Targeted recruitment of a histone H4-specific methyltransferase by the transcription factor YY1

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Methylation of specific residues within the N-terminal histone tails plays a critical role in regulating eukaryotic gene expression. Although great advances have been made toward identifying histone methyltransferases (HMTs) and elucidating the consequences of histone methylation, little is known about the recruitment of HMTs to regulatory regions of chromatin. Here we report that the sequence-specific DNA-binding transcription factor Yin Yang 1 (YY1) binds to and recruits the histone H4 (Arg 3)-specific methyltransferase, PRMT1, to a YY1-activated promoter. Our data confirm that histone methylation does not occur randomly but rather is a targeted event and provides one mechanism by which HMTs can be recruited to chromatin to activate gene expression.

[Keywords: Histone methyltransferase; PRMT1; transcription factor YY1]

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enzymes that methylate core histones, Zhang and colleagues purified PRMT1, which accounts for most of the type I protein arginine methyltransferase activity in cells, as an H4-specific Arg 3 HMT [Wang et al. 2001]. Interestingly, the HMT activity of PRMT1 is required for PRMT1 to function as a coactivator of nuclear hormone receptors, suggesting that the HMT activity of PRMT1 is involved in transcriptional activation. Similarly, a study by Allis and colleagues showed that PRMT1 is the major, if not exclusive, H4 Arg 3-methyltransferase in human 293 cells [Strahl et al. 2001]. It is now clear from these studies that PRMT1 is an H4-specific arginine HMT and that methylation of histone H4 Arg 3 could result in transcriptional activation. However, it is unclear how PRMT1 is targeted to specific promoters or transcriptional regulatory regions.

YY1 (Yin Yang 1) is a 414-amino-acid Krüppel-related zinc finger transcription factor that binds to the CGC CATNNT consensus DNA element located in promoters and enhancers of many cellular and viral genes [Shi et al. 1997; Thomas and Seto 1999]. Like many transcription factors, YY1 requires coactivators and corepressors to function properly. Interestingly, YY1 appears to be equally effective as an activator and as a repressor depending on its relative concentration, its binding partners, and on promoter context. Although reports of the number of genes that might be regulated by YY1 are ever-increasing, the exact mechanisms by which this factor regulates transcription are still unclear.

Over the years, a number of models have been proposed to explain the mechanisms of YY1 action. Of these different models, the recruitment of histone acetyltransferase [HAT] and histone deacetylase [HDAC] enzymes by YY1 is especially appealing and has recently gained the most attention. In the current study, we uncovered an additional histone modification enzyme that could be recruited by YY1 to regulate transcription. Specifically, we found that YY1 binds to PRMT1 and recruits PRMT1 to DNA. The interaction between YY1 and PRMT1 most likely occurs via a bridging protein, the double-stranded RNA-binding protein 76 [DRBP76]. A purified YY1 complex possesses histone H4-specific methyltransferase activity, and results from chromatin immunoprecipitation [ChIP] assays suggest that YY1 directs histone H4 methylation at a YY1-activated, but not a YY1-repressed, promoter. Together, these results provide an example for how one single transcription factor can regulate a diverse number of genes.

Results

Purification of a YY1 complex

To explore how YY1 regulates transcription, we purified a complex containing YY1 by immunoaffinity chromatography using an extract prepared from HeLa cells infected with recombinant adenovirus-expressing Flag epitope-tagged YY1. We found that at least four polypeptides associated specifically with Flag–YY1 [Fig. 1A, lane 2]. As a control, a mock purification was performed on cells infected with an adenovirus expressing green fluorescent protein [GFP; Fig. 1A, lane 1]. Mass spectrometric analysis revealed that the 90-kD YY1-associated protein was either the human interleukin enhancer binding factor 3 [ILF3] or DRBP76, an alternatively spliced product of ILF3 [Fig. 1B, Patel et al. 1999; Duguay et al. 2000]. Based on the molecular mass of the protein and Western blot results with an anti-DRBP76 specific antibody [Fig. 1C], we concluded that the 90-kD YY1-associated protein was DRBP76.

