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Androgen Receptor (AR) Coregulators: A Diversity of Functions Converging on and Regulating the AR Transcriptional Complex

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Androgens, acting through the androgen receptor (AR), are responsible for the development of the male phenotype during embryogenesis, the achievement of sexual maturation at puberty, and the maintenance of male reproductive function and behavior in adulthood. In addition, androgens affect a wide variety of nonreproductive tissues. Moreover, aberrant androgen action plays a critical role in multiple pathologies, including prostate cancer and androgen insensitivity syndromes. The formation of a productive AR transcriptional complex requires the functional and structural interaction of the AR with its coregulators. In the last decade, an overwhelming and ever increasing number of proteins have been proposed to possess AR coactivating or corepressing characteristics. Intriguingly, a vast diversity of functions has been ascribed to these proteins, indicating that a multitude of cellular functions and signals converge on the AR to regulate its function. The current review aims to provide an overview of the AR coregulator proteins identified to date and to propose a classification of these AR coregulator proteins according to the function(s) ascribed to them. Taken together, this approach will increase our understanding of the cellular pathways that converge on the AR to ensure an appropriate transcriptional response to androgens. (*Endocrine Reviews* 28: 778–808, 2007)

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Abbreviations: ADI, Androgen depletion independent; AF, activation function; ANPK, AR-interacting nuclear protein kinase; ANT-1, AR N-terminal domain transactivating protein-1; AR, androgen receptor; ARA, AR-associated; ARE, androgen reponse element; ARIP, AR-interacting protein; ARNIP, AR N-terminal-interacting protein; ARR19, AR corepressor 19kDa; ART-27, AR-trapped clone 27; Asc, activating signal cointegrator; BAF, BRG1-associated factor; BRG1, Brahma-related gene 1; CARM-1, coactivator-associated arginine methyltransferase 1; CBP, CREB-binding protein; CDK6, cyclin-dependent kinase 6; Chip, C-terminal Hsp-interacting protein; ChIP, chromatin immunoprecipitation; CTD, COOH terminal domain; DBD, DNA-binding domain; DHEA, dehydroepiandrosterone; DHT, dihydrotestosterone; DJBP, DJ-1-binding protein; DNA-PK, DNA-dependent protein kinase; E6-AP, E6-associated protein; FHL2, four-and-a-half-LIM-only protein 2; FKBP52, FK506 binding protein of 52kDa; GAK, G-associated kinase; GDI, guanine nucleotide dissociation inhibitor; GSK-3β, glycogen synthase kinase-3β; HAT, histone acetylase; HBO1, human origin recognition complex interacting protein; hBRM, human homolog of *Drosophila* brm gene; HBx, hepatitis B virus nonstructural protein x; HDAC, histone deacetylase; Hey, Hairy/Enhancer of split related with YRPW motif; HIP1, huntingtin-interacting protein 1; HPV, human papillomavirus; Hsp, heat shock protein; LBD, ligand-binding domain; LIM, LIN-11, ISL-1, and MEC-3; LSD1, lysine-specific demethylase 1; MAK, male germ cell-associated kinase; MKRN1, Makorin RING zinc finger protein 1; MNAR, modulator of nongenomic actions of the estrogen receptor; NCoR, nuclear receptor corepressor; NLS, nuclear localization signal; NTD, N-terminal domain; PAK, p21-activated kinase; PCa, prostate cancer; P/CAF, p300/CBP-associated factor; PELP1, proline-, glutamic acid-, and leucine-rich protein-1; PIAS, protein inhibitors of activated STAT; PIC, preinitiation complex; PKC, protein kinase C; PKN, protein kinase N; p54nrb, p54 nuclear RNA binding protein; PP2A, protein phosphatase 2A; PRK, PKC-related kinase; PRMT, protein arginine methyltransferase; PSA, prostate specific antigen; PSF, polypyrimidine tract-binding protein-associated splicing factor; PSP, paraspeckle protein; p-TEFb, positive transcription elongation factor b; RACK1, receptor for activated C kinase 1; RanBPM, Ran-binding protein in the microtubule-organizing center; Rb, retinoblastoma protein; RSK, ribosomal S6 kinase; SCP, small CTD phosphatase; SENP1, SUMO1/sentrin-specific protease 1; siRNA, small interfering RNA; SIRT1, Sirtuin1; SMRT, silencing mediator of retinoid and thyroid receptors; SNURF, small nuclear RING finger protein; SRA, steroid receptor RNA activator; SRC, steroid receptor coactivator; SRCAP, SNF2-related CBP activator protein; SRG, SW13-related gene product; ST, small t antigen; STAT, signal transducer and activator of transcription; SUMO, small ubiquitin-related modifier; SWI/SNF, mating type switching/sucrose nonfermenting; TAU, transactivation unit; TBP, TATA-binding protein; TIF, transcriptional intermediary factor; Tip60, Tat interactive protein 60 kDa; TSG101, tumor susceptibility gene 101; Uba3, ubiquitin-activating enzyme 3; Zac1, zinc-finger protein which regulates apoptosis and cell cycle arrest 1.

I. Introduction

ANDROGENS, WHICH ARE the main male sex steroids, are responsible for the development of the male phenotype during embryogenesis and for male sexual maturation at puberty. In adulthood, androgens remain essential for

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the maintenance of male reproductive function and behavior. In addition to their effects on reproduction, androgens affect a wide variety of nonreproductive tissues including skin, bone, muscle, and adipose tissues. As a consequence, deregulations in the production or action of androgens can affect different organ systems with a variable degree of severity. This is reflected in pathologies ranging from androgen insensitivity syndromes and prostate cancer to an increased risk and susceptibility to gender-related diseases such as hepatocellular carcinomas, to relatively mild conditions such as acne and male pattern alopecia (1–6).

Testosterone, the principal androgen in the male circulation, is synthesized by the testes. The remaining androgens in the bloodstream [~5–10%, including dehydroepiandrosterone (DHEA), androstenediol, and androstenedione] are either produced by the adrenal cortex and can be converted into testosterone in peripheral tissues or are derived from peripheral conversion from testosterone [dihydrotestosterone (DHT)] (7–8). Synthesis of androgens is tightly regulated by the hypothalamic-pituitary-gonadal axis. Pulsatile secretion of LHRH by the hypothalamus stimulates secretion of LH by the anterior pituitary, which in turn induces production of testosterone by the testicular Leydig cells. Testosterone acts through a negative feedback loop to prevent LHRH release by the hypothalamus and to decrease the sensitivity of the pituitary to LHRH. The majority of circulating testosterone is bound to carrier proteins: SHBG or albumin. Therefore, only 1–2% of testosterone exists in an unbound, free form. The major androgens in women include DHEA sulfate, DHEA, androstenedione, testosterone, and DHT. Androgen biosynthesis occurs in both the adrenal and the ovary, and it is regulated by ACTH (adrenal synthesis) and LH (ovarian synthesis) (9, 10).

Upon transportation by the blood to its target tissues, unbound, lipophilic testosterone diffuses into its target cell where it can be rapidly and irreversibly converted into its more potent metabolite DHT by action of 5α-reductase in some but not all target cells (type I or II, depending on the target tissue) (11). Both testosterone and DHT (either locally produced or from the circulation) exert their activities by binding to a cognate receptor, the androgen receptor (AR), a 110-kDa member of the nuclear receptor superfamily of ligand-activated transcription factors. DHT binds the AR with higher affinity, and its biological activity exceeds that of testosterone up to 10 times (12). DHT dissociates from the AR more slowly than testosterone, and AR bound to DHT is more stable, persisting in cells for greater lengths of time (13). In its basal, unliganded state, the AR resides primarily in the cytoplasmic compartment where it exists in a complex with heat shock proteins (Hsps) and immunophilin chaperones such as Hsp70, 90, 56, and p23. Upon ligand binding, alterations occur in the composition of this Hsp complex, and the AR undergoes a conformational change, allowing nuclear translocation of the AR and AR homodimer formation (14). Inside the nucleus, the activated AR binds to specific recognition sequences known as androgen reponse elements (AREs) in the promoter and enhancer regions of target genes. The ARE-bound AR dimer can either interact directly with components of the transcription preinitiation complex or recruit other components that promote such a functional interaction (15–17). Recruited elements may be other transcription factors binding to recognition elements in the vicinity of AREs and forming more complex androgen response units, or they can be coregulator proteins. As a general definition, AR coregulators are proteins that are recruited by the AR and either enhance (*i.e.* coactivators) or reduce (*i.e.* corepressors) its transactivation, but they do not significantly alter the basal transcription rate and do not typically possess DNA binding ability. Instead, coregulators influence AR-mediated transcription by acting at the target gene promoter region to facilitate DNA occupancy, chromatin remodeling, and/or recruitment of general transcription factors associated with RNA polymerase II, or by assuring the competency of the AR to enhance gene expression directly. The latter can be achieved by modulation of the proper folding of the AR, ensuring its stability or correct subcellular localization (16, 17). In the last decade, an overwhelming and ever increasing number of proteins have been identified as AR coregulators. In the current review, we provide an overview of the AR coregulators that have been identified to date. In view of the remarkable functional diversity displayed by these proteins and the vast number of cellular pathways in which they are involved, we propose a classification of AR coregulatory proteins according to their intrinsic primary function. Finally, we discuss the importance of these factors in the regulation of tissue-selective androgen-dependent gene expression under physiological and pathological conditions.

II. The Androgen Receptor (AR)

Like other members of the nuclear receptor superfamily, the AR is characterized by a modular structure consisting of four functional domains: an N-terminal domain (NTD), a DNA-binding domain (DBD), a hinge region, and a ligand-binding domain (LBD) (18, 19). The AR NTD is relatively long and displays the most sequence variability among nuclear receptors. It is very flexible and displays a high degree of intrinsic disorder, which has hampered studies into its three-dimensional structure (20). The AR NTD contains the major transactivation function of the AR, termed activation function (AF) 1. When separated from the LBD, AF-1 gives rise to a constitutively active AR. Two motifs in the AR NTD, 23-FQNLF-27 and to a lesser extent 433-WHTLF-473, have been shown to interact with the LBD, resulting in an NH_2-COOH terminal intra- and/or intermolecular AR interaction that has been proposed to be important for the transcriptional activation of some, but not all, AR target genes (21). AF-1 is highly modular and consists of two transactivation units (TAUs), TAU 1 and TAU 5, that participate in transcriptional activation (22). The AF-1 domain undergoes induced folding when contacted by basal transcription factors such as TFIIF, resulting in a more compact and active conformation that enables further coregulator recruitment and transcription (20). In addition, the NTD harbors a variable number of homopolymeric repeats, the most important of which is a polyglutamine repeat that ranges from 8 to 31 repeats in normal individuals, with an average length of 20. Expansion of the glutamine repeats up to 40 residues or more

results in spinal and bulbar muscular athrophy (SBMA or Kennedy's disease), an X-linked pathology characterized by neurological features and late onset symptoms of mild androgen insensitivity (1, 23, 24). Shortening of the polyglutamine stretch, on the other hand, gives rise to a more transcriptionally active AR, which has been suggested to be associated with a predisposition to prostatic neoplasia (25).

The centrally located DBD is the most conserved region within the nuclear receptor family. This region harbors nine cysteine residues, of which eight are involved in forming two zinc fingers, and a C-terminal extension. The first zinc finger, most proximal to the NTD, determines the specificity of DNA recognition, whereas residues in the second zinc finger are involved in AR dimerization. Two AR monomers in a head-to-head conformation bind as a homodimer to AREs (26), which are direct or indirect repeats of the core 5′-TGTTCT-3′, or more complex response elements harboring diverse arrangements of AREs (27, 28). The C-terminal extension is important for the overall three-dimensional structure of the DBD and plays a role in mediating the AR selectivity of DNA interaction (27).

The hinge region has long been considered to be a flexible linker between the DBD and LBD. More recently, however, this region was shown to be involved in DNA binding as well as AR dimerization and was suggested to attenuate transcriptional activity of the AR (29, 30). Moreover, a ligand-dependent bipartite nuclear localization signal (NLS) is located in the carboxyterminal part of the DBD and the hinge region, implicating the hinge region in AR nuclear translocation (31, 32).

X-ray crystallographic studies indicate that the AR LBD structure is similar to that of the other members of the nuclear receptor superfamily (33–36). The LBD in nuclear receptors consists of 12 discrete α-helices. Insertion of the agonist into the AR ligand-binding pocket has been suggested to change the conformation of the LBD in such a way that helix-12 is stabilized. This leads to the formation of a shallow hydrophobic groove at the top of the ligand binding pocket, generally referred to as AF-2. AF-2 is the major protein-protein interaction surface used by nuclear receptors to recruit LXXLL-motif containing coactivators (37). The AR, however, differs from other nuclear receptors in this respect and interacts with coactivators in a unique manner. The hydrophobic pocket in the AR-LBD binds preferentially to FXXLF motifs, including the 23-FQNLF-27 found in its NTD, and interacts poorly with LXXLL motifs commonly found in coactivators (38–42). Consequently, the hydrophobic pocket within the AR LBD facilitates intramolecular and intermolecular interaction between the AR NTD and its C terminus and is apparently not readily available for coactivator binding. Recent data suggest that the AR N/C terminal interactions occur predominantly when the AR is not bound to DNA (43). Interestingly, several AR-associated coactivators that contain FXXLF motifs have been isolated (44), suggesting that competition exists between these regulatory proteins and the NTD for binding to the AF-2. The implications of such competition and the association of NTD and LBD are not clear, but suggest that additional surfaces outside this well-defined coactivator pocket enable the AR to interact with its coactivators and that different classes of coactivators may interact with different AR surfaces. These observations explain why the AF-2 in the AR LBD displays relatively weak ligand-dependent transactivating properties when compared with the AF-2 of other nuclear receptors. Nonetheless, mutation or deletion of AF-2 markedly reduces transcriptional activation in response to ligand. Apart from forming the ligand binding pocket, the AR LBD mediates interaction between the AR and Hsps (14).

III. AR-Interacting Proteins

In general, proteins that interact with the AR can be divided into three general classes: 1) components of the general transcriptional machinery; 2) functionally diverse proteins with AR coactivating or corepressing properties; and 3) specific transcription factors. AR coregulators differ from general and specific transcription factors in that they do not affect the basal rate of transcription and typically do not bind to DNA.

