A Novel eIF5A Complex Functions As a Regulator of p53 and p53-dependent Apoptosis*

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Although eukaryotic translation initiation factor 5A (eIF5A) was originally designated as an “initiation factor,” recent data have shown it to be also involved in apoptosis. However, the actual function of eIF5A in apoptosis is still unknown. In this study, we performed yeast two-hybrid screens to identify eIF5A-interacting proteins to help us understand the mechanisms of eIF5A. Our results demonstrated that eIF5A and syntenin could engage in a specific interaction both in vitro and in vivo and functioned collaborative to regulate p53 activity. Our findings, for the first time, revealed a new biological activity for eIF5A as the regulator of p53. Overexpression of eIF5A or its EFP domain resulted in up-regulation of p53, and silencing eIF5A by small interfering RNA reduced the p53 protein level. Further analysis by reverse transcription PCR showed eIF5A-activated p53 transcription. The effect of eIF5A on p53 transcriptional activity was further demonstrated by the increasing expressions of p21 and Bax, well known target genes of p53. In contrast, a point mutant of eIF5A, hypusination being abolished, was revealed to be functionally defective in p53 up-regulation. Overexpression of eIF5A led to a p53-dependent apoptosis or sensitized cells to induction of apoptosis by chemotherapeutic agents. However, when eIF5A interacted with its novel partner, syntenin, the eIF5A-induced increase in p53 protein level was significantly inhibited. Therefore, eIF5A seems to be a previously unrecognized regulator of p53 that may define a new pathway for p53-dependent apoptosis, and syntenin might regulate p53 by balancing the regulation of eIF5A signaling to p53 for apoptosis.

The putative eukaryotic translation initiation factor 5A (eIF5A) is an intriguing protein, because it is the only cellular protein known to contain the unique amino acid hypusine, a modification that appears to be required for cell proliferation (1–3). The protein was originally described as a translation initiation factor because of its ability to stimulate the synthesis of methionyl-puromycin in vitro and to transiently attach to ribosomes in the course of initiation of eukaryotic cellular protein synthesis (4, 5). It could promote the formation of the first peptide bond during the initial stage of protein synthesis (6). However, the major evidence for the function comes from a nonphysiological in vitro reaction. Actually, depletion of this factor in yeast caused only a small reduction in the protein synthesis rate (7), suggesting that eIF5A did not function for general protein synthesis. eIF5A was further hypothesized to be involved in the translation of a specific subset of mRNAs, for example, those involved in the cell cycle progression (G1/S transition) (1, 8). Expression of eIF5A has been reported to correlate with cell proliferation; an increase in G1-arrested cells was observed after depletion of this factor in yeast (7).

Although eIF5A was originally designated as an “initiation factor,” the recent in vitro and in vivo data have demonstrated that eIF5A is more than an initiator of protein translation. The finding that eIF5A is a cellular cofactor of human immunodeficiency virus type 1, Rev, and HTLV-1 Rex transactivator proteins in mRNA export suggests that it can have additional activities. Moreover, the factor interacts with the general nuclear export receptor CRM1 during their transportation from the nucleus to the cytoplasm (9). The eIF5A protein expression was normally very low but inducible with T lymphocyte-specific stimuli in human peripheral blood mononuclear cells of healthy individuals, and a significant up-regulation of eIF5A mRNA was found in the peripheral blood mononuclear cells of human immunodeficiency virus type 1-infected patients (10). The eIF5A expression is also significantly increased during dendritic cell maturation, and hypusine formation appears to be essential for this process (11). Further, the protein expression is significantly induced, and the hypusine formation activity increased more than 30-fold in Ras-transformed NIH3T3 cells (12). The importance of post-translational modification of eIF5A is evident, because agents blocking the lysine/hypusine transformation inhibit the growth of mammalian cells, inducing reversible arrest at the G1/S boundary of the cell cycle (1) in Chinese hamster ovary cells and apoptosis in tumor cells (13). We recently reported that eIF5A was involved in the apoptosis of tumor cells induced by inhibition of ubiquitin proteasomes (14). These data suggest that eIF5A may be involved in cell growth and apoptosis. However, the actual function of eIF5A in apoptosis is still unknown. In this study, we demonstrated, for the first time, a new biological activity for eIF5A as the regulator of p53 and that eIF5A and syntenin could engage in a specific interaction both in vitro and in vivo and function collaboratively to regulate p53 activity.
eIF5A Regulates p53-dependent Apoptosis

