RASSF1A Interacts with Microtubule-Associated Proteins and Modulates Microtubule Dynamics

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ABSTRACT

The candidate tumor suppressor gene RASSF1A is inactivated in many types of adult and childhood cancers. However, the mechanisms by which RASSF1A exerts its tumor suppressive functions have yet to be elucidated. To this end, we performed a yeast two-hybrid screen to identify novel RASSF1A-interacting proteins in a human brain cDNA library. Seventy percent of interacting clones had homology to microtubule-associated proteins, including MAP1B and VCY2IP1/C19ORF5. RASSF1A association with MAP1B and VCY2IP1/C19ORF5 was subsequently confirmed in mammalian cell lines. This suggested that RASSF1A may exert its tumor-suppressive functions through interaction with the microtubules. We demonstrate that RASSF1A associates with the microtubules, causing them to exist as hyperstabilized circular bundles. We found that two naturally occurring tumor-associated missense substitutions in the RASSF1A coding region, C65R and R257Q, perturb the association of RASSF1A with the microtubules. The C65R and R257Q in addition to VCY2IP1/C19ORF5 showed reduced ability to induce microtubule acetylation and were unable to protect the microtubules against the depolymerizing action of nocodazole. In addition, wild-type RASSF1A but not the C65R or the R257Q is able to block DNA synthesis. Our data identify a role for RASSF1A in the regulation of microtubules and cell cycle dynamics that could be part of the mechanism(s) by which RASSF1A exerts its growth inhibition on cancer cells.

INTRODUCTION

Loss of RASSF1A expression is one of the most common events in human cancers. Frequent epigenetic inactivation of RASSF1A promoter region has been detected in many common human tumors, including small cell lung cancer, non-small cell lung cancer, and breast and kidney cancers (Refs. 1–5; reviewed in Ref. 6). In addition to its common inactivation, overexpression of RASSF1A in lung (1, 3), kidney (4), and prostate (7) cancer cell lines causes drastic reduction of tumorigenicity both in vitro and in vivo. RASSF1A is the major and longest splice variant coded for by the RASSF1 locus at 3p21.3. The RASSF1A protein contains two putative functional domains. A diacylglycerol binding domain exists at the NH2 terminus, whereas a ras-association (RA) domain is found at the COOH terminus. RASSF1A interacts only weakly with Ras despite containing a RAS-ras-association (RA) domain is found at the COOH terminus. We recently showed that RASSF1A also interacts with p120CAIF (10), a negative modulator of cyclin A expression (11), and more recently, Liu et al. (12) showed RASSF1A to be a microtubule-associated protein able to protect microtubules from the effects of depolymerizing drugs.

Loss of RASSF1A expression is largely attributed to promoter hypermethylation because an exhaustive search for mutations yielded only rare missense substitutions. The significance of many of these missense changes in tumorigenesis have yet to be determined. Recently, Shivakumar et al. (13) showed that RASSF1A, but not RASSF1A mutants A133S or S131F, induce cell cycle arrest by blocking cyclin D1 accumulation. Hence, naturally occurring tumor-associated variants can provide useful tools for the understanding of gene function.

In this study, we provide yeast two-hybrid and colocalization data to support the role of RASSF1A as a microtubule-associated protein. We identify two tumor-associated RASSF1A mutants, which show reduced association with the microtubules. Using these reagents, we provide data that highlight the importance of microtubule association for RASSF1A function in regulating microtubule stability and cell cycle progression.

MATERIALS AND METHODS

Cell Lines and Transfections. The non-small cell lung cancer cell lines NCI-H1299 and NCI-H1437, the green monkey kidney line COS-7, and the neuroblastoma cell line SK-N-AS were routinely maintained in DMEM supplemented with 10% fetal bovine serum (Invitrogen). Transfection was performed using FuGene 6 (Roche) according to the manufacturer’s instructions.

