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Protein arginine methyltransferase 5 (PRMT5) is a novel coactivator of constitutive androstane receptor (CAR)

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ABSTRACT

The constitutive androstane receptor (CAR) plays a key role in the expression of xenobiotic/steroid and drug metabolizing enzymes and their transporters. In this study, we demonstrated that protein arginine methyltransferase 5 (PRMT5) is a novel CAR-interacting protein. Furthermore, the PRMT-dependent induction of a CAR reporter gene, which was independent of methyltransferase activity, was enhanced in the presence of steroid receptor coactivator 1 (SRC1), peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1α) or DEAD box DNA/RNA helicase DP97. Using tetracycline inducible-hCAR system in HepG2 cells, we showed that knockdown of PRMT5 with small interfering RNA suppressed tetracycline -induced mRNA expression of *CYP2B6* but not of *CYP2C9* or *CYP3A4*. PRMT5 enhanced phenobarbital-mediated transactivation of a phenobarbital-responsive enhancer module (PBREM)-driven reporter gene in co-operation with PGC-1α in rat primary hepatocytes. Based on these findings, we suggest PRMT5 to be a gene (or promoter)-selective coactivator of CAR by mediating the formation of complexes between hCAR and appropriate coactivators.

1. Introduction

The constitutive androstane receptor (CAR; NR1I3), a member of the nuclear receptor superfamily, plays a key role in responses to xenochemical stimuli by enhancing the expression of various xenobiotic-metabolizing enzymes and transporters [1–3]. CAR is predominantly localized in the cytoplasm of hepatocytes *in vivo* and in primary hepatocytes, and translocates to the nucleus in response to ligands or activators. 1,4-bis[2-(3,5-dichloro pyridyloxy)]benzene (TCPOBOP) and 6-(4-Chlorophenyl)imidazo [2,1-b] [1,3]thiazole-5-carbaldehyde O-3,4-dichlorobenzyl)oxime (CITCO) are ligands for mouse CAR and human CAR, respectively, whereas phenobarbital (PB) is an indirect CAR activator in both species [1,2,4]. Following nuclear translocation, CAR binds to response elements in the promoters of target genes, forming a heterodimer with retinoid X receptor α (RXRα) [5]. The CAR:RXR heterodimer complex recruits coactivators, such as steroid receptor coactivator 1 (SRC-1) [6], transcriptional intermediary factor 2 (TIF2) [7], SRC-3 [8], DEAD box DNA/RNA helicase DP97 [9] and peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC1α) [10]. Unlike other nuclear receptors, CAR is able to recruit coactivators without ligand binding. Therefore, CAR is often referred to as a constitutively active receptor [5].

Protein arginine methyltransferase 5 (PRMT5) is a type II protein arginine methyltransferase that catalyzes the symmetrical dimethylation of target proteins. PRMT5 is implicated in diverse cellular and biological processes, such as Golgi apparatus structure maintenance [11], cell survival [12], ribosome assembly [13], cell cycle progression [14], and transcriptional regulation. PRMT5 is known to be included in the SWI/SNF chromatin remodeling complex. Human SWI/SNF-associated PRMT5 methylates histone H3 arginine 8 and negatively regulates expression of ST7 and NM23 tumor suppressor genes [15].

In the current study, we identified PRMT5 as a novel CAR-binding protein using co-immunoprecipitation assay. We also showed that it plays a role as a gene selective coactivator of CAR. Furthermore, PRMT5 coactivates the transcriptional activity of CAR independently of its methyltransferase activity.

Abbreviations: CAR, constitutive androstane receptor; PRMT5, Protein arginine methyltransferase 5; CYP2B6, cytochrome P450 2B6; CYP2C9, cytochrome P450 2C9; CYP3A4, cytochrome P450 3A4; PBREM, phenobarbital-responsive enhancer module; SRC-1, steroid receptor coactivator 1; PGC1α, peroxisome proliferator-activated receptor-gamma coactivator 1 alpha.

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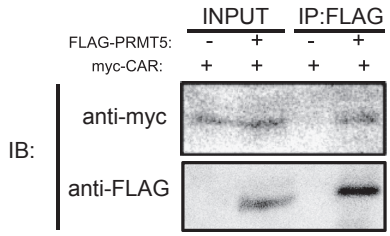

Fig. 1. PRMT5 interacts with CAR. HEK293 cells were transfected with expression plasmids for myc-hCAR and FLAG-PRMT5 (1 μg each), and empty plasmid (1 μg), as indicated. Whole cell extracts were co-immunoprecipitated using Anti-DDDDK-tag mAb-Magnetic beads. Co-precipitants were resolved by SDS-PAGE and detected by western blot analysis using anti-myc and anti-FLAG antibodies.

