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PRMT5 is essential for the eIF4E-mediated 5′-cap dependent translation

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ABSTRACT

It is becoming clear that PRMT5 plays essential roles in cell cycle progression, survival, and responses to external stresses. However, the precise mechanisms underlying such roles of PRMT5 have not been clearly understood. Previously, we have demonstrated that PRMT5 participates in cellular adaptation to hypoxia by ensuring 5′-cap dependent translation of HIF-1α. Given that c-Myc and cyclin D1 expressions are also tightly regulated in 5′-cap dependent manner, we here tested the possibility that PRMT5 promotes cell proliferation by increasing de novo syntheses of the oncoproteins. c-Myc and cyclin D1 were found to be noticeably downregulated by PRMT5 knock-down. A RNA immunoprecipitation analysis, which can identify RNA–protein interactions, showed that PRMT5 is required for the interaction among eIF4E and 5′-UTRs of HIF-1α, c-Myc and cyclin D1 mRNAs. In addition, PRMT5 knock-down inhibited cell proliferation by inducing cell cycle arrest at the G1 phase. More importantly, ectopic expression of eIF4E significantly rescued the cell cycle progression and cell proliferation even in PRMT5-deficeint condition. Based on these results, we propose that PRMT5 determines cell fate by regulating 5′-cap dependent translation of proteins essential for proliferation and survival.

1. Introduction

Protein arginine methyltransferase 5 (PRMT5) belongs to the type II arginine methyltransferase family and is involved in diverse cellular processes such as signal transduction, histone modification, chromatin remodeling, transcriptional silencing or activation, and protein synthesis [1,2]. Because PRMT5 is highly expressed in lymphoma [3,4], breast cancer [5], gastric cancer [6], lung cancer [7,8], malignant melanoma [9], and glioblastoma [10], PRMT5 has been believed to have the oncogenic potential. Indeed, PRMT5 has been reported to be necessary for neoplastic growth [11] and cell cycle progression [8,12–14]. In a viewpoint of mechanism, PRMT5 has been known to promote cell cycle progression in association with multiple signaling pathways mediated by p53 [13], PI3K-AKT [12], E2F-1 [14], and fibroblast growth factor receptor 3 (FGFR3) [8]. Yet, the precise mechanism underlying PRMT5's oncogenic action has not been fully understood.

A key regulatory step in eukaryotic protein synthesis is a translational initiation via the recruitment of eukaryotic initiation factors (eIFs) such as the mRNA 5′-cap-binding protein eIF4E, the RNA helicase eIF4A, and the scaffold protein eIF4G [15,16]. Briefly, eIF4E binds to the 7-methyl guanosine cap structure with triphosphate group (m^7GTP) at the 5′-end of mRNAs and thereby provides the critical interface for the mRNA association with eIF4A, eIF4G and the 40S ribosomal subunit [16]. In cancer cells, eIF4E overexpression facilitates de novo syntheses of tumor-promoting or microenvironment-adaptive proteins, such as c-Myc and cyclin D1, survivin, and VEGF, which may contribute to cancer development and progression [16,17]. Therefore, eIF4E is believed as a reasonable target in developing new anticancer drugs.

In a previous report, we found that PRMT5 participates in the 5′-cap dependent translation of HIF-1α under hypoxic conditions [18], but did not investigate the role of PRMT5 in the translational process. This finding encouraged us to examine whether PRMT5 regulates the expressions of c-Myc and cyclin D1 because these proteins are also translated in a 5′-cap dependent fashion. As a consequence, PRMT5 participates in the interaction between eIF4E and 5′-cap structure of c-Myc or cyclin D1 mRNA, and by doing so promotes cell cycle progression and proliferation in lung cancer cells.

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Our results provide a better understanding of PRMT5's action on cell growth and a rationale for targeting PRMT5 as an anticancer strategy.

2. Materials and methods

2.1. Plasmids and reagents

The structures of small interfering RNA (siRNA) targeting PRMT5 and PRMT5-expressing vector were previously described [18]. To construct the eIF4E-overexpressing plasmid, the human eIF4E cDNA (NM_001968) was cloned by RT-PCR using pfu DNA polymerase, and was inserted into the FLAG and streptavidin-binding protein (SBP) tagged pcDNA plasmid by blunt-end ligation, which was designated F/S-eIF4E. MG132 and cycloheximide were purchased from Sigma–Aldrich (St. Louis, MO). Anti-PRMT5 antibody was purchased from Millipore (07-405), and antibodies against cyclin D1 (sc-753), c-Myc (sc-40), Hsp90 (sc-69703), or ATF4 (sc-200) from Santa Cruz Biotechnology (Santa Cruz, CA). Antibodies recognizing the cap-dependent translation-related proteins eIF4E (9742), p-eIF4E (9741), eIF4G (2498), p-eIF4G (2441), eIF4A (2013), and 4E-BP1 (4923) were purchased from Cell Signaling (Danvers, MA).

