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N-myristoyltransferase 1 enhances human immunodeficiency virus replication through regulation of viral RNA expression level

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ABSTRACT

N-myristoyltransferase (NMT) catalyzes protein *N*-myristoylation. It has been suggested that the isozyme NMT1 enhances the replication of human immunodeficiency virus type-1 (HIV-1). However, the details of the mechanism by which NMT1 does so remain unclear. In this study, we investigated NMT1-binding proteins by co-immunoprecipitation and mass spectrometry. As a result, several RNA-binding proteins including ribosomal proteins, NMT isozymes, and hnRNP A2/B1 were observed to bind to NMT1, as mediated mainly by RNA. Interestingly, only hRNP A2/B1 was found to associate with NMT1 without mediation by RNA. It was also suggested that hnRNP A2/B1 contributes to the formation of complexes of high molecular weights involving NMT1. Knockdown of hnRNP A2/B1 resulted in the enhancement of viral replication with an increase in the expression level of viral RNA in HIV-1-producing cells. On the other hand, knockdown of NMT1 resulted in the attenuation of viral replication with the decrease in the expression level of viral RNA in HIV-1-producing cells. Additionally, overexpression of NMT1 induced the enhancement of viral replication with the increase in the expression level of the viral RNA. These findings suggest that both NMT1 and hnRNP A2/B1 take part in the regulation of HIV-1 RNA expression through their mutual opposite effects on the viral RNA expression in HIV-1-producing cells.

1. Introduction

N-myristoyltransferase (NMT) is an enzyme catalyzing protein *N*-myristoylation [1]. NMT is detected in the cytosolic and ribosomal fractions prepared by biochemical subcellular fractionation [2]. The basic amino acid sequence in the *N*-terminal region of NMT contributes to ribosomal targeting [3]. *N*-Myristoylation generally confers substrate proteins the membrane-targeting ability, which is essential for the function of the substrate proteins [4].

N-Myristoylation of the viral structural precursor protein $Pr55^{gag}$ is essential for human immunodeficiency virus type 1 (HIV-1) replication [5]. The isozyme NMT1 [6,7] is reported to be closely associated with the replication of HIV-1, in which NMT1 knockdown attenuates HIV-1 replication [8]. Additionally, NMT1 knockdown perturbs the appropriate membrane localization of $Pr55^{gag}$ [8]. However, the detailed mechanism underlying the promotive effect of NMT1 on HIV-1 replication has remained unclear.

To investigate how NMT1 contributes to HIV-1 replication, first we investigated NMT1 binding proteins using proteomics technology. The binding of NMT1 to hnRNP A2/B1, which was resistant to nuclease treatment, was observed, indicating that the binding was not mediated by RNA. Interestingly, NMT1 and hnRNP A2/B1 were respectively associated with the up-regulation and down-regulation of HIV-1 RNA in HIV-1-producing cells. Here, it was suggested that the association between NMT1 and hnRNP A2/B1 is involved in the regulation of HIV-1 RNA expression level through their reciprocal opposite effects; by this mechanism, NMT1 partly enhances HIV-1 replication.

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2. Materials and methods

2.1. Material

TZM-bl cells were obtained from the National Institutes of Health AIDS Research and Reference Reagent Program.

2.2. Construction of NMT1 and NMT2 expression vectors

The expression vectors of NMT1 and NMT2, which were tagged with the Xpress epitope and 6× His epitopes at the *N*-terminus, were constructed by cloning into the pcDNA4/HisMax vector (Life Technologies) [3]. The expression vector of NMT1 with the HA-tag at the *N*-terminus was also constructed by using the pcDNA3 vector (Life Technologies).

2.3. Transfections of plasmids and siRNAs

Human embryonic kidney 293 (HEK293) cells were transfected using a Lipofectamine LTX reagent (Life Technologies) for plasmid DNAs [3] and a Lipofectamine RNAiMAX transfection reagent (Life technologies) for siRNAs. siRNAs for hnRNPA2/B1 (sc-43841), NMT1 (sc-61132), and control (sc-37007) were obtained from Santa Cruz Biotechnology Inc. To prepare HEK293 cells permanently expressing His-tagged NMT1, HEK293 cells transfected with pcDNA4/HisMax-NMT1 were treated with 500 μg/ml Zeocin™ (Life Technologies) and cultured. Then, His-tagged-NMT1-expressing HEK293 cells were selected and named HEK293/His-tagged NMT1 cells.

