Androgen Receptor Interacts with the Positive Elongation Factor P-TEFb and Enhances the Efficiency of Transcriptional Elongation*

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Androgen receptor (AR) may communicate with the general transcription machinery on the core promoter to exert its function as a transcriptional modulator. Our previous report demonstrated that the AR interacted with transcription factor III (TFIIF) under physiological conditions and that overexpression of Cdk-activating kinase, the kinase moiety of TFIIH, enhanced AR-mediated transcription in prostate cancer cells. In an effort to further dissect the mechanisms implicated in AR transactivation, we report here that AR interacts with PITALRE, a kinase subunit of positive elongation factor b (P-TEFb). Cotransfection of the plasmid encoding the mutant PITALRE (mtPITALRE), defective in its RNA polymerase II COOH-terminal domain (CTD)-kinase activity, resulted in preferential inhibition of AR-mediated transactivation. Indeed, AR transactivation in PC-3 cells was preferentially inhibited at the low concentration of 5,6-dicloro-1-β-D-ribofuranosylbenzimidazole (DRB), a CTD kinase inhibitor. These results suggest that CTD phosphorylation may play an important role in AR-mediated transcription. Furthermore, a nuclear run-on transcription assay of the prostate-specific antigen gene, an androgen-inducible gene, showed that transcription efficiency of the distal region of the gene was enhanced upon androgen induction. Taken together, our reports suggest that AR interacts with TFIIH and P-TEFb and enhances the elongation stage of transcription.

Molecular studies of eukaryotic transcription suggest that the process of transcription can be divided into the following steps: preinitiation complex assembly on the core promoter, initiation, promoter clearance, elongation, and termination (1). To initiate transcription, general transcription factors need to be recruited to the promoter either in a stepwise fashion or in a form of holoenzyme (1). The promoter clearance is defined as a point when RNA polymerase II leaves the initiation complex to start elongation of transcripts (2). Phosphorylation of the COOH-terminal domain (CTD)

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The abbreviations used are: CTD, COOH-terminal domain of RNA polymerase II largest subunit; AR, androgen receptor; DHT, dihydrotestosterone; DRB, 5,6-dicloro-1-β-D-ribofuranosylbenzimidazole; NELF, negative elongation factor; PSA, prostate-specific antigen; P-TEFb, positive-transcription elongation factor b; TFIIH and TFIIF, transcription factor IIF and IIH, respectively; FBS, fetal bovine serum; MMTV, murine mammary tumor virus; AR-NDDB, AR amino-terminal and DNA-binding domain.

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nucleolar receptors in the absence of ligands, recruit histone deacetyltransferase, and lead to condensation of nucleosomal structures for repression of transcription (6, 18).

The amino-terminal domain of steroid receptors contains a ligand-independent activation function-1, which is under the control of activation function-2 (10). The amino-terminal domain of steroid receptors has been reported to interact with general transcription factors, as exemplified by AR interaction with transcription factor IIF (TFIIF) (19) and transcription factor III (TFIIH) (20). Transcription factor IIB has been reported to interact with thyroid receptor (21), vitamin D receptor (22), and hepatocyte nuclear factor 4 (23). However, the molecular mechanism by which activation function-1 synergistically activates transcription remains unclear.

We reported previously that the AR interacted with TFIIH under physiological conditions and that overexpression of Cdk-activating kinase, the kinase moiety of TFIIH, enhanced AR-mediated transactivation in prostate cancer cells (20). In an effort to further dissect the mechanisms implicated in AR transactivation, we found that AR interacts with PITALRE, a kinase subunit of positive elongation factor b (P-TEFb) (24), and that cotransfection of the plasmid encoding the mutant PITALRE (mtPITALRE), which is defective in its CTD kinase activity (25), results in preferential inhibition of AR-mediated transactivation. AR transactivation is also preferentially inhibited at the low concentration of DRB, a CTD kinase inhibitor.

In addition, a nuclear run-on transcription assay of the PSA gene, an androgen-inducible gene, using LNCaP nuclei showed that the transcription efficiency of the distal region of the gene was enhanced upon androgen induction. These results suggest that AR interacts with TFIIH and P-TEFb and enhances the elongation stage of transcription.

MATERIALS AND METHODS

Plasmids—The complementary DNA fragments for PITALRE and mtPITALRE were generous gifts (25) and subcloned into the eukaryotic expression vector pSG5 (Stratagene). The complementary DNA fragment for negative elongation factor-D (NELF-D) (26) was generated by polymerase chain reaction and subcloned into pSG5.

