



Molecular communication between androgen receptor and general transcription machinery

Dong Kun Lee, Chawnshang Chang*

*George Whipple Laboratory for Cancer Research, Departments of Pathology, Urology, and the Cancer Center,
601 Elmwood Avenue, P.O. Box 626, Rochester, NY 14642, USA*

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Abstract

The androgen–androgen receptor (AR) signaling pathway plays a key role in proper development and function of male reproductive organs. Like other transcriptional regulators, AR may communicate with the general transcription machinery on the core promoter to exert its function as a transcriptional modulator. The molecular communication between AR and the general transcription machinery may be achieved either by the direct protein–protein interaction between AR and the general transcription machinery or by the indirect interaction mediated by coregulators. Analyses of AR-mediated transcription suggest that the orchestrated interaction of AR with the transcription factors IIF (TFIIF) and IIIH (TFIIH), and positive transcription elongation factor b (P-TEFb), may increase efficiency of transcriptional elongation from the androgen target genes, such as prostate specific antigen (PSA). Based on studies so far, AR may regulate transcription not by enhanced assembly of preinitiation transcription complex but by regulating promoter clearance and elongation stage of transcription.

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1. Introduction

Androgens, testosterone (T) and 5 α -dihydrotestosterone (DHT), play key roles in proper development and function of male reproductive organs, such as prostate and epididymus, as well as nonreproductive organs, such as muscle, hair follicles, and brain [1,2]. The action of androgens is mediated by androgen receptor (AR), a member of the steroid hormone receptor superfamily, that is composed of a variable amino-terminal domain, a highly conserved DNA-binding domain, and a ligand-binding domain [3–5]. Upon T or DHT binding, AR undergoes a series of conformational changes that allow AR to interact with androgen elements (AREs) in various androgen target genes [6]. The ligand-binding domain mediates activation function-2 (AF-2), while the amino-terminal domain mediates ligand-independent activation function-1 (AF-1) that is under control of AF-2 [7]. The functional significance of AR in male sex differentiation has been demonstrated by various natural AR mutations that cause partial or complete androgen insensitive syndromes [8,9]. Patients with com-

plete androgen insensitive syndrome are phenotypic females with female external genitalia, while patients with partial androgen insensitive syndrome are males with a spectrum of defects that vary from near-normal male phenotypes to near-normal female phenotypes [8,9]. In addition to androgen insensitive syndromes, somatic mutations in AR have been frequently found in metastatic prostate cancer, indicating that AR plays an important role in development and maintenance of normal prostate as well as prostate cancer [9–11].

Although AR is a member of the steroid hormone receptor superfamily that requires ligand to function as a transcription factor, numerous studies suggest that AR can be activated by the castration level of androgens in advanced androgen-independent prostate cancer [12–14]. Regardless of whether AR is activated in the presence or absence of androgens, AR may modulate the general transcription machinery on the core promoter in order to regulate gene expression. Therefore, fundamental analysis of AR-mediated gene expression with respect to the general transcription machinery is absolutely necessary to develop effective therapies for the prostate cancer patients. This review will describe the mechanisms by which AR communicates with the general transcription machinery.

* Corresponding author. Tel.: +1-585-273-4500; fax: +1-585-756-4133.
E-mail address: chang@urmc.rochester.edu (C. Chang).

2. Modulation of chromatin structure at the promoter regions of androgen target genes

2.1. Role of chromatin remodeling in transcription

In order to initiate transcription, chromatin structure around the promoter region of androgen target genes needs to be reorganized. Acetylation at the lysine residues in the NH₂-terminal domain of the core histones destabilizes DNA–histone contacts in nucleosomes and allows chromatin to be accessible to DNA-binding proteins [15,16]. Several coregulators for nuclear receptors, such as AIB1/ACTR/pCIP/RAC3, CBP, p300, GRIP1/TIF2, PCAF, and SRC-1, have been reported to possess histone acetyltransferase (HAT) activity [17–24]. In addition to HAT, the SWI/SNF complexes have been reported to disrupt DNA–histone interaction within nucleosomes [25,26]. The SWI/SNF complexes utilize energy from ATP hydrolysis to displace DNA–histone contacts [25]. The SWI/SNF complexes can be recruited to the transcription machinery by coregulators or RNA polymerase II [26]. In contrast to histone acetylation, histone deacetylation by histone deacetyltransferase (HDAC) leads to condensation of nucleosomal structures for transcriptional repression [27]. Corepressors for nuclear receptors, such as NCoR or SMRT, have been demonstrated to recruit HDAC activity [28–31].