2. Materials and methods

2.1. Chemicals and plasmid construction

Tetracycline (Tet) and PK11195 were purchased from Sigma Aldrich (St. Louis, MO). The construction of human CAR (pcDNA-hCAR) expression plasmids has been reported previously [9,16,17]. The hCAR gene was subcloned into pcDNA5/TO (Invitrogen, Carlsbad, CA) with N-terminal myc or FLAG tags. Full-length human *PRMT5* was amplified from a human hepatoma HepG2 cell cDNA and inserted in-frame into pCMV-3Tag-6 (Stratagene Santa Clara, CA). The methyltransferase activity-deficient PRMT5 mutant (PRMT5Δ5), in which the AdoMet binding site GAGRG (residues 365–369) was deleted [18], were constructed by inverse PCR. The DR4-driven luciferase reporter plasmid (pDR4-Luc) was constructed by inserting three tandem repeats of the DR4 motif into pGL4.24 (Promega).

2.2. Cell culture

The HepTR/hCAR cell line was established in HepG2 cells; hCAR was expressed only in the presence of Tet, using the T-REx system (Invitrogen) [9]. Human embryonic kidney HEK293, HepG2 and HepTR/hCAR cells were cultured in Dulbecco's modified Eagle's medium (DMEM; Wako, Osaka, Japan) containing 10% fetal bovine serum (FBS) and penicillin–streptomycin at 37 °C in a humidified atmosphere containing 5% CO_2.

2.3. Co-immunoprecipitation assay

Cells seeded in 60-mm plates were transfected with expression plasmids for FLAG-PRMT5 alone or in combination with myc-hCAR using PEI Max reagent (Polysciences Inc., Warrington, PA). At 48 h post-transfection, cells were harvested after being washed twice with ice-cold phosphate-buffered saline (PBS) and suspended in lysis buffer (50 mM Tris–HCl, 1 mM EDTA, 150 mM NaCl, and 1% Triton X-100) containing a protease inhibitor cocktail (Roche Diagnostics). Supernatants were incubated with Anti-DDDDK-tag mAb-Magnetic beads (MBL, Nagoya, Japan) at 4 °C for 4 h. The beads were washed three times with wash buffer (50 mM Tris–HCl, 1 mM EDTA, 650 mM NaCl, and 0.1% Triton X-100) and then suspended in sodium dodecyl sulfate (SDS) sample buffer. The co-immunoprecipitated proteins were then separated by SDS–polyacrylamide gel electrophoresis (SDS–PAGE) and detected by western blotting using anti-myc-tag and anti-DDDDK-tag antibodies (MBL). The signals were captured by Typhoon 9500 (GE health care).

2.4. Luciferase reporter assay

HEK293 cells were transfected using PEI Max reagent and the appropriate expression plasmids, with pGL4.74 (hRluc/TK; Promega) used as an internal standard. After overnight incubation, luciferase activity was measured using the Dual-Luciferase Reporter Assay System (Promega). The activities of firefly luciferase were normalized against those of Renilla luciferase.

2.5. Knockdown experiment

HepTR/hCAR cells were transfected with *PRMT5*-targeting or control small interfering RNA (siRNA; Invitrogen) using Lipofectamine RNAiMAX reagent (Invitrogen) according to the manufacturer's instructions.