Cell Culture and Transfection Assay—DU145 and PC-3 cells were maintained in Dulbecco’s modified Eagle’s medium (Life Technologies, Inc.) supplemented with 10% heat inactivated fetal bovine serum (FBS) and Dulbecco’s modified Eagle’s medium/F-12 supplemented with 7% FBS, respectively. Non-prostate cancer H1299 and HeLa cells were maintained in Dulbecco’s modified Eagle’s medium supplemented with 10% FBS. All media contain 50 units/ml penicillin and 50 μg/ml streptomycin. Cells were seeded to a density of 50–60% confluence for transfection. Cells in 35-mm dishes were refed with fresh medium 2 h before transfection and transfected with 2 μg of DNA according to the “SuperFect transfection” instructions (Qiagen). After 2–3-h incubation, cells were treated with medium supplemented with charcoal-dextran-treated FBS containing either ethanol or 1 nM DHT. Cells were incubated at 37°C for 24 h, washed with PBS, and harvested. Cells were resuspended in 10 mM Tris–HCl (pH 7.4), 10 mM NaCl, 3 mM MgCl2, 0.5% Nonidet P-40 and incubated on ice for 10 min. The nuclei pellets were spun down at 500 × g and resuspended in 10 mM Tris–HCl (pH 8.0), 40% glycerol, 5 mM MgCl2, and 0.1 mM EDTA. Nuclei were frozen and stored in liquid nitrogen in portions of 100 μl corresponding to 2 × 107 nuclei. The nuclei were mixed with 100 μl of 10 mM Tris–HCl (pH 8.0), 5 mM MgCl2, 300 mM KCl, 0.5 mM each ATP, CTP, UTP, and 100 μl of [α-32P]CTP (800 Ci/mmol) and incubated for 30 min at 30°C. RNase free DNase I was added, and the incubation was continued for 10 min at 37°C. Protease K was added to a final concentration of 300 μg/ml in 0.1% SDS, and the reaction mixture was incubated 30 min at 37°C. The labeled RNA transcripts were isolated by phenol extraction, phenol/chloroform extraction, and ethanol precipitation. Nuclear transcripts were separated from unincorporated nucleotides using Sephadex G-50 columns equilibrated with 10 mM Tris–HCl (pH 7.8), 0.5 mM EDTA, and 0.3% SDS.

The DNA fragments containing the PSA exons 1 and 2 were obtained by polymerase chain reaction of the plasmid containing the genomic PSA. The DNA fragments were gel-purified and digested with EcoRI. The distal and proximal PSA DNA fragments (Fig. 6A) were gel-purified. The plasmid-containing 75K gene (29) was digested with PstI. Each DNA fragment was denatured and immobilized onto the nylon membrane using a slot blot (Schleicher & Schuell) as described elsewhere (28). The membrane was prehybridized for 2 h at 60°C in 6× SSC, 10× Denhardt’s reagent, 1% SDS, and 100 μg/ml denatured salmon sperm DNA. Hybridization was carried out at 60°C for 4 h in 6× SSC, 1% SDS, 100 μg/ml denatured salmon sperm DNA, and 1 × 106 cpm of labeled RNA transcripts. The filters were washed twice in 2× SSC for 30 min at 60°C and then treated in 2× SSC containing RNase A (5 μg/ml) for 20 min at 30°C to remove unhybridized regions of RNA. The filters were washed twice in 2× SSC for 10 min at 37°C. Signals were detected using a Molecular Dynamics PhosphorImager.

RESULTS

AR Interaction with TFIIH—Biochemical studies of protein-protein interactions between AR and the general transcription factors indicated that AR may interact with TFIIH and TFIIH under physiological conditions (19, 20). Recruitment of TFIIH completes the assembly of the preinitiation complex on the promoter and results in promoter opening and/or the early elongation/promoter clearance steps (1, 3). The kinase activity of TFIIH has been reported to phosphorylate the CTD of the largest subunit of RNA polymerase II (3) and to stimulate the elongation stage of transcription by several activators (8). TFIIH-mediated CTD phosphorylation could lead to promoter clearance by dissociation of proteins recruited for the initiation steps of the preinitiation complex assembly, resulting in establishing an elongation-competent transcription complex (30). The significance of CTD phospho-
rualion for the elongation stage of transcription was demonstrated by Yankulov et al. (31). The elongation stage of transcription in Xenopus oocytes was inhibited by microinjection of antibodies against TFIIH subunits, but not by microinjection of antibodies against TFIIA, a general transcription factor specific for transcription initiation. In summary, phosphorylation of the CTD of RNA polymerase II may be associated with the transition from the initiation to the elongation stage of transcription (30). Based on intensive molecular and biochemical studies of transcription mechanisms, interaction of AR with TFIIH reported in our previous study led us to analyze whether AR enhances transcription mainly at the elongation stage of transcription.