2.2. PSA as a model of androgen target gene

Prostate specific antigen (PSA) is the most well studied AR target gene that encodes a kallikrein-like serine protease [32–35]. It is a tissue-specific tumor marker widely used by oncologists and urologists to monitor treatment response, prognosis, and progression of prostate cancer [36,37]. The sequence analyses of the PSA gene revealed AP-1 and SP-1 binding sites as well as ARE in the 5' flanking upstream region, but PSA gene expression is tightly regulated by AR [38–41]. In vivo mapping of the DNase I hypersensitive sites in the 5' flanking sequences of the PSA gene using AR-positive prostate cancer LNCaP cells identified AREs in the promoter-proximal region, at approximate positions –170 bp (ARE-I) and –394 bp (ARE-II), and in the enhancer region, at approximate position –4200 bp (ARE-III) [41]. Reporter gene assays demonstrated that mutations in the ARE-I and the ARE-II resulted in 80 and 50% reduction, respectively, while mutations in the ARE-III resulted in 99% reduction of the PSA promoter activity [41]. This result indicates that the ARE-III in the enhancer region is absolutely required for the PSA gene expression. The mechanism by which these three AREs cooperate with each other for the highest PSA gene expression remains unclear.

Given the fact that the degree of histone acetylation is correlated with the rate of transcription, chromatin immunoprecipitation (ChIP) assay using anti-acetylated histone antibodies has been employed to analyze the molecular dynamics of transcription complexes by AR [42,43] and

ER [44]. ChIP assays demonstrated that the androgen–AR signaling pathway resulted in histone acetylation around the AREs-I, -II, and -III [43]. The results obtained by ChIP assay are well consistent with the results by in vivo mapping of the DNase hypersensitive sites [41], indicating reorganization of chromatin structure in the AREs to recruit the general transcription machinery. Coactivators, such as CBP and GRIP1, were recruited to all three AREs upon androgen induction [43]. However, corepressors, such as NCoR and SMRT, were recruited to the ARE-I and ARE-II, but not to the ARE-III, only in the presence of antiandrogen casodex, indicating that antiandrogen bound AR is actively engaged in gene repression by recruiting histone deacetylase activity [43]. Neither corepressors nor coactivators were recruited to the AREs in the absence of ligands [43]. Certain nuclear receptors, such as thyroid receptor and retinoic acid receptor, have been demonstrated to recruit NCoR and SMRT in the absence of ligand [28–31].

3. Commanding the general transcription machinery on the PSA gene promoter

3.1. Transcriptional regulation

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, transcription initiation, promoter clearance, elongation, and termination [45–48]. The promoter clearance is defined as a point when RNA polymerase II leaves the initiation complex to start transcriptional elongation [47].

In order to initiate transcription, general transcription factors and RNA polymerase II need to be recruited to the promoter either in a stepwise fashion or in a form of holoenzyme [45–48]. Accurate and efficient eukaryotic mRNA synthesis by RNA polymerase II requires general transcription factors, such as, TFIIA, TFIIB, TATA-binding polypeptide (TBP) or TBP containing multi-protein TFIID, TFIIE, transcription factors IIF (TFIIF), and IIH (TFIIH) [45–48] (Table 1). TBP was named for its function to interact with the TATA element located at around –30 bp in the promoter, but is absolutely required for transcription from both the TATA containing and TATA-less promoters [49]. TFIIA interacts with TBP, dissociates negative regulators, and stabilizes TBP binding to DNA [50]. TFIIB has been reported to interact with TBP and to recruit RNA polymerase II/TFIIF on the core promoter [51]. TFIIF associates with RNA polymerase II and prevents RNA polymerase II from nonspecific interaction to DNA, resulting in specific interaction of RNA polymerase II at the promoter [52]. In addition, TFIIF has been reported to play a role in regulating transcriptional elongation [53]. TFIIE has been reported to recruit TFIIH and modulate TFIIH helicase activity, and may participate in DNA unwinding around the transcription initiation site [54]. Recruitment of TFIIH completes the assembly of the preinitiation complex