EXPERIMENTAL PROCEDURES

Plasmids, Cell Lines, Transfection, and Antibody—eIF5A and its truncation mutants were prepared by PCR-specific primers and cloned in-frame into the pGBK7 vector and the human syntenin cDNA was isolated from a human mammary cDNA library and cloned into the GAL4 DNA-binding domain. The resultant plasmid and a mammary cDNA for syntenin was then obtained from a mammary library (Clontech Laboratories, Inc.). Eight positive clones of 1.75 million clones were screened, and then we restreaked three positive clones to be syntenin. Full-length syntenin cDNA was then isolated from 10^6 cells by using TRIzol Reagent (15596-026, Invitrogen) according to the manufacturer’s instructions. We used M-MLV Reverse Transcriptase (M1701, Promega) for semiquantitative reverse transcription PCR following the manufacturer’s instructions. We performed PCR amplifications of 20 cycles for glyceraldehyde-3-phosphate dehydrogenase and 30 cycles for a 420-bp fragment of p53, respectively. Primer sequences were 5'-GTC-3 and 3'-CTTCTTTGGCT GGGGAGAGGAG-3' for phosphatase and 5'-AGGCTTATGAC CTGGGAGGGGG-3' for the p53 fragment (GenBank™ accession number X02469).

Analysis of Apoptosis by Flow Cytometry—For flow cytometry, cells were harvested and followed by a washing with phosphate-buffered saline. Cells were fixed in cold ethanol (70%) overnight and stained with 50 μg/ml propidium iodide in phosphate-buffered saline containing 1 mg/ml RNase for 30 min at 4 °C in the dark. Percentages of cells in the different phases of the cycle were measured by flow cytometric analysis of propidium iodide-stained nuclei using CellQuest software (FACSalibur, BD Biosciences). Proportions of apoptotic cells were indicated as a percentage of the sub-G1 fraction in FACS analysis.

RESULTS

Identification of Syntenin as eIF5A-binding Protein—The eIF5A protein comprises two well defined domains, GST (N-terminal) and eIF5A (C-terminal). In the attempt to identify eIF5A-binding proteins that could clarify the role of eIF5A in the cell, we performed a yeast two-hybrid screen using the EFP domain of eIF5A as bait to screen an oligo(dT)-primed human cDNA library. Eight positive clones of yeast transformants were found. Among them, the inserts from three positive clones were identified to be syntenin. Full-length cDNA for syntenin was then obtained from a mammary library, encoding 298 amino acid residues and containing two PDZ domains in tandem. These two PDZ domains span amino acids 113–193 (PDZ1) and 198–273 (PDZ2), respectively. The PDZ domains span amino acids 113–193 (PDZ1) and 198–273 (PDZ2), respectively. With different N-terminal and C-terminal deletions of eIF5A being tested, protein-protein interaction was assayed in yeast transformants grown on media containing 1 mg/ml 3-AT. The yeast transformants were then assayed for interaction with syntenin using FRET assays. In FRET assays, syntenin was expressed in yeast cells by the GAL4 activation domain vector pGADT7 (Clontech Laboratories, Inc.). Syntenin cDNA was ligated into the pDsRed-N1 vectors (Clontech Laboratories, Inc.). Rabbits polyclonal anti-syntenin antibodies were purchased from Cell Signaling Technology, Inc. The anti-syntenin antibodies were used to prepare the GST-syntenin fusion protein (Clontech Laboratories, Inc.). An EFP fused to the Syntenin cDNA was prepared in our laboratory against human eIF5A expressed from p53WT and H1299 (p53-/-) cells. To test if the eIF5A and its domains (EFP, eIF5A, eIF5AkoA, and eIF5AkoD) were cloned into the pXJ40HA mammalian expressing vector. The constructs were sequenced to confirm the correct orientation. For fluorescence resonance energy transfer (FRET) assays, the eIF5A DNA and eIF5AkoA were amplified and ligated into the pEGFP-N1 vectors (Clontech Laboratories, Inc.). Syntenin cDNA was ligated into the pDsRed-N1 vectors (Clontech Laboratories, Inc.).