A. General transcription factors

As is the case for other transcription factors, enhanced transcription by the AR depends on the recruitment of RNA polymerase II to promoters of its target genes. This is achieved by the assembly of general transcription factors that make up the preinitiation complex (PIC). A detailed description of transcription initiation is beyond the scope of this manuscript and has been reviewed previously (45). Briefly, formation of the PIC is accomplished by binding of TFIID, which is composed of TATA-binding protein (TBP) and TBP-associated factors, in the proximity of the transcriptional start site. TFIIB then binds TBP and recruits RNA polymerase II and TFIIF, which ensures specific interaction of RNA polymerase II at the promoter. TFIIE and TFIIH are recruited to RNA polymerase II to facilitate strand separation, which allows transcription initiation. Although many AR-associated coregulators facilitate and mediate communication between the AR and the general transcriptional machinery, the AR has also been shown to interact directly with components of the basal transcriptional machinery. For instance, the AR NTD interacts with RAP74, a large subunit of TFIIF. Binding of RAP74 induces α-helical structure in AF-1 and facilitates interaction between the AR and the p160 coactivator steroid receptor coactivator (SRC)-1 (20, 46–50). Modest binding to the RAP30 subunit of TFIIF and TBP has also been described (46). Moreover, the AR has been shown to interact with TFIIH, and overexpression of the cdk-activating kinase subunit of TFIIH markedly stimulates the AR-mediated transcription (50). the AR interaction with TFIIH may enhance phosphorylation of the RNA polymerase COOH terminal domain (CTD), an event necessary to transition from transcription initiation to transcriptional elongation, suggesting that the AR may increase the efficiency of transcriptional elongation of AR target genes. Consistent with this hypothesis, an interaction between the AR and positive transcription elongation factor b (p-TEFb) has been described (51). The small subunit of p-TEFb, PITALRE (also known as CDK9), harbors protein kinase activity that is able to phosphorylate the CTD of the largest subunit of RNA polymerase II, which

is necessary to progress from PIC formation on the promoter to transcriptional elongation. Remarkably, both TFIIH and p-TEFb possess CTD kinase activity, but these activities act at different stages of transcription (15). In addition to its contacts with several general transcription factors, the AR also interacts directly with RNA polymerase II through association with its subunit RPB2. Coexpression of RPB2, which is involved in transcriptional elongation, stimulates AR-mediated transcription of target genes (52). Interaction of the AR with and regulation of AR-mediated gene expression by other subunits of RNA polymerase II has not been observed. Taken together, these findings indicate that the AR may regulate transcription of target genes by regulating both transcriptional initiation and elongation events.

B. AR coregulators

More than 200 nuclear receptor coregulators have been identified since the isolation of the first nuclear receptor coactivator, SRC-1, in 1995 (53). By mining peer-reviewed literature accessible through PubMed (www.pubmed.gov) and consulting specialized websites dedicated to AR function [the AR gene mutation database (androgendb.mcgill.ca) and the Nuclear Receptor Signaling Atlas (NURSA) database (www.nursa.org)], we have attempted to provide an up-to-date overview of proteins that have been listed as putative coregulators for the AR. As of May 2007, the list of proteins that have been classified as potential AR coregulators contains 169 members. Remarkably, these coregulators display a diverse array of functions and are involved in multiple cellular pathways. There are many ways one could categorize or group these proteins. We have chosen to arrange these proteins according to their apparent primary function, *i.e.*, the function for which they are best recognized, even if, in some cases, this particular activity may not be critical for their effect on AR action. Overall, we feel that such a classification, rather than classification by their function as a coactivator or a corepressor, will provide a broader picture of the cellular events that converge on and regulate the transactivation properties of the AR. As will be discussed below, this does not preclude the possibility that some multifunctional AR coregulators can be assigned to multiple categories. For reasons of simplicity and to keep our overview comprehensive, we chose not to include information on the specific cell systems or specific target genes used to ascertain the coregulator properties of the AR cofactors in this section. This information will be addressed in *Sections IV and V*.

1. Components of the chromatin remodeling complex. Transcription occurs on a chromatin template, in which DNA is wound around a core of four basic histone proteins (H2A, H2B, H3, and H4) to form nucleosomes. DNA-histone interactions limit the accessibility of the nucleosomal DNA to transcription factors and form a major obstacle to transcription. Chromatin remodeling complexes alter and unwrap the histone-DNA contacts in an ATP-dependent manner catalyzed by ATPases, leading to reorganization of the nucleosomal structure and eventually to a chromatin status that is more permissive to transcription (54, 55). Several AR coregulator proteins have been identified as components of the chromatin remodeling complex. One of the first indications that components of the chromatin remodeling complex may play a role in AR-mediated transcription came from the identification of AR-interacting protein (ARIP) 4, a nuclear ATPase that belongs to the SNF2-like family of chromatin remodeling proteins. ARIP4 interacts with the AR zinc-finger region and stimulates AR-dependent transactivation in cotransfection experiments (56). Alhough ARIP4 displays DNA-dependent ATPase activity, its specific activity was subsequently shown to be considerably lower than that of SNF2-family members, suggesting that it may not be a classical chromatin remodeling protein. Nonetheless, ARIP4 mutants that do not possess ATPase activity behave as dominant-negative regulators of AR function (56, 57). Subsequently, the ATPases Brahma-related gene 1 (BRG1) and human homolog of *Drosophila* brm gene (hBRM), two core components required for nucleosome repositioning by the mating type switching/sucrose nonfermenting (SWI/SNF) chromatin remodeling complex, were shown to stimulate AR activity potently (58). Depending on the gene context, however, different requirements for these ATPases were noted, with some genes relying solely on hBRM and others relying on both hBRM and BRG1 for androgen regulation (58). The BRG1-associated factor (BAF) 57 subunit, an accessory component of this remodeling complex, is also required for AR-dependent transactivation (59). The AR coactivation function of BAF57 depends on SWI/SNF ATPase activity and cooperates with other classes of coactivators. BAF57 directly binds to the AR and is recruited to AR target genes upon ligand stimulation (59). Interestingly, the SWI3-related gene product (SRG3/BAF155), another component of the SWI/SNF complex, is also able to enhance transactivation by the AR. SRG3 interacts with the AR DBD-hinge region and exists in a complex with the AR on promoters of AR targets genes (60). SRG3 appears to initiate at least some of its coactivation properties by enlisting the SRC-1 coactivator. Remarkably, SRG3 function may not be entirely dependent on the presence of BRG1 or hBRM (60). Furthermore, the SNF2-related CREB-binding protein (CBP) activator protein (SRCAP) is able to coactivate transcription by the AR (61). Direct interaction of SRCAP with the AR, however, has not been reported. Similarly, hOsa1 (BAF250) and hOsa2, the largest subunits of the SWI/SNF complex, stimulate transcription by the AR, but association of these proteins with the AR has not been demonstrated (62).

Overall, the recruitment of these chromatin remodeling proteins to the AR transcriptional complex is consistent with the altered DNA topology and the loss of canonical nucleosomal ladder that is observed at AR target genes after exposure to androgens (63).

2. Histone modifiers: acetyltransferases and deacytelases. In addition to chromatin remodeling, which represents a higher order level of chromatin reorganization and involves repositioning of components of the nucleosome structure, modification of histone residues can affect transcription efficiency and provide a more localized control over transcriptional events in chromatin (54, 55). Modifications such as acetylation, methylation, phosphorylation, ubiquitination, ADP-ribosylation, and glycosylation of histone residues have been described. In most cases, modification of a histone residue

changes the net charge of the nucleosome, which results in loosening or tightening of the DNA-histone interactions. For example, acetylation of a histone lysine residue attenuates its positive charge and abrogates its interaction with the negatively charged DNA. Some of these histone modifications are associated with transcriptional activation (*e.g.*, acetylation), and others are indicative of active or repressed genes (*e.g.* methylation). Also, the position of the modified histone residue can affect the activation status of a gene. The concept that a combination of such marks affects binding of transcriptionally effector proteins lies at the basis of the histone code (54, 55).

In keeping with this notion, several dynamic changes in the covalent histone modification status have been associated with androgen-stimulated transcription. These include activating modifications at histone 3 such as acetylation of lysine 9 and lysine 14, dimethylation of arginine 17, phosphorylation of serine 10, and dimethylation as well as trimethylation of lysine 4 (64). In addition, removal of repressive marks has been described, such as demethylation of mono-, di-, and trimethyl marks at lysine 9 of histone 3 and decrease in the dimethylation status of lysine 20 at histone 4 (65–68). The significance of these modifications will be discussed in more detail in sections of the text describing enzymes executing these events. A summary of the histone modifications associated with androgen action can be found in Fig. 1.

Recruitment of histone acetylase (HAT) activity to chromatin is associated with transcriptional activation. Conversely, deacetylation of these marks by histone deacetylase (HDAC) activity renders the chromatin environment transcriptionally repressed. Several HATs and HDACs have been shown to interact with the AR and modulate its transactivating properties.

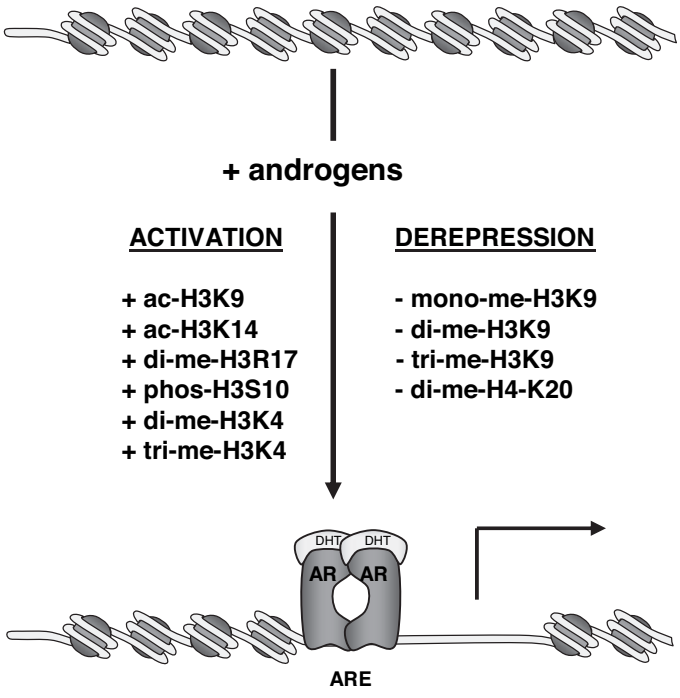

FIG. 1. Covalent histone modifications associated with androgen action.

For example, two members of the p160 SRC gene family, SRC-1 and SRC-3 [p300/CBP interacting protein (p/CIP), receptor-associated coactivator-3 (RAC3), acetyltransferase (ACTR), amplified in breast cancer-1 (AIB1), or thyroid hormone receptor activator molecule-1 (TRAM1)] have been reported to possess HAT activity. Similar to SRC-2 [also known as glucocorticoid receptor-interacting protein-1 or transcriptional intermediary factor (TIF)-2], the third member of this family that does not possess HAT activity, SRC-1 and SRC-3 interact directly and ligand-dependently with the AR to enhance AR-mediated transcription (16, 53, 69–77). Although the LXXLL motif-containing p160 family members have been shown to interact with AR AF-2, they interact primarily with the AR N terminus and possibly the DBD. Moreover, all three SRC family members function as scaffold proteins that attract additional coactivator proteins, including factors with histone-modifying potential (78). Indeed, SRCs have been shown to recruit p300, the p300 homolog CBP, as well as p300/CBP-associated factor (P/CAF), all coactivator proteins that possess HAT functions that are intrinsically stronger than those found in SRC-1 and -3. Moreover, *in vitro* experiments have demonstrated a direct, SRC-independent interaction between p300, CBP, and P/CAF and the AR (79). The potentiation of ligand-induced AR transactivation by these three coactivators (79–81) relies on the presence of a functional HAT domain. In addition to their effects on histones, CBP, p300, and P/CAF can acetylate proteins such as transcription factors and coregulators. Noteworthy, p300, as well as P/CAF, acetylates the AR at three lysine residues in its DBD-hinge region (79). Point mutations in these AR acetylation sites selectively prevent androgen induction of androgen-responsive genes, hamper coactivation of the AR by SRC-1, p300, Tip 60, and Ubc9, and result in a 10-fold increase in the binding of the corepressor nuclear receptor corepressor (NCoR) (81). It should, however, be noted that the lysine residues that are acetylated by p300 and P/CAF are part of the AR NLS and that mutations of these sites may therefore be expected to disrupt AR activity regardless of acetylation events at these sites. Nonetheless, histone acetylation by p300 and CBP facilitates recruitment of the SWI/SNF and Mediator coactivator complexes (63). Furthermore, CBP and p300 function as a direct bridge between DNA-bound AR and the basal transcriptional machinery (79). They may also serve as a scaffold interacting with and assembling a number of other transcriptional regulators (79).

Another coregulator that harbors HAT activity is Tat interactive protein 60 kDa (Tip60). Tip60 interacts with the AR LBD and enhances AR-mediated transcription by acetylating histones as well as the AR. Acetylation of AR lysine residues in the AR-hinge region by Tip60 is a requisite for Tip60-mediated coactivation of the AR. Remarkably, action of Tip60 on AR transactivation is counteracted by HDAC1 (82–84).

Human origin recognition complex interacting protein (HBO1) is another HAT protein that ligand dependently associates with the AR DBD-LBD region. Contrary to the HAT proteins listed above, HBO1 acts as an AR corepressor, inhibiting hormone-dependent AR activation (85). The direct involvement of the HAT function of HBO1 in these events is

not clear, because HBO1 has been reported to harbor a relatively weak HAT function. Moreover, histone acetylation by HBO1 has not been demonstrated. Therefore, HBO1 has been proposed to acetylate histones as part of a multisubunit complex (86).

The importance of acetylation and deacetylation of histone and nonhistone proteins in AR-mediated transcription is further emphasized by the functional antagonism between the nicotinamide adenine dinucleotide-dependent HDAC Sirtuin1 (SIRT1) (and p300 at sites of AR acetylation). SIRT1 (Sir2, a class III HDAC) represses androgen-induced AR signaling by a mechanism that involves direct binding to the AR hinge and requires both the nicotinamide adenine dinucleotide-dependent catalytic function of SIRT1 and deacetylation of the lysine residues 630/632/633 in the AR-hinge region that are targeted by p300 and P/CAF (87). Moreover, SIRT1 inhibits p300-mediated interaction between the AR N and C termini. On the other hand, ligand-induced repression of AR function by the class II HDAC HDAC7 is independent of these acetylation sites. Moreover, the deacetylase activity of HDAC7 is at least partly dispensable in the repression of AR function (88). In addition to SIRT1, several HDACs of classes I and II negatively affect AR transactivation. Contrary to SIRT1 and HDAC7, which can interact directly with the AR, recruitment of HDACs to the AR transcriptional complex is usually indirect through association with multisubunit corepressor complexes such as NCoR and silencing mediator of retinoid and thyroid receptors (SMRT) or as binding partners for other AR corepressors (17).

