-GAA CCT TGA AGC CTG TG-3', respectively, and the amplified PCR product was a 486 bp DNA fragment. PCR conditions were 95°C for 5 minutes, 30 amplification cycles (95°C for 30 seconds, 72°C for 1 minute), and a final extension at 72°C for 5 minutes. The PCR products from each sample were subjected to electrophoresis in 2% agarose gels, stained with ethidium bromide, and photographed.

Small interfering RNA assay. The double-stranded small interfering RNA (siRNA) oligonucleotide used for targeting RASSF1A was synthesized by Ambion, Inc. (Austin, TX). The sequences used have been published previously (8): sense 5'-GACCUCUGGCGACUUCAATT-3' and antisense 5'-UGAAUGCGCCACAGGUCC-3'. H1299 cells were plated onto six-well cell culture plates in normal growth medium and grown to 70% confluence. After 24 hours, 10 g siRNA were added in 1 mL serum-free, antibiotic-free RPMI 1640 (Life Technologies).

Cell cycle analysis. Cell cycle distributions were determined by the flow cytometric analysis of propidium iodide–labeled cells. Cells were seeded at 5 × 10$^3$ cells/60 mm plate. After 48 hours, the cells were collected, fixed in 70% ethanol, and stored at −20°C. They were then washed twice with ice-cold PBS and incubated with RNAse and propidium iodide. Cell cycle analysis was done by FACScan flow cytometry (BD Biosciences, San Jose, CA).

Western blot analysis. Total cell lysates (50 μg) were resolved on 12% SDS-PAGE gel and then transferred onto nitrocellulose membranes (Amersham Pharmacia Biotech, Little Chalfont, United Kingdom). Membranes were blocked using 5% nonfat milk/TBS for 60 minutes and incubated overnight at 4°C with each primary antibody (1:500). After washing, membranes were incubated for 1 hour with a peroxidase-labeled secondary antibody (1:5,000; Amersham Pharmacia Biotech) at room temperature. After rewashing, bands were visualized using a peroxidase-linked enhanced chemiluminescence detection system (Amersham Pharmacia Biotech). All experiments were repeated in triplicate.

In vitro kinase assay. Kinase assays were done using a SAPK/JNK Kinase Assay kit (Upstate Biotechnology, Lake Placid, NY) according to the manufacturer's instructions. Briefly, cells (1 × 10$^6$) that had been maintained in RPMI 1640 containing 0.5% FBS for 24 hours were treated with SP600125, PD98059, or rapamycin for 48 hours. They were then washed twice with ice-cold PBS and the collected cells were lysed with 10 μL of dilution buffer containing 20 mmol/L MOPS (pH 7.2), 25 mmol/L β-glycerophosphate, 5 mmol/L EGTA, 1 mmol/L sodium orthovanadate, 1 mmol/L DTT, and protease inhibitors (100 μg/mL phenylmethylsulfonyl fluoride, 1 μg/mL aprotinin, and 1 μg/mL leupeptin). The reaction was done at 30°C for 30 minutes in 20 μL kinase reaction buffer containing diluted [γ-32P]ATP (10 μCi/10 μL), cell lysates, and 1 μg glutathione S-transferase (GST)-c-Jun or bovine serum albumin (BSA; Sigma Chemical, Co., St. Louis, MO). After incubating the mixture, the reaction was terminated by adding an equal volume of 4 × SDS sample buffer, and this was then heated at 95°C for 5 minutes and then resolved by SDS-PAGE. Separated proteins were transferred to nitrocellulose membranes and radioactivity incorporated into GST-c-Jun or BSA was visualized by autoradiography at 41 kDa. Membranes were then stripped and reprobed for immunoblot analysis with antibodies to pan-c-Jun or β-actin to determine the amounts of labeled c-Jun.