RESULTS

Identification of Syntenin as eIF5A-binding Protein—The eIF5A protein comprises two well defined domains, GST (N-terminal) and eIF5A (C-terminal). In the attempt to identify eIF5A-binding proteins that could clarify the role of eIF5A in the cell, we performed a yeast two-hybrid screen using the EFP domain of eIF5A as bait to screen an oligo(dT)-primed human cDNA library. Eight positive clones of yeast transformants were found. Among them, the inserts from three positive clones were identified to be syntenin. Full-length cDNA for syntenin was then obtained from a mammary library, encoding 298 amino acid residues and containing two PDZ domains in tandem. These two PDZ domains span amino acids 113–193 (PDZ1) and 198–273 (PDZ2), respectively. With different N-terminal and C-terminal deletions of eIF5A being created (Fig. 1A), the EFP domain was further determined to be essential for the interaction of eIF5A with syntenin in yeast cotransformed with syntenin (in pGADT7) and either eIF5A or its mutants (in pGBK7) and scored for β-galactosidase activity (Fig. 1A).

To further define which domain of eIF5A was required for
the interactions with syntenin, a GST pull-down experiment was performed in vitro. As shown in Fig. 1B, the full-length eIF5A and EFP domain were both specifically associated with syntenin, which is consistent with the results of yeast two-hybrid screens. In contrast, no association was found between other mutations of eIF5A and syntenin or between syntenin and GST protein (Fig. 1B). We also constructed different deletions of syntenin to define the region, which determines the binding behavior of syntenin with respect to eIF5A. Fig. 1C shows that the N-terminal sequence of syntenin was necessary for its interaction with eIF5A.

To further verify the interaction in vivo, we carried out co-immunoprecipitations by transient co-transfection experiments in 293T cells. A lysate of human 293T cells expressing Myc-eIF5A and HA-syntenin was immunoprecipitated with an anti-HA antibody, followed by immunoblotting with an anti-myc antibody. Western blot analysis of equal amounts of cell extracts was also performed in parallel. E, in vivo interaction of eIF5A with syntenin in MDA-MB-435 cells. Cell lysates were immunoprecipitated with anti-eIF5A antibody followed by immunoblotting with anti-eIF5A and anti-syntenin. Control immunoprecipitation was performed with pre-immune serum.

To observe the physical association of eIF5A with syntenin in living cells, we employed the FRET microscopy to visualize it in vivo. The method was described by Xia and Liu (15) to perform a direct pixel-by-pixel analysis in living cells, and it could show FRET intensities with high spatial resolution. The three-filter method was applied in all FRET experiments, and GFP, DsRed (referred to as RFP below), and FRET filter images are used to calculate a NFRET. Fusion protein GR-6, in which GFP and
p53 functions as a transcription factor to regulate target genes involved in apoptosis. To determine the transcriptional activity of the eIF5A-induced p53 protein, the expression of p21, a well-known target gene of p53, was examined. As shown in Fig. 3D, the expression level of p21 was increased in eIF5A-overexpressed cells. We next investigated whether the up-regulated p53 modulated the expression of Bax, Bcl-2, and Mdm2. Bax, a pro-apoptotic member of the Bcl-2 family, expression was low in control cells but was dramatically increased after eIF5A transfection (Fig. 3D). The kinetics of Bax expressions was similar to the expression of p53 (Fig. 3A). Mdm2 expression level also increased after eIF5A transfection (Fig. 3D). In contrast, Bcl-2 expression decreased (Fig. 3D). Thus, up-regulation of p53 induced expression of Bax and Mdm2 but decreased Bcl-2 expression.

To define which domain of eIF5A is required for p53 up-regulation, we constructed two plasmids containing EFP and eif5a domain of eIF5A, respectively. The truncation sites are indicated in the predicted structure for the human eIF5A (Fig. 1A). After transfection, expression of the EFP domain of the eIF5A proteins, with the expected molecular sizes, was confirmed by Western blot using anti-eIF5A and showed to be necessary to regulate p53 expression (Fig. 4A). In contrast, the eif5a domain was not able to induce p53 expression (Fig. 4A).

Furthermore, because the hypusine residue (residue 50) in the EFP domain is essential for eIF5A function, we then assessed whether the modification is essential to the eIF5A-induced up-regulation of p53. As shown in Fig. 4B, the eIF5A mutant, in which lysine 50 was replaced by alanine and hypusination was abolished, was revealed to be functionally defective in up-regulation of p53, whereas the expression level of the mutant form was almost similar to that of the tagged wild type eIF5A. These results, therefore, demonstrated that p53 up-regulation by eIF5A depends on the post-translational modification of eIF5A.