Reflecting the importance of the action of HATs and HDAC enzymes at genomic sites mediating AR transcriptional activity, the acetylation status of histone 3 and 4 residues is often assessed as a marker for the transcriptional activation status of a particular AR target gene.

3. Histone modifiers: methyltransferases and demethylases. Although histone acetylation is generally associated with active gene transcription, histone methylation can be indicative of both the active and repressed transcriptional states of the chromatin (54, 55). The position of the histone residue affected by this modification is important for making this distinction. For example, methylation of lysine 4 on histone 3; arginines 2, 17, and 26 on histone 3; and arginine 3 on histone 4 is associated with active genes, whereas methylation of lysine 9 on histone 4 is predominantly associated with repressed genes. Moreover, lysine residues can be monomethylated, dimethylated, or trimethylated, and the extent of the methylation serves as an important indication of its transcriptional status. Although methylation has long been considered to be an irreversible epigenetic mark, recently, demethylases that mediate active demethylation of repressive histone segments have been identified (54, 55).

AR-dependent transcription relies on both methyltransferase and demethylase activities. Coactivator-associated arginine methyltransferase 1 (CARM-1) or protein arginine methyltransferase (PRMT)-5, a histone methyltransferase acting at H3R17, was identified initially by its ability to interact with SRC coactivators. Due to its indirect recruitment to ligand-bound nuclear receptors including the AR, CARM-1 has been classified as a secondary coactivator (89). Androgen stimulation leads to recruitment of CARM-1 to androgen-responsive enhancers (90). CARM-1 stimulation of AR transactivation depends entirely on the presence of SRC family members. Moreover, the presence of CARM-1 enhances AR transactivation by p160 family members. Loss of CARM-1 reduces transcription of androgen-responsive genes. Mutation of its S-adenosyl methionine binding site abrogates its methyltransferase activity and prevents CARM-1 from exerting its coactivator function. In addition to its effects on histones, CARM-1 methylates proteins in the transcriptional complex including CBP/p300 and several RNA binding proteins (89, 90). Noteworthy, CARM-1 may also be recruited to the AR transcriptional complex through p44 (MEP50), a component of the methylosome. p44 interacts directly with the AR and CARM-1, is found on promoters of AR target genes upon androgen stimulation, and stimulates the transcription of some AR-target genes. In addition, p44 and CARM-1 synergistically cooperate to enhance transactivation by the AR (91). Similar to CARM-1, PRMT1 is recruited to the AR transcriptional complex and stimulates AR-dependent gene expression via SRC proteins (92). PRMT1, however, preferentially methylates H4R3, which facilitates subsequent acetylation of histone 4 tails by p300. Remarkably, acetylation of histone 4 inhibits its methylation by PRMT1. Like CARM-1, PRMT1 depends on an intact S-adenosyl methionine binding site to fulfill its cofactor function.

Methylation of lysine 9 on histone 3 by the methyltransferase G9a is predominantly associated with repression of transcription. However, for some nuclear receptors including the AR, G9a functions as a coactivator, although weakly (93). Nonetheless, G9a cooperates synergistically with TIF-2, CARM-1, and p300 in activating transcription by the AR. This synergy is strongly dependent on the arginine-specific protein methyltransferase activity of CARM-1, suggesting a link between histone arginine and lysine methylation in AR-mediated transcription. Noteworthy, PRMT methyltransferases cannot substitute for CARM-1 in this respect. On the other hand, cooperation between G9a, CARM-1, and SRC-2 does not absolutely require the enzymatic activity of G9a. The dependency of G9a on SRC-2 indicates that SRC-2 may function as a scaffold to recruit G9a. G9a associates with regulatory regions in AR target genes in the presence as well as the absence of androgens, and loss of G9a expression hampers androgen-induced AR-dependent stimulation of target genes (93).

Recently, histone methyltransferase activity with a specificity for H3-K36 and H4-K20 has been attributed to nuclear receptor-binding Su(var)3-9, Enhancer-of-zeste, Trithorax (SET) domain-containing protein-1 (NSD1, also known as AR-associated (ARA) protein 267α) (94). Based on its ability to interact with the AR DBD-LBD region, to stimulate AR transactivation in an androgen-dependent manner, and to cooperate with other AR coregulators, ARA267 has been classified as an AR-associated coactivator (95). Although this possibility remains to be proven, it is tempting to speculate that the AR-coactivating properties of ARA267 are mediated by its histone methyltransferase moiety.

The concept that demethylation of histones is involved in transcriptional activation by the AR has emerged only re-

cently. Interest was triggered by the observation that lysine-specific demethylase 1 (LSD1), which specifically demethylates monomethylated and dimethylated H3K9, interacts with the AR (NTD, DBD, as well as LBD), and stimulates AR-dependent transcription (65). Down-regulation of LSD1 expression abrogates androgen-induced transcriptional activation. Chromatin immunoprecipitation (ChIP) analysis demonstrated that AR and LSD1 form chromatin-associated complexes in a ligand-dependent manner. Androgen exposure leads to a robust decrease in mono-, di-, and trimethyl H3K9 marks at the promoter of AR target genes. Small interfering RNA (siRNA)-mediated loss of LSD1 prevents ligand-induced changes in mono- and dimethyl H3K9 but does not affect trimethyl H3K9 (65). Similar to LSD1, JHDM2A, which demethylates mono- and dimethylated H3K9, interacts directly with the AR and coactivates androgen-mediated transcription (66). Contrary to LSD1, which is constitutively present at AR target genes, JHDM2A exhibits hormone-dependent recruitment. Overexpression of JHDM2A greatly reduces the H3K9 methylation level. A knockdown of JHDM2A expression results in increased dimethyl K9 levels at the promoter region of AR target genes concomitant with a decrease in their expression. Loss of LSD1 does not affect the binding of the AR to promoter regions of target genes or the ligand-induced recuitment of JHDM2A, but it does partially impair hormone-induced reduction of dimethyl H3K9 (66). In addition to LSD1 and JHDM2A, a third demethylase, JMJD2C, interacts with and functions as a coactivator for the AR (67). Interestingly, JMJD2C is a histone tridemethylase able to remove mono-, di-, and trimethyl marks from H3K9. Like LSD1, JMJD2C is constitutively present at promoter regions of AR target genes. Both JMJD2C and LSD1 interact with and stimulate AR-dependent gene transcription in a cooperative manner. Upon androgen treatment, AR, LSD1, and JMJD2C assemble on chromatin, resulting in demethylation of mono-, di-, and trimethyl H3K9 and stimulation of AR-dependent transcription. Conversely, knockdown of JMJD2C inhibits androgen-induced removal of trimethyl H3K9 and transcriptional activation by the AR (67). Taken together, these observations indicate that androgen-dependent gene transcription requires the assembly and coordinate action of methyl transferases and demethylases with distinct substrate specificities.

4. Components of the ubiquitination/proteasome pathway. Ubiquitination is a reversible posttranslational modification of cellular proteins in which a 76-amino acid polypeptide, ubiquitin, is attached to lysines in target proteins. Ubiquitination of a substrate involves the action of an activating E1 enzyme that transfers ubiquitin to a conjugating E2 enzyme, which in turn enlists an E3 ligase to deliver the ubiquitin tag to the intended target protein. Target proteins can be either polyubiquitinated or monoubiquitinated. The former usually serves as a signal for degradation of the substrate protein by the 26S proteasome, whereas the latter tends to function as a signal that regulates protein stability and protein-protein recognition, activity, and intracellular localization. Both modes of ubiquitination play vital roles in transcriptional regulation because they allow proper progression through rounds of transcription and appropriate assembly of the necessary protein complexes, and they modulate the activation status of transcription factors and coregulators (96, 97). Not surprisingly, several AR coregulator proteins function in the ubiquitin-proteasome pathway. Most of these coregulators demonstrate E3 ligase activity; this is the case for instance for E6-AP, Mdm2, PIRH2, SNURF/RNF4 and Chip. The E3 ligase E6-associated protein (E6-AP) interacts with the AR NTD in a hormone-dependent manner, demonstrates hormone-dependent recruitment to the promoter region of AR target genes, and enhances the transactivation function of the AR (98). E6-AP may also modulate the protein level of the AR because E6-AP null mice demonstrate increased AR levels in androgen-responsive prostate tissues, and overexpression of E6-AP markedly reduces AR protein expression in cells in culture (98). In addition, Mdm2 interacts with the AR and catalyzes its ubiquitination and proteolysis. The interaction of Mdm2 with the AR NTD and DBD is at least in part dependent on its E3 ubiquitin ligase activity (99). After androgen stimulation, Mdm2 complexes with the AR and HDAC1 at active AR target gene promoters and attenuates AR activity. Both the AR and HDAC1 are ubiquitinated in response to androgen. HDAC1 and Mdm2 cooperate to reduce AR-mediated transcription, and this functional interaction is attenuated by the HAT activity of the AR coactivator Tip60 (100). This suggests an interplay between acetylation status and receptor ubiquitylation in AR regulation. Supporting this possibility, Tip60 also interacts with PIRH2, another E3 enzyme. Similar to Mdm2, PIRH2 interacts directly with the AR (NTD) and HDAC1 (101). However, PIRH2 enhances AR-mediated transcription by reducing HDAC1 protein levels and inhibition of HDAC1-mediated transcriptional repression. PIRH2 is recruited to AREs in AR target genes and is required for optimal expression of these genes. The E3 ubiquitin ligase small nuclear RING finger protein (SNURF/RNF4) was isolated as an AR coregulator based on its ability to interact with the AR NLS in a hormone-dependent manner (102). SNURF does not influence the binding of the AR to cognate DNA sequences, but it appears to enhance transactivation by the AR by facilitating its import into the cell nucleus (103). SNURF also retards AR nuclear export on hormone withdrawal (104). To date, there is no evidence of SNURF-mediated changes in the ubiquitination pattern of the AR. In addition to its E3 ubiquitin ligase function, C-terminal Hsp-interacting protein (Chip) acts as a molecular chaperone involved in the folding and hormone binding of nuclear receptors. Interaction between Chip and the AR NTD, which occurs in a highly specific and sequence-dependent manner, suggests a functional link between these processes in the regulation of AR activity (105). Chip negatively regulates AR transcriptional activity by promoting AR ubiquitination and degradation (105, 106). Noteworthy, these effects of Chip are not fully reversed by proteasome inhibitors, suggesting that mechanisms different from proteasome-mediated degradation are involved. Indeed, Chip overexpression reduces the rate of AR degradation, which is consistent with an effect on AR folding (107). Thus, its effect on AR action might not be entirely dependent on its ubiquitin ligase activity.

Other proteins that have been identified as AR coregulators and have been suggested to possess E3 ubiquitin ligase

function are ARNIP, ARA54 and MKRN1 (108–111). AR N-terminal-interacting protein (ARNIP) interacts with the AR NTD, although it does not affect AR ligand-binding kinetics or AR transcriptional activation. However, AR N-terminal-C-terminal interaction is reduced in the presence of ARNIP (108). ARA54 has been isolated based on its ability to ligand-dependently associate with the AR LBD and was subsequently shown to enhance AR-mediated transactivation (109). The ubiquitously expressed Makorin RING zinc finger protein 1 (MKRN1) inhibits the transcriptional activity of the AR (111). Interestingly, disruption of the ubiquitin ligase activity of MKRN1 does not affect its inhibitory transcriptional activity. Whether ARNIP, ARA54, and MKRN1 affect the ubiquitination status of the AR or its associated complex has not been assessed.

In addition to these E3 ubiquitin ligases, proteins with other functions in the ubiquitin/proteasome pathway have been shown to modulate AR-mediated transcription. For instance, the ubiquitin-specific protease USP10 interacts directly with the AR and is part of DNA-bound AR complexes (112). USP10, but not an enzymatically inactive mutant USP10, stimulates AR-dependent transcription. Conversely, loss of USP10 expression impairs responsiveness to androgens. Similarly, the E2 ubiquitin-conjugating enzyme UBCH7 stimulates AR-mediated transactivation in a hormone-dependent manner (113). The ubiquitin conjugation activity of UBCH7 is required for this response. Tumor susceptibility gene 101 (TSG101), an E2-like enzyme deprived of ubiquitin conjugase activity, which has been proposed to act as a dominant-negative inhibitor of polyubiquitination, also modulates the AR transactivating potential. TSG101 was originally shown to repress ligand-dependent AR transcriptional activation (114). Interestingly, in an independent study TSG101 was reported to act as a coactivator for AR-mediated transcription (115). TSG101 enhances monoubiquitination of the AR in a ligand-dependent manner, and this correlates with enhanced transactivating capacity. A dominant-negative mutant of ubiquitin preventing polyubiquitination also stimulates AR-mediated transcription, which cannot be enhanced by TSG101 (115).

These reports establish multiple effectors of distinct steps in the ubiquitinylation pathway as important regulators of the AR transactivating function. Interestingly, the role of the proteasome in these events does not appear to be restricted solely to degradation of the AR or its associated proteins in the cytoplasm (Ref. 116, and also discussed below). Instead, the proteasome itself may be actively involved in AR-governed transcriptional events in the cell nucleus. This hypothesis is supported by the observation that overexpression of the proteosomal subunit PSMA7 enhances AR transactivation (117). Moreover, inhibition of the proteasome prevents the nuclear translocation of the AR, blocks interaction between the AR and several of its coregulators, and ultimately abolishes androgen-induced target gene expression (117). In addition, after androgen treatment, the 19S proteasomal subcomplex is recruited to AR target genes, where its occupancy parallels that of the AR (118).