The Mutant PITALRE (mtPITALRE) Inhibits AR Transactivation in Prostate Cancer Cells—Given the fact that general elongation factors, such as P-TEFb, transcription factor IIS, and Elongins, also regulate the elongation stage of transcription (4), we analyzed the effects of positive and negative elongation factors on AR-mediated transcription. P-TEFb is composed of 124- and 43-kDa polypeptides and a key regulator controlling RNA polymerase II in the elongation stage of transcription (24). The small subunit of P-TEFb, PITALRE, possesses protein kinase activity capable of phosphorylating the CTD of the largest subunit of RNA polymerase II, which has been known to be a key step required to enter an elongation mode from the preinitiation complex formation on the promoter (4). Recent studies show that the Tat protein encoded by the human type 1 immunodeficiency virus (HIV-1) genome, a notable transcriptional modulator, which activates the expression plasmid encoding NELF-D, a subunit of a recently identified negative elongation factor (26), was performed. Cotransfection of the NELF expression plasmid inhibited both AR-mediated transcription and SV40 enhancer-mediated transcription to about the same degree in PC-3 (Fig. 2A) and HeLa cells (data not shown), resulting in little preferential inhibition of AR-mediated transcription. These results suggest that there might be another factor(s), which modulates activity of P-TEFb in prostate cancer PC-3 and DU145 cells and enhances AR-mediated transcription more efficiently. Since our preliminary data indicate that AR activates androgen-responsive genes mainly at the elongation stage of transcription, we propose that the specific factor(s) modulating activity of PITALRE might play a role in prostate cancer progression. To analyze whether AR utilizes a specific set of general elongation factors for regulation of AR transactivation, a cotransfection assay of the expression plasmid encoding NELF-D, a subunit of a recently identified negative elongation factor (26), was performed. Cotransfection of the NELF expression plasmid inhibited both AR-mediated transcription and SV40 enhancer-mediated transcription to about the same degree in PC-3 (Fig. 2A) and DU145 (data not shown) cells, resulting in no preferential inhibition of AR transactivation by NELF.

AR Interaction with PITALRE—Results demonstrating preferential inhibition of AR-mediated transcription by mtPI-
TALRE led us to analyze whether PITALRE interacts with AR in prostate cancer cells. The whole cell extract of AR-positive LNCaP prostate cancer cells was prepared and used for a coimmunoprecipitation assay with protein A-Sepharose beads coupled with anti-PITALRE antibody. The immunoprecipitated samples were analyzed by a Western blot assay using anti-hAR antibody (NH27). As shown in Fig. 4A, AR was detected in the immunoprecipitated samples obtained using protein A-Sepharose beads coupled with anti-PITALRE antibody, but not in the samples obtained using protein A-Sepharose beads alone, indicating AR interaction with PITALRE in a ligand-independent manner under physiological conditions. This interaction was also analyzed using AR-negative prostate cancer PC-3 cells with cotransfection of plasmids encoding AR and PITALRE (Fig. 4B). AR interaction with P-TEFb in a ligand-independent manner was further confirmed by a biochemical binding assay (Fig. 4C). Since glutathione S-transferase fused with the AR NH2-terminal plus DNA-binding domain (AR-NDBD) was incubated with Ni2+-resins. The resins were incubated with 35S-labeled TNT-expressed PITALRE and extensively washed with 20 mM HEPES (pH 7.8), 20% glycerol, 0.5 mM EDTA, and 400 mM NaCl. Proteins were eluted and analyzed on SDS-polyacrylamide gels, followed by a PhosphorImager. For the control, bacterial lysate without histidine-tagged AR-NDBD was used in parallel (lane 2). About 5% of TNT-expressed samples was loaded on lane 1.

**Fig. 2.** No preferential inhibition of AR-mediated transactivation by mutant PITALRE in non-prostate cancer cell line H1299 cells. Experiments were performed and analyzed as described in the legend to Fig. 1 using non-prostate cancer H1299 cells.