Endogenous YY1 and DRBP76 associate in vivo

To determine whether YY1 interacts with DRBP76 under normal physiological conditions, we tested whether the proteins could be coimmunoprecipitated from a nuclear extract without overexpression of either protein. Indeed, a significant fraction of DRBP76 was coprecipitated by an anti-YY1 antibody, as detected via Western blot analysis with the anti-DRBP76 antibody [Fig. 2A, lane 1]. In contrast, no DRBP76 was detected in anti-Flag precipitates or in a precipitate where no primary antibody was used [Fig. 2A, lanes 2,3].

Taking advantage of the fact that YY1, with its unusually long stretch of consecutive histidines [Shi et al. 1991], binds strongly to a nickel affinity column, we purified an endogenous native YY1 complex from HeLa cells using a simple conventional chromatography procedure [Fig. 2B]. In-gel tryptic digestion of the 90-kD YY1-associated protein followed by sequencing by microcapillary HPLC ion trap mass spectrometry again revealed that the 90-kD protein was DRBP76. This result unequivocally confirms that DRBP76 partners with YY1 in vivo.

DRBP76 binds YY1 through residues 261–333 of YY1

To identify the YY1 domain that interacts with DRBP76, we tested the ability of different GST–YY1 fusion proteins to bind DRBP76. DRBP76 was captured by full-length YY1 (1–414) fused to GST, but not by the GST polypeptide alone [Fig. 3, lanes 5,6,7,8]. Extensive analysis of YY1 segments indicated that DRBP76 interacted with residues 261–333 of YY1. Interestingly, this same conserved region of YY1 binds HDACs [Yao et al. 2001].

Interaction between YY1 and PRMT1

ILF3 is known to bind specifically to PRMT1 [Tang et al. 2000]. Because DRBP76 is nearly identical to ILF3, we predicted that DRBP76 would also interact with PRMT1, and we sought to determine whether YY1 interacts with PRMT1, possibly through DRBP76. As expected, anti-Flag antibody coprecipitated PRMT1 from extracts of cells that expressed Flag–DRBP76 [Fig. 4A, lane 3]. Intriguingly, anti-Flag antibody also specifically coprecipi-
Figure 1. YY1 physically associates with DRBP76. (A) Silver-stained SDS-PAGE of the Flag–YY1 complex. “Control” indicates an anti-Flag immunopurified sample prepared from HeLa cells transduced with adenovirus expressing GFP. In addition to Flag–YY1, arrows indicate proteins copurified, in approximately stoichiometrically equivalent amounts, with Flag–YY1. (B) Amino acid sequence of DRBP76 and ILF3. Each dash (–) indicates an amino acid in ILF3 that is identical to the corresponding one in DRBP76. Peptide sequences obtained by microsequencing are underlined. (C) An immunoblot of the purified Flag–YY1 complex using an anti-DRBP76 antibody.
tated PRMT1 from extracts of cells transfected with a Flag–YY1 expression vector or infected with recombinant adenovirus that expressed Flag–YY1 (Fig. 4B, lane 1, C, lane 1). The interaction between PRMT1 and YY1 remains intact under stringent immunoprecipitation conditions, suggesting that PRMT1 binds avidly to YY1 in vivo (Fig. 4C, lane 4).

To address the likelihood that YY1–DRBP76–PRMT1 exists as a tricomplex, we performed Western blot analysis on the Flag–YY1 complex where we identified DRBP76. Although at this time we cannot rule out the possibility that the YY1–PRMT1 interaction takes place without DRBP76, the presence of PRMT1 in the purified Flag–YY1 complex (Fig. 4D, lane 3) clearly favors the idea that DRBP76 acts as a bridging protein between YY1 and PRMT1.

Recruitment of histone H4-specific methyltransferase activity by YY1

Because PRMT1 selectively methylates Arg 3 of histone H4 (Strahl et al. 2001; Wang et al. 2001), we determined whether the YY1–PRMT1 interaction could result in the recruitment of H4-specific HMT enzymatic activity by YY1. Immunoprecipitates from Flag–DRBP76 transfected cells were prepared using an anti-Flag antibody, and assayed for HMT activity. As shown in Figure 5A, the Flag–DRBP76 immunocomplex contains unique H4-specific HMT activity (Fig. 5A, lane 3). Similarly, a Flag–YY1 immunocomplex efficiently methylated H4, but not H2A, H2B, or H3 (Fig. 5B, lane 3), thus reinforcing the idea that YY1 specifically binds PRMT1 and recruits H4-specific HMT activity.