5. Components of the sumoylation pathway. The small ubiquitin-related modifier SUMO posttranscriptionally modifies several proteins involved in regulation of transcription and chromatin structure. The machinery responsible for the sumoylation of target genes displays remarkable similarity to that mediating protein ubiquitination because it consists of E1-activating enzymes, an E2-conjugating enzyme, and several E3 ligases. SUMO E1, -2, and -3 enzymes are, however, distinct from their counterpart enzymes in the ubiquitin/proteasome pathway. Similar to the non-proteasomal roles of ubiquitin, SUMO modification of a protein primarily regulates localization and activity (119). Multiple proteins involved in several aspects of the sumoylation pathway can modulate the AR transcriptosome. First, SUMO homologs have been shown to affect AR-mediated transcription. SUMO-1 decreases, whereas SUMO-2 and -3 enhance AR transcriptional activity (120, 121). SUMO-3 interacts with the AR NTD. The positive effect of SUMO-3 on AR-transcriptional activity does not depend on either the sumoylation sites of the AR or the sumoylation function of SUMO-3 (121). Sumoylation of the AR NTD by SUMO-1 is stimulated by androgens, and mutation of the sumoylation sites in the AR NTD increases AR transactivation, indicating that sumoylation serves to attenuate AR function (120). Second, the SUMO E2 conjugating enzyme Ubc9 interacts with the NLS in the AR-hinge region and acts as a AR coactivator (122). Interestingly, the effects of Ubc9 on AR activity occur independently of its SUMO-1 conjugating catalytic activity (122, 123). Third, protein inhibitors of activated STAT (PIAS) family members that function as SUMO E3 ligases can either positively or negatively affect transcription by the AR (124–132). PIAS proteins (PIAS-1, -3, -xα, or ARIP3, -xβ, and -y) bind the AR DBD (126). Although homologous, PIAS proteins can differ markedly in their ability to sumoylate the AR and/or AR-associated coactivators such as TIF-2 (131). PIAS-y, which acts as a corepressor for the AR, does not rely on its E3 ligase activity to influence AR-mediated transcription (132). Moreover, the decision for a particular PIAS protein to function as a corepressor or coactivator depends on the cell type and the target gene (127). Furthermore, the PIAS-like SUMO E3 ligases Zimp7 and Zimp10 both function as AR coactivators (133–135). Zimp10 was shown to interact with the AR NTD (133). AR sumoylation is enhanced in the presence of Zimp10, and mutation of the AR sumoylation sites abrogates the augmentation of AR activity by Zimp10 (133, 135). Fourth, AR-mediated transcription is markedly enhanced by SENP1, a member of the SUMO-specific protease family (136). Although the AR is a target for SENP1, the ability of SUMO1/sentrin-specific protease 1 (SENP1) to enhance AR-dependent transcription is not mediated through desumoylation of the AR, but rather through its ability to deconjugate HDAC1, thereby reducing its deacetylase activity. The repressive effect of HDAC1 on AR-dependent transcription can be reversed by SENP1 and by deletion of its sumoylation sites. In contrast, SENP2 and SENP3 have only modest effects on AR transactivation (136).

In addition to the ubiquitination/proteasome and sumoylation pathways, activity of the related neddylation pathway appears to be involved in AR-mediated transcription. Ubiquitin-activating enzyme 3 (Uba3), the catalytic subunit of the activating enzyme of the ubiquitin-like NEDD8 (neural precursor cell expressed developmentally down-regulated) con-

jugation pathway, inhibits transactivation by the AR. The neddylation activity of Uba3 is required for its inhibition of steroid receptor transactivation. Direct interaction between Uba3 and the AR has not been reported (137).

Overall, the identification of numerous proteins with functions in the ubiquitination, SUMOylation as well as NEDDylation pathways as AR coregulators points toward the critical importance of tight regulation of the turnover, stability, degradation, and subcellular relocalization of components of the AR transcriptional machinery in androgen-regulated gene transcription.

6. Proteins involved in splicing and RNA metabolism. Primary transcripts undergo several modifications before a mature mRNA is generated that can serve as a template for translation. Because the steps from transcription to translation are mechanistically and functionally coupled (138, 139), it is not surprising that several proteins, which demonstrate AR coregulator characteristics, belong to or share high functional or structural homology to members of the family of RNA processing enzymes. For instance, the pre-mRNA splicing proteins PSF (polypyrimidine tract-binding protein-associated splicing factor), PSP1 (paraspeckle protein 1) and PSP2 interact with AF-1 of the AR (140). p54nrb (p54 nuclear RNA binding protein, NonO), another component of the U1snRNP prespliceasome, interacts with the AR NTD in a ligand-dependent manner and potentiates AF-1 function (140). Because p54nrb and PSF also directly interact with the RNA polymerase II CTD, a molecular link between the AR transcriptional and splicing machinery is apparent (138). Furthermore, p102 U5snRNP has been isolated as a protein interacting with AR AF-1, termed ANT-1 (AR N-terminal domain transactivating protein-1). ANT-1 enhances the ligand-independent AF-1 function of the AR but does not affect ligand-dependent AF-2 activity (141, 142).

The splicing factor hnRNPA1 is recruited to the AR through association with the AR interacting coactivator ARA54 and selectively suppresses ARA54-enhanced AR transactivation via interruption of AR-ARA54 interaction (143). Finally, the previously discussed methyltransferases CARM-1 and p44 (MEP50) are components of the methylosome complex that methylates snRNP complex proteins, suggesting that they also fulfill roles in splicing events.

7. Proteins involved in DNA repair. In a targeted approach to discover components that comprise the AR apo- and holoreceptor complex using tandem mass spectroscopy analysis, the trimeric DNA-dependent protein kinase (DNA-PK) complex was isolated (144). The DNA-PK complex is best known for its role in DNA repair and has emerged as a part of the transcriptional machinery. The AR-LBD interacts directly with the Ku70 and Ku80 regulatory subunits of DNA-PK in a DNA-independent manner. Interaction between the AR and the catalytic DNA-PK subunit has not been observed. Ku proteins bind the AR in both the cytoplasm and the nucleus. Ku proteins are recruited in an androgen-dependent manner to the promoter of AR target genes. Ku70 and Ku80 as well as DNA-PK enhance AR activity in transactivation assays. Ku70 and Ku80 have been shown to exert these effects through recycling of transcriptional factors (144). Other proteins with roles in DNA repair and damage control have been demonstrated to modulate AR-mediated transcription. For instance, the checkpoint protein Rad9 acts as a corepressor to suppress AR transactivation (145). The AR interacts with the C terminus of Rad9 via its LBD. The FXXLF motif within the C terminus of Rad9 interrupts the androgen-induced interaction between the N terminus and C terminus of the AR. Moreover, the tumor suppressor genes BRCA1 and BRCA2 are AR coactivators (146–148). BRCA2 is an integral component of the homologous recombination machinery, whereas BRCA1 possesses both E3 ubiquitin ligase activity and DNA repair activity. BRCA1 interacts with the AR NTD and enhances transcription of AR target genes. BRCA1-enhanced AR transactivation can be further induced synergistically with AR coregulators SRCs, CBP, ARA55, and ARA70 (146, 147). BRCA2, but not a truncated mutant of BRCA2, synergizes with SRC-2 to enhance transcriptional activation by the AR. BRCA2 associates with the AR NTD and LBD, as well as SRC-2, and further cooperates with P/CAF and BRCA1 to enhance AR- and SRC-2-mediated transactivation (148).

In general, components of the DNA repair machinery are recruited when the transcriptional machinery runs into obstacles or DNA lesions that prevent proper transcription of target genes. The identification of several proteins with functions in DNA repair as coregulators for the AR indicates that this mechanism holds true also for AR-mediated transcription.

8. Chaperones and cochaperones. In the absence of androgens, the molecular chaperone complex is critical to maintain the AR in a stable, inactive, intermediate configuration that has a high affinity for androgenic ligands. Upon binding of androgens and folding of the AR into an active conformation, selective molecular chaperones remain associated with the AR and are important for downstream events such as AR translocation, AR transcriptional activity, disassembly of the AR transcriptional complex, and AR degradation. The sustained importance of these proteins in overall AR activity is reflected in the interactions between the AR and multiple components of chaperone complexes throughout the life cycle of the AR (14). In the early stages of the AR activation process, AR LBD interacts transiently with Hsp40 (Ydj1), Hsp70 (HSc70), Hip, Hps90, Hop, and p23, leading to an equilibrium in which the AR is maintained in an overall high-affinity ligand-binding state. In this respect, Hsp40 is necessary for hormone binding to the AR (149). Mutations in Hsp40 result in a reduction of AR-Hsp70 complex formation and defects in AR folding (150). In contrast, loss of the Hsp70 cochaperone DjA1 in a knockout mouse model leads to increases in AR protein levels and enhanced transcription of several androgen-responsive genes in Sertoli cells, giving rise to severe defects in spermatogenesis (151). In the same study, DjA1 was suggested to function as a negative regulator of transactivation by the AR. Hormone binding causes the AR to undergo a sequential loss of chaperones (14). With the assistance of Hsp90, the AR is transformed into a DNA-binding competent state. Receptor activation leads to unmasking of the NLS, resulting in Hsp90-dependent translocation of the AR to the nucleus (14). Cdc37 (p50) also functions down-stream of hormone-binding as an Hsp90-

associated protein involved in AR trafficking. Mutant forms of cdc37 induce defects in AR transactivation while leaving AR protein levels unaltered (152). Hsp70 and Hsp40 are also believed to reassociate with the AR in the presence of ligand and to facilitate transport of the receptor into the nucleus (14). Hsp90 binding cochaperone FKBP52 (FK506 binding protein of 52kDa) interacts with AR complexes (153). *In vivo* studies using FKBP52-deficient mice indicate that FKBP52 does not affect hormone binding by the AR or AR nuclear translocation but is critical for AR transactivation (153, 154). FKBP52 enhances AR-mediated transcription, and this effect depends on its ability to interact with Hsp90 (153). FKBP52 may also be necessary to maintain AR protein levels (153). The related cochaperone FKBP51 forms complexes with the AR and stimulates AR transactivation, although these observations could not be confirmed by a second, independent study (154, 155). Apart from their effects on AR folding and trafficking, experimental evidence supports a direct involvement of molecular chaperones in the transcriptional activation of AR target genes. Bag-1 Hsp70 cochaperones, in particular the Bag-1L isoform, bind directly to the TAU 5 domain in the AR NTD and function as a coactivator for the AR (156, 157). Bag-1L relies on its association with Hsp70 to interact with the AR, and loss of this interaction domain markedly suppresses its abilitity to stimulate AR-mediated transactivation. Moreover, Bag-1L as well as Hsp70 are recuited with the AR to promoter regions of AR target genes (156). Noteworthy, Bag-1L harbors a ubiquitin-like domain that facilitates association of Bag-1L with the proteasome, enabling Bag-1L to function as a coupling factor between the chaperone and proteolytic complex (158). This is reminescent of the dual function of Chip as both an E3 ubiquitin ligase and a cochaperone. In fact, AR degradation by an Hsp70-Chip governed system has been reported (158). Bag-1 and Chip interact directly and cooperate with each other during the sorting of chaperone substrates to the proteasome. Taken together, these findings suggest an interdependency between AR-mediated transcription, AR degradation, and folding events.

9. Cytoskeletal proteins. Actin is a major component of the cytoskeleton. Although the cytoplasmic roles of actin and actin organization in the cytoplasm have been well established, the possibility for a role for actin in the nucleus has been controversial. However, it is now generally accepted that actin plays a role in transcriptional events. Actin as well as actin binding proteins have been shown to mediate nuclear translocation of transcriptional regulators. Moreover, actin is found as part of chromatin remodeling complexes and ribonucleoprotein particles and interacts directly with RNA polymerases (159). Actin binding proteins and actin monomers bind to the AR, indicating that they also play an important role in AR-mediated transcription. For example, supervillin, an actin-binding protein, is able to interact with the AR NTD and DBD-LBD (160). This association is enhanced in the presence of androgens. Supervillin increases AR transactivation and cooperates with other AR coregulators, such as ARA55 or ARA70. Moreover, three different actin isoforms cooperate with supervillin to stimulate further AR transactivation in an additive manner (161). Conversely, an actin chelator that reduces the availability of monomer actin attenuates the coactivator properties of supervillin (161). Supervillin has no effect on cytoplasmic-nuclear translocation of the AR, nor does it affect the half-life of the AR (160). Similar to their effect on supervillin, androgens increase the interaction between the AR DBD-LBD and gelsolin, another actin-binding protein, in a dose-dependent manner. Gelsolin interacts with the AR during nuclear translocation and enhances ligand-dependent AR activity (162). In addition, the F-actin cross-linking protein filamin, which was originally identified as a protein that facilitates nuclear transport of the AR, interacts with the AR DBD-LBD in a ligand-independent manner. However, this interaction is enhanced in the presence of androgens. The absence of filamin hampers androgen-induced AR transactivation (163). A second, smaller 90- to 100-kDa (instead of the 280-kDa form) fragment of filamin (termed filamin A) is capable of nuclear translocation and colocalizes with the AR to the nucleus (164, 165). This naturally occurring filamin fragment represses AR transactivation and disrupts AR interdomain interactions as well as hampers SRC-2-activated AR function. Another cytoskeletal protein, α-actinin-2, enhances the transactivation activity of SRC-2 and serves as a primary coactivator for the AR, acting in synergy with SRC-2 to increase AR transactivation function (166). α-Actinin-4 also binds to the AR and exhibits coregulating properties (167). Finally, the actin binding protein transgelin suppresses AR function via interruption of AR-ARA54 heterodimerization, resulting in the cytoplasmic retention of the AR and ARA54. Transgelin does not directly interact with the AR but exerts its effects through recruitment to ARA54 (168).

Like actin, microtubules constitute a principal component of the cytoskeleton and have been proposed to play an important role in nuclear receptor function. In the case of AR-mediated transcription, ARA67/PAT1/APPBP, which shows homology to kinesin light chain and binds microtubules, interacts with the AR NTD. ARA67/PAT1 functions as a corepressor for the AR. Interruption of AR cytoplasmic-nuclear shuttling may play a major role in ARA67/PAT1-mediated suppression of AR activity (169).