Results

Exogenous expression of RASSF1A blocks the c-Jun-NH$_2$-kinase pathway. It has been reported that the introduction of RASSF1A into H1299 lung carcinoma cells induces cell cycle arrest at the G1 phase (8). However, the signal pathway causing this cell cycle arrest is not yet fully understood. To identify the pathway upstream of RASSF1A-induced Cyclin D1 down-regulation, we transfected H1299 cells with RASSF1A and, then, we did Western blot analysis. As shown in Fig. 1A, RASSF1A was efficiently expressed in H1299 cells transiently transfected with RASSF1A. It is interesting that phosphorylated JNK was down-regulated in the H1299 cells (Fig. 1B). The downstream mediators of JNK were also examined by Western blot analysis. As shown in Fig. 1B, the exogenous expression of RASSF1A inhibited the phosphorylation of c-Jun and reduced the
expression of Cyclin D1. This result is consistent with a previous report, which showed that the exogenous expression of RASSF1A down-regulated the expression of Cyclin D1 (8). To examine the same effect as was observed in the cells transiently transfected with RASSF1A, we made stable transfectant cells expressing RASSF1A and confirmed the expression of RASSF1A by Western blot analysis (Fig. 2A). These cells showed a marked reduction in colony formation compared with control vector–transfected cells (Fig. 2B). As mentioned above, a previous report showed that the exogenous expression of RASSF1A induces cell cycle arrest at the G1 phase (8). Figure 2C also shows that RASSF1A overexpression induced cell cycle arrest at the G1 phase in the same cell line. To confirm that the ectopic expression of RASSF1A inhibits JNK phosphorylation, Western blot analysis was done on cells ectopically expressing RASSF1A. JNK phosphorylation was inhibited in cells stably expressing RASSF1A, and the phosphorylation inhibition of JNK substrates, such as c-Jun and ATF-2, was then accompanied (Fig. 2D). We also observed that Cyclin D1 was down-regulated in cells stably expressing RASSF1A. In addition, the inhibition of JNK phosphorylation by RASSF1A was examined in multiple cell lines. First, we used Western blot analysis with anti-phospho-JNK antibody to examine phospho-JNK expression levels in two selected nontumorigenic cell lines (MRC-5 and BEAS-2B) and one tumorigenic cell line (MCF-7), in all of which the ectopic expression of RASSF1A inhibited JNK phosphorylation (Fig. 3A). Next, we examined whether RASSF1A expression inhibits cell growth in these three cell lines; we found that the introduction of RASSF1A into these cell lines induced growth inhibition (Fig. 3B). To examine the same effect in stably transfected cells, MCF-7 cells were transfected with RASSF1A, treated with G418, and the clones were pooled. RASSF1A expression and reduced JNK phosphorylation were observed in

![Figure 2A](image)

![Figure 2B](image)

![Figure 2C](image)

![Figure 2D](image)

**Figure 2.** The restoration of RASSF1A expression by 5-Aza-dC treatment reduces the phosphorylation of JNK. A, RASSF1A expression was analyzed by RT-PCR in various cancer cell lines. B, the restoration of RASSF1A expression by 5-Aza-dC treatment was analyzed by RT-PCR in MCF-7, H1299, and A549 cells. Cells were treated with the indicated concentrations of 5-Aza-dC for 48 hours. BEAS-2B cells were used as a positive control (Con) and β-actin was used as an internal loading control. Columns, restoration of RASSF1A expression. Average band densities were measured in a Gel Doc image analyzer (Bio-Rad) by using Quantity One software. RASSF1A expression densities were normalized versus β-actin levels. C, reduced phosphorylation of JNK by 5-Aza-dC treatment was analyzed by Western blotting in cancer cell lines. β-actin and pan-JNK were used as an internal loading controls.
the stably transfected MCF-7 cells by Western blot analysis (Fig. 3C). These cells showed markedly inhibited cell growth compared with the control vector (Fig. 3D).