Recruitment of PRMT1 to a YY1-inducible promoter

Earlier reports suggested that methylation of Arg 3 of histone H4 by PRMT1 resulted in transcriptional activation [Strahl et al. 2001; Wang et al. 2001]. We therefore hypothesized that YY1 could recruit PRMT1 to YY1-activated, but not YY1-repressed, promoters. To test this, ChIP assays were performed with the mouse c-myc promoter, which is known to be positively regulated by YY1 (Riggs et al. 1993). For comparative purposes, ChIP assays also were done using the YY1-repressed c-fos promoter (Gualberto et al. 1992; Natesan and Gilman 1993). Chromatin prepared from untreated NIH3T3 cells, or
NIH3T3 cells expressing various amounts of YY1, was immunoprecipitated with anti-YY1, anti-PRMT1, or anti-methyl arginine antibodies. PCR analyses showed that PRMT1 associated with the c-myc promoter (Fig. 6A, lanes 4–6), but not the c-fos promoter. Further, the amount of PRMT1 present on the c-myc promoter was directly proportional to the amount of YY1 expressed in cells. Importantly, increased arginine methylation occurred in response to increased expression of YY1 at the c-myc, but not at the c-fos promoter (Fig. 6A, lanes 7–9). Consistent with our observations that YY1 binds PRMT1, and that the YY1-containing complex possesses H4-specific HMT activity, methylation of histone H3 at Arg17 was not affected by YY1 abundance (Fig. 6A, lanes 10–12). Neither PRMT1 nor arginine methylation level changed at the c-myc promoter by overexpression of the GFP protein (Fig. 6B). Semiquantitative reverse transcriptase PCR (RT–PCR) analysis (Wang et al. 2002) was performed to confirm activation of c-myc by YY1 (Fig. 6C). Together, our results provide firm evidence that YY1 specifically targets histone H4 for methylation.

Further experimental evidence showing that YY1 recruits PRMT1, through DRBP76, to activate transcription

To obtain additional evidence that YY1 recruits PRMT1 via DRBP76, we performed transfection-reporter assays with a c-myc promoter luciferase construct (Fig. 7A). Consistent with earlier studies (Riggs et al. 1993), a plasmid that expresses wild-type YY1 activated the c-myc promoter in a dose-dependent fashion (Fig. 7B, top graph). Importantly, in agreement with the observation that YY1 interacts with DRBP76 through residues 261–333, the ability to activate the c-myc promoter was completely abolished by a YY1 mutant containing a deletion of residues 261–333. In a similar experiment, wild-type, but not a C-terminally truncated, DRBP76 activated the c-myc promoter (Fig. 7B, bottom graph).

Finally, to prove that the ability of YY1 to bind PRMT1 correlates with activation, we employed a DNA vector-based RNAi method to suppress PRMT1 expression in HeLa cells, and determined the consequences of YY1-dependent transcription on the c-myc promoter. siRNA synthesized from the BS/U6 template (Sui et al. 2002) was targeted to PRMT1 and efficiently inhibited endogenous PRMT1, but not the control protein β-actin, with expression monitored by immunoblotting analysis (Fig. 7C, bottom, lanes 3,6). Mock transfected cells or cells transfected with the BS/U6 vector had no effect on the PRMT1 gene product (Fig. 7C, bottom, lanes 1,2). In total agreement with the observation that YY1 targets PRMT1 to activate the c-myc promoter, luciferase activity was significantly reduced from the c-myc promoter reporter [SN-Luc] in the presence of the pBS/U6–PRMT1 construct (Fig. 7C, top left panel). Expression of siRNA
from the pBS/U6–PRMT1 plasmid had no effect on c-myc promoter reporters with mutated (mmSN-Luc) or deleted (AN-Luc) YY1-binding sites (Fig. 7C, top middle and right panels). Taken together, these results provide strong supporting evidence that YY1 recruits PRMT1 to activate transcription.