2.2. Cell culture and transfection

A549 human lung adenocarcinoma cells were cultured in 10% fetal bovine serum (FBS) and 25 mM glucose contained Dulbecco's modified Eagle's medium (DMEM) at 20% O_2/5% CO_2 (normoxia) or at 1% O_2/5% CO_2 (hypoxia). Cells were transiently transfected with plasmids or siRNAs using Lipofectamine 2000 (Life Technologies Korea, Seoul, Korea), when cells are 40% confluent. The transfected cells were allowed to stabilize for 48 h before experiments.

2.3. Immunoprecipitation and immunoblotting

Total protein extracts were prepared using a cell lysis buffer containing 1% IGEPAL, 150 mM NaCl, 50 mM Tris–HCl (pH 7.9), 10 mM NaF, 0.1 mM EDTA, and a protease inhibitor cocktail (Sigma–Aldrich). Total proteins were incubated with a primary antibody overnight at 4 °C, and then the immune-complexes were pulled-down using protein A/G-agarose beads (Santa Cruz Biotechnology). For Western blot, proteins were electrophoresed on SDS–polyacrylamide gels and transferred to PVDF membrane (Millipore). Transferred membranes were incubated with a primary antibody (1:1000) in 5% bovine serum albumin overnight at 4 °C, and then a HRP-conjugated secondary antibody (1:10,000) was incubated for 1 h at room temperature. Proteins levels were visualized using an ECL Prime (GE healthcare, NJ).

2.4. RNA immunoprecipitation (RIP) assay

The RNA-Binding Protein Immunoprecipitation Kit (Millipore, USA) was used for performing RNA immunoprecipitation (RIP). In brief, cytoplasmic extracts were prepared in a lysis buffer containing 0.5% IGEPAL, 120 mM KCl, 50 mM Tris–HCl (pH7.9), 2 mM EDTA, 100 U/ml RNase inhibitor, and a protease inhibitor cocktail, then cell lysates were immunoprecipitated with an antibody recognizing eIF4E or PABP overnight at 4 °C. Co-precipitated RNAs were amplified by RT-PCR and visualized on an agarose gel with ethidium bromide. The gene-specific primers were designed to amplify 5′-UTR regions of target mRNAs. The sequences (5′–3′) of the primers are CTTCAACGTTTCAGGACCTCG and CTTCTGCACACA TTTGAAGTA for cyclin D1; GAGCGACATCATTAAGGTCGC and AGGTCATAGTTCCTGTTGGTG for c-Myc; TCTATTCAAGACTTG-CAGCTT and AGGTCATAGTTCCTGTTGGTG for HIF-1α.

2.5. m^7GTP pull down assay

Cell lysates (0.3 mg protein) were incubated with 30 L of m^7GTP-Sepharose beads (GE Healthcare) at 4 °C for 1 h. The m^7GTP interacting complexes were washed five times with 600 μL of phosphate buffered saline containing 2 mM $MgCl_2$ and 0.5 mg/mL of heparin, and then eluted proteins were analyzed by Western blotting.

2.6. Cell cycle analysis

A549 cells were harvested and resuspended in 200 μL of phosphate-buffered saline and fixed in 75% ethanol on ice for 30 min. Cells were labeled with 0.05 mg/mL of propidium iodide in the presence of 0.5 mg/mL of RNase A, and further incubated for 30 min. DNA contents were analyzed using a Becton Dickinson FACStar flow cytometer (BD Biosciences, San Jose, CA).

2.7. Clonogenic assay

For clonogenic assay, A549 lung cancer cells (1×10^4) were cultured in DMEM containing 25 mM glucose and 10% fetal bovine serum for 6 days. Cells were fixed with 10% formalin and stained with crystal violet.