To further examine the inhibition of JNK phosphorylation by RASSF1A, we did an in vitro kinase assay using GST-c-Jun as substrate for JNK. Consistent with the results shown in Figs. 1 and 2, which show a high level of phosphorylated JNK expression, JNK kinase activity was highly retained in H1299 cells (Fig. 4). Treatment with SP600125, a specific JNK inhibitor (24), blocked GST-c-Jun phosphorylation. However, the MAP/extracellular signal-regulated kinase (ERK) kinase inhibitor PD98059 did not inhibit JNK activity and neither did the mTOR inhibitor rapamycin, which inhibits the phosphorylation and activation of p70S6K. In agreement with the Western blot analysis results, an in vitro kinase assay showed that JNK activity in cells stably expressing RASSF1A was markedly reduced as was observed for cells treated with SP600125 (Fig. 4).

Restoration of RASSF1A by 5-aza-2'-deoxycytidine inhibits c-Jun-NH2-kinase activity. It has been reported that RASSF1A is epigenetically inactivated in various cell lines (5). Consistent with these reports, RASSF1A was not expressed in H1299, MCF-7, or A549 cell lines, whereas RASSF1A expression was detected in BEAS-2B, SNU638, and HeLa cell lines by RT-PCR (Fig. 5A). RASSF1A expression was also observed in H1299 cells transiently transfected with the RASSF1A gene. We next examined whether RASSF1A expression suppressed by aberrant methylation could be recovered by treating with 5-aza-2'-deoxycytidine (5-Aza-dC), an inhibitor of DNA methylation. Three cell lines (H1299, MCF-7, and A549) were treated with 5-Aza-dC for 48 hours at various concentrations and RASSF1A expression was analyzed by RT-PCR. As expected, its expression was restored in 5-Aza-dC–treated cells (Fig. 5B). We next examined whether the restoration of RASSF1A expression by 5-Aza-dC treatment inhibited JNK activity. Cell lysates were prepared from cells treated with 5-Aza-dC and then subjected to Western blot analysis. The phosphorylation of JNK was reduced in H1299 and MCF-7 cells treated with the high concentration (10 μmol/L) of 5-Aza-dC (Fig. 5C). However, A549 cells showed no reduction in JNK phosphorylation by 5-Aza-dC treatment because the endogenous level of phosphorylated JNK in A549 cells was low.

RASSF1A inhibits cell growth via the c-Jun-NH2-kinase pathway. To identify if reduced JNK activity by RASSF1A inhibits cell growth, we blocked the JNK pathway by introducing JNKDD into H1299 cells and we then did a colony formation assay; p53 was used as a positive control. Cells transfected with p53 showed a reduction in colony formation of >90% (Fig. 6A). Similarly, cells transfected with RASSF1A showed a reduction in colony-forming activity of 40%. It was previously reported that JNKDD-expressing NCI-H82 cells show no colony formation in low-serum medium but not in complete medium (19). It is interesting that the ability of JNKDD-expressing cells to colonize was completely abolished in complete medium. Growth inhibition by JNKDD expression was also examined. H1299 cells were transfected with JNKDD, treated with G418 (to eliminate untransfected cells), and surviving cells were counted. Consistent with the results of the colony formation assay, JNKDD expression was found to inhibit cell growth (Fig. 6B). The downstream mediator of JNKDD was also examined by Western blot analysis. As shown in Fig. 6C, the exogenous expression of JNKDD inhibited the phosphorylation of c-Jun. These results show that RASSF1A-inhibited JNK phosphorylation induces H1299 growth inhibition.

Inhibition of RASSF1A expression revives c-Jun-NH2-kinase phosphorylation. We used siRNA to inhibit RASSF1A expression as previously reported (8). Transient transfection of RASSF1A siRNA into BEAS-2B or RASSF1A-overexpressing H1299 cells efficiently down-regulated RASSF1A expression (Fig. 7A). We
then examined whether the siRNA-mediated blocking of RASSF1A expression could release this cell cycle arrest at the G1 phase in cells stably expressing RASSF1A. As shown in Fig. 7B, flow cytometric analysis showed that RASSF1A expression induced cell cycle arrest at the G1 phase and that siRNA treatment released cells from RASSF1A-induced cell cycle arrest. We also tested whether the siRNA-mediated blocking of RASSF1A expression enhanced JNK activity in BEAS-2B and RASSF1A-overexpressing H1299 cells. Western blot analysis showed that siRNA treatment enhanced the phosphorylation of JNK in both cell lines (Fig. 8A). In particular, JNK phosphorylation in RASSF1A-overexpressing cells was more evidently enhanced than in BEAS-2B cells. In addition, an in vitro kinase assay was done on these cell lines. As shown in Fig. 8B, the siRNA-mediated blocking of RASSF1A expression enhanced JNK activity in both cell lines. Taken together, these results show that RASSF1A suppressed the JNK pathway and inhibited the cell cycle progression of lung cancer cells.