Table 1
General transcription factors (GTF) in human cells

TFIIA	Number of subunits (kDa)	Function
TFIIB	3 (12, 19, 35)	Dissociates repressors from TBP and stabilizes TBP binding to DNA
TFIIB	1 (35)	Interacts with TBP and recruits RNA polymerase II
TFIID		
TBP	1 (38)	Recognizes TATA sequences
TAFs	12 (15–250)	Regulates TBP activity
TFIIE	2 (34, 57)	Recruits TFIIF and modulates helicase, ATPase, and kinase activity of TFIIF
TFIIF	2 (34, 74)	Increases specific interaction of RNA polymerase II with DNA and suppresses RNA polymerase II pausing
TFIIH		
CAK	3 (32, 38, 40)	Phosphorylates CTD of RNA polymerase II
Core subunits	6 (34–89)	Unwinds DNA helix by helicase and ATPase activity

on the promoter and results in ATP-dependent unwinding of the DNA template around the transcription initiation site and/or the early elongation/promoter-clearance steps [47].

Human RNA polymerase II consists of 12 polypeptides with molecular weights ranging from 220 to 10 kDa [55,56]. Structural analysis of RNA polymerase II demonstrates that the two largest subunits of RNA polymerase II, RPB1 and RBP2, interact with DNA and form the core of the RNA polymerase II with the remaining subunits at the surface area [57]. The largest subunit of RNA polymerase II, RPB1 has been most studied due to its intriguing feature of repeated hepta-amino acid sequences at the COOH-terminal domain (CTD) [58,59]. The CTD of RPB1 has been reported to interact with proteins whose functions range from formation of preinitiation complex, such as TBP [60], to post-transcription modification, such as, splicing factors and cleavage/polyadenylation factors [61]. Most importantly, the CTD has been demonstrated to play a key role in regulating transcriptional elongation [62,63]. The kinase activity in TFIIF has been reported to phosphorylate the CTD of RPB1 [64–66], which is required to establish and maintain the transcriptional elongation complex [46,63]. TFIIF-mediated CTD phosphorylation could lead to promoter clearance by dissociation of general transcription factors recruited for the initiation steps of the PIC assembly, resulting in establishing an elongation-competent transcription complex [47,63]. TFIIF has been reported to interact with several activators that stimulate the elongation stage of transcription by several activators [67,68]. The significance of CTD phosphorylation by TFIIF for the elongation stage of transcription was demonstrated by Yankulov et al. [69]. The elongation stage of transcription in *Xenopus* oocytes was severely inhibited by microinjection of antibodies against TFIIF subunits, but not by microinjection of antibodies against TFIIB, a general transcription factor involved in the early stage of preinitiation complex assembly [69].

Activators have been demonstrated to stimulate one or more steps of the transcription cycle by direct or indirect communication with the general transcription factors [46].

In addition, activators may also interact with auxiliary factors, called coregulators, to enhance recruitment of the general transcription machinery on the promoter [70–73]. Direct interactions of activators with coregulators and/or general transcription factors have been suggested to be mechanisms for transcriptional activation [70–75]. Nuclear run-on transcription and RNase protection analyses revealed three classes of activation domains [67]. Type 1 activators, such as Sp1 and CTF, stimulate an initiation stage of transcription. Type 2A activators, such as Tat encoded by human immunodeficiency virus type 1, stimulate an elongation stage, thus type 2A activators may prevent abortive elongation by arrest of RNA polymerase II at poorly defined sites. Type 2B activators, such as VP16 and p53, stimulate both an initiation and an elongation stage.