The protein p53 activity is commonly regulated at the transcriptional level and/or through post-translational stabilization that blocks its ubiquitin-dependent degradation by the 26 S proteasome (16, 17). To explore the mechanism leading to the increase in p53 protein level, we tested both possibilities and found that mRNA transcript levels of p53, determined by reverse transcription PCR, were significantly increased in the cells overexpressing eIF5A (Fig. 5A). No significant change in the ubiquitinated p53 level was observed with Western blot approaches by anti-p53 antibodies (data not shown), but Mdm2 expression level increased after eIF5A transfection (Fig. 3D). As the phosphorylation of p53 at multiple sites commonly leads to its stabilization, further analysis was conducted to determine the phosphorylated site(s) of p53 in response to eIF5A overexpression by Western blot analysis using phosphorylation site-specific antibodies. Fig. 5B shows phosphorylation at serine 6 and 392 significantly increased among the phosphorylation sites tested. Taken together, p53 up-regulation by eIF5A expression was mainly associated with transcriptional activation of the p53 gene.

**eIF5A Regulates p53-dependent Apoptosis—**In our experiments, the eIF5A expression through transfection affected p53

[FIG. 2. eIF5A interaction with syntenin in living cells. The interaction of eIF5A with syntenin in living COS-7 cells using FRET analysis by confocal microscopy. A, positive control. The cells expressing GFP-RFP fusion protein showed strong positive signals for protein interaction. B and C, negative control. The cells co-expressing either GFP-eIF5A and RFP or GFP and RFP-syntenin proteins showed no signals for their interactions. D, FRET signal for protein interaction was showed in the cells co-expressing GFP-eIF5A and RFP-syntenin. E, FRET signal for protein interaction was showed in the cells co-expressing GFP-eIF5A<sub>50AA</sub> and RFP-syntenin. Scale bar represents 20 μm. Color scales for FRET intensity are displayed. Red and blue indicate high and low intensity, respectively.

RFP was linked by a 6-amino acid peptide, was prepared as a positive control (Fig. 2A), and co-transfection with GFP and RFP was used as a negative control (data not shown). As a result, we found the NFRET signals in COS-7 cells co-transfected with GFP-eIF5A and RFP-syntenin, indicating the interaction of eIF5A and syntenin in living cells (Fig. 2D). The same result was also observed using GFP-eIF5A<sub>50AA</sub> to substitute for GFP-eIF5A (Fig. 2E), suggesting the binding was not affected by hypusine modification. In contrast, in the cells co-transfected with GFP and RFP-syntenin, or GFP-eIF5A and RFP, no NFRET signals were found (Fig. 2B and C).

A New Biological Activity for eIF5A as the Regulator of p53—In our efforts to identify the functional significance for the interaction of eIF5A with syntenin, we unexpectedly found that p53 protein level was obviously enhanced in response to eIF5A transfection. As shown in Fig. 3, after transient transfection in COS-7 cells, almost 4-fold of myc-tagged eIF5A relative to the level of endogenous eIF5A was observed and led to an increase in p53 protein level, which was further shown both in a time- and dose-dependent manner (Fig. 3, A and B). In contrast, neither an unrelated euakaryotic initiated factor family member (eIF4A) nor control vector pXJ40 had a similar effect on the levels of p53 expression (Fig. 3A). To further demonstrate the implication of endogenous eIF5A in p53 regulation, RNA interference was employed to specifically knockdown the eIF5A level. After the transfection with the siRNA specific for eIF5A, eIF5A expression was markedly decreased compared with the control, and the observed eIF5A knockdown led to a significant reduction in p53 expression (Fig. 3C). In contrast, the p53 protein level was not affected in the control transfected cells. These results indicated that suppression of the endogenous eIF5A expression through eIF5A siRNA could reduce p53 protein level.
Fig. 3. eIF5A regulated p53 protein expression. A, an increase in p53 protein level was induced by eIF5A expression through transfection. COS-7 cells were transiently transfected with the eIF5A expression vector, the eIF4A expression vector, and the control plasmid pXJ40 at 2 μg, respectively, and then cultured at indicated time points. Cell lysates were analyzed by immunoblotting with antibodies to p53 and myc. The expression level was normalized to glyceraldehyde-3-phosphate dehydrogenase (GAPDH). B, eIF5A induced p53 expression in a dose-dependent manner. COS-7 cells were transiently transfected with varying amounts of the eIF5A expression vector for 24 h. Cell lysates were analyzed by immunoblotting with antibodies to p53. The p53 expression level was normalized to glyceraldehyde-3-phosphate dehydrogenase. C, silencing eIF5A inhibited p53 expression. The siRNA targeting eIF5A mRNA was constructed and transfected into COS-7 cells for 48 and 72 h, respectively. Cell lysates were analyzed by immunoblotting with antibodies to p53 and eIF5A. D, the effects of eIF5A on the expressions of p21, Bax, Bcl-2, and Mdm2. After transient transfection with the eIF5A expression vector for 24 h, COS-7 cell lysates were subjected to Western blot analysis with antibodies to p21, Bax, Bcl-2, and Mdm2, respectively.