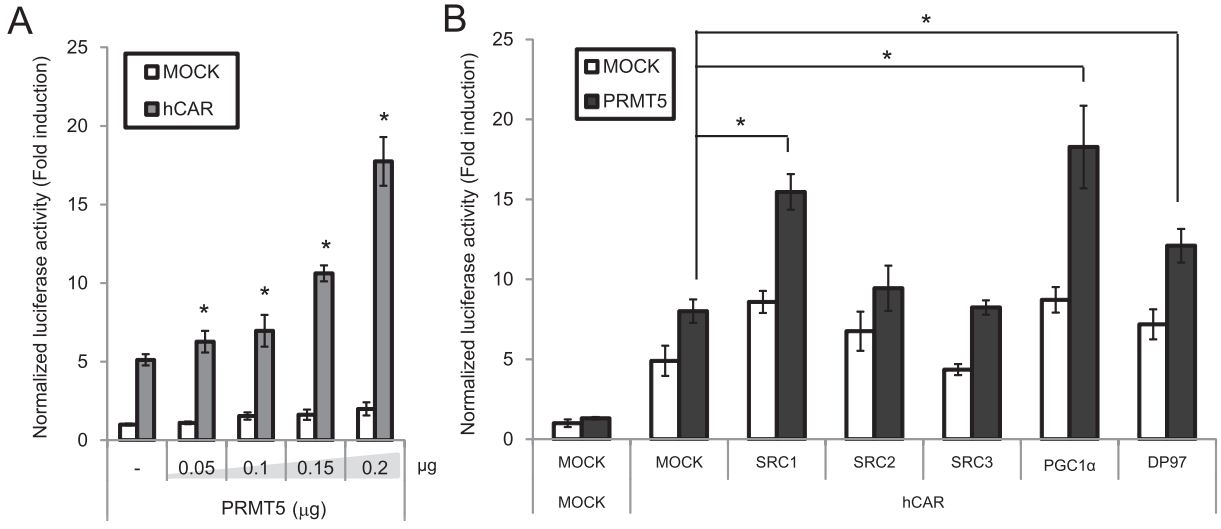

Fig. 2. PRMT5 enhances the transcriptional activity of CAR. (A) HEK293 cells were co-transfected with the DR4-luciferase reporter plasmid (0.1 μg), pGL4.74 (0.01 μg) and expression plasmids for hCAR (0.05 μg) and PRMT5 (0.05–0.2 μg), and empty plasmid, as indicated. Cells were harvested and luciferase activity was measured at 24 h post-transfection. Results are presented as Renilla-normalized luciferase activity and expressed as the mean ± S.D. (*$p < 0.05$; $n = 4$). The Graph was represented one of three independent experiments. (B) HEK293 cells were co-transfected with the DR4-luciferase reporter plasmid (0.1 μg), pGL4.74 (0.01 μg) and expression plasmids for hCAR(0.05 μg), PRMT5(0.15 μg), SRC-1, SRC-2, SRC3, PGC1α and DP97(0.1 μg each), and empty plasmid, as indicated. Cells were harvested and luciferase activity was measured at 24 h post-transfection. Results are presented as Renilla-normalized luciferase activity and expressed as the mean ± S.D. ($n = 3$).

2.6. Quantitative RT-PCR

Total RNA was isolated using ISOGEN II (Nippon Gene Co. Ltd, Tokyo, Japan) and cDNA was synthesized using a ReverTraAce qPCR RT Kit (Toyobo Co., Osaka, Japan). Quantitative RT-PCR (qRT-PCR) was conducted in a final volume of 25 μl using the THUNDERBIRD™ SYBR qPCR Mix (Toyobo) according to the manufacturer's protocol and using 7500 fast system SDS software (Applied Biosystems). The specific primers used were as follows: *CYP2B6* (5′-AAG CGG ATT TGT CTT GGT GAA-3′ and 5′-TGG AGG ATG GTG GTG AAG AAG-3′), *CYP3A4* (5′-CCA AGC TAT GCT CTT CAC CG-3′ and 5′-TCA GGC TCC ACT TAC GGT GC-3′), *CYP2C9* (5′-AAC ATG CAGAAA AGA AAT GCC-3′ and 5′-CCT CCA TTA CGG AGA GTT TCC-3′), UGT1A1(5′-AGTG-GATGGCAGCCACTGGCT-3′ and 5′-CAGTAAGTGGGAACAGCCAGA-3′), PR*MT5* (5′-AAC CAT CAA AAC AAG AAC AG-3′ and 5′-CAC CAA TCT ATG AAG ACC TC-3′) and *β-actin* (5′-TCC TCCTGA GCG CAA GTA CTC-3′ and 5′-CTG CTT GCT GAT CCA CAT CTG-3′).

2.7. Statistical analysis

Statistical comparisons were performed with one-way analysis of variance (ANOVA) followed by Dunnett's multiple comparison test as the post hoc test, and differences were considered statistically significant at $^{*}p < 0.05$.

3. Results

3.1. PRMT5 interacts physically with CAR

We have previously shown by co-immunoprecipitation assays that the DEAD box DNA/RNA helicase DP97 is among the CAR binding proteins [9]. Furthermore, DP97 was found to coactivate the transcriptional activity of hCAR. In the same co-immunoprecipitate, PRMT5 was also identified as a CAR interacting protein. We therefore initially confirmed the physical interaction between hCAR and PRMT5 by co-immunoprecipitation assays in HEK293 cells transfected with FLAG-tagged PRMT5 (FLAG-PRMT5) and myc-tagged hCAR (myc-hCAR), as shown in Fig. 1.