Plasmids and Antibodies. The bait plasmid pGBKKT7-RASSF1A and pGEX-IT1-RASSF1A were constructed by restriction digest of full-length RASSF1A from pcDNA3.1 using EcoRI and cloned in frame into yeast vector pGBKKT7 (BD Clontech) and the glutathione S-transferase expression vector pGEX-IT1, respectively (Amersham Pharmacia Biotech). pcDNA3HA/RASSF1A contains the complete coding region of RASSF1A as a BamHI-Xho1 fragment in pcDNA3HA. The RASSF1A mutant variants K21Q, C65R, S131F, A133F, R201H, V211A, R257Q, Y325C, and A336T were created by PCR-based site-directed mutagenesis using pcDNA3HA/RASSF1A as a template. pEGFP-C2-RASSF1A contains the coding region of RASSF1A as an EcoRI fragment. The complete coding region of VCY2IP1/C19ORF5 was cloned in frame of the HA- and GFP- in pcDNA3 and pEGFP-C2, respectively. Rabbit polyclonal anti-hemagglutinin (HA) antibody (Y-11) was from Santa Cruz Biotechnology. Mouse monoclonal Anti-myc antibody was from Clonetech. Goat polyclonal anti-MAP1B (N-10) antibody was from Santa Cruz Biotechnology. Mouse monoclonal antibodies against α-tubulin (DM1A), β-tubulin (TUB 2.1), and acetyl-α-tubulin (6-11B-1) and anti-HA (HA-7) were from Sigma. Mouse monoclonal anti-RASSF1A antibody (ebi14) was from ebiosciences. HRP-conjugated Rabbit antimouse IgG and HRP-conjugated goat antirabbit IgG secondary antibodies were purchased from DAKOcyto- mation. Alexafluor-488-conjugated goat antirabbit IgG and Alexafluor-594 conjugated rabbit antimmune IgG were purchased from Molecular Probes.

Yeast Two-Hybrid Screen. Yeast two-hybrid screening was performed as described previously (10) Briefly, the bait vector pGBKKT7-RASSF1A was transformed in yeast strain Saccharomyces cerevisiae AH109 (RASSF1A-BD) using the Lithium Acetate/Polyethylene glycol method and selected on Trp plates. Strain AH109 includes four reporter genes ADE2, HIS3, lacZ, and...
MEL18 whose expression is regulated by GAL4 responsive upstream activating sequences and promoter elements. The bait RASSF1A-BD was then used to screen a pretransformed MATCHMAKER brain library cloned in pACT2 and introduced into yeast strain S. cerevisiae Y187. A total of 6 × 10^6 colonies were screened, of which 103 were positive for α-galactosidase expression and turned blue. Clones were rescued and retransformed into yeast to reconfirm positive interactions. Positive clones were sequenced using automated DNA sequence analysis (ABI) and homologies identified using National Center for Biotechnology Information BLASTN/BLASTX.

**Immunoprecipitation and Western Blot Analysis.** Generation of the glutathione S-transferase-RASSF1A and the in vitro-translated HA-VCY2IP1/C19ORF5 and myc-RASSF1A was performed as described previously (10). The translated/tagged protein products were mixed and immunoprecipitated using anti-HA antibody and protein G/A agarose beads. The protein complexes were then solubilized by addition of 15 μl of 2× SDS sample buffer and denatured before loading onto a 7.5–14% SDS-PAGE minigel. Western blotting was performed according to standard procedures. Membranes were then probed with the antibodies indicated.

**Microtubule Cosedimentation Assay.** The microtubules cosedimentation assay was done as described previously (14). Cells were washed with ice-cold PBS, scraped into 1 ml of PBS, and collected by centrifugation. The cells were resuspended in 60 μl of precleared cell supernatant and incubated for 30 min at 37°C. Samples were then centrifuged for 30 min at 20,000 × g and HA-RASSF1A content was analyzed by SDS-PAGE (L/H11003).

**Immunofluorescence.** Exponentially growing NCI-H1299 cells were plated on coverslips and transfected the next day with indicated constructs using Fugene 6 as described by the manufacturer. After 48 h of transfection, cells were fixed in 4% paraformaldehyde, permeabilized in acetone at −20°C for 5 min, and then treated with 2 μl HCl for 10 min. BrdU incorporation was visualized with mouse monoclonal anti-BrdU antibody and alexafluor-594 secondary antibody. HA-RASSF1A-expressing cells were visualized with anti-HA antibody and alexafluor-488-conjugated secondary antibody.