Our findings revealed a new biological activity for eIF5A as the regulator of p53 and p53-dependent apoptosis. Recently, higher eIF5A protein expression was found in tumors with p53 expression and further promoted the transcription of Bax as well as p21, the most intuitive links between p53-mediated transactivation and apoptosis. To further determine the biological role of eIF5A, we examined its effect on apoptosis in a FACS assay. A pair of human lung carcinoma cells (H1299 (p53	extsuperscript{+/+}) and H460 (p53	extsuperscript{−/−})) were transfected with the pXJ40 control vector or the pXJ40 vector encoding either eIF5A or eIF4A and cultured for 24 h. Then, FACS analysis was performed, which showed that eIF5A could induce apoptosis in H460 cells expressing wild type p53 but had no significant effect on p53-null H1299 cells (Fig. 6A), indicating that the induction of apoptosis by eIF5A is dependent on p53. The effect of eIF5A on the apoptosis of H460 cells was more observable after the cells were further treated with camptothecin (1 μM) for an additional 8 h at 24 h after the transfections. As shown in Fig. 6, B and C, FACS analysis indicated that the effect of eIF5A on apoptosis was significantly enhanced in H460 cells treated with camptothecin (Fig. 6, B and C) but not in camptothecin-treated p53-null H1299 cells. Similar results were also obtained in the cells treated with etoposide and cisplatin (data not shown). These data indicated that the eIF5A-induced apoptosis was p53-dependent.

Effect of eIF5A on p53 Was Affected by Syntenin—To further investigate the functional significance of the interaction of eIF5A with syntenin, we assessed whether the effect of eIF5A on p53 expression was affected by syntenin in COS-7 cells co-transfected with eIF5A and syntenin together. As shown in Fig. 7A (lane 3), our results found that the eIF5A-induced increase in p53 protein level was inhibited to almost 50% by syntenin co-transfected expression (Fig. 7A). In contrast, the eIF5A-led increase in p53 expression level was not affected by the co-transfection of either the pXJ40 control vector or the pXJ40-eIF4A expression vector (Fig. 7A, lanes 2 and 5). The effect of syntenin on p53 became more observable with the increasing doses of the pXJ40-eIF5A expression vector (Fig. 7B). To further investigate whether the antagonizing effect was via a direct physical association, we constructed a syntenin mutant (SYNmut) (Fig. 1C, PDZ1 + 2), in which the N-terminal domain (∆1–101) was deleted, and the interaction with eIF5A was abolished (Fig. 1C). After co-transfection of the syntenin mutant and eIF5A together, our results indicated that the syntenin mutant no longer inhibited the eIF5A-led increase in p53 protein level (Fig. 7A, lane 7). Thus, these data showed that when eIF5A interacted with syntenin, the eIF5A-induced increase in the p53 protein level was significantly inhibited.