3.2. Communication between AR and general transcription machinery

AR may communicate with the general transcription machinery on the core promoter to exert its function as a transcriptional modulator. The molecular communication between AR and the general transcription machinery may be achieved either by the direct protein–protein interaction between AR and the general transcription machinery or by the indirect interaction mediated by coregulators. The mechanisms by which coregulators modulate AR transactivation have been extensively discussed elsewhere [73], thus this review will focus on the molecular communication between AR and the general transcription machinery. TFIIB interaction with nuclear receptors has been extensively studied to explain mechanisms implicated in transcriptional activation, since TFIIB has been reported to recruit RNA polymerase II to the preinitiation complex. TFIIB has been reported to interact with thyroid receptor [76], Vitamin D receptor [67], and hepatocyte nuclear factor 4 [77], and enhance their activities in transfection and/or cell free transcription assays. However, recruitment of TFIIB does not seem to be a rate-limiting step for AR- (Lee and

Chang, unpublished observation) and ER-mediated transcription [78]. Biochemical binding assays showed that TFIIB interacted with ER, but over-expression of TFIIB did not enhance ER-mediated transcription [78], indicating that recruitment of TFIIB to the preinitiation complex may not be a rate-limiting step for ER-mediated transcription. Co-immunoprecipitation assays using nuclear extracts from AR-positive prostate cancer LNCaP cells demonstrated that AR did not interact with TFIIB under the physiological conditions (Lee and Chang, unpublished observation). Over-expression of TFIIB did not enhance AR-mediated transcription (Lee and Chang, unpublished observation). Instead, androgen and estrogen receptors seem to enhance recruitment of transcription factors, such as TFIIE or TFIIH, in the later stage of preinitiation complex assembly [78–80].

The general transcription factors that may modulate AR-mediated transcription through protein–protein interactions have been identified by biochemical binding and co-immunoprecipitation assays [79,80]. Detailed biochemical binding assays demonstrated that the AR N-terminal domain ranging from 142 to 485 amino acids interacts with RAP74, a large subunit of TFIIF [79]. Excess amounts of the polypeptide AR_{142–485} inhibited the AR AF1-mediated transactivation in cell free transcription system. Addition of purified recombinant TFIIF, but not purified recombinant TBP, reversed the inhibitory effect of the peptide on AR AF1-mediated transactivation, indicating that AR interaction with TFIIF might be one of the rate-limiting steps for AR-mediated transcription [79].

Co-immunoprecipitation assay of AR-positive prostate cancer LNCaP cell nuclear extracts using anti-AR antibody demonstrated that AR interacts with TFIIH under the physiological conditions [80]. TFIIH is composed of six core subunits and three catalytic subunits, cdk7, cyclin H, and MAT1, for the kinase moiety [81]. The three catalytic subunits of TFIIH, called cdk-activating kinase (CAK), have been reported to phosphorylate ER α [82], RAR α [83], the POU domain of Oct1 [84], and the CTD of RNA polymerase II [81]. The functional significance of AR interaction with CAK was demonstrated by transient transfection assays. Over-expression of CAK enhanced AR-mediated transcription around three- to four-fold in prostate cancer cells [80]. The interaction between AR and TFIIH could enhance AR-mediated transcription through two different pathways. First, the free CAK or TFIIH-associated CAK may phosphorylate AR and enhance AR transactivation. Phosphorylation of the receptor can play a pivotal role in the regulation of the receptor activity, such as nuclear translocation, DNA binding, and interaction with regulatory proteins [12]. Second, the AR interaction with TFIIH may enhance phosphorylation of the RNA polymerase II CTD, which subsequently facilitates a transition from an initiation mode to an elongation mode of transcription. The detailed mechanism by which AR may enhance transcriptional elongation of androgen target genes is extensively discussed in the next section.