2.8. Quantitative RT-PCR

RNAs were extracted from cells using TRIzol® reagent (Life Technologies). cDNAs were synthesized from 1 μg of RNAs using the EasyScriptTM cDNA Synthesis Kit (Applied Biological Materials, Richmond, BC). The cDNAs were amplified using the ABI StepOne™ Real-Time PCR (Applied Biological Materials). mRNA levels were quantified by calculating Ct (threshold cycle) values and presented as percents of β-actin levels. The sequences of PCR primers (5′–3′) are GGACCTGACTGACTACCTCA and AGCTTCTCCTTAATGTCACG for β-actin; GACCTACTGCTGTCAGGAAG and ACCAAAATTCAGCTCC TGTA for PRMT5; GGAGGAGAACAAACAGATCA and GTAGGACAGG AAGTTGTTGG for cyclin D1; TCTGAGGAGGAACAAGAAGA and GTAGTTGTGCTGATGTGTGG for c-Myc; CACCATTAGAAAGCAGTTCC and GTGGCATTAGCAGTAGGTTC for HIF-1α.

2.9. Statistical analyses

All data were analyzed using the unpaired Student *t*-test in Microsoft Excel 2010. Data are represented as means and standard deviations. $p < 0.05$ was considered statistically significant.

3. Results

3.1. PRMT5 is required for the de novo syntheses of c-Myc, cyclin D1, and HIF-1α

To induce the intracellular accumulation of HIF-1α protein, A549 cells were treated with a proteasome inhibitor MG132 that blocks HIF-1 degradation even under normoxia. As was previously reported [18], the synthesis of HIF-1 protein was noticeably reduced by PRMT5 knock-down (Fig. 1A). Given that c-Myc and cyclin D1 proteins are also synthesized via 5′-cap dependent translation, we examined whether PRMT5 is needed to synthesize c-Myc and cyclin D1 proteins. Interestingly, c-Myc and cyclin D1 were accumulated in the presence of MG132, which was abolished by PRMT5 knock-down (Fig. 1B). In contrast, Hsp90 and ATF4,