2.4. Cell lysis and western immunoblot analysis

Cell lysis, sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), and western immunoblot analysis were conducted as described previously [9]. For immunoreactions, HIV-1-positive plasma, an anti-hnRNP A2/B1 antibody (Santa Cruz Biotechnology), an anti-Xpress antibody (Life Technologies), an anti-NMT1 rabbit polyclonal antibody (Santa Cruz Biotechnology), an anti-lactate dehydrogenase (LDH) goat polyclonal antibody (CHEMICON International), and an anti-actin (Ab-1) antibody (Millipore, Billerica) were used as the primary antibodies. An appropriate secondary antibody conjugated with peroxidase (POD) against each primary antibody used was utilized.

2.5. Detection of N-myristoylation using click chemistry

Click chemistry reagents (Life Technologies) were used for detecting *N*-myristoylation of $Pr55^{gag}$. HEK293 cells were transfected with or without pNL-CH or pNL-CH/gag Gly^2 to Ala^2 (G2A) [3]. After 48 h of cultivation, the HEK293 cells were treated with 20 μM Click-IT myristic acid azide for 5 h. After cell lysis, biotin-alkine and $CuSO_4$ were added to the lysate for azide–alkine reaction, and the lysate was subjected to SDS-PAGE and streptavidin blotting.

2.6. Co-immunoprecipitation

To isolate NMT1-binding proteins, HEK293/His-tagged NMT1 cells or the parent HEK293 cells were lysed with Triton X-100 lysis buffer (50 mM Tris–HCl, pH 8.0, 150 mM NaCl, 0.5% Triton X-100, and protease inhibitor cocktail) for 30 min at 4 °C. After centrifugation, each obtained lysate was treated with or without 500 unit/ml benzonase nuclease (Merck Millipore) and purified using a His-tagged protein purification kit (MBL).

2.7. Protein identification by mass spectrometry

The gels obtained after SDS-PAGE were subjected to silver staining. Specifically stained proteins in gel pieces were digested with trypsin, and digested products were analyzed in the MS and MS/MS modes of MALDI-TOF/TOF UltrafleXtreme (Bruker Daltonics Inc.) [10]. The NCBI nr database was searched using Mascot software (Matrix Science).

2.8. Blue native PAGE

Blue native PAGE was performed using NativePAGE™ Novex Bis-Tris Gel system (Life Technologies) in accordance with the manufacturer's instruction.

2.9. Quantification of HIV-1 p24 antigen in supernatant

Each cell-free supernatant was filtered using a 0.45-μm-pore-size filter and the filtrate was subjected to ELISA to quantify HIV p24 (ZeptoMetrix Corporation).

2.10. Measurement of viral infectivity

TZM-bl cells were used for the measurement of viral infectivity of supernatants as previously described [11].

2.11. Quantitative RT-PCR

Total RNA was extracted and cDNA was synthesized using the SuperScript™ III First-Strand Synthesis system. EvaGreen™ Supermix (Bio-Rad Laboratories) reagent was used for quantitative real-time PCR analysis. Thermocycling was carried out using the DNA Engine OPTICON®2 system (MJ Research, Inc.). mRNA expression level was normalized to the expression level of the transcript of the actin gene. The oligonucleotide primers used for the PCR were as previously described [12].