In addition to AR, TFIIH has been reported to interact with and phosphorylate ER α [82], RAR γ [83], and RAR α [85] in vitro or in vivo. The helix 12 in the ER ligand-binding domain appears to interact with p62 and XPD subunits of TFIIH [82]. In a GST pull-down assay, the addition of 17 the amino acid peptide containing the LXXLL motif in p62 subunit interfered with TFIIH interaction with ER α [82]. TFIIH interaction with ER results in phosphorylation of ser118 and enhancement of ER transactivation in a ligand-dependent manner [82]. The TFIIH-mediated phosphorylation site of RAR α has been mapped at position ser87 [83]. CAK could not enhance the mutant form of RAR S77A in transient transfection assays, indicating that phosphorylation is required for CAK-mediated enhanced RAR transactivation [83]. The TFIIH-mediated phosphorylation site(s) in AR has not yet mapped.

A recent report demonstrates the physiological significance of TFIIH interaction with nuclear receptors [86]. Mutations in XPD subunit of TFIIH result in the rare inherited genetic disorder *Xeroderma pigmentosum* with high photosensitivity of skin following sun exposure [87]. The XPD was initially identified as a subunit of DNA repair enzyme, but later demonstrated to have dual functions, DNA repair and transcription as a subunit of TFIIH [81]. The cells carrying mutations in the *xpd* gene showed reduced ligand-dependent transactivation by RAR α , ER α , and AR [86]. The mutations in the *xpd* gene appear to weaken the association of CAK subunits with the core TFIIH subunits, resulting in reduced phosphorylation of RAR α by CAK [86]. This striking report gave a clue to answer the few symptoms of *X. pigmentosum* patients that could not be explained only as a DNA repair deficiency syndrome, such as immature sexual development.

3.3. Enhanced transcriptional elongation of AR target genes by the androgen–AR signaling pathway

Based on intensive molecular and biochemical studies of transcription mechanisms, interaction of AR with TFIIF and TFIIH suggests that AR may increase efficiency of transcriptional elongation of androgen target genes. In addition to TFIIF and TFIIH, the general elongation factors, such as positive transcription elongation factor b (P-TEFb), transcription factor IIS, and Elongins, also play a key role in regulating the elongation stage of transcription [53]. So far, P-TEFb has been demonstrated to interact with AR by co-immunoprecipitation and GST pull-down assays [68]. P-TEFb is composed of 124 and 43 kDa polypeptides and a key regulator controlling RNA polymerase II in the elongation stage of transcription [88]. The small subunit of P-TEFb, PITALRE (also known as cdk9), 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 PIC formation on the promoter [63,81]. Both TFIIH and P-TEFb possess subunits that can phosphorylate the

CTD domain of RNA polymerase II [53,63,81]. However, the CTD kinase activity of TFIIF and P-TEFb plays a role at different stages of transcription. TFIIF is required for promoter clearance, which is defined as a point when RNA polymerase II leaves the initiation complex to start formation of transcripts [47], while P-TEFb is required to prevent arrest of RNA polymerase II within a few hundred nucleotides of the promoter [53].

Co-transfection of the expression plasmid encoding the mutant type of PITALRE (mtPITALRE) defective in its CTD kinase activity [68] showed inhibition of AR-mediated transcription in prostate cancer PC-3 and DU145 cells. Other studies also demonstrate that the Tat protein encoded by the human type 1 immunodeficiency virus (HIV-1) genome, a notable transcriptional modulator, which activates the elongation stage of transcription, requires P-TEFb kinase activity for the efficient transactivation both in vivo and in vitro [89,90]. In conclusion, the inhibition of AR-mediated transcription by mtPITALRE indicates that AR may enhance androgen target genes mainly at the elongation stage of transcription by communicating with P-TEFb, TFIIF, and TFIIF. P-TEFb has been reported to be required for the efficient transcription of many, but not all, genes, which explains preferential inhibition of AR-mediated transcription.