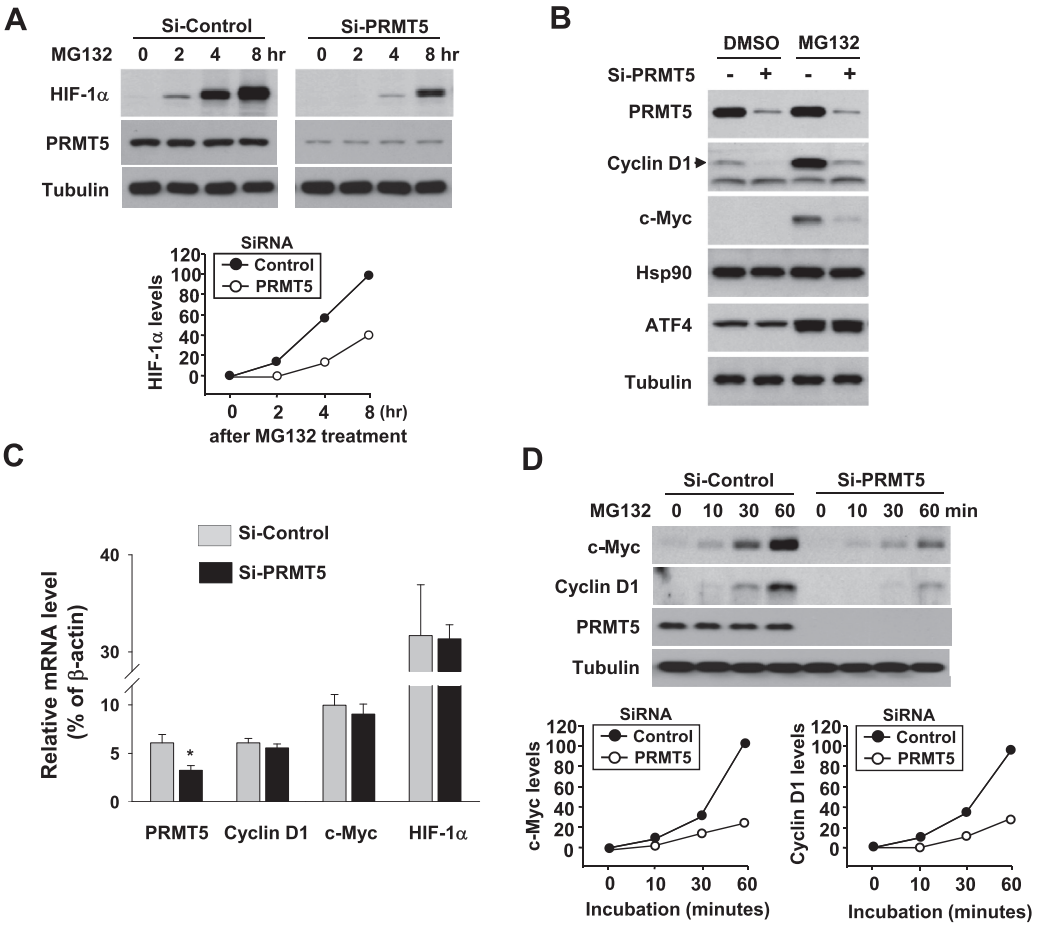

Fig. 1. PRMT5 is required for the syntheses of c-Myc, cyclin D1, and HIF-1α proteins. (A) A549 cells, which had been transfected with 40 nM PRMT5 siRNA, were treated with 20 M MG132 under normoxia. Proteins were detected by immunoblotting (top) and their intensities were quantified using Image J software (NIH, USA). Results (means of three experiments) are plotted as a function of incubation time (bottom). (B) A549 cells, which had been transfected with siRNAs, were incubated with MG132 for 2 h. Proteins were immunoblotted with the indicated antibodies. (C) mRNAs extracted from the transfected A549 cells were reverse-transcribed and quantified using real-time PCR. Each assay was done in quadruplicate and the result was divided by β-actin level in the corresponding sample. Final results (means + s.d.) were obtained from four independent experiments, and *denotes $p < 0.05$. (D) siRNA-treated A549 cells were incubated with cycloheximide for 1 h, and then washed with PBS. Cells were cultured in a fresh medium containing MG132, and then protein levels were immunoblotted (upper) and quantified by Image J (bottom).

whose translations can be mediated cap-independently, were expressed consistently regardless of PRMT5 knock-down. We next measured their mRNA levels to rule out the possibility that c-Myc and cyclin D1 expressions are regulated at the pre-translational level. Quantitative RT-PCR analyses verified the PRMT5 knock-down and showed that cyclin D1, c-Myc and HIF-1 mRNA expressions were not regulated by PRMT5 (Fig. 1C). To examine whether PRMT5 is involved in de novo syntheses of c-Myc and cyclin D1 proteins, A549 cells were pre-incubated with cycloheximide for 12 h to remove preexisting proteins, and then cells were incubated in a fresh medium containing MG132 to restart protein synthesis. Consequently, c-Myc and cyclin D1 syntheses were significantly attenuated by PRMT5 knock-down (Fig. 1D). As it does in HIF-1α translation, PRMT5 is likely to play a crucial role in the 5′-cap dependent translation of c-Myc and cyclin D1.

3.2. PRMT5 does not interact with the translation initiation complex

For the initiation of 5′-cap dependent translation, eIF4E should dissociate from the inhibitor 4E-BP1, which results from the mammalian target of rapamycin complex 1 (mTORC1)-mediated phosphorylation of 4E-BP1. Free eIF4E binds to 5′-cap structure of target mRNAs and recruits eIF4G, eIF4A and eIF3, which further recruits 40S ribosomal subunit and poly(A)-binding protein (PABP) to form the translational initiation complex. Since PRMT5 functions to methylate proteins at arginine residues, we tested the possibility that PRMT5 binds and methylates some of eIF members or PABP. However, the immunoprecipitation analyses showed that PRMT5 associates with none of eIF4E, eIF4G, eIF4A, and PABP (Fig. 2A). To strengthen this result, we further examined the interaction between PRMT5 and eIF4E under overexpressing condition. Consistently, ectopic PRMT5 did not bind to ectopic eIF4E (Fig. 2B). Next, we examined whether PRMT5 joins to the eIF4F complex which is composed of eIF4E, eIF4G, and eIF4A. However, PRMT5 knock-down did not affect the co-assembly among eIF4E, eIF4G and eIF4A (Fig. 2C). The activity of 5′-cap dependent translation depends on the phosphorylation status of eIF4E, which is stimulated through the growth factor signaling pathways. We thus examined whether PRMT5 regulates the activation process of eIF4E, but found no effect of PRMT5 knock-down on the serum-induced phosphorylation of eIF4E. Taken together, PRMT5 may not directly regulate the components in the translation initiation complex.