3. Results

3.1. NMT1 associates with hnRNP A2/B1, which is not mediated by RNA

The cell lysates of HEK293/His-tagged NMT1 cells and the parent HEK293 cells as the control experiment were prepared for the immunoprecipitation of His-tagged NMT1. His-tagged NMT1 was immunoprecipitated using anti-His tag beads, and the obtained immune complex was subjected to SDS-PAGE, followed by silver staining. As shown in Fig. 1A, at least nineteen specific bands (shown by open and closed arrow heads) were observed for the immune complex with His-tagged NMT1 compared with the case of the control experiment. The specific bands were analyzed by mass spectrometry. As a result, ten (closed arrow heads) of the nineteen proteins in the complex with His-tagged NMT1 were identified, which included six ribosomal proteins (L4, L12, L19, L24, S16, and S24). Additionally, two types of endogenous NMT1 isozyme, which could be NMT1L, NMT1M, or NMT1S [6,7], endogenous NMT2, and hnRNP A2/B1 were identified. Since NMT1 can localize to ribosomes [2,3], each component of the complex was considered to potentially bind to His-tagged NMT1, as mediated by ribosomal RNA or other types of RNA such as mRNAs. To determine whether there are any proteins among the nineteen proteins whose specific binding to His-tagged NMT1 is not mediated by RNAs, each cell lysate was treated with nuclease to digest nucleic acids, followed by immunoprecipitation of His-tagged NMT1. Interestingly, only hnRNP A2/B1 among the nineteen specifically bound proteins