The hypothesis that the AR interaction with TFIIF, TFIIF, and P-TEFb may increase CTD phosphorylation, resulting in enhanced efficiency of transcriptional elongation from androgen target genes has obtained a solid base through several different approaches [68]. The purine nucleotide analog, 5,6-dichloro-1- β -D-ribofuranosylbenzimidazole (DRB), has been known to preferentially reduce the synthesis of promoter-distal transcripts and has a minimal effect on the synthesis of promoter-proximal transcripts both in vitro and in vivo, thus it is an inhibitor for the elongation stage of transcription by RNA polymerase II [91,92]. The mechanism of DRB inhibition at the transcriptional elongation stage was well characterized by the finding that DRB is an inhibitor for CTD kinases [93]. Co-transfection assays in the presence of various concentrations of DRB demonstrated that AR-mediated transcription was markedly inhibited from 4×10^{-6} M DRB, while SV40 enhancer-mediated transcription was not inhibited [68]. These results indicate that efficient AR-mediated transcription is highly dependent on the efficient CTD phosphorylation of RNA polymerase II, which is a key step required to enter the elongation stage [63,82]. Since the CTD kinase activity of P-TEFb has been reported to be sensitive to DRB [53], inhibition of AR-mediated transcription by DRB is consistent with the results obtained with preferential inhibition of AR-mediated transcription by mtPITALRE.

In addition, a nuclear run-on transcription assay of the endogenous *PSA* gene, an androgen-inducible gene, using nuclei prepared from AR-positive prostate cancer LNCaP cells demonstrated that the transcription efficiency from the distal region of the *PSA* gene was indeed enhanced upon androgen induction [68]. The results of nuclear run-on

transcription assay of the *PSA* gene have provided another solid evidence indicating that the androgen-AR signaling pathway may increase efficiency of transcriptional elongation of AR target genes. Together, AR interacts with TFIIF and P-TEFb, and enhances the elongation stage of transcription from AR target genes upon androgen induction.

3.4. AR interaction with RNA polymerase II

The importance of CTD phosphorylation in the largest subunit of RNA polymerase II (RPB1) for efficient transcriptional elongation has been well documented [63,81]. In addition to the CTD of RPB1, biochemical and genetic studies indicated that the second largest subunit of RNA polymerase II (RPB2) may also play important roles in transcriptional elongation [94,95]. Mutations in RPB2 inhibited interaction with the general elongation factor SII and severely increased transcriptional arrest, demonstrating that RPB2 may play important roles in transcriptional elongation [95].

Since several studies indicated that AR interacts with TFIIF, TFIIF, and P-TEFb that play roles in transcriptional elongation [68,79,80], it is likely that RPB2 may also play a role in AR transactivation. This hypothesis was supported by GST pull-down and co-immunoprecipitation assays. A GST pull-down assay indicated that the amino-terminal domain of RPB2 interacted with AR (Lee and Chang, unpublished observation). Co-expression of RPB2 enhanced AR-mediated transcription around three-fold, while it did not enhance SV40 enhancer-mediated transcription or ER α transactivation (Lee and Chang, unpublished observation). Co-expression of the other subunits of RNA polymerase II as well as TFIIB did not show enhancement of AR-mediated transcription (Lee and Chang, unpublished observation). Since co-expression of RPB2 did not enhance SV40 enhancer-mediated transcription or ER α transactivation, over-expression of RPB2 may selectively interact with AR and enhance its activity. All together, the interaction of RPB2 with AR may recruit transcription factors, such as P-TEFb, that interact with RPB2 in the transcription machinery and enhance AR transactivation. The transcription factors interacting with RPB2 may be required for the efficient AR-mediated transcription, while those are not required for SV40 enhancer-mediated transcription or ER-mediated transcription. RPB2 has been reported to play a key role in transcriptional elongation [94,95], which supports the hypothesis that AR may increase the efficiency of transcriptional elongation based on our previous studies. In addition, the early report suggests that RPB2 interacts with RPB1 [56], therefore, it is possible that interaction between AR and RPB2 may allow AR to influence the function of RPB1. The enhanced phosphorylation of CTD in RPB1 has been reported to be required for efficient transcriptional elongation [53,63,81]. Interaction of RPB2 with AR may recruit CTD kinases to the transcription machinery and enhance the efficiency of CTD phosphorylation.