3.2. PRMT5 enhances CAR-mediated transcriptional activation in synergy with SRC-1, PGC1α and DP97

We analyzed the effect of PRMT5 on CAR-mediated transactivation using a DR4-luciferase reporter plasmid (DR4-luc) in HEK293 cells. PRMT5 significantly enhanced hCAR-mediated transactivation of DR4-luc in a dose-dependent manner (Fig. 2A). Furthermore, we investigated the effect of other known CAR coactivators, SRC-1, SRC-2, SRC-3, PGC1α and DP97, on the transcriptional activity of hCAR in either the presence or absence of PRMT5 (Fig. 2B). SRC-1, SRC-2, PGC1α, DP97 and PRMT5 individually enhanced hCAR-mediated transactivation. Synergistic activation of hCAR was observed when PRMT5 was co-expressed with SRC-1, PGC1α or DP97.

3.3. The methyltransferase activity of PRMT5 is not required for coactivation of CAR

PRMT5 is a type II protein arginine methyltransferase. Methylation of histone protein is required for PRMT5 to trigger the transcriptional repression of genes. To investigate whether the methyltransferase activity is required for coactivation of CAR by PRMT5, the S-adenosyl-L-methionine (AdoMet) binding site-deletion mutant (PRMT5Δ5) was used [18]. The interaction of PRMT5Δ5 with hCAR was observed as in the case of wild-type PRMT5 (Fig. 3A). PRMT5Δ5 enhanced hCAR-mediated transactivation similarly to wild-type PRMT5 (Fig. 3B). These observations indicate that the methyltransferase activity of PRMT5 is not required for the regulation of CAR-mediated transactivation.

3.4. PRMT5 selectively enhances the CAR-mediated expression of CYP2B6

To investigate the effects of PRMT5 on the expression of endogenous genes that are regulated by CAR, *PRMT5* was knocked down by *PRMT5*-targeting siRNA in HepG2 cells Tet-dependently expressing hCAR (HepTR/hCAR) (Fig. 4A). The up-regulation of mRNA levels of CAR target genes, such as *CYP2B6*, *CYP2C9*, *CYP3A4* and *UGT1A1*, was investigated after treatment with Tet for 24 h. Knockdown of *PRMT5* with siRNA suppressed Tet-inducible *CYP2B6* mRNA expression. In contrast, the induction of *CYP2C9*, *CYP3A4* and *UGT1A1* mRNA was not affected by knockdown of *PRMT5* (Fig. 4B).