Discussion

YY1 is a protein with dual potential and may either activate or repress the transcription of a long list of genes (Shi et al. 1997; Thomas and Seto 1999). YY1 was the first sequence-specific DNA-binding transcription factor shown to recruit HDACs to repress transcription (Yang et al. 1996). In the study presented here, we found that YY1 recruits an additional histone-modifying enzyme, PRMT1. In this respect, YY1 is similar to the retinoblastoma (Rb) protein that not only binds HDACs but also forms a complex with HMT to target histone methylation (Brehm et al. 1998; Magnaghi-Jaulin et al. 1998; Nielsen et al. 2001; Vandel et al. 2001). Unlike YY1, Rb targets Lys 9 of histone H3 for methylation by associating with SUV39H1 and consequently repressing transcription. A recent study also showed that the transcription factor E2F-6 contributes to gene silencing by recruiting HMTase1 and G9a to methylate Lys 9 of H3 independent of Rb (Ogawa et al. 2002). In addition, HP1 recruits SUV39H1 to heterochromatin and simultaneously associates with MTR, HDAC4, and HDAC5 to repress transcription (Zhang et al. 2002). To date, YY1 is the only human sequence-specific DNA-binding transcription factor that associates with HDACs for transcriptional repression and with PRMT1 for transcriptional activation. An important question that needs to be addressed in the near future is whether recruitment of multiple histone modification enzymes by a single factor is a general feature for many sequence-specific DNA-binding transcription factors.

ILF3, with an apparent molecular mass of 110 kD, is one of several proteins that can bind to the antigen receptor response element 2 (ARRE-2) sequence (Li et al. 1992). Several double-stranded RNA-binding proteins, including NF90, MMP4, TCP80, and DRBP76, are either polymorphic variants or products of alternative splicing of the ILF3 transcript. In addition to double-stranded RNA binding, NF90 is involved in specific DNA binding (Corthesy and Kao 1994; Kao et al. 1994; Sakamoto et al. 1999) and TCP80 might regulate protein translation (Xu and Grabowski 1999). The product of the MMP4 gene, which was initially isolated as an incomplete cDNA of DRBP76, was identified as an M-phase phosphoprotein, suggesting that it may have a special function in cell
division [Matsumoto-Taniura et al. 1996]. In addition, DRBP76 has been reported to serve as a substrate for the interferon-induced protein kinase, PKR, and contribute to a role for PKR in cell-cycle regulation. Our finding that DRBP76, like ILF3, interacts with PRMT1 provides an additional function for this protein not previously described.

We have precisely mapped the DRBP76-interacting domain to residues 261–333 of YY1. However, we do not yet know the exact PRMT1-interacting domain within DRBP76. Earlier studies demonstrated that the C-terminal region of ILF3 [residues 622–910] is responsible for the interaction between PRMT1 and ILF3 [Tang et al. 2000]. The absence of a DRBP76 C terminus corresponding to residues 701–910 of ILF3 suggests that the minimal PRMT1-interacting domain may reside within residues 622–700 of DRBP76. Our finding that a DRBP76 C-terminal deletion mutant, DRBP76 (1–588) failed to activate the c-myc promoter supports this arrangement.

It is well known that many proteins besides histone H4 can be methylated by PRMT1 (McBride and Silver 2001). Consistent with a recent report [Gabellini et al.

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**Figure 5.** A purified YY1 complex methylates histone H4. Anti-Flag immunoprecipitates obtained either from HeLa cells transfected with plasmids expressing Flag-DRBP76 (A) or from immunopurification of Flag–YY1 (B) were assayed for methylase activity in the presence of core histones. “Flag competitor” corresponds to the addition of excess Flag peptide immunogen. Negative controls include immunoprecipitates from mock transfected cells and anti-Flag immunopurified materials from cells transduced with adenovirus expressing the GFP. Purified recombinant SUV39H1 was used as a positive control for histone H3 methylation. Each blot was stained with Amido black to ensure proper protein transfer.