3.3. PRMT5 is essential for the eIF4E recruitment to the 5′-cap of mRNAs

A key step in the cap-dependent translation initiation is the recruitment of eIF4E to the mRNA 5′-end which contains a 7-methylguanosine (m^7GTP) cap [19]. We next tested the possibility that

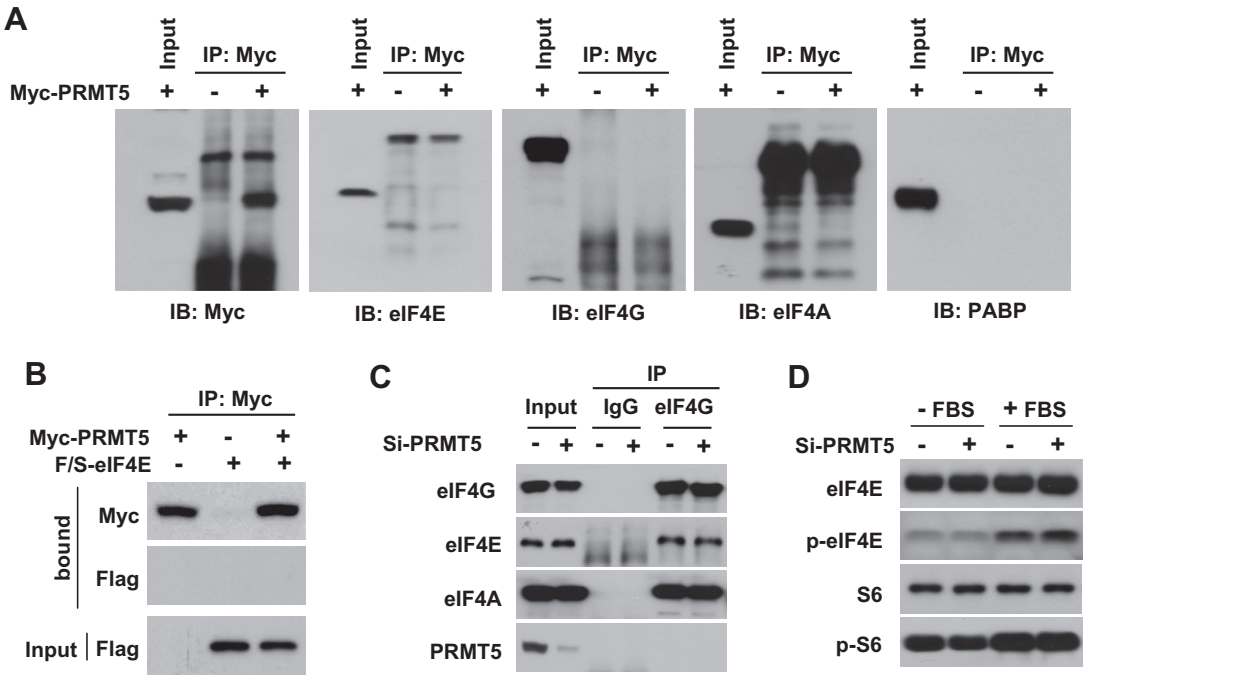

Fig. 2. PRMT5 does not bind to translation initiation factors. (A) HEK293T cells were transfected with the empty or Myc-PRMT5 vector and stabilized for 24 h. Cell lysates (1 mg of proteins) were incubated with 1 μg of anti-Myc antibody overnight at 4 °C, the immune complexes were pulled-down using protein A/G-agarose beads, and the bound proteins were immunoblotted with the indicated antibodies. (B) HEK293T cells, which had been co-transfected with Myc-PRMT5 and F/S-eIF4E, were subjected to immunoprecipitation and immunoblotting. (C) A549 cells, which had been transfected with control or PRMT5 siRNA, were subjected to immunoprecipitation and immunoblotting. (D) The transfected A549 cells were cultured overnight without fetal bovine serum (FBS), and further incubated in the absence or presence of 10% FBS for 1 h. Total and phosphorylated eIF4E proteins were analyzed by immunoblotting.