**Fig. 3.** No preferential inhibition of AR-mediated transactivation by the negative elongation factor NELF in PC-3 cells. PC-3 cells were transiently transfected with 800 ng of pMMTV-luciferase, 10 ng of pRVL540-luciferase, 30 ng of AR expression plasmid, and without or with increasing amounts of NELF expression plasmids as indicated. Total amounts of plasmids were adjusted to 2 μg using psG5. Experiments were analyzed as described in the legend to Fig. 1.

**Fig. 4.** AR interaction with PITALRE. A, whole cell extracts of LNCaP (1 μg each) were prepared as described elsewhere (27) and used for coimmunoprecipitation. Lanes 1 and 4 were obtained with whole cell extract from ethanol-treated cells. Lanes 2 and 5 were obtained with whole cell extracts from 1 μM DHT-treated cells. About 0.5% of input was loaded in lanes 4 and 5. The immunoprecipitated samples with anti-PITALRE antibody-bound protein A-Sepharose were loaded in lanes 1 and 2. The immunoprecipitated sample with protein A-Sepharose was loaded in lane 3 as a control. B, PC-3 cells were transiently transfected with the plasmids encoding AR and wild type PITALRE as described in the legend to Fig. 1. Whole cell extracts were prepared as described elsewhere (27) and used for coimmunoprecipitation. Lanes 1 and 2 were obtained with whole cell extract from ethanol-treated cells. Lanes 3 and 4 were obtained with whole cell extracts from 1 μM DHT-treated cells. About 7.5% of input was loaded in lanes 1 and 3 as a control. Immunoprecipitated samples were loaded in lanes 2 and 4. C, bacterial lysate containing histidine-tagged AR amino-terminal plus DNA-binding domain (AR-NDBD) was incubated with Ni2+-resins. The resins were incubated with 35S-labeled TNT-expressed PITALRE and extensively washed with 20 mM HEPES (pH 7.8), 20% glycerol, 0.5 mM EDTA, and 400 mM NaCl. Proteins were eluted and analyzed on SDS-polyacrylamide gels, followed by a PhosphorImager. For the control, bacterial lysate without histidine-tagged AR-NDBD was used in parallel (lane 2). About 5% of TNT-expressed samples was loaded on lane 1.
Although eukaryotic RNA polymerase II pausing or arrest signals are poorly characterized, RNA polymerase II pausing or arrest are frequently caused within a few hundred nucleotides from the initiation. The exons 1 and 2 of the PSA gene are separated by 1200 nucleotides, thus the exon 1 and 2 were chosen as a proximal and distal probe, respectively. As shown in Fig. 6B, the ratio of the signal detected by the distal probe to that detected by the proximal probe increased ~2–3-fold upon androgen induction. This result clearly indicates that preferential inhibition of AR-mediated transcription was due to bona fide characteristics of AR-mediated transcription.

**DISCUSSION**

AR is required to communicate with the general transcription machinery on the core promoter to exert its function as a transcriptional modulator. AR interaction with TFIIH and P-TEFb has been reported to possess a DRB-sensitive CTD kinase activity. A cotransfection assay was performed in the presence of various concentrations of DRB to analyze the significance of AR modulation during transcriptional elongation. As shown in Fig. 5, transcription from both the reporter pMMTV-luciferase and the control pRL-luciferase was slightly enhanced at the concentration of DRB lower than $10^{-6}$ M, presumably due to the inhibition of nonspecific random initiation of RNA polymerase II resulting in an increase in specific initiation. However, AR-mediated transcription was markedly inhibited from $4 \times 10^{-6}$ M DRB, while SV40 enhancer-mediated transcription was not inhibited. These results indicate that efficient AR-mediated transcription is highly dependent on the CTD phosphorylation of RNA polymerase II, which is a key step required to enter the elongation stage (3). Together with cotransfection results obtained with the mtPITALRE, preferential inhibition of AR-mediated transcription by DRB indicates that AR may enhance androgen responsible genes mainly at the elongation stage of transcription by communicating with P-TEFb and TFIIH.