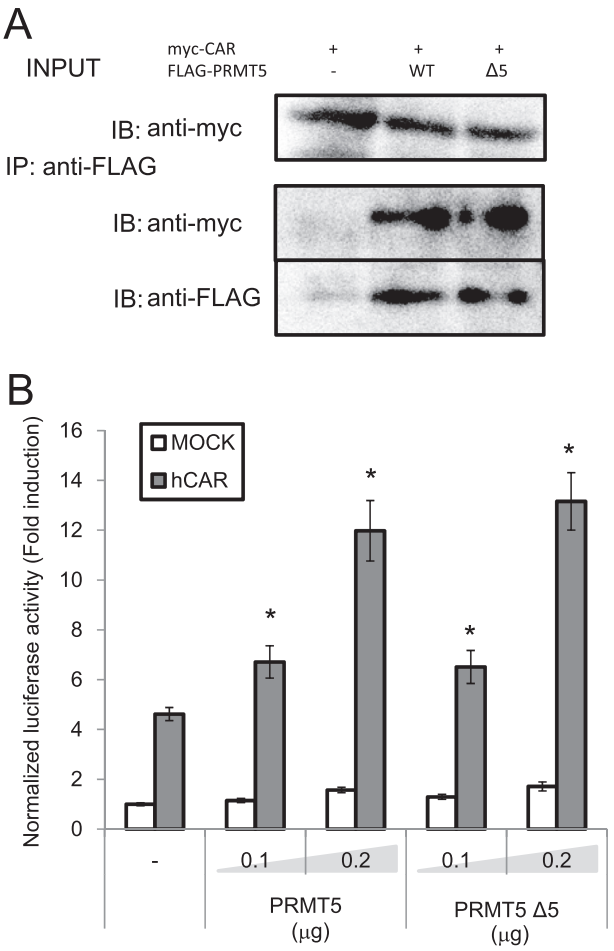

Fig. 3. Enhancement of CAR transcriptional activity by PRMT5 is methyltransferase activity independent. (A) HEK293 cells were co-transfected with expression plasmids for myc-hCAR and FLAG-PRMT5(WT), FLAG-PRMT5Δ5(Δ5) (1 μg each), or empty plasmid, as indicated. Whole cell extracts were co-immunoprecipitated using anti-Anti-DDDDK-tag mAb-Magnetic beads. Co-precipitants were resolved by SDS-PAGE and detected by western blot analysis using anti-myc and anti-FLAG antibodies. (B) HEK293 cells were co-transfected with the DR4-luciferase reporter plasmid (0.1 μg), pGL4.74 (0.01 μg) and expression plasmids for hCAR (0.05 μg), PRMT5 or PRMT5Δ5 (0.1 μg or 0.2 μg each), and empty plasmid (0.1 μg), as indicated. Luciferase activity was measured at 24 h post-transfection. Cells were harvested and luciferase activity measured. Results are presented as Renilla-normalized luciferase activity and expressed as the mean ± S.D. ($^{*}p < 0.05$; n = 4). The Graph was represented one of three independent experiments.

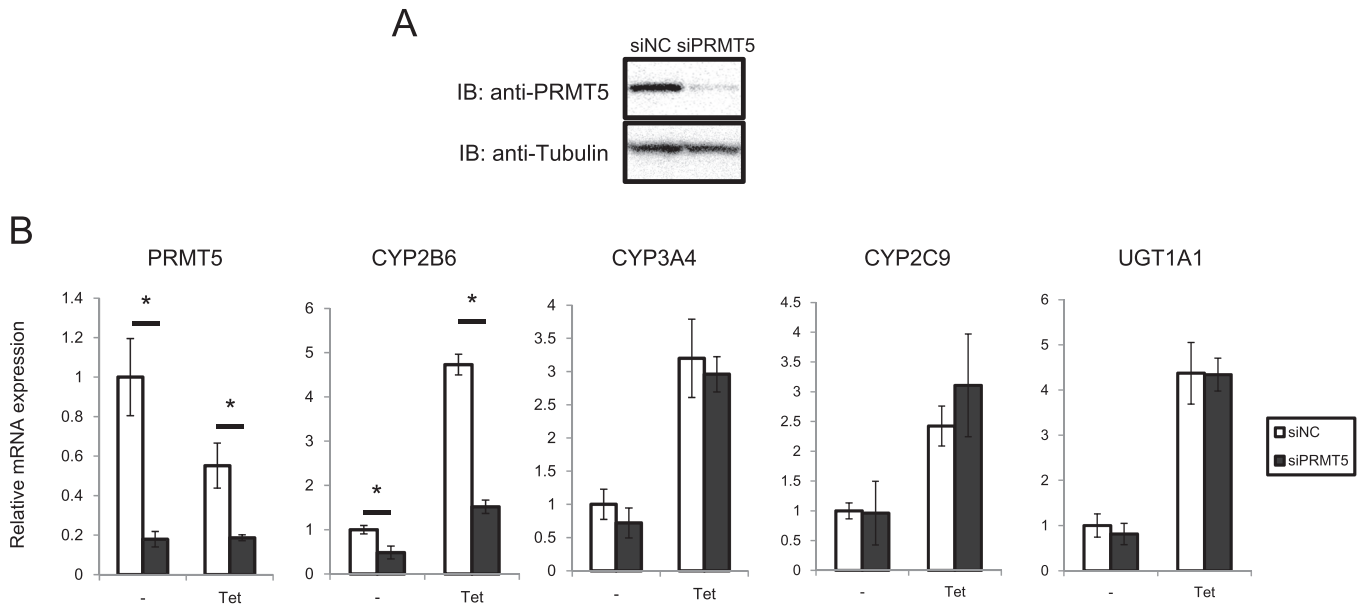

Fig. 4. Gene-specific regulation of PRMT5. HepTR/hCAR cells were treated with PRMT5-targeting or control siRNA. After 48 h, cells were treated with Tet or solvent for an additional 24 h. (A) Whole-cell lysates were resolved by SDS-PAGE, and protein was detected by immunoblotting using anti-PRMT5 and anti-tubulin antibodies. (B) The levels of PRMT5, CYP2B6, CYP3A4 and CYP2C9 mRNA were measured by qRT-PCR. Results were normalized against those for β-actin and expressed as the mean ± S.D. (*$p < 0.05$; $n = 3$). The Graph was represented one of three independent experiments.