**DISCUSSION**

Our results demonstrated, for the first time, that eIF5A and syntenin could engage in a specific interaction both in vitro and in vivo, and functioned collaboratively to regulate p53 activity. The eIF5A signaling to p53 required both the EFP domain of eIF5A and hypusine formation through modifications but was interfered with by its negative regulator syntenin. To date, although a large number of cellular genes transcriptionally regulated by p53 have been described, limited genes are known to regulate p53 and p53-dependent apoptosis (17). Thus, the identification of the interaction of eIF5A with syntenin will generate new insights into the mechanisms by which p53 activity is tightly regulated in cell proliferation and apoptosis.
accumulation and poor differentiation (18). However, the correlation between them is unclear. In the present study, both eIF5A expression through transfection and eIF5A silencing through RNA interference significantly altered the p53 protein level, suggesting that the regulation of eIF5A activity is an upstream event to p53 activation. The eIF5A protein was also reported to have significantly increased in the v-HA-Ras oncogene-transformed mouse NIH3T3 cells, implying that the regulation of eIF5A activity is a downstream event controlled by the Ras-mitogen-activated protein signal transduction pathway (12). Moreover, the eIF5A protein expression was markedly elevated in lung adenocarcinomas containing K-Ras mutation, compared with wild type K-Ras tumors (18). Therefore, we hypothesize that eIF5A mediates the effect of Ras mutation on p53 activation. Further investigations are being done to confirm the eIF5A involvement in the p53 pathway.

Syntenin contains two closely located PDZ domains that share some (ephrinB1, EphA7) interacting proteins with PICK1 and GRIP. The PDZ domains of syntenin can recognize type I (neurofascin, ProTGFα), type II (syndecans, ephrin-B2, and EphA7), and nonconserved PDZ binding motifs (Schwannomin-FEEL) (19–23). For the majority of the known partners of syntenin, PDZ domains are usually the sites for their interaction. However, some soluble partners, for example sox4 transcriptional factor, bind directly to the NH2 termini of syntenin, not to PDZ domains (24), which is similar to our results (Fig. 2B). The interaction of eIF5A with syntenin was mapped to the EFP domain of eIF5A. Although hypusine formation in the EFP domain is essential for eIF5A function in p53 regulation,
our data showed it was not essential for the interaction of eIF5A with syntenin. The regulation of p53 function is complex. The known mechanisms for regulation include an increased rate of transcription and translation and a post-translational stabilization of the protein (17). Thus, the increase in p53 protein level could also possibly occur through stabilization and accumulation of p53 via down-regulation of Mdm2 expression (25). However, p53 activation by eIF5A in our results was accompanied with the increase in Mdm2 expression (Fig. 3D).

This was possibly because of the negative-feedback loop in which p53 activation induced Mdm2 expression (26–28), but phosphorylation of p53 at various sites could prevent p53 to interact with the up-regulated Mdm2 (Fig. 5B) (29, 30). The Mdm2 up-regulation in p53 activation was also found in Ras signaling, inducing Mdm2 in a p53-dependent manner, thereby blunting p53 activation in response to different stress (31, 32).

One perplexing aspect of eIF5A protein is that it can promote both cell survival and cell death. In yeast expression, eIF5A has been reported to correlate with cell proliferation (7). Further, eIF5A expression was induced in activated human T lymphocytes (10). This paradox could be reconciled by viewing the mechanisms of eIF5A not as isolated circuits, but as part of a coordinated process, which targets key nodes of cell signal networks for cell growth or apoptosis. Moreover, the seemingly contradictory biological outcomes can also be found in Ras (a regulator of eIF5A activity), mediating both life and death decisions by distinct effector pathways (33). As the downstream target of eIF5A, p53 is also implicated in diversified functions, such as cell growth, cell cycle arrest, differentiation, or cellular senescence, in addition to apoptosis (31). For example, higher eIF5A protein expression was present in tumors with p53 accumulation but showing poor differentiation (18). Certain levels of p53 expression in human mammary epithelial cells may resist cells to extracellular matrix-induced apoptosis (34).
Moreover, p53 protein in human mammary epithelial cells is detected frequently in women at high risk for the development of breast cancer (35). How this seemingly discordant choice of cell death versus survival for eIF5A protein is achieved is not known. However, clarifying these complexities represents a challenge and offers hope for a more selective intervention of the p53 apoptotic program.

In conclusion, our findings demonstrated a new biological activity for eIF5A as the regulator of p53 and that eIF5A and syntenin could engage in a specific interaction both in vitro and in vivo and demonstrated that eIF5A functioned collaboratively to regulate p53 activity. These findings generated new insights into the mechanisms by which p53 is tightly regulated in apoptosis and generated a better understanding for the new function of eIF5A. The interaction of eIF5A with syntenin could possibly unravel novel pathways for p53 control and permit the p53 network to be manipulated in a more selective and sensitive manner. Moreover, the ability of eIF5A to sensitize cells to agents of chemotherapy can also be exploited for therapeutic purposes or may be suggested for rational strategies to improve therapy.

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