10. Proteins involved in endocytosis. Endocytosis mediates the selective uptake of specific macromolecules into the cell. The best-characterized form of endocytosis is that mediated by the budding of clathrin-coated vesicles from specialized regions of the plasma membrane. Clathrin-coated vesicles fuse with endosomes, and the content of the vesicle is sorted for intracellular transport or recycled to the plasma membrane (170). Endocytosis can also be achieved in a clathrin-independent manner by uptake of molecules in small invaginations of the plasma membrane termed caveolae, which are coated with caveolin (171). Interestingly, multiple proteins involved in both mechanisms of endocytosis have been shown to interact with the AR and to influence AR-mediated transcription. One of the adaptor proteins involved in clathrin-mediated uptake, huntingtin-interacting protein 1 (HIP1), associates with the AR and reduces the rate of AR protein degradation (172). Moreover, HIP1 is recruited to AREs upon androgen stimulation. Overexpression of HIP1 enhances AR-mediated transcription. Conversely, transcrip-

tion by the AR is significantly repressed after knockdown of HIP1 expression. Androgen stimulation results in nuclear translocation of HIP1, an event that relies on a nuclear localization signal at the COOH terminus of HIP1 (172). Remarkably, another endocytic protein termed APPL (adapter protein containing PH domain, PTB domain, and leucine zipper motif), that translocates to the nucleus upon growth factor stimulation, down-regulates AR-mediated transcription in a dose-dependent manner. Interaction between the AR and APPL is mediated by Akt (173). In addition, HAP1 (huntingtin-associated protein 1), which functions in endocytosis of membrane receptors and endosomal trafficking, interacts with the AR through its LBD (174). This interaction is dependent on the length of the AR polyglutamine stretch (stronger with increasing length), and the addition of androgens diminishes the strength of this association. Cyclin G-associated kinase (GAK), or auxilin 2, is an essential cofactor for Hsp70-dependent uncoating of clathrin-coated vesicles. GAK interacts with the AR NTD and enhances the AF-1 function of AR activity in a ligand-dependent manner (175). Caveolin is a principal component of caveolae membranes that serve as a scaffold protein of many signal transduction pathways. Caveolin-1 ligand-dependently interacts with the AR NTD and LBD (176). Overexpression of caveolin-1 significantly increases nuclear localization of the AR and potentiates ligand-dependent AR activation (177). In contrast, down-regulation of caveolin-1 expression diminishes androgen-induced AR-mediated transcription (176).

Overall, these findings support the concept that several proteins involved in different aspects of endocytosis exert AR coregulatory characteristics.

11. Signal integrators and transducers, scaffolds, and adaptors. In line with the AR coregulator properties of endocytic scaffold proteins such as caveolin-1, several proteins involved in cell-cell contacts and cell-substrate adhesion complexes are able to interact with the AR and regulate its activity. This is the case also for a number of proteins that function as scaffolds and adaptors for multiple signal transduction pathways. Among these are LIN-11, ISL-1, and MEC-3 (LIM) domain-containing proteins that can associate with focal adhesions, such as ARA55/Hic, paxillin and four-and-a-half-LIM-only protein 2 (FHL2). ARA55 binds to the AR-LBD in a ligand-dependent manner and relies on three LIM domains in its C-terminal half for this interaction. ARA55 enhances transcriptional activity of the AR (178). Interestingly, the focal adhesion kinase (FAK) Pyk2 is able to repress AR transactivation by interacting with and phosphorylating ARA55 (179). The ARA55-related protein paxillin also localizes within focal adhesions and can participate in a number of signal transduction pathways. Paxillin directly interacts with the AR, and overexpression of paxillin results in increased targeting of the AR to the nuclear matrix (180). Paxillin functions as a coactivator for the AR. Moreover, like ARA55, paxillin relies on its COOH-terminal LIM domain to interact with the AR. The four-and-a-half LIM domain protein FHL2, which also functions at focal adhesions as well as in the nucleus, directly associates with full-length AR and stimulates AR-mediated transcription in an agonist- and AF-2-dependent manner (181). FHL2 has been found to interact with PELP1/MNAR (proline-, glutamic acid-, and leucine-rich protein-1/modulator of nongenomic actions of the estrogen receptor), which serves as a scaffolding protein that couples nuclear receptors with various signaling complexes (182). The PELP/MNAR interactome harbors transcriptional regulators, chromatin regulators, splicing factors, cell cycle proteins, cytoskeletal regulators, and proteins involved in nongenomic signaling. PELP1/MNAR interacts with the AR and enhances FHL2-mediated AR transactivation. Conversely, knockdown of PELP1/MNAR reduces FHL2-induced AR transactivation (182). Thus, PELP1 functions as a molecular adaptor, coupling FHL2 with the AR. Another focal adhesion protein, vinexin α, has been identified as a vinculin-binding protein that plays a key role in cell spreading and cytoskeletal organization. The AR binds to vinexin α, and the ligand-induced transactivation function of the AR is stimulated by vinexin α (183).

In addition to focal adhesion components, several proteins involved in G-coupled receptor signaling affect AR-induced transcription and/or interact with the AR. The Rho GTPase guanine nucleotide exchange factor (GEF) Vav3 activates Rho family GTPases by promoting the exchange of GDP for GTP. Vav3 potentiates AR transcriptional activity (184, 185). In contrast, knockdown of Vav3 results in decreased AR transactivation. The increase in AR activity by Vav3 involves AF-1 of the AR. However, Vav3 does not interact with the AR, nor does it increase AR levels. Whether its GEF function is required for the stimulation of AR transactivation is still under debate (184, 185). Rho guanine nucleotide dissociation inhibitor (Rho GDI) was originally identified as a negative regulator of the Rho family of GTP binding proteins. Overexpression of Rho GDI increases AR transcriptional activation, suggesting an AR coactivator role (186). Physical interaction between Rho GDI and the AR has not been assessed. Interplay between activated Cdc42-associated tyrosine kinase Ack1 and the AR has also been described. Ack1 binds the AR and phosphorylates several tyrosine residues in its NTD (187). Activated Ack1 is recuited to AREs and promotes induction of AR target gene expression in both the presence and absence of androgens. Moreover, knockdown of Ack1 decreases androgen-stimulated recruitment of the AR to AREs in target genes, suggesting that Ack1 is required for optimal androgen-regulated DNA binding of the AR (187). Protein kinase C-related kinase (PRK) 1/protein kinase N is a member of the protein kinase C (PKC) superfamily of serine/threonine kinases and is one of the first identified effectors for RhoA GTPases. The AR interacts with PRK1 through the TAU 5 domain (188). Blocking of endogenous PRK signaling severely impairs agonist-dependent AR transactivation. Similar effects are seen for the related PRK2. Conversely, stimulation of the PRK signaling cascade results in a ligand-dependent superactivation of the AR. Furthermore, PRK1 promotes a functional complex of AR with the coactivator SRC-2 (188). RanBPM (Ran-binding protein in the microtubule-organizing center) was originally identified by its interaction with the small Ras-like GTPase Ran. RanBPM interacts directly with the AR-NTD and DBD in the presence of ligand and enhances androgen-dependent transcription by the AR (189). RanBPM may also play a role in Ran-dependent nuclear transport. It is noteworthy that Ran/

ARA24 interacts with the AR NTD and acts as a coactivator for the AR (190), suggesting that RanBPM, Ran, and the AR work in a multiprotein complex.

The p21-activated kinase (PAK6) that contains a putative amino-terminal Cdc42/Rac interactive binding motif and a carboxyl-terminal kinase domain interacts with either the AR-hinge region or LBD (191–193). In contrast to most PAKs, PAK6 activity is not stimulated by Cdc42 or Rac, but can be stimulated by AR binding. In response to androgens, PAK6 cotranslocates into the nucleus with the AR and represses AR-mediated transcription. This suppression requires its kinase activity but does not depend upon GTPase binding to PAK6 and is not mimicked by the closely related PAK1 and PAK4 isoforms. Active PAK6 inhibits nuclear translocation of the stimulated AR, suggesting a possible mechanism for inhibition of AR responsiveness (191–193). Interaction with PAK6 could provide a mechanism for the AR to cross-talk with other signal transduction pathways. In keeping with this concept, the adaptor/scaffolding protein receptor for activated C kinase 1 (RACK1) interacts with the AR through its LBD (194). RACK1 facilitates ligand-independent AR nuclear translocation upon PKC activation and suppresses both ligand-dependent and -independent AR transactivation through PKC activation. ChIP assays reveal a decrease in AR recruitment to AR target genes after stimulation of PKC. These observations support a role for RACK1 as a scaffold for the association and modification of the AR by PKC, enabling translocation of the AR to the nucleus but rendering the AR unable to activate transcription of its target genes (194). An independent study confirmed the repressive effect of RACK1 on androgen-dependent gene expression and showed that androgens can enhance the association between RACK1 and the AR (195). Moreover, RACK1 facilitates the interaction between the AR and Src kinase, which results in increased tyrosine phosphorylation of the AR (195). It is noteworthy that tyrosine phosphorylation by Src is important for AR nuclear translocation (196).

In line with the concept that adaptors for multiple signal transduction pathways can modulate AR-driven transcription, several effectors of such cascades are able to interact with the AR and positively or negatively alter the transcriptional events it mediates. For instance, signal transducer and activator of transcription (STAT)-3 can bind the AR and enhance AR transactivation (125, 197–199). STAT3 has been described to stimulate the transcriptional activity of the AR in a hormone-dependent manner acting synergistically with SRC-1, P/CAF, CBP, and SRC-2 (197). Conversely, DHT-induced AR activity is increased by IL-6, a cytokine activating and signaling through STAT3 (198). In addition, association of the AR with STAT3 enhances the activity of STAT3 (199). AR activation overcomes the inhibitory effect on STAT3-mediated transcription by PIAS3. The AR relieves STAT3 from STAT3-PIAS3 complex formation (199). Similarly, Smad3, a key component in the TGF β signaling cascade modulates AR-mediated transcription (200–203). Depending on the experimental setting and the target gene studied, Smad3 can act as an AR coactivator or corepressor. Protein-protein interaction between AR and Smad3 involves the AR DBD-LBD region. Moreover, ligand-bound AR inhibits TGF-β transcriptional responses through selectively repressing Smad3 signaling (203).

Ligand-enhanced binding of Ebp1, an ErbB-3 binding protein, to the AR NTD suggests a link also between ErbB receptor and AR signaling (204). Indeed, ectopic expression of Ebp1 inhibits ligand-mediated transcriptional activation of AR target genes (204–206). Ebp1 participates in the transcriptional regulation by the AR via its interaction with the corepressors HDAC and Sin3 (207).

Supporting the possibility for cross-talk between Notch and androgen-signaling pathways, Hairy/Enhancer of split related with YRPW motif 1 (Hey1), a member of the basic helix-loop-helix-orange family of transcriptional repressors that mediate Notch signaling, interacts with the AR in a ligand-independent manner (208). Androgen-dependent AR transcriptional activity is inhibited by Hey1, and expression of a constitutively active form of Notch represses transactivation by the AR. It is noteworthy that Hey2, another member of the Hey family, is also able to repress AR transcription. The inhibiting effects of Hey1 on AR transactivation are mediated by AF-1 (208). Similarly, the AR (through its LBD) and the interferon-activated RNase L interact in a ligand-dependent manner (209). In addition, overexpression of RNase L in the presence of interferon reduces androgen-mediated AR transcriptional activity. Conversely, androgens are able to interfere with induction of gene expression by interferon, indicating a functional cross-talk between DHT and interferon signaling (209). Finally, the Wnt signaling pathway also modulates androgen signaling at multiple levels. Androgens promote the cytoplasmic-nuclear translocation of beta-catenin, a critical component of this signaling pathway. Moreover, beta-catenin is able to bind to the AR LBD in a ligand-dependent manner, is recruited to AREs in AR target genes, and enhances transcriptional activity by the AR (210–214). Furthermore, glycogen synthase kinase-3β (GSK-3β), a protein serine/threonine kinase that regulates beta-catenin degradation, phosphorylates and interacts with the AR and suppresses its ability to activate transcription (215, 216). In contrast, some reports mention a GSK-3β-mediated increase in AR transactivation (217). Furthermore, T cell factor 4, one of the targets of Wnt signaling that relies on beta-catenin for transcriptional activation, interacts with the AR DBD and functions as a corepressor for the AR (214, 218).

12. Cell cycle regulators. Interestingly, several proteins involved in the regulation of cell cycle progression also associate with the AR and modulate its transcriptional activity. For example, cyclin E increases the transactivation activity of the AR in the presence of DHT. Cyclin E binds directly to the NTD of the AR and enhances its AF-1 transactivation function. Interaction with the AR does not require complex formation with CDK2, nor does it involve phosphorylation of the AR (219). Cdc25B is a cell cycle regulator that functions as a dual-specific phosphatase to mediate cell cycle progression by activating the cyclin-dependent kinases. Cdc25B interacts directly with the AR and stimulates AR-dependent transcription independent of its protein phosphatase activity (220–222). Moreover, P/CAF and CBP interact and synergize with Cdc25B and further enhance its coactivation activity (220). Furthermore, cyclin-dependent kinase 6 (CDK6) binds

to and is activated by cyclin D1 and as such enhances the transition of cells through the G_1 phase of the cell cycle. CDK6 also associates with the AR and stimulates its transcriptional activity in the presence of DHT. This effect does not require its kinase activity and is inhibited by cyclin D1 and p16INK4a (223). Moreover, CDK6 is present in association with the AR at the promoter region of AR target genes. Contrary to the coactivator properties exhibited by these cell cycle regulators, cyclin D1 functions as a corepressor for the AR (224–229). Ligand-mediated transcriptional activation of AR target genes is inhibited by cyclin D1 as well as cyclin D3 (224). This function of cyclin D1 is independent of its role in cell cycle progression. Cyclin D1 directly binds to the AR in a ligand-independent manner. Cyclin D1 targets the AF-1 transactivation function. Corepressor activity of cyclin D1 can be explained by its ability to recruit HDACs and its inhibition of AR N- and C-terminal interactions (224–229). A second isoform of cyclin D1, termed cyclin D1b, is compromised in its ability to regulate AR activity, although it retains the ability to associate with the AR (230). The retinoblastoma protein (Rb) functions as a tumor suppressor by controlling progression through the cell cycle. Rb has been described to bind to the AR in an androgen-independent manner and enhances AR transcriptional activity in the presence of DHT (231, 232). Rb and ARA70 cooperate with each other to activate transcription by the AR (231). Interestingly, pp32, which interacts with Rb, also functions as an AR coactivator (233). The presence of Rb modulates this activity. The splicing factors p54nrb and PSF are additional components of the pp32-Rb complex (233). Furthermore, Rb-associated Krüppel protein (RbaK) interacts with the AR LBD in a ligand-dependent manner (234). Finally, apoptosis-antagonizing transcription factor (AATF), also termed Che-1, which has been shown to bind Rb and promote cell cycle progression, enhances AR-mediated transactivation in a hormone- and dose-dependent manner and acts as cooperative coactivator for TSG101 (115).