**Nuclear Run-on Transcription Assay of PSA Gene**—Since the specific sequences of certain genes play a role in pausing or premature termination of RNA polymerase II (36), a nuclear run-on transcription assay of PSA gene, an androgen-inducible gene, was performed to exclude a possibility that preferential inhibition of AR-mediated transcription was due to androgen sensitivity. RNA polymerase II pausing or arrest signals are poorly characterized. RNA polymerase II pausing or arrest are frequently caused within a few hundred nucleotides from the initiation. The exons 1 and 2 of the PSA gene are separated by 1200 nucleotides, thus the exon 1 and 2 were chosen as a proximal and distal probe, respectively. As shown in Fig. 6B, the ratio of the signal detected by the distal probe to that detected by the proximal probe increased ~2–3-fold upon androgen induction. This result clearly indicates that preferential inhibition of AR-mediated transcription was due to bona fide characteristics of AR-mediated transcription.
inhibition of AR-mediated transcription was not observed with cotransfection of the expression plasmid encoding NELF, a recently identified negative elongation factor (26). These results indicate that AR utilizes a specific set of elongation factors for efficient AR-mediated transcription. The working model for AR-mediated transcription based on our results is shown in Fig. 7.

Both TFIIH and P-TEFb possess subunits that can phosphorylate the CTD domain of RNA polymerase II (3, 4). However, TFIIH and P-TEFb function at different stages of transcription. TFIIH is required for promoter clearance, which is defined as a point when RNA polymerase II leaves the initiation complex to start formation of transcripts (30), while P-TEFb is required to prevent arrest of RNA polymerase II within a few hundred nucleotides of the promoter (4). P-TEFb has been reported to be required for the efficient transcription of many, but not all, genes, which explains inhibition of both SV40 enhancer-mediated transcription and AR-mediated transcription. However, AR-mediated transcription appears to suffer more severely from the frequent arrest of RNA polymerase II than SV40 enhancer-mediated transcription. This difference may reflect the possibility that the preinitiation complexes on the pRLSV40 promoter for SV40 enhancer-mediated transcription differ from those on the pMMTV promoter for AR-mediated transcription. Development of a well-defined transcription system may be necessary to characterize the mechanisms by which AR enhances transcription.

Since AR interacts with both TFIIH and P-TEFb, it is plausible to speculate that AR activates transcription mainly at the elongation stage. Given the fact that PITALRE is a DRB-sensitive CTD kinase (4), the effect of DRB on AR-mediated transcription was analyzed to demonstrate that CTD phosphorylation is a rate-limiting step for efficient AR transactivation. DRB dramatically increases the frequency of RNA polymerase II arrest within a few hundred nucleotides from the transcription initiation site by inhibiting phosphorylation of the CTD (32, 33). SV40 enhancer-mediated transcription was not inhibited in the presence of 10−6 M DRB, while AR-mediated transcription was severely inhibited. Transcriptional activators, such as AP-2, PU.1, Sp1, and TEF-1, modulate SV40 enhancer-mediated transcription (37), thus phosphorylation of the CTD by P-TEFb may not be a rate-limiting step for efficient transcription by these activators. This result is consistent with the observation that most transcriptional activators enhance the rate of transcriptional initiation (8). SV40 enhancer-mediated transcription was inhibited only at the high concentration (5 × 10−5 M) of DRB (data not shown). This result indicates that AR-mediated transcription requires efficient CTD phosphorylation. Consistent with the results obtained by a reporter gene assay using mPITALRE and DRB, a nuclear run-on transcription assay of the PSA gene, an androgen-inducible gene, using LNCaP nuclei indicated that transactivation efficiency of the distal region of the PSA gene was enhanced upon androgen induction (Fig. 6). This result clearly suggests that preferential inhibition of AR-mediated transcription by mPITALRE or DRB was not due to the artifact of a reporter gene assay (e.g. RNA polymerase II pausing or arrest signal in a reporter gene). The preinitiation transcription complex activated by AR may require a high level of CTD phosphorylation for efficient transactivation. All together, AR may increase the processivity of RNA polymerase II upon androgen induction. A reporter gene assay with a reporter gene containing only the multicopy of AR-responsible elements did not give detectable induction by androgens (data not shown). This phenomenon may result from the possibility that AR enhances transcriptional elongation. AR may need other activators to enhance transcriptional initiation. A recent study of androgen regulation of the p21 gene indicated that binding sites for AR and Sp1 on the p21 promoter showed synergistic activation (38). Given that fact, AR enhances the rate of transcriptional initiation (8), this study suggests a cooperation between an activator for elongation and an activator for initiation for efficient transcription of p21 gene. Characterization of mechanisms implicated in AR transactivation may facilitate identification of additional coregulators required for efficient AR transcription as well as development of potential therapeutic drugs for effective prevention of prostate cancer.

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FIG. 7. A working model for AR-mediated transcription. Nucle-ar-specific coregulators and general coregulators are omitted in the figure to simplify the relative positions of TFIIH and P-TEFb with AR.
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