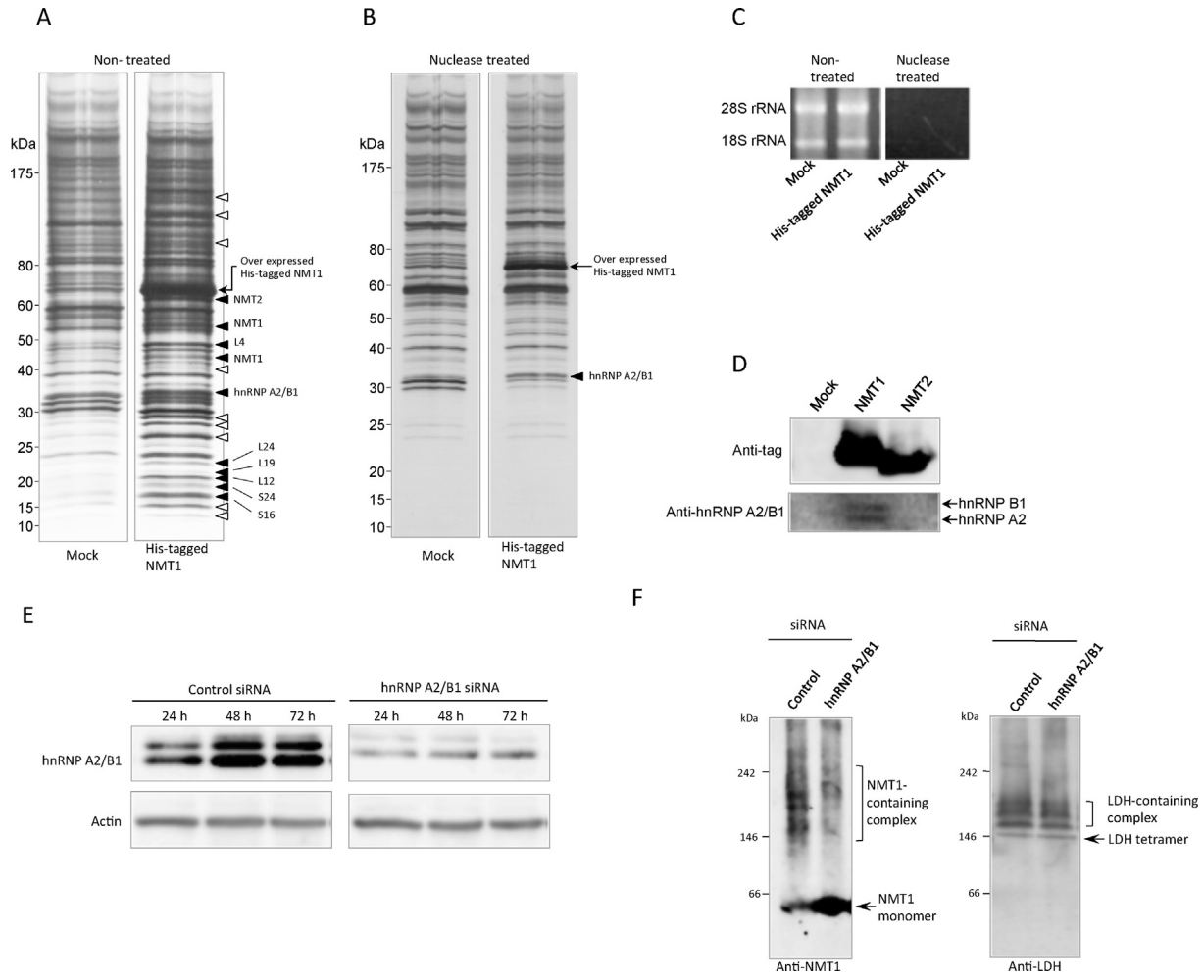

Fig. 1. Identification of association of NMT1 with hnRNP A2/B1. Lysate from 3×10^8 HEK293/His-tagged NMT1 cells or parental HEK293 cells was treated with (B) or without (A) benzonase nuclease, followed by addition of anti-His tagged beads. The eluate from the beads treated with 6xHis peptide solution was subjected to SDS-PAGE followed by silver staining. Proteins specifically binding to His-tagged NMT1 were identified by mass spectrometry. RNA was extracted from an aliquot of each lysate and subjected to agarose gel electrophoresis, followed by ethidium bromide staining (C). HEK293/His-tagged NMT1, HEK293/His-tagged NMT2, or parental HEK293 cells were lysed and immunoprecipitated using the anti-His antibody. The immune complex was subjected to SDS-PAGE and western immunoblot analysis to detect His-tagged NMTs and hnRNPA2/B1 (D). The effect of siRNA on hnRNPA2/B1 knockdown in HEK293 cells was examined by western immunoblot analysis at the indicated time for lysates from HEK293 cells transfected with siRNA (E). HEK293 cells at 72 h posttransfection of each siRNA were lysed and subjected to blue-native PAGE, followed by western immunoblot analysis to detect the endogenous NMT1 and LDH (F).

remained after the nuclease treatment (Fig. 1B). The complete nucleic acid digestion was confirmed by detection of 28S and 18S ribosomal RNAs (Fig. 1C). The association of NMT1 with hnRNP A2/B1 after nuclease treatment was confirmed by western immunoblot analysis (Fig. 1D), which clarified that hnRNP A2/B1 co-immunoprecipitated with NMT1 but not with NMT2. hnRNP A2/B1 predominantly localizes in the nucleus and shuttles between the nucleus and the cytoplasm [13]. On the other hand, NMT1 is present in the cytoplasm and can localize to ribosomes [2,3]. Accordingly, it is considered that a relatively small amount of hnRNP A2/B1 co-immunoprecipitated with overexpressed His-tagged NMT1 (Fig. 1 D).

To investigate whether the shift of the apparent molecular weight of endogenous NMT1 could be observed with or without hnRNPA2/B1 knockdown, HEK293 cells were transfected with hnRNPA2/B1 siRNA or control siRNA and cultured for 72 h. The cell lysates treated with nuclease were subjected to blue-native PAGE, and endogenous NMT1 was detected by western immunoblot analysis. The efficacy of hnRNPA2/B1 knockdown for 72 h by the siRNA used was confirmed (Fig. 1E). As shown in the control lane of the left panel of Fig. 1F, not only monomeric NMT1 of 60 kDa (shown by an arrow) but also NMT1s of high molecular weights from 150 kDa to 250 kDa (shown by a single bracket) were detected, indicating that NMT1 exists in complex with proteins in cells. From this finding, we examined the effect of hnRNPA2/B1 knockdown on the formation of complexes containing NMT1. In comparison with the case of the control siRNA, the relative amount of the endogenous NMT1s in the complexes was decreased and that of monomer NMT1 of about 60 kDa was increased by hnRNP A2/B1 knockdown (left panel of Fig. 1F). The equivalent protein loading was confirmed by the level of the tetramer lactate dehydrogenase (LDH) detected (Fig. 1F right panel). Additionally, not only a tetramer of LDH (146 kDa) but also several high-molecular-weight complexes containing LDH were also observed, which were not affected by hnRNP A2/B1 knockdown, suggesting that the shift of the apparent molecular weight of NMT1 with hnRNP A2/B1 knockdown specifically occurred. These results suggest that endogenous NMT1 associates with hnRNP A2/B1, which is not mediated by RNA, and contributes to the formation of complexes containing NMT1. The details about the association between NMT1 and hnRNP A2/B1 and the

