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Androgen Signaling in Prostate Cancer

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The androgen-signaling axis plays a pivotal role in the pathogenesis of prostate cancer. Since the landmark discovery by Huggins and Hodges, gonadal depletion of androgens has remained a mainstay of therapy for advanced disease. However, progression to castration-resistant prostate cancer (CRPC) typically follows and is largely the result of restored androgen signaling. Efforts to understand the mechanisms behind CRPC have revealed new insights into dysregulated androgen signaling and intratumoral androgen synthesis, which has ultimately led to the development of several novel androgen receptor (AR)-directed therapies for CRPC. However, emergence of resistance to these newer agents has also galvanized new directions in investigations of prereceptor and postreceptor AR regulation. Here, we review our current understanding of AR signaling as it pertains to the biology and natural history of prostate cancer.

It has now been more than 70 years since Huggins and Hodges (1941) first exposed the central role of androgen signaling in prostate cancer by showing that orchiectomy induces considerable tumor regression. Their seminal discovery was recognized with the Nobel Prize in Medicine in 1966 and, to this day, gonadal testosterone depletion remains a mainstay of therapy for advanced disease (Mohler et al. 2012). It is now evident that the majority of prostate cancers express the androgen receptor (AR) throughout the course of the disease (Sadi et al. 1991; Ruizeveld de Winter et al. 1994; Attard et al. 2009), and, in recent years, deeper interrogation into the molecular basis of androgen signaling has offered a better understanding of how AR specifically directs cancer cell behavior. Taken together, these findings have solidified the importance of androgen signaling in prostate cancer pathogenesis.

Nevertheless, androgen-deprivation therapy (ADT) by chemical or surgical castration is invariably followed by the recurrence of castration-resistant prostate cancer (CRPC) within a median of 14–20 months (Sharifi et al. 2005). Once thought to be an androgen-independent state, it is now recognized that this is generally not the case (Mohler 2008). Progression to CRPC is typically heralded by a rising prostate-specific antigen (PSA) despite castrate concentrations of testosterone, suggesting that inappropriate restoration of the AR signaling

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axis remains pivotal to this progressive and lethal form of disease (Scher and Sawyers 2005; Ryan and Tindall 2011). Efforts to identify the mechanisms underlying CRPC have revealed new insights into dysregulated androgen signaling, including how AR may incur gain-of-function through mutations, splice variants, and aberrant coregulation (postreceptor regulation), as well as how intracrine steroidogenesis (prereceptor regulation) critically contributes to tumor progression. This has ultimately led to the development of several novel AR-directed therapies, which have since clinically validated many of these concepts (Sharifi 2010; Chang and Sharifi 2012). In this work, we review our current understanding of the androgen signaling axis as it directly pertains to the biology of prostate cancer in its various stages, highlighting aspects of prereceptor and postreceptor regulation (Ryan and Tindall 2011; Heemers 2014), as well as emerging AR-directed therapeutic strategies and ongoing areas of research.

ANDROGEN BIOSYNTHESIS IN NORMAL MALE PHYSIOLOGY

Androgens play an essential role in the development and maintenance of normal male physiology (Griffin 1992). The biosynthesis of all steroid hormones begins with 27-carbon cholesterol, which undergoes stepwise modification by a small complement of enzymes first to 21-carbon steroids (progestins) and subsequently to 19-carbon androgens (Fig. 1). In normal male physiology, early steps in steroidogenesis occur efficiently in two tissues—the adrenal cortex and the testes—so that these tissues together play a major role in the synthesis of circulating steroids (Sharifi and Auchus 2012). Further downstream reactions in the steroidogenic pathways are then refined by specific isoenzymes in target tissues to meet site-specific requirements.