13. Regulators of apoptosis. In addition to proteins that govern progression through the cell cycle, a few proteins with prominent roles in the execution of apoptosis act as AR coregulators. For example, the proapoptotic caspase-8 represses AR-dependent gene expression (236). It does this by disrupting AR N/C interaction and inhibiting androgen-induced AR nuclear localization. Noteworthy is the fact that caspase-8 does not depend on its apoptotic protease activity to exert these functions. Caspase-8 interacts directly with the AR NTD FXXLF and WXXLF sequences, and mutations of these AR motifs prevent its repressive effect on AR-mediated transcription. In addition, knockdown of caspase-8 by RNA interference specifically affects the androgen-dependent expression of AR-targeting genes (236). Par-4, another proapoptotic protein, on the other hand, acts as an AR coactivator (237). Par-4 physically interacts with the AR DBD, is recruited to the promoter of an AR-driven gene in the presence of androgens, enhances association of the AR with DNA, and increases AR-dependent transcription. Androgen-induction of this gene is counteracted by a dominant-negative form of par-4 (237).

14. Viral oncoproteins. The human papillomavirus (HPV) E2 oncoprotein has been suggested to act as an AR coactivator by physical and functional interactions with the AR as well as the AR-associated coactivators SRC-2 and Zac1 (zinc-finger protein which regulates apoptosis and cell cycle arrest 1). SRC-2 and Zac1 are both able to act synergistically with HPV E2 proteins on AR-dependent transcriptional activation (238, 239). Similarly, HPV E6 and E7 are able to interact directly with the AR in the absence and presence of androgens (240). Depending on the cell type and the promoter context, these oncoproteins display AR coactivator or corepressor properties. Interestingly, also the hepatitis B virus nonstructural protein x (HBx) can enhance AR activity (241, 242). HBx dose-dependently increases androgen-stimulated AR-mediated transcription. HBx does not physically associate with ligand-bound AR in the nucleus, and it likely augments AR activity by increasing the phosphorylation of the AR through HBx-mediated activation of the c-Src kinase signaling pathway (242).

15. Other functionally diverse proteins

a. Nuclear receptor coregulators. A number of proteins that have been identified as AR coregulators cannot be readily classified into the categories listed above. Some of these have been reported to either positively or negatively regulate ligand-dependent transcription by nuclear receptors. General nuclear receptor coactivators that have been shown to enhance androgen-dependent transcription by the AR include Asc-1 (activating signal cointegrator-1) (243), Asc-2 (244), components of the Trap/Mediator complex (63, 245), CoCoA (coiled-coiled coactivator) (246), NRIP (nuclear receptor interaction protein) (247), PNRC (proline-rich nuclear receptor coregulatory protein) (248), TIF-1α (249), MRF1 (modulator recognition factor 1) (250), PDIP1 (PPARγ-DBD-interacting protein 1) (251), Zac1 (252), GT198 (253), and ARA70 (254). Corepressors that negatively affect transactivation of the AR as well as other nuclear receptors comprise Alien (255), AES (aminoterminal enhancer of split) (256), components of the SMRT and NCoR repressor complexes (17, 257), RIP140 (receptor interacting protein 140 kDa) (258), PATZ (POZ-AT hook-zinc finger protein) (259), and TGIF (5′TG3′ interacting factor) (260). This group of proteins also contains some coactivators [*e.g.*, ART-27 (AR-trapped clone 27) (261) and ARA160 (262)] as well as corepressors [*e.g.*, Tip110 (263), TZF (testicular zinc finger protein) (264–266), and ARR19 (AR corepressor 19kDa) (267)] that specifically interact with the AR. The coregulators listed here interact with the AR and affect its transcription activity via different regions of the receptor.

b. Kinases and phosphatases. Relatively few AR coregulators are protein kinases and phosphatases. Some of these have been listed above. Others have been identified, including male germ cell-associated kinase (MAK). MAK physically associates with the AR (AR NTD-DBD and DBD-LBD fragments) (268). MAK and the AR are corecruited to promoters of AR target genes, and MAK is able to enhance the AR transactivation potential in an androgen- and kinase-dependent manner. To this end, MAK acts in synergy with SRC-3 (268). In addition, the Ser/Thr protein kinase AR-interacting

nuclear protein kinase (ANPK) interacts with the DBD-hinge region of the AR in a ligand-dependent manner (269). Overexpression of ANPK enhances AR-dependent transcription. The AR does not appear to be a substrate for ANPK (269). Remarkably, also Dyrk1A, a dual specificity tyrosine phosphorykation-regulated kinase that shares homology with ANPK, coactivates transactivation by the AR. This effect of Dyrk1A is mediated at least in part through physical and functional interaction with ARIP4, which is independent of its kinase activity (270). Similarly, ERK8 negatively regulates transcriptional coactivation of the AR by ARA55 in a kinase-independent manner (271). The serine/threonine protein kinase p90-kDa ribosomal S6 kinase (RSK), an important downstream effector of MAPK, also enhances the expression of AR target genes, an effect that was reversed by inhibiting RSK activity. This apparent coactivating activity of RSK involves both RSK kinase activity and its ability to associate with p300 (272).

Small CTD phosphatase (SCP)-2 interacts with the AR NTD (273). SCP2 and two other family members, SCP1 and SCP3, attenuate AR transcriptional activity and are recruited in an androgen- and AR-dependent fashion onto the promoter of an AR-target gene. Silencing of SCP2 increases androgen-dependent transcription and augments AR loading to target gene promoter and enhancer. SCP2 is involved in promoter clearance during androgen-activated transcription (273). Finally, mediated by tumor antigen simian virus 40 small t antigen (ST), protein phosphatase 2A (PP2A) can be transferred onto the ligand-activated AR (274). Transfer by ST is strictly dependent on the agonist-activated conformation of the AR, occurs within minutes of the addition of androgen to cells, and can occur in either the cytoplasm or the nucleus. ST rapidly dissociates from the complex upon PP2A binding to the AR. PP2A is transferred onto the LBD of the AR, and the phosphatase activity is directed to five phosphoserines in the NTD AF-1, with a corresponding reduction in AR transactivation (274).

c. Diverse functions. The remaining AR coregulators include the tumor suppressor genes LATS/KPM and PTEN. LATS2/KPM, which possesses kinase activity, interacts with the AR-LBD. This interaction is ligand-enhanced. LATS2 inhibits androgen-regulated gene expression by a mechanism that involves the inhibition of AR N- and C-terminal interaction. ChIP assays revealed the presence of LATS2 and the AR at the promoter of AR target genes (275). PTEN also functions as an AR corepressor via a phosphatidylinositol-3-OH kinase/Akt-independent pathway (276–278). The direct interaction between the AR (amino acids 483–651) and PTEN inhibits AR nuclear translocation and promotes AR protein degradation (278).

Tob1 and the closely-related Tob2, members of an antiproliferative protein family and negative regulators of osteoblast proliferation and differentiation both suppress AR-dependent transcriptional activity. Tob1 inhibits the nuclear foci formation of DHT-bound AR (279).

The multifunctional DJ-1/PARK7 oncoprotein and neuromodulator was identified as an AR coactivator by its ability to interact with PIASx α/ARIP3 and to restore AR transcription activity by absorbing the corepressor PIASx α from the AR-PIASx α complex (280). DJ-1 interacts directly with the AR as well (281). DJ-1-binding protein, DJBP, binds the DBD of the AR in an androgen-dependent manner and colocalizes with DJ-1 or AR in the nucleus (282). DJBP represses androgen-dependent AR transactivation activity by recruiting a HDAC complex. DJ-1 partially restores the activity of the AR by abrogating the DJBP-HDAC complex.

Interestingly, apart from DJ-1, a second protein implicated in Parkinson's disease possesses AR coregulator activity. Indeed, L-dopa-decarboxylase interacts with the AR LBD and NTD and enhances AR transactivation activity (283).

Melanoma antigen gene protein MAGEA11 is an AR coactivator of particular interest (284). It specifically binds the AR N-terminal FXXLF motif, resulting in stabilization of the ligand-free AR and, in the presence of an agonist, increases exposure of AF-2 to the recruitment and activation by the SRC/p160 coactivators. AR transactivation increases in response to MAGEA11 and the SRC/p160 coactivators through mechanisms that include but are not limited to the AF-2 site. Thus, MAGEA11 functions as a unique AR coregulator that increases AR activity by modulating the AR interdomain interaction.

Steroid receptor RNA activator (SRA) was originally isolated as a coactivator for several nuclear receptors, including the AR, which acts as an RNA transcript (285). SRA transcripts exist in distinct ribonucleoprotein complexes that contain also SRC-1. SRA is translated as well, and three SRA isoforms (SRA1–3) enhance AR-mediated transcription (286).

C. Specific transcription factors

Further regulation of the transcriptional output by the AR is achieved by transcription factors that bind to specific cognate DNA sequences. Over the last decade, multiple transcription factors have been shown to interact physically and functionally with the AR (287–324) (for an overview, see Table 1). Regulation of AR-mediated transcription by these factors is governed by different mechanisms. Some of these proteins interact directly with the AR [*e.g.*, DAX-1 with the AR LBD (287)] and affect its ability to interact with AREs without binding directly to DNA themselves. Others [*e.g.*, AP-1 (80)] compete with the AR for coregulators that are present in limited supply within the cell. Alternatively, some transcription factors [*e.g.*, Foxa2 (288)] bind to DNA sequences that are interspersed between or in close proximity to AREs, allowing cooperation in and coregulation of transcription of the target genes. The importance of this latter mechanism of regulatory cross-talk between the AR and multiple DNA-binding transcription factors is underscored by the results of several recent ChIP-on-chip approaches aimed at mapping the genome-wide recruitment of the AR and characterizing the loci of AR enrichment (325–327). In these studies, a minority of the sites of AR occupancy meet the criteria that define a canonical ARE. Instead, most of the AR binding sites contain only an ARE half-site. A small fraction harbors no ARE-like motif at all. Strikingly, the sites of AR recruitment are selectively enriched in binding motifs for multiple specific transcription factors including Foxa1,

TABLE 1. An overview of transcription factors that modulate AR activity

Transcription factor	A/R	Direct/indirect	Ref.
AML3/CBFα1	A	Direct	289
AP-1	R	Direct–NTD, LBD	80, 290, 291
ATF2	R	Direct–DBD	292
Brn-1	A/R	Direct	293
c-Jun	A/R	Direct–DBDh, DBD-LBD	294, 295
c-rel	R	Direct	296
c/EBPα	R	Direct–NTD, DBDh	297
Dax1	R	Direct–LBD	287, 298
EGR1	A	Direct–NTD	299
ERα	R	Direct–NTD	300
FKHR	R	Direct–NTD, LBD	301, 302
Foxa1	A	Direct–DBDh	303, 304, 325
Foxa2	A/R	Direct–DBD	288, 304
FoxH1	R	Direct–NTD-DBD	305
GATA-2	A	ND	306, 325
GATA-3	A	ND	306
GR	R	Direct–DBD	307
HoxB13	R	Direct	308
NF1	A	ND	309
Oct-1	A/R	Direct–DBD	293, 310, 325
Oct-2	ND	Direct–DBD	310
Pod-1	R	Direct–DBDh	311
p53	R	Indirect	312, 313
PDEF	A	Direct–DBD	314
RelA	R	Direct–NTD-DBD	315
RXR	A/R	Direct–LBD	316
Sox9	A/R	Direct–DBD	317
Sp1	A	Direct	309, 319
SRY	R	Direct–DBD	318
SHP	R	Direct–NTD, LBD	320
SF1	A	Direct–DBD	321
TR2	R	Direct	322
TR4	R	Direct–NTD, DBD, LBD	323
USF2	A	Direct	324

A/R, Transcription factor activates (A) or represses (R) AR function; direct/indirect, the transcription factor interacts directly or indirectly with the AR; ND, not determined; DBDh, DBD-hinge.

Oct1, GATA2, ETS1, AP-1, RAR, ZNF42, HNF-4α, and EGR (325–327). Occupancy at AR binding sites has been confirmed for a subset of these transcription factors (325). The presence of these transacting factors, in some cases observed in the absence of androgens, is critical for the recruitment of the AR and/or RNA polymerase II (325). Full and timely androgen induction of AR target gene expression requires normal expression of these factors and relies on the presence of intact consensus binding motifs for these factors (325). Moreover, silencing of one transacting factor can negatively affect the reciprocal occupancy of the AR binding sites by another (325). Overall, these studies offer a first glance at a hierarchical network of transcription factors that act at and regulate distinct steps in the generation of the AR transcriptional output. Moreover, they indicate that collaborating transcription factors can aid the AR in binding to sites other than canonical AREs. Such collaboration can offer insights into the manner by which the AR is able to exert finely tuned and spatiotemporal regulation of target gene expression in a gene- and cell-specific manner, because composite response elements are likely to function as points of regulatory cross-talk. Recent array-based methods aimed at unraveling the AR interactome have isolated more DNA-binding transcription factors that are able to interact with the AR, including for instance AP-2, GATA-3, GATA-4, and E47 (296), suggesting that the number of transacting factors able to steer AR recruitment and transcriptional activity in a similar manner may be substantial. It will be challenging but important to characterize the mechanism(s) of cross-talk between the AR and its associated transcription factors at loci of AR transcriptional activity and to ascertain the distribution and activity of AR coregulators at these sites.