functional significance of the complexes have not been clarified. Previous studies indicated that bovine and murine NMTs exist as a mixture with apparent molecular weights of up to about 390 kDa [14,15], suggesting that the existence of complexes of NMT isozymes might be universal in mammalian species.

3.2. hnRNP A2/B1 knockdown does not affect Pr55^{gag} *N*-myristoylation but increases the expression levels of HIV-1 proteins

NMT1 catalyzes *N*-myristoylation of substrate proteins. HIV-1 Pr55^{gag} *N*-myristoylation is essential for HIV-1 replication [5]. Additionally, it was reported that one of the NMT isozymes, NMT1, is closely associated with HIV-1 replication [8]. We examined the effect of hnRNP A2/B1 knockdown on Pr55^{gag} *N*-myristoylation in HEK293 cells transfected with an HIV-1 expression vector with wild-type Pr55^{gag} or G2A mutation. *N*-myristoylation was detected using click chemistry [16]. As shown in Fig. 2, Pr55^{gag} *N*-myristoylation was detected in wild-type Pr55^{gag} but not in the G2A mutant, as expected. Additionally, the expression level of Pr55^{gag} with G2A mutation was slightly higher than that of wild-type Pr55^{gag}, as expected, which could be explained as being due to the accumulation of the G2A mutant instead of its release as viral particles (third panel of Fig. 2). Under this condition, the apparent *N*-myristoylation level of Pr55^{gag} in HEK293 cells with hnRNP A2/B1 knockdown was clearly higher than that without the knockdown (second panel of Fig. 2). Although this finding was interesting, the expression levels of not only Pr55^{gag} but also gp120 in HEK293 cells with hnRNP A2/B1 knockdown were clearly higher than those in HEK293 cells without the knockdown (third and fourth panels of Fig. 2). The equivalent protein loading was confirmed by the expression level of actin detected (fifth panel of Fig. 2). Altogether, these findings indicate that the hnRNP A2/B1 knockdown does not affect Pr55^{gag} *N*-myristoylation but interestingly increases the expression levels of HIV-1 proteins.

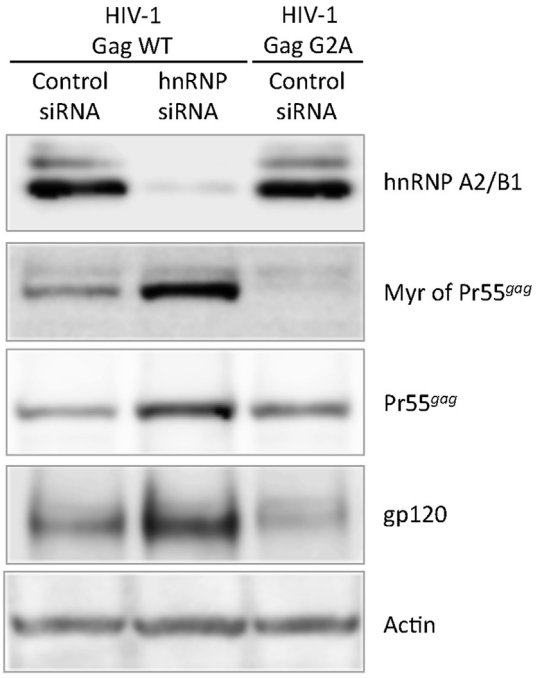

Fig. 2. Effects of hnRNP A2/B1 knockdown on expression of viral proteins and *N*-myristoylation of Pr55^{gag}. HEK293 cells were transfected with hnRNPA2/B1 or control siRNA. After 24 h of cultivation, HEK293 cells were transfected with pNL-CH and cultured for 48 h pNL-CH/gagG2A was used for the expression of Pr55^{gag} without *N*-myristoylation. The cells were lysed and subjected to SDS-PAGE and western immunoblot analysis to detect hnRNPA2/B1, Pr55^{gag}, gp120, and β-actin. For detection of *N*-myristoylation of Pr55^{gag}, click chemistry was used.