**Statistical Analysis.** Comparisons were made by Fisher’s exact test or t test when appropriate. Ps of <0.05 were taken as statistically significant.

**RESULTS**

**RASSF1A Interacts with Microtubules-Associated Proteins Both in Vitro and in Vivo.** We performed yeast two-hybrid screen to identify proteins that interact with RASSF1A. Approximately 6 × 10^6 independent transformations were screened, of which 103 clones were positive for α-galactosidase expression. After excluding clones that contained genomic repeats, we found 58 independent clones that included known and novel genes that were able to interact with RASSF1A in the yeast two-hybrid system. Thirty-two clones were homologous to the VCY21 (also known as C190RF5, NP_060644) gene, which has high overall similarity with MAP1A and MAP1B. The NH2 terminus of VCY21 (residues 3–564 aa, NP_060644) has 58% similarity with the NH2 terminus of MAP1B (residues 16–650 aa, NP_005900). The COOH terminus of VCY21 (residues 649–848 aa, NP_060644) has a 42% similarity with the COOH terminus of MAP1B (residues 2009–2225 aa, NP_005900). Similarly, the NH2 terminus of VCY21 (residues 205–544 aa, NP_060644) has 57% similarity with the NH2 terminus of MAP1A (residues 2–390 aa, 101 60644).

Fig. 1. RASSF1A interacts with microtubule-associated proteins. A, endogenously expressed MAP1B was pulled down by glutathione S-transferase-RASSF1A (GST-RASSF1A)-coated Sepharose beads from SK-N-AS cell lysates. Extracts were resolved by SDS-PAGE, and MAP1B was visualized using anti-MAP1B (N-10) antibody after Western blotting (WB). B, RASSF1A is associated with MAP1B in SK-N-AS cells. pDNA3-HA and pDNA3-HA-RASSF1A were transiently transfected into SK-N-AS cells. Recombinant proteins were immunoprecipitated (IP) using anti-hemagglutinin (HA) antibody (Y-11), and bound MAP1B was visualized as above. C, Myc-RASSF1A interacts with HA-VCY21 (C190RF5 clone37D in vitro. Anti-Myc antibody (Clontech) was used to IP Myc-RASSF1A from a mixture of in vitro-generated Myc-RASSF1A and HA-VCY21/190RF5 clone37D. The IP was resolved by SDS-PAGE, and bound HA-VCY21/C190RF5 clone37D was visualized with anti-HA antibody. Input proteins are shown and Myc-Lamda (Lam) was used for control. D, exogenously overexpressed RASSF1A and HA-VCY21/C190RF5 associate in COS-7 cells. HA-VCY21/C190RF5 was immunoprecipitated with anti-HA antibody from extracts of COS-7 cells cotransfected with RASSF1A and HA-VCY21/C190RF5. RASSF1A was detected using the eb114 antibody (E Bioscience). E, HA-RASSF1A expressed in COS-7 cells coexpressed with in vitro-polymerized tubulin. Protein extracts from COS-7 cells transfected with HA-RASSF1A were incubated with 50 μg of tubulin polymerized in vitro in the presence or absence of 50 μM Taxol. The mixture was spun down, fractionated into a supernatant (S) and pellet (P), and HA-RASSF1A content was analyzed by SDS-PAGE (L = 10 μl of lysate).
NP_002364). The COOH terminus of VCY2IP1/C19ORF5 (residues 566–860 aa, NP_002364) has a 36% similarity with the COOH terminus of MAP1A (residues 2234–2597 aa, NP_002364). We also identified 9 independent clones that contained the MAP1B gene. In total, there were 41 RASSF1A-interacting clones that were microtubule-associated proteins. In contrast, we identified only 10 clones for MST1 and MST2 that already have been shown to interact with RASSF1A. The interaction between RASSF1A and MAP1B was confirmed in vitro, using glutathione S-transferase-RASSF1A fusion protein and extracts from the neuroblastoma cell line SK-N-AS. As shown in Fig. 1A, glutathione S-transferase-RASSF1A bound efficiently to MAP1B from SK-N-AS cell lysates. The interaction was additionally confirmed in SK-N-AS cells transiently transfected with HA-RASSF1A; Fig. 1B shows that exogenously overexpressed HA-RASSF1A immunoprecipitated with endogenously expressed MAP1B.