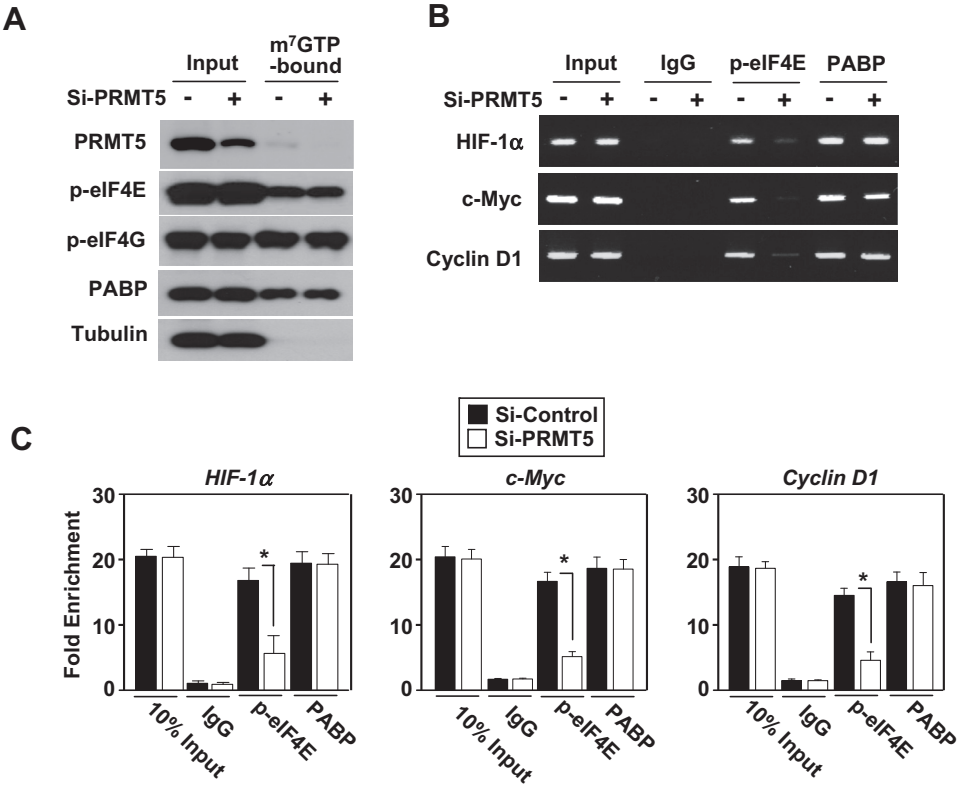

Fig. 3. PRMT5 is involved in the recruitment of eIF4E to 5′-cap of c-Myc, cyclin D1 or HIF-1α mRNA. (A) Lysates (1 mg) from the transfected A549 cells were incubated with 15 L of m^7GTP-conjugated Sepharose beads for 2 h. The bound proteins were analyzed by immunoblotting using the indicated antibodies. (B, C) Cytoplasmic proteins (1 mg) extracted from the transfected A549 cells were precipitated using 1 μg of indicated antibodies (marked above the gels) for 6 h. The precipitated proteins–mRNA complexes were treated with proteinase K to elute mRNAs from the complexes, and then the mRNAs were amplified by RT-PCR. The PCR products were electrophoresed on 2% agarose gels, stained with ethidium bromide, and visualized under UV (B). The PCR band intensities were quantified using Image J software (NIH, USA), and results (means + s.d., $n = 3$) are plotted as bars (C), *denotes $p < 0.05$.

PRMT5 is involved in the association with the translation initiation factors and the m^{7}GTP cap of mRNAs. However, an m^{7}GTP-pull down assay showed that PRMT5 did not either associate with the cap structure nor affect the cap-binding of activated (phosphorylated) eIF4E, eIF4G, and PABP (Fig. 3A). Because the m^{7}GTP-pull down assay was performed in a test tube, we re-examined the role of PRMT5 in cellular levels using RIP analysis. Surprisingly, phospho-eIF4E, not PABP, could not be recruited to c-Myc, cyclin D1, and HIF-1α mRNAs in PRMT5-knocked down cells (Fig. 3B and C). These results suggest that PRMT5 indirectly promotes the eIF4E recruitment to the 5′-cap structure of target mRNAs.