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**Figure 6.** YY1-dependent recruitment of PRMT1. (A,B) Cross-linked chromatin from NIH3T3 cells nontransduced or transduced with YY1- or GFP-expressing adenovirus was immunoprecipitated with the indicated antibodies and analyzed by PCR using primers specific for DNA surrounding YY1 sites in the c-myc and c-fos promoters. Identical results were obtained from multiple experiments. (C) Semiquantitative RT–PCR was performed to analyze expression of the c-myc gene in YY1-expressing cells. PCR products of cDNA samples are shown.
Figure 7. DRBP76- and PRMT1-dependent activation by YY1. (A) Schematic diagram of effector and reporter plasmids. (B,C) Expression plasmids and reporter plasmids were transfected together into HeLa cells as indicated. Luciferase activities are the averages ± S.D. from three separate experiments. Western blots were performed to monitor protein expression.
2002), we found that nucleolin, a protein that induces chromatin decondensation by binding to histone H1, co-purified with YY1 [data not shown]. Additionally, a human homolog of the yeast protein RRP5 was identified in our Flag–YY1 complex [data not shown]. Like DRBP76, both nucleolin and RRP5 contain conserved RNA-binding domains, a hallmark of many PRMT1 substrates [Wada et al. 2002]. In future studies, it will be important to determine whether nucleolin and RRP5 can also serve as substrates for YY1-bound PRMT1 and to determine the biological role of YY1 in these potential PRMT1 substrates.

It is interesting to note that the HMT-interacting domain of YY1 is identical to one of the HDAC-interacting domains. At this time, we do not know if the interaction of YY1 with HMT and HDACs is mutually exclusive or synergistic. In vitro, the acetylated histone H4 tail is a poor substrate for PRMT1 [Wang et al. 2001]. It is conceivable then, that YY1 could facilitate H4 Arg 3 methylation by targeting PRMT1 to chromatin regions undergoing active histone deacetylation [Fig. 8]. Perhaps deacetylation of lysines in histone tails by YY1-bound HDACs conveniently accelerates the rate or efficiency with which YY1-targeted PRMT1 can methylate Arg 3 of H4. The challenge ahead is to determine the signal that dictates the recruitment of these two different activities by YY1.

**Materials and methods**

**Plasmids**

pBS/U6–PRMT1 was constructed by inserting an oligodeoxynucleotide corresponding to nucleotides 977–998 of PRMT1 cDNA [5′-GGCGAGGAGATCTTCGGCACCAA-3′ (forward) and 5′-AGCTTTGGTGCCGAAGATCTCCTCGCC-3′ (reverse)] into pBS/U6 [Sui et al. 2002] between the Apal and HindIII sites. The second inverted sequence [5′-AGCTTTGGTGCCGAA GATCTCCTCGCC-3′ (forward) and 5′-AATTCAAA AAGGGCAGGAGATCTCCTCGCCACCAA-3′ (reverse)] then was inserted into the intermediate plasmid between the HindIII and EcoRI sites to generate the final product. Details of all other plasmid constructions are available upon request.

![Figure 8](https://example.com/figure8.png)

**Figure 8.** A model of gene activation and repression by YY1 through recruitment of histone-modifying enzymes.

**Immunological reagents and techniques**

Anti-Flag and anti-β-actin antibodies were obtained from Sigma Biochemical. Anti-DRBP76 and anti-YY1 antibodies were obtained from BD Biosciences and Santa Cruz Biotechnology, respectively. Anti-PRMT1, anti-methyl arginine, and anti-R17H3 antibodies were obtained from Abcam. Immunoprecipitations were performed in a solution of PBS containing NP-40 and protease inhibitors, as described [Laherty et al. 1997]. Immunocomplexes were washed six times with the same buffer, and immunoprecipitated proteins were removed from protein A beads by boiling in gel loading buffer. For Western blot analyses, proteins were resolved on SDS–polyacrylamide gels and transferred to nitrocellulose membranes. After blocking with nonfat dried milk, the membranes were probed with antibodies and developed with the SuperSignal West Pico Chemiluminescent Substrate (Pierce).