We confirmed the interaction of VCY2IP1/C19ORF5 with RASSF1A in vitro using sequences from one of the positively interacting clones, clone 37D, that contained the COOH terminus 2.5 kb of the 3.183 kb of the complete coding region of VCY2IP1/C19ORF5 (Fig. 1C). The interaction was additionally confirmed by immunoprecipitation of HA-VCY2IP1/C19ORF5 and probing with anti-RASSF1A antibody (eb114) from cotransfected COS-7 cells (Fig. 1D). This data are supported by immunofluorescence staining that showed HA-RASSF1A and GFP-VCY2IP1/C19ORF5 colocalize in NCI-H1299 cells (Fig. 2A).

**RASSF1A Colocalizes with Microtubules and Promote Their Stability.** The high frequency with which microtubule-associated proteins were identified by the yeast two-hybrid screen suggested RASSF1A localized to the microtubules. This was confirmed by immunofluorescence staining in several cell lines transfected with HA-RASSF1A (NCI-H1299, A549, MCF7, and COS-7). Fig. 2, B and D, shows that HA-RASSF1A colocalized with β-tubulin and α-tubulin, respectively, in NCI-H1299 cells and all other cell lines studied (data not shown). Furthermore, overexpression of RASSF1A appeared to rearrange the microtubules into either circular or bundled perinuclear rings, whereas the untransfected cells show the microtubules radiating from a microtubule-organizing center located at the centrosome. This phenotype is consistent with microtubule staining in cell lines with or without endogenous RASSF1A expression (Fig. 2C). RASSF1A-negative cell lines (NCI-H1299, A549, and MCF7) displayed unbundled microtubules radiating from 

![Figure 2](image_url)

**Fig. 2.** RASSF1A associates with tubulin and VCY2IP1/C19ORF5 and promotes microtubule stabilization. A, RASSF1A (HA-RASSF1A) colocalized with VCY2IP1/C19ORF5 (HA-C19ORF5). NCI-H1299 cells were transfected with green fluorescent protein-VCY2IP1/C19ORF5 (GFP-C19ORF5) and HA-RASSF1A. HA-RASSF1A was visualized using anti-HA (HA7; Sigma) antibody (red), GFP-VCY2IP1/C19ORF5 (green), and 4,6-diamidino-2-phenylindole (DAPI) counterstained (blue). B, RASSF1A colocalized with β-tubulin. NCI-H1437 non-small cell lung cancer cells were transfected with HA-RASSF1A, which was visualized using anti-HA (Y11) antibody (green), and β-tubulin was stained with TUB2.1 antibody (Sigma). C, NCI-H1437 cell line with endogenous RASSF1A expression and NCI-H1299 (RASSF1A−/−) were grown on coverslips and stained for β-tubulin as above. The magnified images shows the differences in the microtubules orientation and structure in both lines. D, wild-type RASSF1A protects microtubules from drug-induced depolymerization. NCI-H1299 cells were transfected with the indicated constructs (see "Materials and Methods"). Forty-eight h after transfection, cells were treated with 10 μM nocodazole or vehicle for 1 h. α-Tubulin was visualized with DM1A antibody (red), and transfected proteins were stained green. E, wild-type RASSF1A is associated with acetylated α-tubulin. NCI-H1299 cells were transfected with the indicated constructs and stained as before. Acetylated α-tubulin was visualized using 6-11B-1 antibody (red).
from the microtubule-organizing center. RASSF1A-positive cell lines (NCI-H1437, NCI-H1792, and HeLa) display a more bundled and circular microtubules. Similar phenotype was observed when pEGFP-RASSF1A was used instead of HA-RASSF1A (data not shown). The interaction with the microtubules was confirmed in vitro using a microtubule cosedimentation assay with extracts of HA-RASSF1A expressing COS-7 cells. Fig. 1E shows RASSF1A cosedimented with in vitro polymerized microtubules.