3.4. PRMT5 promotes hypoxic response and cell proliferation by facilitating the eIF4E-mediated cap-dependent translation

We next addressed whether PRMT5 promotes HIF-1α, c-Myc, or cyclin D1 expression through the eIF4E-mediated translation. The overexpression of eIF4E rescued HIF-1α synthesis upon PRMT5 knock-down (Fig. 4A). When PRMT5 was knocked down in A549 cells, the cell cycle was arrested at the G1 phase, causing the reduction in S-phase population (Fig. 4C). Given that c-Myc and cyclin D1 facilitate the G1-to-S transition, the G1 arrest by PRMT5 knock-down may be attributed to the suppression of these proteins (Fig. 4B). However, eIF4E overexpression rescues the expressions of c-Myc and cyclin D1 and cell cycle progression even upon PRMT5 knock-down (Fig. 4B and C). Consistently, the overexpression of eIF4E significantly rescued clonogenic cell growth in PRMT5 knocked-down A549 cells (Fig. 4D). These results suggest that PRMT5 promotes cellular response to hypoxia and cell proliferation via the eIF4E-mediated translation of HIF-1α, c-Myc, and cyclin D1.

4. Discussion

The arginine methyltransferase PRMT5 participates in diverse cellular processes, such as signal transduction, histone modification, and protein synthesis [2]. In particular, PRMT5 has been received attention as a tumor-promoting factor. Indeed, nuclear PRMT5 epigenetically inactivates tumor suppressor genes by methylating histones H3R8 and H4R3 [1,2], and also cytoplasmic PRMT5 methylates and activates the epidermal growth factor receptor and the ribosomal protein S10 [20,21]. Accordingly, PRMT5 in both the nucleus and the cytoplasm sets intracellular conditions for cell proliferation. We here identified a novel role of PRMT5 in protein synthesis, that is, PRMT5 employs eIF4E as a mediator to initiate the 5′-cap dependent translation. We also found that c-Myc and cyclin D1 proteins are synthesized depending on PRMT5. This mechanism seems to underlie the tumor-promoting action of PRMT5.

In the present study, PRMT5 was found to participate in the interaction between eIF4E and the 5′-cap structure of its target mRNAs. However, the direct target for the PRMT5′s action is not uncovered. Giving the enzymatic function of PRMT5, it is expected that PRMT5 binds and methylates eIF4E per se or other protein(s) modulating the eIF4E recruitment to the mRNA cap. Therefore, we performed co-immunoprecipitation analysis to identify the PRMT5 binding to eIF4E, but could not detect the interaction. This result encouraged us to propose the indirect action of PRMT5 on the eIF4E-mediated translation. However, in case the immunoprecipi-