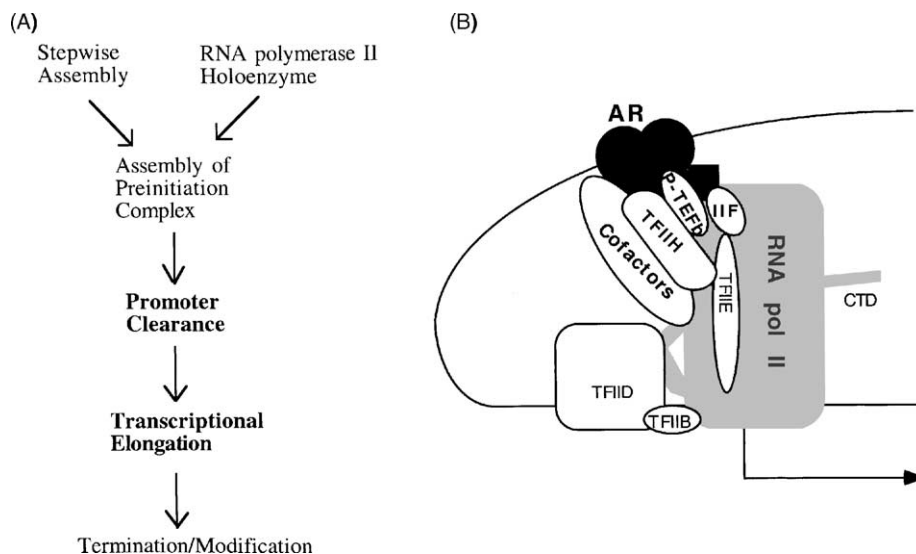


Fig. 1. Working model of AR-mediated transcriptional regulation. (A) The transcriptional stages that the androgen–AR signaling pathway may influence are bold-faced. (B) Protein–protein interactions of AR with the general transcription machinery on the core promoter are shown. The transcription factors that have been demonstrated to interact with AR are bold-faced. Coregulators that may regulate AR activity are well described elsewhere [73].

4. Concluding remarks/future directions

Regulation of transcription from androgen target genes by AR is an end-point of the androgen–AR signaling pathway. Transcriptional activators have been demonstrated to enhance transcription by several different ways. Enhanced assembly of preinitiation complex on the core promoter by activators is well documented [46,74,75]. Interaction of activators with TBP or TFIIB has been demonstrated to explain activation through enhanced assembly of preinitiation complex. Based on studies so far, AR may regulate transcription not by enhanced assembly of preinitiation complex but by regulating promoter clearance and elongation stage [68,79,80]. Analyses of AR-mediated transcription suggest that the orchestrated interaction of AR with TFIIF, TFIIH, P-TEFb, and RPB2 may increase efficiency of the CTD phosphorylation of RPB1 in the transcription machinery to enhance transcription from the androgen target genes, such as PSA. However, the hypothesis that the androgen–AR signaling pathway may increase efficiency of CTD phosphorylation is based on results obtained by transfection assays using a CTD kinase inhibitor, DRB. Thus, further studies are necessary to prove the hypothesis by demonstrating enhanced phosphorylation of CTD in AR-mediated transcription complexes upon androgen induction.

Several coregulators have been suggested to bridge transcriptional activators and general transcription machinery [70–72]. However, the available information on AR coregulators is not sufficient to draw a clear blueprint of molecular bridging between AR and the general transcription machinery by AR coregulators. A recent study shows that TRAP 220, a subunit of TRAP/DRIP complexes, has been reported to interact with the AR AF2 domain in a ligand dependent

manner [96]. Association of TRAP/DRIP complexes with AR results in enhanced AR-mediated transcription [96]. The TRAP/DRIP complex, initially identified as thyroid receptor/Vitamin D receptor associated polypeptides [97,98], is a part of RNA polymerase II holoenzyme which mediates transcriptional activation for a broad range of activators (reviewed in [99]). Thus, it is likely that AR coregulators may not only recruit HAT and/or SWI/SNF complexes but also communicate with the general transcription machinery. Further studies are required to understand roles of the complicated mediator complexes in AR-mediated transcription. Fig. 1 shows a working model of AR regulation of the transcription machinery.

Acknowledgements

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