**Mutant Forms of RASSF1A Show Loss of Microtubule Association.** We compared the subcellular localization of wild-type HA-RASSF1A with nine naturally occurring tumor-associated variant forms of the protein. All variants of RASSF1A showed similar levels of expression in COS-7 cells (Fig. 3A). However, with all mutants, aberrant localization of RASSF1A was observed (Figs. 2D and 3B). Variants C65R and R257Q showed the most drastic change in the subcellular localization of RASSF1A. The majority of cells expressing HA-tagged C65R and R257Q variants showed atypical localization of RASSF1A, where it existed in the nucleus or in other undefined cytoplasmic compartments.

**Loss of Microtubule-Association Correlated with Loss of Microtubule Stability.** Fig. 2D shows that the wild-type HA-RASSF1A protected the microtubules against depolymerization induced by treating NCI-H1299 cells with 10 μM nocodazole for 1 h. The same effect was seen in MCF7 or when pEGFP-RASSF1A was used (data not shown). Examination of the RASSF1A variants showed that the C65R and R257Q were not able to protect the microtubules against depolymerization when RASSF1A localized to the nucleus (Fig. 2D). In general, the microtubules were protected against nocodazole-induced depolymerization whenever wild-type RASSF1A or any of the variants colocalized with the microtubules.

**RASSF1A-Induced Acetylation of Microtubules.** Acetylation of α-tubulin is a marker for increased microtubules stability. Cells transfected with wild-type HA-RASSF1A expressed high levels of acetylated α-tubulin (Fig. 2E). However, this phenotype was lost or greatly reduced in cells expressing C65R and R257Q variants (Fig. 2E).

**VCY2IP1/C19ORF5 Does Not Stabilize Microtubules.** Because HA-VCY2IP1/C19ORF5 appeared to colocalize with RASSF1A, its ability to stabilize microtubules was examined. However, unlike wild-type RASSF1A, VCY2IP1/C19ORF5 did not cause the microtubules to exist in circular bundles and was not able to protect the microtubules from nocodazole-induced depolymerization. In addition, VCY2IP1/C19ORF5 was not able to induce the acetylation of α-tubulin (Fig. 2, D and E).

**Loss of RASSF1A Association with the Microtubules Affects Its Ability to Delay the Cell Cycle.** We used BrdU incorporation assay to compare the ability of wild-type RASSF1A and variants C65R/R257Q to stop DNA synthesis in NCI-H1299 cells (Table 1). Wild-type RASSF1A caused a significant decrease in BrdU incorporation compared with the mutant variants (P < 0.001). Wild-type RASSF1A blocked BrdU incorporation in at least 77 ± 3.00% of cells, whereas variants C65R and R257Q blocked BrdU incorporation in only 54.66 ± 2.08 and 29.66 ± 4.04% of cells, respectively.

**DISCUSSION**

The data presented in this study support previous studies, suggesting that the RASSF1A tumor suppressor is a microtubule-associated protein. We used a yeast two-hybrid screen to show that RASSF1A interacts with microtubule-associated proteins, which comprised 70% of the interacting clones. Consistent with these findings, we show that RASSF1A colocalized with α- and β-tubulin in mammalian cell lines, protected microtubules from nocodazole-induced depolymerization, and induced acetylation of α-tubulin. We identified two tumor-associated RASSF1A variants (C65R/R257Q), which have drastically reduced ability to associate with the microtubules. C65R and R257Q variants failed to protect against drug-induced microtubule depolymerization and did not induce acetylation of α-tubulin. Furthermore, unlike wild-type RASSF1A, the mutant forms did not block DNA synthesis. Taken together, these data suggest that association of RASSF1A with the microtubules is central to its function and disruption of this association may promote tumorigenesis.