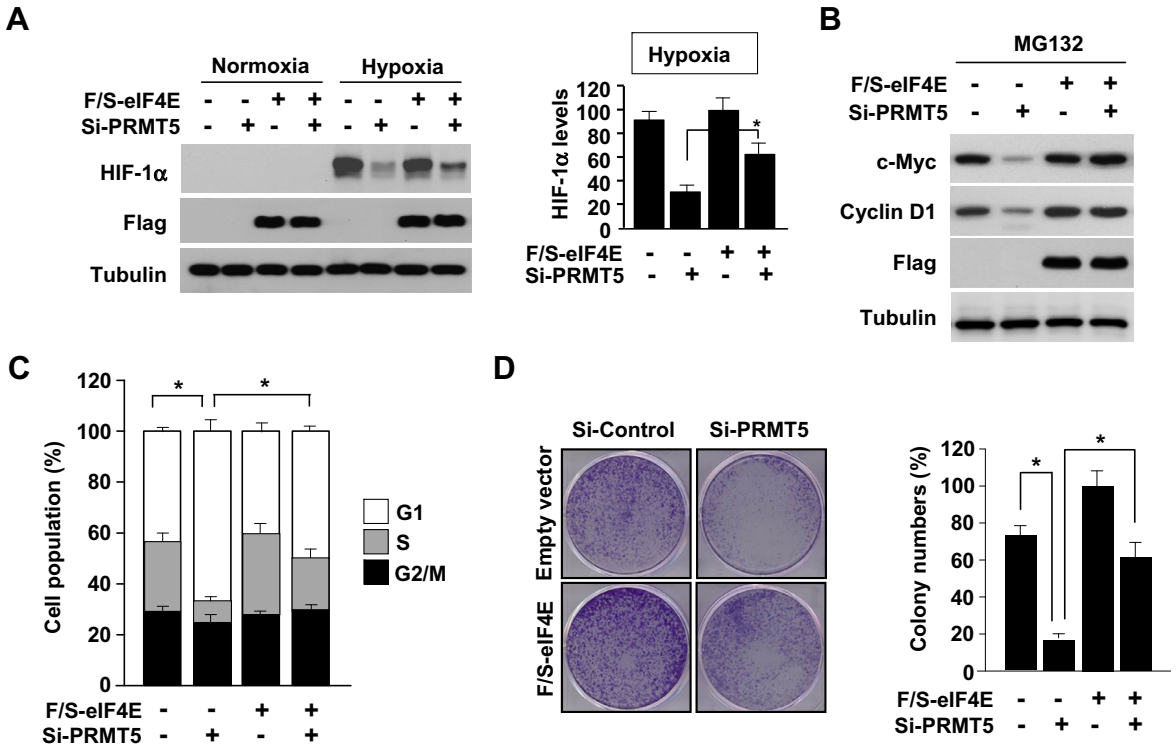

Fig. 4. eIF4E overexpression reverses the effects of PRMT5 knock-down on protein syntheses and cell proliferation. (A) A549 cells, which had been transfected as indicated, were incubated under normoxia (20% O_2) or hypoxia (1% O_2) for 8 h. HIF-1α levels were analyzed by immunoblotting (left) and quantified using Image J. Results (means + s.d., $n = 3$) are plotted in the right panel, *denotes $p < 0.05$. (B) The transfected A549 cells were incubated in the absence or presence of MG132 for 2 h, and cell lysates were subjected to immunoblotting. (C) After A549 cells were transfected as indicated, cell cycle was analyzed by propidium iodide staining and flow cytometry. The population at each cell cycle phase was represented as mean + s.d. from three different experiments, *denotes $p < 0.05$. (D) The transfected A549 cells were incubated for 6 days, fixed using formalin, and stained with crystal violet (left). Colonies were counted under a microscope, and their numbers (mean + s.d.) are represented as bars (right), *denotes $p < 0.05$.

tation analysis was not sensitive enough to detect the transient PRMT5–eIF4E interaction occurring during the enzyme reaction, the possibility of direct interaction between PRMT5 and eIF4E still remains open. More sensitive methods other than immunoprecipitation would be applied for confirming whether or not they are associated.

A previous study suggested that PRMT5 promotes the proper assembly of ribosomes by methylating ribosomal protein S10 at R158 and R160 and by doing so facilitates protein synthesis [20]. If the methylation of ribosomal protein S10 is critical for ribosomal assembly, PRMT5 should be generally involved in protein synthesis that is always done on the ribosomal complex. However, we here found that de novo syntheses of Hsp90 and ATF4 proteins were not attenuated by PRMT5 knock-down whereas c-Myc, cyclin D1 and HIF-1α syntheses were impaired. This finding suggests that PRMT5 selectively regulates protein synthesis and the eIF4E-mediated 5′-cap dependent translation is the case. Given the previous report and our results, proteins are synthesized through very complicated processes and PRMT5 seems to regulate the processes in multiple steps.

Increasing evidence suggests that the tumor-promoting activity of PRMT5 is attributed to cell cycle progression [8,12–14], but the molecular mechanism underlying the PRMT5 regulation of cell cycle has not been fully understood. We also observed that PRMT5 knock-down in A549 cancer cells arrested cell cycle at the G1 phase along with decreased c-Myc and cyclin D1 levels. More importantly, cell cycle and the expression of c-Myc and cyclin D1 were substantially rescued by eIF4E overexpression. These results suggest that eIF4E acts as a downstream player in the PRMT5-mediated cancer cell proliferation. Then, does eIF4E become an anticancer target? In fact, eIF4E inhibition has been investigated as an emerging anticancer strategy [16,17,22]. Antisense oligonucleotide targeting eIF4E has been demonstrated to inhibit tumor growth and angiogenesis with down-regulation of c-Myc, cyclin D1 and VEGF in mice [17]. 4EGI-1, which is a small molecule inhibiting the eIF4E–eIF4G interaction, has shown anticancer effect in association with cyclin D1 and HIF-1α suppression in human lung cancer cells [23]. Although we did not inhibit eIF4E in this work, such a role of eIF4E can be deduced from our result showing that eIF4E overexpression robustly enhanced cell cycle progression and colony formation (used as an in vitro tumorigenesis assay) in PRMT5-deficient A549 cells.

In conclusion, we propose that PRMT5 promotes eIF4E-mediated 5′-cap dependent translation of c-Myc, cyclin D1 and HIF-1α, and also that this mechanism underlies the tumor-promoting action of PRMT5. This study provides not only insight into the mechanism by which PRMT5 regulates protein synthesis, but also rationale for PRMT5-targeting anticancer strategy.

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