**Purification of YY1 complexes**

A nuclear extract was prepared from HeLa cells transfected with recombinant adenovirus expressing Flag–YY1. Affinity purification of the Flag–YY1 complex with anti-Flag antibody was performed according to the protocol used for purification of a Flag–PCAF complex [Ogryzko et al. 1998]. Purified samples were concentrated, resolved by SDS–PAGE, and analyzed by silver staining. A Coomassie blue-stained sample was prepared in parallel and the band corresponding to p90 was excised; samples were sequenced by peptide mass spectrometry. For purification of an endogenous YY1 complex, a HeLa cell nuclear extract was prepared and fractionated on 20 mL of P11 phosphocellulose [Whatman] using a 0.1–1 M KCl step gradient in a buffer containing 20 mM Tris-HCl (pH 8.0), 4 mM EDTA, 10% glycerol, 1 mM PMSE, and 0.5 mM DTT. Fractions containing active YY1 were loaded onto a Q Sepharose column (Pharmacia), washed, and eluted using a 0.1–1 M linear gradient. Active fractions from this second column were combined and loaded onto a Ni-NTA resin column (Novagen). The final column was washed with 50 mM imidazole, and the YY1 complex was eluted with 300 mM imidazole.

**Electrophoretic mobility shift assays (EMSSAs)**

Single-stranded oligodeoxynucleotides corresponding to a consensus YY1-binding site (5′-AGGGCTTCCATTTTGAAGC-3′ and its complement) were labeled individually with γ32P-ATP and T4 polynucleotide kinase, heated together to 65°C, and allowed to anneal by slow cooling to room temperature. Each 12 µL reaction mixture contained 12 mM Hepes (pH 7.9), 10% glycerol, 5 mM MgCl2, 60 mM KCl, 1 mM DTT, 0.5 mM EDTA, 50 µg/mL bovine serum albumin, 0.05% NP-40, 0.1 µg poly(dI–dC), purified proteins, and 5 fmole radiolabeled DNA. Reactions were incubated for 10 min at room temperature, separated on 4% nondenaturing polyacrylamide gels, dried, and autoradiographed.

**GST pull-down assays**

GST, GST–YY1, and GST–YY1 deletion mutants were expressed and purified as described [Yang et al. 1997]. 5′S-DRBP76 was prepared using the coupled transcription-translation rabbit reticulocyte lysate system [Promega]. Equimolar quantities of GST or GST–YY1 conjugated to glutathione-Sepharose beads were incubated with radiolabeled DRBP76. Binding reactions, washing conditions, electrophoretic analysis, and subsequent autoradiography were performed as previously described [Yang et al. 1997].
Methyltransferase assay
For each reaction, 4 µg of chicken core histones were incubated with 0.55 µCi of S-adenosyl-L-[methyl-3H]methionine (Perkin Elmer) in MTase buffer [50 mM Tris at pH 8.0] for 1 h at 30°C in a final volume of 50 µl. The reactions were terminated by the addition of SDS gel loading buffer followed by heating for 10 min at 95°C. Samples were separated by SDS-PAGE and transferred onto PVDF membranes. Membranes were exposed to X-ray film in the presence of a Kodak transcreen LE.

ChIP assay
ChIP assays were performed essentially as described (Weinmann et al. 2001). Briefly, mouse NIH3T3 cells were treated with formaldehyde, and chromatin was purified on CsCl-equilibrium gradients. After ultracentrifugation, DNA containing fractions were dialyzed and kept frozen at −80°C in aliquots. Equal amounts of purified chromatin were incubated overnight with different antibodies and collected on protein A beads. Cross-linked products were reversed by heating overnight at 65°C, and the immunoprecipitated DNA was purified by protein A beads. Cross-linked products were reversed by heating overnight at 65°C, and the immunoprecipitated DNA was purified by protein A beads. Cross-linked products were reversed by heating overnight at 65°C, and the immunoprecipitated DNA was purified by protein A beads. Cross-linked products were reversed by heating overnight at 65°C, and the immunoprecipitated DNA was purified by protein A beads.

Transfection and luciferase assay
HeLa cells were transfected with different combinations of plasmids directing the synthesis of various effector proteins or siRNA plus a luciferase reporter using the Fugene 6 transfection reagent (Roche). All transfections were normalized to equal amounts of DNA with parental expression vectors. Forty-eight hours later, cells were collected and luciferase activity was determined using the Dual Luciferase Reporter Assay System (Promega).

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