3.3. hnRNP A2/B1 knockdown induces significant enhancement of not only viral production but also the efficient maturation of viral particles

Next, we investigated the effect of hnRNP A2/B1 knockdown on HIV-1 replication. HEK293 cells with or without hnRNP A2/B1 knockdown were transfected with the HIV-1 expression vector. The p24 antigen amount indicating viral production level and the viral infectivity of the supernatants after 24 h and 48 h were examined. As shown in Fig. 3A and B, the level of viral production and the relative viral infectivity in supernatants at 48 h from HEK293 cells with the hnRNP A2/B1 knockdown were significantly higher than those without the knockdown. To examine HIV-1 maturation, supernatants of the same p24 antigen amount were assayed for viral infectivity. As shown in Fig. 3C, the relative infectivities of supernatants at 24 h and 48 h from HEK293 cells with hnRNP A2/B1 knockdown were significantly higher than those without the knockdown. Altogether, these results indicate that the hnRNP A2/B1 knockdown induces not only the significant enhancement of viral production but also the efficient maturation of viral particles.

3.4. NMT1 has the function to increase expression level of HIV-1 RNA

Since increased expression levels of HIV-1 proteins were observed after hnRNP A2/B1 knockdown, the HIV-1 RNA expression level in the HEK293 cells with the hnRNP A2/B1 knockdown was quantified by RT-qPCR analysis, in which a primer pair for the detection of HIV-1 unspliced RNA was used [12]. Additionally, to investigate the significance of the association between NMT1 and hnRNP A2/B1, the HIV-1 RNA expression level in HEK293 cells with NMT1 knockdown was also measured. The hnRNP A2/B1 knockdown by siRNA was again confirmed to be very effective (first panel of Fig. 4 A). The NMT1 knockdown by siRNA was also observed to be effective (second panel of Fig. 4A). hnRNP A2/B1 knockdown did not affect the NMT1 expression level, and again it was also observed to increase the expression levels of Pr55^{gag} and gp120. The NMT1 knockdown did not affect the hnRNP A2/B1 expression level (first panel of Fig. 4A). On the other hand, the expression levels of Pr55^{gag} and gp120 in HEK293 cells with NMT1 knockdown were slightly higher than those in control HEK293 cells (third and fourth panels of Fig. 4A). The HIV-1 RNA expression level in HEK293 cells with hnRNP A2/B1 knockdown was significantly higher than that with control siRNA, whose expression level was about sixfold the control level (Fig. 4B). On the other hand, the HIV-1 RNA expression level in HEK293 cells with NMT1 knockdown was significantly lower than that in the cells with control siRNA, which showed only a partial decrease (Fig. 4B). Additionally, it was confirmed that NMT1 knockdown induces a significant decrease in HIV-1 infectivity (Fig. 4C), which was in agreement with a previous report [8]. The NMT1 knockdown induced not only a significant decrease in HIV-1 RNA expression level (Fig. 4B) but also a slight increase in the expression level of Pr55^{gag} (third panel of Fig. 4A). Since the NMT1 knockdown induces an abnormal distribution of Pr55^{gag} in virus-producing cells and decreases in HIV-1 replication [8], and Pr55^{gag} with the G2A mutant accumulates within the cells instead of being released as viral particles [17] (also see Fig. 2, third panel), it is therefore speculated that the slight increase in the expression level of Pr55^{gag} despite the slight decrease in that of HIV-1 RNA with NMT1 knockdown may be due to the accumulation of viral Pr55^{gag}