IV. Implications and Significance of the Convergence of a Multitude of Diverse Functions on the AR

A. Accurate transcriptional output by the AR requires the concerted action of numerous cellular pathways and processes

A glance at the overview of the AR coregulators reported to date and summarized in Table 2 reveals a daunting level of functional diversity among these proteins (see also Fig. 2). Some of the functions listed in Table 2 can be anticipated. For instance, because the AR transcriptional complex needs to get access to the template genomic DNA to execute target gene expression successfully, it stands to reason that the AR enlists the help of regulatory proteins that can alleviate the constraints imposed by the chromatin structure. The recruitment of proteins that are able to unwind higher order chromatin structures or loosen DNA-histone interactions is a means to achieve this goal. Because the (de)acetylases and (de)methylases involved in this latter process can modify not only histones but also several components of the AR transcriptional complex, with severe consequences for the activity level and interplay between the individual components of this complex, this allows for another level of tuning the transcriptional output (*e.g.*, Refs. 63, 79, 81, 84, 87, 91). The chromatin environment can also be altered by ubiquitination and sumoylation (54, 55). Several AR coregulators possess the enzymatic activities required to induce these modifications and accordingly can modify the AR and several of its associated cofactors, again with severe consequences for the intrinsic activity, stability, and functional interactions of these proteins in the AR transcriptional complex (99–101, 115, 120, 123). Whether these events correspond with alterations in the local ubiquitination or sumoylation pattern in the chromatin environment of AR target genes has not yet been assessed. Similarly, from a mechanistic perspective, interaction of the AR as well as several of its associated coregulators with multiple components of the general transcription machinery makes sense. A number of proteins that are part of the spliceosome and/or function in RNA metabolism have been identified as coregulators for the AR. Traditionally, events involved in the maturation of (pre-)mRNAs have been designated to be posttranscriptional. An emerging view, however, is that all steps from transcription to translation are functionally and mechanistically coupled and that the different steps of the gene expression process should therefore be considered as cotranscriptional (138, 139). Underlining the linkage between the transcriptional events leading to the production of a prema-

TABLE 2. Overview of AR coregulators identified to date

Coregulator	coA/coR	Direct/indirect	Ref.
1. Components of the chromatin remodeling complex			
ARIP4	coA–def	Direct	56, 57
BRG1	coA–def	ND–ChIP	58, 63
hBRM	coA–def	ND	58
BAF57	coA–DN	Direct–ChIP, CoIP	59
SRG3/BAF155	coA–over	Direct–ChIP, CoIP	60
SRCAP	coA	ND	61
hOsa1/BAF250	coA	ND	62
hOsa2	coA	ND	62
2. Histone modifiers: acetyltransferases and deacetylases			
SRC-1	coA	Direct–ChIP	53, 63, 70, 72–75
SRC-2	coA	Direct–ChIP, CoIP	64, 69–73, 75, 213
SRC-3	coA–over	Direct–ChIP	63, 73, 75, 76, 337
p300	coA–si	Direct and indirect–ChIP	78, 79–81, 337
CBP	coA	Direct and indirect–ChIP	64, 78, 80
P/CAF	coA	Direct and indirect	78–81
Tip60	coA	Direct–ChIP	82–84
HBO1	coR	Direct	85
SIRT1	coR	Direct–CoIP	87
HDAC7	coR	Direct	88
HDACs, several	coR–si	Indirect–ChIP, CoIP	17, 63, 82–84
3. Histone modifiers: methyltransferases and demethylases			
CARM1/PRMT5	coA–si	Indirect–ChIP	89–91
PRMT1	coA–over	Indirect	92
G9a	coA–si	Indirect–ChIP	93
NSD1/ARA267α	coA	Direct	94, 95
LSD1	coA–si	Direct–ChIP	65, 67
JHDM2A	coA–si	Direct–ChIP	66
JMJD2C	coA–si	Direct–ChIP, CoIP	67
4. Components of the ubiquitination/proteasome pathway			
E6-AP	coA–def, over	Direct–ChIP	98
Mdm2	coR–over	Direct–ChIP, CoIP	99, 100
PIRH2	coA–si	Direct–ChIP, CoIP	101
SNURF/RNF4	coA	Direct	102–104
Chip	coR	Direct	105–107
ARNIP	ND	Direct	108
ARA54	coA	Direct	109
MKRN1	coR	ND	111
USP10	coA	Direct	112
UBCH7	coA	ND	113
TSG101	coA/coR	ND	114, 115
5. Components of the sumoylation pathway			
SUMO-1	coR	ND	120, 121
SUMO-2	coA	ND	121
SUMO-3	coA	Direct	121
Ubc9	coA	Direct	122, 123
PIAS1	coA/coR	Direct	126–128, 130, 131
PIAS3	coA/coR	Direct	124, 127, 128, 131
PIASxα/ARIP3	coA/coR	Direct	127, 130, 131
PIASxβ	coA/coR	Direct	127, 128, 131
PIASy	coR	Direct	132
Zimp7	coA	ND	134, 135
Zimp10	coA	Direct	133, 135
SENP1	coA–si, over	Indirect	136
Uba3	coR	ND	137
6. Proteins involved in splicing and RNA metabolism			
PSF	ND	Direct–MS	140
PSP1	ND	Direct–MS	140
PSP2	ND	Direct–MS	140
p54nrb	coA	Direct–MS	140
p102 U5snRNP/ANT-1	coA	Direct	141, 142
hnRNPA1	coR–si, over	Indirect	143
p44/MEP50	coA–def	Direct–ChIP	91
7. Proteins involved in DNA repair			
Ku70	coA	Direct–ChIP, CoIP, MS	144
Ku80	coA–si	Direct–ChIP, CoIP, MS	144
DNA-PKc	coA	Indirect–MS	144
Rad9	coR–over	Direct–CoIP	145
BRCA1	coA–over	Direct	146, 147
BRCA2	coA	Direct	148

(*Continued*)

TABLE 2. *Continued*

Coregulator	coA/coR	Direct/indirect	Ref.
8. Chaperones and cochaperones			
Hsp40	coA	Direct	14, 149, 150
Hsp90	coA	Direct–MS	14, 167
Hsp70	coA	Direct–MS, ChIP	14, 167, 156
DjA1	coR–def	Indirect	151
Cdc37	coA	Indirect	152
FKBP52	coA–def	Indirect	153, 154
FKBP51	coA–over	Indirect–CoIP	154, 155
Bag-1L	coA	Direct–ChIP, CoIP	156, 157
9. Cytoskeletal proteins			
Actin	coA	ND	161
Supervillin	coA	Direct	160, 167
Gelsolin	coA	Direct–MS	162, 167
Filamin	coA	Direct–CoIP, MS	163
Filamin-A	coR	ND, direct–CoIP	164, 165
α-actinin-2	coA	Indirect	166
α-actinin-4	coA/coR–si	ND–MS	167
Transgelin	coR–si, over	Indirect	168
ARA67/PAT1/APPBP	coR–over	Direct	169
10. Proteins involved in endocytosis			
HIP1	coA–si	ND–ChIP	172
APPL	coR–over	Indirect	173
GAK/auxillin2	coA	Direct–CoIP	175
Caveolin-1	coA	Direct–CoIP	176, 177
11. Signal integrators and transducers, scaffolds and adaptors			
ARA55	coA–si, DN	Direct–ChIP	178
Paxillin	coA	Direct	180
FHL2	coA	Direct	181
PELP1/MNAR	coA	Direct–CoIP, MS	182, 167
Vinexin-α	coA	Direct	183
Vav3	coA–si, over	Indirect	184, 185
Rho GDI	coA	ND	186
Ack1	coA–si, over	Direct–ChIP	187
PRK1	coA	Direct–ChIP	188
RanBPM	coA	Direct–CoIP	189
ARA24/Ran	coA	Direct	190
PAK6	coR	Direct	191–193
RACK1	coR–si	Direct–CoIP	194, 195
STAT3	coA	Direct–CoIP	125, 197–199
Smad3	coA/coR–over	Direct–CoIP	200–203
Ebp1	coR–si	Direct–ChIP, CoIP	204–207
Hey1	coR	ND–CoIP	208
Hey2	coR	ND	208
RNase L	coR	Direct–CoIP	209
β-catenin	coA–si	Direct–ChIP, CoIP	210–214
GSK-3β	coA/coR	Direct	215–217
TCF4	coR	Direct–CoIP	218
12. Cell cycle regulators			
Cyclin E	coA–over	Direct	219
cdc25B	coA	Direct	220–222
CDK6	coA–over	Direct–ChIP	223
Cyclin D1	coR–over	Direct–CoIP	224–229
Rb	coA	Direct	231, 232
pp32	coA	ND–CoIP	233
RbaK	coA	Direct	234
AATF/Che-1	coA	ND	115
13. Regulators of apoptosis			
Caspase 8	coR–si	Direct–CoIP	236
Par-4	coA–DN	Direct–ChIP	237
14. Viral oncoproteins			
E2	coA	Direct	238, 239
E6	coA/coR	Direct	240
E7	coA/coR	Direct	240
Hbx	coA	Indirect	241, 242
15. Other functionally diverse proteins			
Nuclear receptor coregulators			
Asc-1	coA	Direct	243
Asc-2	coA	Indirect–ChIP	244
Trap/Mediator complex proteins	coA–si	Direct–ChIP, CoIP	63, 245

TABLE 2. *Continued*

Coregulator	coA/coR	Direct/indirect	Ref.
CoCoA	coA	Indirect	246
NRIP	coA–si	Direct	247
PNRC	coA	Direct	248
TIF1-α	coA–si	Indirect	249
MRF1	coA	Direct	250
PDIP1	coA	ND	251
Zac1	coA	Indirect	252
GT198	coA	Direct	253
ARA70	coA–DN	Direct	235, 254
Alien	coR–over	Direct–ChIP, CoIP	255
AES	coR	Direct	256
SMRT	coR–si	Direct and indirect–ChIP, CoIP	17
NCoR	coR–si	Direct and indirect–ChIP	17, 257
RIP140	coR	Direct–ChIP	258
PATZ	coR–AS	Indirect	259
TGIF	coR	Direct	260
ART-27	coA	Direct	261
ARA160	coA	Direct	262
TIP110	coR–over	Direct	263
TZF	coR	Direct	264–266
ARR19	coR	Direct	267
Kinases and phosphatases			
MAK	coA–si, DN	Direct–ChIP, CoIP	268
ANPK	coA	Direct	269
Dyrk1A	coA	Indirect	270
ERK8	coR	Indirect	271
RSK	coA	Indirect	272
SCP2	coR–si	Direct	273
PP2A	coR	Direct	274
Diverse functions			
LATS2/KPM	coR–over	Direct–ChIP	275
PTEN	coR–def, over	Direct–CoIP	276–278
Tob1	coR	ND	279
Tob2	coR	ND	279
DJ-1/PARK7	coA	Direct and indirect–CoIP	280, 281
DJBP	coR	Direct	282
L-dopa-decarboxylase	coA	Direct	283
MAGEA11	coA	Direct	284
SRA	coA	ND–CoIP	285, 286

coA, Coactivator; coR, corepressor; direct/indirect, direct or indirect association with the AR; ND, not determined. For those coregulators for which interaction between endogenously expressed coregulator and AR has been described, the method by which this information was obtained is noted as CoIP (coimmunoprecipitation), MS (mass spectrometry) or ChIP. Similarly, coregulators for which the function has been confirmed by assessing the expression of AR target genes have been marked as si (confirmation of function on endogenously expressed AR target genes obtained by siRNA-mediated knockdown of coregulator expression), AS (confirmation obtained via antisense oligos), DN (verification of coregulator function by dominant-negative isoforms), def (coregulator-deficient cells were used to verify function), or over (overexpression experiments were performed).

ture mRNA and its subsequent processing, splicing factors interact not only with the AR but also with RNA polymerase II subunits (138). Moreover, the nuclear compartments specifically enriched in splicing factors seem to be in close proximity of and potentially overlap with those where active transcription is taking place (138). Similarly, coupling between transcription and DNA repair allows for the removal and repair of obstacles and DNA lesions (329–331). Thus, AR coregulators, which also function in DNA repair mechanisms, may therefore not be completely unexpected. It is noteworthy that transcription-DNA repair linkage typically involves chromatin remodeling activity as well as the action of the ubiquitin/proteasome pathway.

Some of the functions assigned to AR-associated coregulators may, at least at first sight, be harder to reconcile with active transcription taking place in the cell nucleus. For example, the identification of several AR coregulatory proteins with an active role in endocytosis, a process that originates at the plasma membrane and takes place predominantly in the cytosol, appears counterintuitive. It is important to keep in mind, however, that endocytic proteins are intrinsically connected with the actin cytoskeleton and function as scaffolds that are able to link several functionally related or even seemingly unrelated cellular processes. As discussed above, components of the (actin) cytoskeleton as well as transducers and effectors of multiple intracellular signaling pathways have been assigned AR coregulator properties. Moreover, at least for some endocytic proteins, including HIP1, fractions of their cellular pool are able to undergo nucleocytoplasmic shuttling. About half of the cellular HIP1 translocates to the nucleus in an androgen-dependent manner where it is recruited to AREs, directly linking the endosomal compartment and the AR transcriptional complex (172). Finally, it is reasonable to consider that the endocytic compartment in AR-mediated transcription is related to receptor-mediated uptake. This concept has been proposed for some nuclear

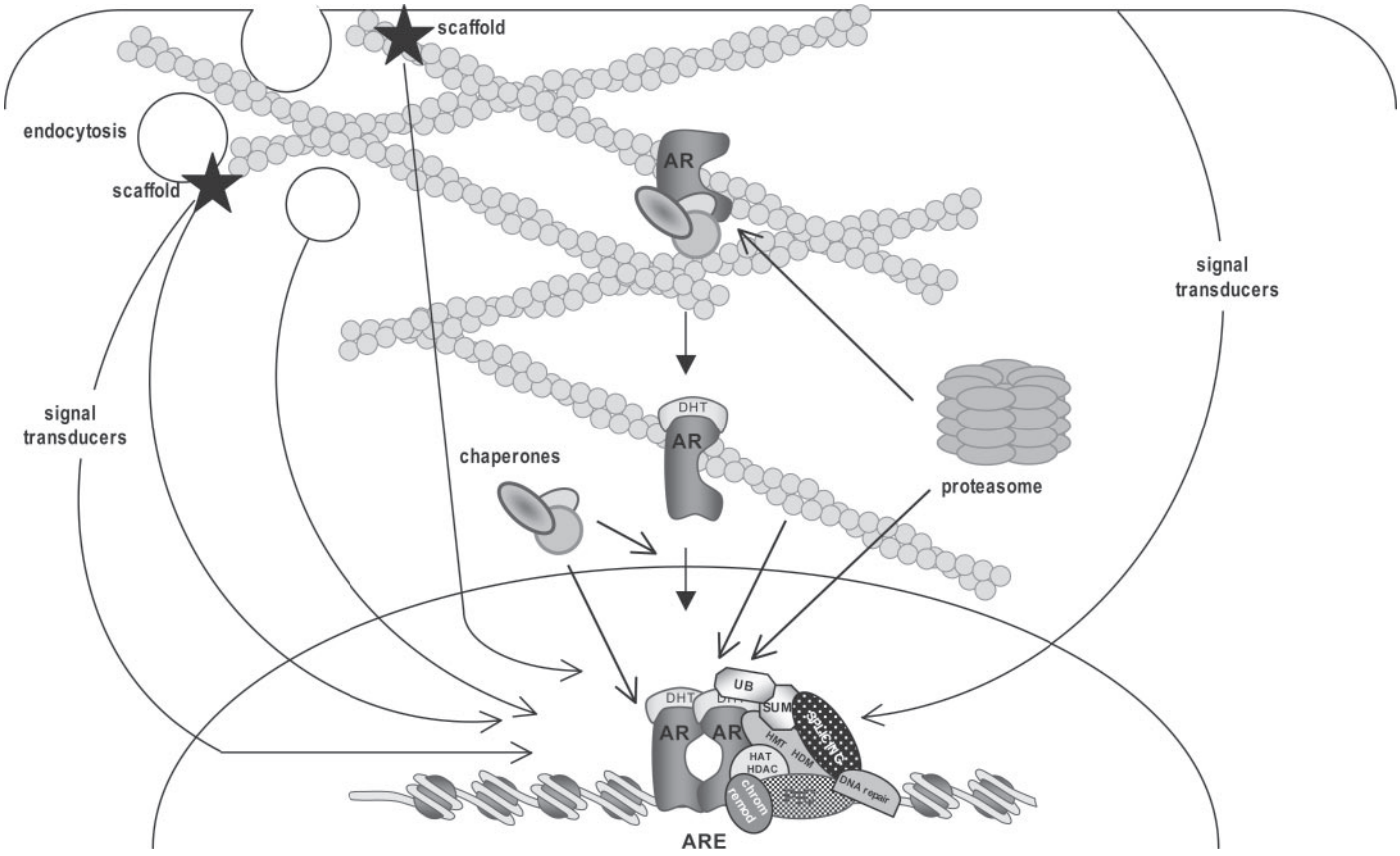

FIG. 2. Schematic overview of the cellular pathways and processes converging on the AR. chrom remod, Chromatin remodeling; HMT, histone methyltransferase; HDM, histone demethylase; UB, components of the ubiquitination/proteasome pathway; SUMO, components of the sumoylation pathway.