**Discussion**

RASSF1A is inactivated in many human cancers. Although the LOH and epigenetic inactivation of the RASSF1A promoter has been reported to cause a loss of gene expression in tumor and cancer cell lines, the precise mechanism by which RASSF1A functions as a tumor suppressor is not fully understood. RASSF1A contains a RAS association domain and is a known Ras effector. RASSF1A has also been shown to heterodimerize with Nore 1 (25). Although many investigators have been interested in the role of RASSF1A in the Ras downstream pathway, more efforts have been focused on elucidating the precise mechanism of RASSF1A. A recent study found that the exogenous expression of RASSF1A induced cell cycle arrest at the G1 phase by down-regulating Cyclin D1 (8). In agreement with this report, we also observed that the ectopic expression of RASSF1A blocked G1-S transition in the same cell line. In the next experiment, we investigated the MAPK signaling pathway as a downstream mediator of RASSF1A. We first examined the effect of RASSF1A on the ERK and p38 MAPK pathways. No change in their activations was observed in cells transfected with RASSF1A. It has been reported that oncogenic RAS phosphorylates and activates the JNK pathway (26), and that activated JNK induces target genes, which include Cyclin D1 (27, 28). Currently, the contribution of RASSF1A to the Ras-JNK pathway is unknown. In particular, the signaling mechanisms by which RASSF1A inhibits the proliferation of lung cancer cells by G1 phase arrest are poorly understood. Here we show that RASSF1A reduces the phosphorylation of JNK and then inhibits cell growth. We found that the exogenous expression of RASSF1A in H1299 cells, in which RASSF1A expression was not previously detectable, resulted in growth inhibition and a reduction in phosphorylated JNK. We also confirmed, by performing an in vitro kinase assay, that RASSF1A inhibits the phosphorylation of JNK. RNA interference–mediated blocking of RASSF1A expression in RASSF1A-expressing cells was found to revive JNK activity. Based on these results, we suggest that JNK plays a...
The role of JNK in oncogenic transformation has been suggested by several investigators. The activation of the JNK pathway is required for transformation by such oncogenes as the Bcr-Abl leukemia oncogene and the Met oncogene (14, 29). Oncogenic Ras has also been reported to stimulate JNK activation (19) and it was shown that the JNK pathway (JNK/c-Jun/activator protein-1) is essential for lung cancer cell transformation. In the present study, a high level of JNK phosphorylation was detected in H1299 cells, and the introduction of RASSF1A into these cells reduced the JNK phosphorylation level and caused growth inhibition. To show that RASSF1A-induced growth inhibition is mediated by the reduced phosphorylation of JNK, we transfected JNKDD into H1299 cells and then did a colony formation assay. As shown in Fig. 6A, when the cells were transfected with JNKDD, no colonies were formed. This result is consistent with previous results presented by Xiao and Lang (19). Thus, it seems reasonable to presume that JNK is activated during H1299 cell transformation and that this activation is essential for cell survival.

Taken together, although many efforts have been made to elucidate the role of RASSF1A as a tumor suppressor, the precise mechanism by which RASSF1A functions as the tumor suppressor remains to be elucidated. The present study shows that RASSF1A inhibits JNK activity and that this results in lung cancer cell growth inhibition. Based on the results of the present study, we suggest that the tumor-suppressing activities of RASSF1A stem from its suppression of JNK activation. Thus, this activity may play an important role in preventing the malignant transformation of normal lung cells.

References

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