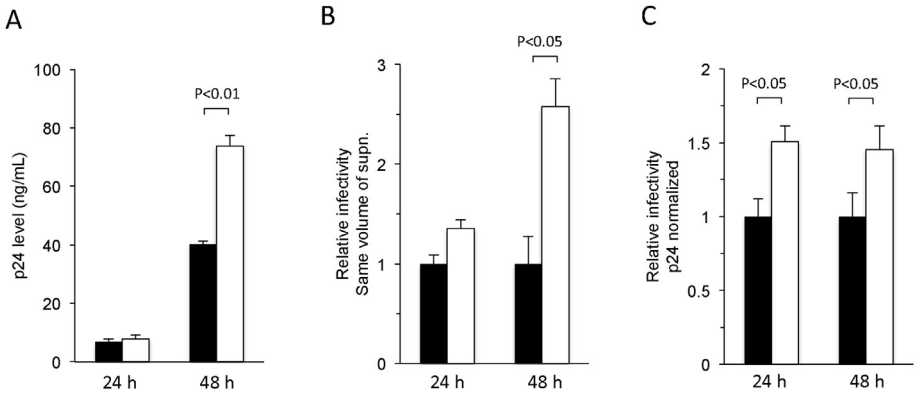

Fig. 3. Effect of hnRNP A2/B1 knockdown on HIV-1 replication. HEK293 cells were transfected with hnRNPA2/B1 or control siRNA. After 24 h of cultivation, HEK293 cells were transfected with pNL-CH. The HIV-1 p24 antigen in the supernatants at 24 h and 48 h posttransfection was quantified by p24 ELISA (A). The HIV-1 infectivity of the same volume of supernatant (B) or p24 antigen-normalized supernatant (C) was examined using TZM-bl cells. Each bar represents the mean standard deviation (n = 3). *p was calculated using Student's *t*-test.