receptors, including the AR (332). The structural association of the cytoskeleton as well as scaffold proteins and signal transducers with endosomes does not preclude a role for these elements in AR-mediated transcription that is independent of endocytosis. The importance of the cytoskeleton in AR transactivation seems to be related mainly to the successful translocation of the AR to the nucleus, although both actin and actin-binding proteins are present in the nuclear AR transcriptional complex. Similarly, the importance of chaperone and cochaperones in AR-governed transcription is not merely related to their role in assuring the proper folding that enables the AR to bind its ligand—an event that is closely linked to proteasomal degradation. In addition, (co)chaperones are needed to ensure the conformation of the ligand-bound AR that allows its nuclear entry (14). Moreover, several of these proteins have been found to complex with the AR within the chromatin environment of target genes (156). Noteworthy is the fact that chaperones also fulfill important functions in the coating and/or uncoating of endosomes. Recent studies confirm the interaction of the AR with multiple components of the cellular pathways summarized here (167). It should be noted also that the classification we put forward does not preclude additional roles for AR-interacting regulatory proteins in the transcriptional process, such as an architectural function in the assembly of nucleoprotein structures as has been proposed for SNURF/RNF4 (333).

B. Assembly of the AR transcriptional complex

The isolation of a multitude of proteins with AR coregulatory properties leads to speculation about the manner in which the formation of the AR transcriptional complex is orchestrated. Most of the work aimed at resolving this issue has been done using the gene encoding prostate specific antigen (PSA) as a model gene system. As is the case for most other AR target genes identified to date, androgen regulation of the PSA gene involves enhancer and promoter elements. Due to the presence of AREs (ARE I and II in the promoter region, ARE III in the enhancer region), the PSA enhancer and promoter region each display androgen responsiveness, but maximal androgen regulation requires the involvement of both regions (334, 335). Thus far, a rather limited set of coregulators has been evaluated in the formation of the AR transcriptional complex at the PSA gene (64, 336–338). This group consists mainly of regulatory proteins that are common, core components of the transcriptional complexes formed by many nuclear receptors and specific transcription factors, such as SRC-1, SRC-2, SRC-3, p300, P/CAF, BRG1, TRAP220 and CARM-1. Upon androgen stimulation, the AR is recruited to both the enhancer and the promoter of the PSA gene, followed by the recruitment of these coactivators and RNA polymerase II. Contrary to RNA polymerase II, which displays an overall higher occupancy at the promoter region, the relative abundance of the AR and its associated coacti-

vators is higher at the enhancer region. Of the coactivators studied, CARM-1 is the only exception, being recruited solely to the enhancer region. Overall, a combinatorial rather than a sequential recruitment of coactivators appears to be involved, with members of the p160 family of coactivators fulfilling a central role. The levels of proteins bound at the regulatory regions of the PSA gene rise gradually, reaching a maximum at 16 h after stimulation and then slowly declining. The kinetics of AR coactivator binding to the PSA regulatory regions correlate well with those of PSA gene transcription (337). Elegant molecular approaches have led to the proposal of an integrated chromosomal looping/RNA polymerase II tracking model resulting from the enhancer-promoter interaction. In this model, the recruitment of AR and its coactivators at both the enhancer and promoter regions creates a chromosomal loop that allows enhancer-bound AR and promoter-bound AR to share a common coactivator complex. At the same time, it permits RNA polymerase II to track from the enhancer along the looped chromatin to the promoter region (337).

As indicated in Table 2, the presence of several other AR coregulators at regulatory regions of the PSA gene has been confirmed. Because these studies have focused primarily on the recruitment of a single coregulator to a particular genomic AR binding site, they do not provide further information regarding the overall assembly of the AR transcriptional complex, the dynamics of its formation, or the relative importance of recruitment to the enhancer and the promoter. Resolving these issues will require concerted efforts of multiple research groups working in this field. Similarly, it will be vital to assess whether the manner in which the AR coregulator complex is assembled at the PSA gene can be generalized to other AR target genes. In this respect, the formation of the AR transcriptional complex at the KLK2 gene, a AR target gene with an enhancer/promoter organization that is similar to that of the PSA gene, appears to progress along the same lines (64). Very recently, several system approach studies aimed at evaluating the genome-wide binding of the AR suggest that many, if not most, of the target genes identified differ considerably in their genomic organization and in the localization, composition, and clustering of AREs governing androgen-regulated transcription of these genes (325–327). Follow-up studies will therefore be critical to addressing the manner in which AR coregulators are recruited to these regulatory regions. Finally, the impact of cell type-specific context on these events will need to be explored.

C. Accommodation of coregulators by the AR

An intriguing question relates to the manner in which the AR can accommodate physical interaction with such a perplexing number of cofactors. Although some of these regulators are recruited to the AR transcriptional complex through an intermediary protein, the majority of them seem to be able to associate directly with the AR (Table 2). Interaction of coregulators with different regions of the AR may offer some relief. Another means toward reducing the complexity of the AR-cofactor interaction could lay in the temporal recruitment and release of coregulators to and from the receptor. Definite insights into these matters will require concerted and extensive ChIP and Re-ChIP approaches and will most likely depend on collaborative efforts from several research groups working in this field.

Some AR-associated coregulators have been claimed to display specificity for the AR. In most cases, these observations were performed at the time of isolation of the protein in question, with further characterization indicating a broader range of interaction and coregulation. For example, ARA70, the first AR coactivator to be identified by a yeast two-hybrid approach, was initially put forward as an AR-specific coregulator, but has since been shown to modulate transcription by several other nuclear receptors (254, 339). FHL2, on the other hand, does display specificity for the AR when compared with other nuclear receptors but is known to act also as a cofactor for several specific transcription factors (340). Therefore, the number of truly AR-specific coregulators is likely to be very small. Based on the information available to date, ART-27 and ARR19 appear the only coregulators that can be qualified as AR-specific.

On the other hand, coregulators have been shown to display selectivity in the particular set of AR target genes with which they associate (58, 341). Detailed exploration of this pattern of selectivity may require ChIP-on-chip approaches. Moreover, the tissue and cell type-selective expression pattern observed for some coregulators and androgen-regulated changes in the expression of AR coactivators (341–344) may allow further modification of AR-coregulator association. Along the same lines, evidence for agonist- or antagonist-mediated induction of changes in the posttranslational modification status of AR-associated coregulatory machinery is starting to emerge (257, 345). Such changes may predispose coregulators to interact selectively with particular regulatory components of the AR transcriptional complex or lead to the release of cofactors from this complex.

V. AR Coregulators in (Patho)Physiology

The dependency of the AR on its coregulators to form a productive transcriptional complex suggests an important role for these regulatory proteins in the development and maintenance of androgen-responsive tissues as well as in pathologies that are associated with aberrant AR function. In keeping with this notion, some AR-associated coregulators display selective or enriched expression in androgen-dependent tissues such as prostate and testis. A higher level of selectivity can be achieved by restricting the expression to specific cell types. For instance, FHL2 is selectively enriched in epithelial cells of the prostate, whereas ARA55/Hic-5 is preferentially expressed in the prostatic stromal compartment (181, 346). Moreover, tissue-selective AR coregulator splice variants have been described, and, interestingly, such alternative splice forms can exhibit a change in activity from corepressor to coactivator or vice versa (266). The idea that androgen-responsive tissues rely on AR-coactivator expression for their functional and structural integrity is supported by knockout mouse models. Some AR coregulator-deficient mice demonstrate embryonic lethality, which suggests an important role early in development and/or an activity that

TABLE 3. Selection of coregulator-deficient mouse models showing varying degrees of androgen resistance

Coregulator targeted	Phenotype	Ref.
BRM$^{-/-}$	Slightly reduced testis weight	348
E6-AP$^{-/-}$	Reduced testis weight, reduced fertility, defects in sperm production and function, attenuated growth and development of the prostate gland	98, 349
FKBP52$^{-/-}$	Mild to severe hypospadias, ambiguous external genitalia, malformation of the seminal vesicles, reduction of anterior prostate, mild dysgenesis of dorsolateral and ventral prostate	153, 154
SRC-1$^{-/-}$	Reduced testis weight, decreased growth and development of the prostate	350
SRC-2$^{-/-}$	Hypofertility, defects in spermiogenesis, testicular degeneration	351

is critical for overall physiology (347). In contrast, other models appear to be phenotypically normal, suggesting that the function of the coregulator that is being targeted may overlap with and be rescued by the action of other cofactors (347). The actual involvement of the AR in these phenotypes, however, is hard to ascertain. Loss of other coregulators, such as those listed in Table 3 (98, 153, 154, 348–351), gives rise to hormone-resistant phenotypes with varying degrees of severity ranging from compromised fertility to hypospadias and changes in the composition of prostate, seminal vesicles, and testis.

Interestingly, AR-associated coregulators have been shown to be important for the development of pathologies that are linked to aberrant AR action. Prostate cancer (PCa) is a prominent example of such a condition. PCa cells depend on androgens for proliferation, a characteristic that is being exploited for therapeutic intervention. So-called androgen ablation therapy either targets the production of androgens or interferes with the activity of the AR (352). Although androgen ablation therapy is initially successful in the majority of cases, eventually most tumors will find a way to circumvent this form of treatment and emerge as androgen depletion-independent (ADI) cancers (353). Remarkably, despite the castrate levels of circulating androgens in these patients, the AR is still a critical determinant for ADI PCa cell proliferation (3, 354, 355). The unexpected "reactivation" of the AR in ADI PCa cells has been attributed to mechanisms of AR hypersensitivity (AR amplification and/or mutations), promiscuous activation of the AR (by adrenal androgens, nonandrogenic steroids, and even antiandrogens), outlaw AR pathways (AR activated by growth factors and cytokines, thereby bypassing the need for androgens), and local intracrine production of androgens (independent of the low circulating serum androgens levels) (356, 357). Over the last few years, the importance of the involvement of AR coactivator proteins in ADI AR activation is increasingly being recognized (358). In the progression of PCa, a subset of AR coactivators has been shown to be overexpressed. Deregulated expression of AR coactivators tends to increase with tumor dedifferentiation and to correlate with aggressive disease and poor prognosis. Moreover, overexpression of these regulatory factors has been demonstrated to contribute substantially to the ADI mechanisms of AR activation described above. Therefore, overexpression of AR coactivators is considered to be a valuable target for therapeutic intervention (358). The molecular machinery underlying the aberrant expression of these critical cofactors in PCa disease progression is under intense investigation as a potential therapeutic target for the treatment of this severe disease (343, 344). Similarly, efforts are being directed toward defining those regions within the AR that can mediate critical interactions with clinically relevant cofactors. Recent work from our laboratory led to the isolation of a discrete WXXLF motif in the AR NTD that is essential for ligand-independent AR activity that is resistant to antiandrogens such as bicalutamide (359, 360).

In addition to PCa, at least one case of complete androgen insensitivity syndrome, which is typically linked to an inactivating mutation of the AR (1, 2), has been suggested to be causally related to a defect in or an absence of an AR-interacting regulatory protein, rather than to an aberration of the receptor itself (361). Very recently, an intriguing interplay between HBx, a nonstructural hepatitis B virus protein acting as a coactivator for the AR, and the AR of host hepatocytes has been proposed to underly the male predominance of hepatocellular carcinoma (242). Because other viral oncoproteins have been suggested to be able to regulate the transcriptional activity of the AR (239, 240), and because males are known to be more vulnerable to microbial infections, this mechanism may be more generally applicable. Finally, coactivators of the AR may also play a role in relatively mild conditions such as androgenic alopecia (362).

VI. Conclusions and Future Directions

As illustrated by this overview, a multitude of coregulators with diverse functions have the potential to converge on the AR and regulate its transcriptional output. A considerable part of this information has been derived from *in vitro* studies and the use of promoter-reporter constructs that may not fully recapitulate the activity of the AR in a chromatin environment. It will, therefore, be vital to monitor the construction of the AR transcriptional complex and the transcriptional output it generates in model systems that express an endogenous AR. Such studies will also help to determine the importance of tissue selectivity in the recruitment of coregulators to the AR and the selective involvement of particular cellular pathways in these events.

Although an impressive number of different functions have already been ascribed to the regulatory proteins involved in the formation of a productive AR transcriptional complex, additional properties allowing these proteins to modulate transactivation by the AR cannot be ruled out.

Typically, investigation into the functional interactions between the AR and its coregulators remains limited to the impact of coregulators on AR activity. The AR may, however, have a reciprocal effect on the intrinsic activity of its coregulators. This possibility is supported by the observation that the AR, independently of its DNA binding ability, dramatically increases the intrinsic transcriptional activity of SRC-2, CBP, and p300 that are tethered to DNA (363). This kind of

"triggering" phenomenon might also be important in the nongenomic actions of the AR (which have not been addressed in the current manuscript). Moreover, mounting evidence suggests that the AR feeds back to regulate the composition and activity of its coregulator complex by modulating the expression of its cofactors (341–344). Similarly, it has been suggested that coactivators such as SRC-3 undergo posttranslational modifications upon androgen treatment, resulting in specific modification "codes" that govern preferences in its interaction with other regulatory proteins (345).

An emerging view is that coregulators also function as signal integrators, relaying information from the cell surface to the nucleus (328). It will be important to determine whether this holds true also for the AR and to identify the signaling mechanisms involved.

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