The interactions between RASSF1 and VCY2IP1/C19ORF5 was previously reported but not confirmed (15). The identification of MAP1B as an RASSF1A-interacting protein is a novel finding. We have confirmed the interaction between RASSF1A and VCY2IP1/C19ORF5 and MAP1B using in vitro-generated proteins and with whole cell lysates. Consistent with these findings, immunofluorescence staining showed RASSF1A colocalized with VCY2IP1/C19ORF5. However, unlike RASSF1A, overexpression of VCY2IP1/C19ORF5 did not protect microtubules from drug-induced depolymerization or induced acetylation of α-tubulin. These findings are consistent with the observed weak association of VCY2IP1/C19ORF5 with the microtubules in the absence of RASSF1A. VCY2IP1/C19ORF5 is an interacting partner for VCY2, a testis-specific protein.
located in the frequently deleted AZFc region on chromosome Yq (16). VCY2 in turn interacts with UBE3A, a ubiquitin-protein ligase E3A (17). Previously, VCY2IP1/C19orf95 has also been shown to interact with LRPPRC, the mitochondrial inner membrane NADH dehydrogenase I and cytochrome c oxidase I (15). MAP1B is the earliest microtubule-associated protein expressed in the developing nervous system (18) and is thought to have roles on axonal transport and neurite outgrowth (19). More recently, MAP1B has been shown to be phosphorylated by glycogen synthase kinase-3β through the TrkA receptor and this correlates tightly with outgrowth of neuritis (20). Similar to RASSF1A, MAP1B is localized to microtubules and protects against depolymerization induced by nocodazole (21). Hence, it is possible that RASSF1A localizes to the microtubules through interaction with MAP1B in neuronal cells or with other microtubule-associated proteins in other cellular backgrounds.

It is suggested that RASSF1A association with the microtubules is required for its ability to induce mitotic arrest in COS-7 similar to the effect caused by the microtubule-polymerizing drug Taxol (12). Using naturally occurring RASSF1A mutants, we argue that the association of RASSF1A with the microtubules is essential for it to mediate its functions. We show that wild-type RASSF1A blocks BrdU incorporation in NCI-H1299 cells. This effect is abrogated by the C65R and R257Q missense changes. These mutants are found in lung, breast, and kidney cancers and have reduced ability to associate fully and efficiently with the microtubules. The C65R variant has been previously shown to affect RASSF1A’s ability to suppress growth of kidney cancer cells (4). The cause(s) for this loss of association is not clear. The C65 codon is a highly conserved residue, and it is part of the consensus sequence of the C1/DAG domain in RASSF1A. The R257Q change is conserved in the RasGTP effector AF-6 protein, the prototype protein for the RAS-association domain. RASSF1A-C65R is predicted to contain a zinc binding domain ZnF-NFX, which according to the Simple Modular Architecture Research Tool (SMART) prediction program3 is found in the human transcriptional repressor NK-X1 found in the nucleus. In addition, the C1/DAG domain prediction becomes less efficient. These changes could also render the RASSF1A amenable to aggregation and misfolding, which eventually results in its inactivation. Similar changes have been found to cause the inactivation of PARKIN, the gene responsible for autosomal recessive Parkinsonism, by sequestration into insoluble aggregates (22).

Acetylation of α-tubulin is an important posttranslational modification process of the microtubules. Acetylation of lysine 40 in α-tubulin can be detected specifically using the antibody 6-11B-1 (23). The acetylation of microtubules is widely regarded as a process associated with stable, less dynamic microtubules. Migratory cells such as the fibroblasts have no acetylated microtubules at their leading edge, a highly dynamic structure devoid of stable microtubules and involved in cell motility (24). This suggests that inhibition of microtubule acetylation could result or at least is associated with increased motility and vise versa. Recently, it has been shown that HDAC6 inhibits the acetylation of microtubules and increases cell motility and migration (25). However, it is not clear whether the increase in cell motility is caused by a decreased level of stable microtubules or by just the reduction in the level of acetylated microtubules (26). Our unpublished data suggest that cells stably transfected with wild-type RASSF1A have reduced motility compared with controls. Microarray expression profiling has shown that genes involved in cell adhesion and motility such as zyxin and CDH2 are significantly up-regulated after expression of RASSF1A in A549, which might indicate a role for RASSF1A in the control of cell migration and adhesion (27).

Overall, the evidence presented here confirms the localization of RASSF1A to the microtubules. Our data suggest that through interaction with the microtubules and microtubule-associated proteins, RASSF1A regulates cell cycle progression and may also modulate cell migration.

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