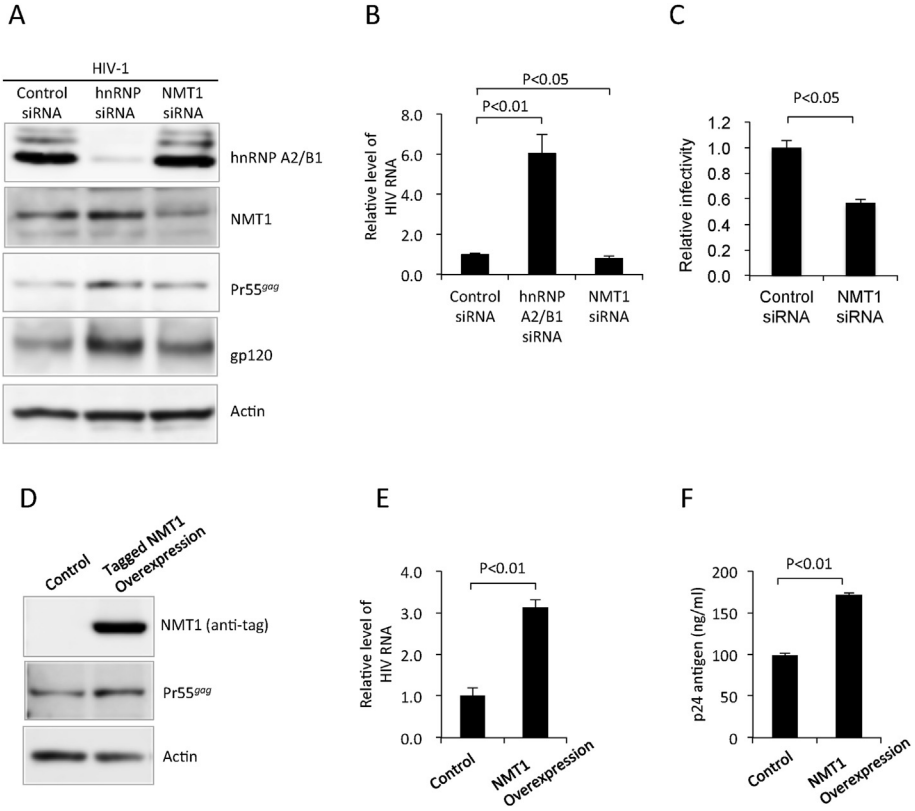

Fig. 4. Effects of NMT1 knockdown and NMT1 overexpression on HIV-1 replication. HEK293 cells were transfected with hnRNPA2/B1, NMT1, or control siRNA. After 24 h of cultivation, HEK293 cells were transfected with pNL-CH and cultured for 48 h. The cell lysates were subjected to SDS-PAGE and western immunoblot analysis to detect hnRNP A2/B1, NMT1, $Pr55^{gag}$, gp120, and β-actin (A). The cellular RNAs were extracted for HIV-1 RNA quantification by RT-PCR analysis (B). The HIV-1 infectivity of each supernatant was examined using TZM-bl cells (C). pNL-CH was transfected into HEK293 cells with or without the NMT1 expression vector and the cells and supernatant at 48 h were collected. The cell lysates were subjected to SDS-PAGE and western immunoblot analysis to detect overexpressed tagged NMT1, $Pr55^{gag}$, and β-actin (D). Cellular RNAs were extracted for HIV-1 RNA quantification by RT-PCR analysis (E). HIV-1 p24 antigen levels in supernatants were examined by p24 ELISA (F).

without *N*-myristoylation in the HEK293 cells. Additionally, the slight increase in gp120 expression level was an interesting observation in the HEK293 cells with the NMT1 knockdown (fourth panel of Fig. 4A). Because there was no increase in the expression level of gp120 from HIV-1 proviral DNA that introduced the G2A mutation in $Pr55^{gag}$ (the fourth panel of Fig. 2), the increase in gp120 expression level is considered to be a secondary effect of NMT1 knockdown on cellular factors involved in viral replication.

To investigate the effect of NMT1 overexpression on HIV-1 RNA level, two types of plasmid that encode NMT1 and an infectious HIV-1 clone were cotransfected into HEK293 cells. The expressions of NMT1 and HIV-1 $Pr55^{gag}$ in HEK293 cells were verified by western immunoblot analysis (Fig. 4D). The expression level of $Pr55^{gag}$ in the NMT1-overexpressing HEK293 cells was higher than that in the control HEK293 cells. Under this condition, the HIV-1 RNA expression level in the NMT1-overexpressed HEK293 cells was significantly higher than that in the control HEK293 cells. The

HIV-1 production level in the supernatant of the NMT1-overexpressing HEK293 cells was also significantly higher than that of control HEK293 cells.

4. Discussion

Altogether, these findings indicate that the increases in the expression levels of HIV-1 proteins, viral production level, and viral infectivity by hnRNP A2/B1 knockdown were basically due to the increase in the expression level of HIV-1 RNA. Interestingly, the NMT1 knockdown induced a significant decrease in the expression level of HIV-1 RNA, and the NMT1 overexpression induced a significant increase in that of HIV-1 RNA, suggesting that NMT1 has a role in the increase in the expression level of HIV-1 RNA in HIV-1-producing cells. Our findings of the increases in the expression levels of HIV-1 RNA (Fig. 4B) and viral proteins (Fig. 2) in HIV-1-producing cells and the increases in the amount of released HIV-1 and viral infectivity (Fig. 3) with hnRNP A2/B1 knockdown are basically in agreement with previous reports [12,18]. However, our novel finding in this study is that the action of NMT1 on HIV-1 replication is in contrast to that of hnRNP A2/B1, especially regarding the HIV-1 RNA expression level (Fig. 4B and E). Taking the association between NMT1 and hnRNP A2/B1 into consideration (Fig. 1), we here hypothesize that NMT1 regulates the function of hnRNP A2/B1. Although the *N*-myristoylation of HIV-1 proteins by NMT1 could primarily and directly contribute to HIV-1 replication, the novel function of NMT1 in increasing HIV-1 RNA expression level might secondarily contribute to HIV-1 replication, in which hnRNP A2/B1 is involved. The verification of this hypothesis is required in future studies.

Conflict of interest

All authors declare no conflict of interest.

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Transparency document

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