4. Discussion

The chromatin remodeling complex SWI/SNF is known to regulate the transcription of several genes by controlling chromatin structure in an ATP-dependent manner. PRMT5 has been identified, as part of the SWI/SNF complex, to be present in promoter complexes. It is proposed that PRMT5 hypermethylates promoter histones, H3R8 and H4R3, and may function as a transcriptional repressor of genes, such as *E-cadherin*, *Cyclin E*, *P14ARF*, *P16INK4*, *ST7 and NM23* [15,19–21]. Moreover, PRMT5 regulates transcription by post-translational modification of transcriptional factors. The p65 subunit of NFκB (RelA) is known to be post-translationally modified by PRMT5. Arginine methylation of E2F1 and p53 by PRMT5 reportedly influences protein stability; therefore PRMT5 regulates cell cycle progression and cell death [14,22,23].

Type I PRMTs, PRMT1 and PRMT4/CARM-1 (coactivator-associated arginine methyltransferase 1), are reported to be coactivators of hormone and orphan nuclear receptors [24–27]. CARM-1 methylates arginines 2, 17 and 26 of histone H3. CARM1 acts as an androgen receptor (AR) coactivator, but requires the presence of a p160 coactivator to potentiate AR activity. CARM1 does not bind directly to AR; rather, it is associated with AR through its direct binding to p160 coactivator. Reducing CARM-1 expression diminishes AR-dependent transcription, increases prostate cancer cell proliferation, and induces apoptosis. The correlation between Type II PRMT, PRMT5, and AR has been reported [28]. PRMT5 complexes with AR-interacting protein p44, thereby enhancing AR-mediated transcription in a methyltransferase-independent manner.

In this study, we show that a complex between PRMT5 and CAR was observed for the first time. Luciferase reporter assays demonstrated that PRMT5 enhanced the transcriptional activity of CAR in a dose dependent manner. This PRMT5-enhanced transactivation of CAR was co-operatively affected by the other CAR coactivators, SRC-1, SRC-2, PGC1α and DP97. Interestingly, the methyltransferase activity-deficient mutant of PRMT5 (PRMT5Δ5) enhanced the transcriptional activity of CAR to levels similar to those produced by the wild-type PRMT5. These observations suggest that PRMT5 may be enrolled in the coactivator complex of CAR as an intermediary protein without dependence on methyltransferase activity.

To clarify the role of PRMT5 in CAR-mediated regulation of endogenous genes, we used HepTR/hCAR cells, in which the expression of the CAR gene was induced by Tet. This was necessary because ectopically expressed CAR spontaneously migrates into the nuclear compartment and transactivates CAR target genes in the cultured cell line even in the absence of any ligand [9]. Upon Tet treatment, the mRNA expression of CAR target genes was triggered. The knockdown of PRMT5 reduced the level of CYP2B6 mRNA, whereas the CAR-mediated up-regulation of CYP2C9, CYP3A4 and UGT1A1 mRNA was insensitive to PRMT5 knockdown. These results suggest that PRMT5 acts as a promoter or gene-specific co-regulator of CAR. We previously reported that DP97 was a target gene-selective co-regulator of CAR. The Knockdown of DP97 reduced CAR-mediated mRNA levels of CYP2B6 and UGT1A1 but not of CYP3A4. These observations suggest that CAR-mediated target gene activation is selectively regulated depending on the species of co-factors, as is the case for PRMT4 in promoter-specific NFkB target gene expression [29].

Interestingly, hCAR expression inversely regulated the levels of PRMT5 mRNA (Fig. 4B) and protein (data not shown), suggesting that PRMT5 is a novel target gene of CAR. PRMT5 was recently reported to enhance gluconeogenic gene expression via histone H3R2 methylation [30]. It is known that CAR represses the expression of gluconeogenic genes, such as *G6Pase* and *PEPCK* [31,32]. We speculate that CAR-mediated repression of guluconeogenesis might be partly due to the down-regulation of PRMT5. However, further study will be required.

In summary, we showed that PRMT5 enhanced the transcriptional activity of CAR independently of its methyltransferase activity. The coactivator effect of PRMT5 on the expression of CAR target genes is gene or promoter selective. PRMT5 may play the role of intermediary protein in CAR coactivator complexes.

Conflict of interest

None.

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Transparency document

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