The testes are responsible for the biosynthesis of the majority of testosterone in circulation, with comparatively minor input from the

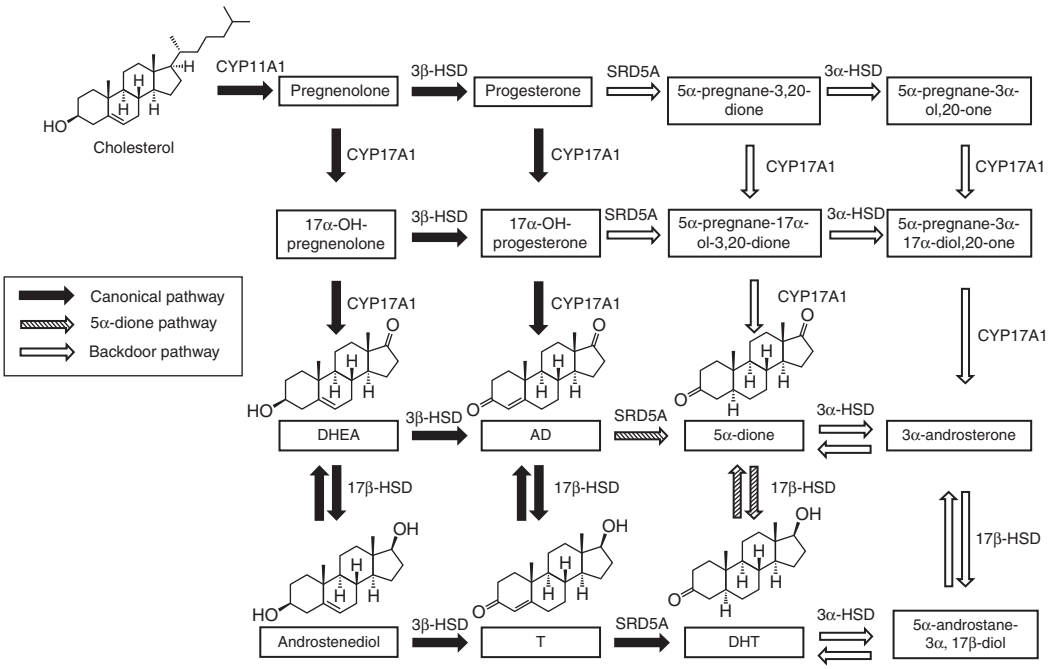

Figure 1. Pathways of androgen biosynthesis in normal physiology and prostate cancer. Key enzymes are denoted next to arrows for each reaction. Specific isoenzymes responsible for particular reactions are discussed in the main text. DHEA, dehydroepiandrosterone; AD, androstenedione; T, testosterone; DHT, dihydrotestosterone.

adrenal glands (Nakamura et al. 2009). In both the zona reticularis of the adrenal cortex and Leydig cells of the testes, steroidogenesis starts with the side-chain cleavage of cholesterol by CYP11A1 (cholesterol side-chain cleavage enzyme, P450scc) to generate pregnenolone. Pregnenolone is then converted by CYP17A1 (17-hydroxylase/17,20-lyase, P450c17) to 17-OH-pregnenolone and subsequently to dehydroepiandrosterone (DHEA). Although much of the nascent DHEA in the adrenal cortex is readily sulfonated by sulfotransferase (SULT2A1) for eventual secretion into circulation, testicular Leydig cells lack SULT2A1 and abundantly express 3β-hydroxysteroid dehydrogenase 2 (3β-HSD2), which enables further downstream metabolism of DHEA to testosterone (Sharifi and Auchus 2012). Two final steps are required for the generation of testosterone in the testes, primarily mediated by 3β-HSD2 and 17β-hydroxysteroid dehydrogenase 3 (17β-HSD3). A requirement for the latter enzyme is shown by loss-of-function mutations that lead to pseudohermaphroditism (Geissler et al. 1994). Following synthesis, testosterone is secreted into serum, in which it is mostly bound to sex hormone–binding globulin (SHBG) and albumin (Dunn et al. 1981; Rosner et al. 1991). The degree of bound and unbound testosterone probably exists at equilibrium, with free testosterone thought to readily undergo cellular uptake through passive diffusion into peripheral tissues (Dunn et al. 1981). Intriguingly, some studies have shown that exogenous administration of testosterone and dihydrotestosterone (DHT) leads to increased levels of serum but not necessarily intraprostatic androgens (Page et al. 2011; Thirumalai et al. 2016), indicating that currently underappreciated mechanisms may be at play to tightly regulate intracellular androgens within a narrow concentration range.

In prostate cells, testosterone may act directly on AR or be irreversibly converted to DHT by 5α-reductase, of which there are two isoenzymes (SRD5A1, SRD5A2) (Russell and Wilson 1994; Zhu and Imperato-McGinley 2009). In particular, SRD5A2 is the predominant enzyme present in benign prostatic tissue that mediates the testosterone→DHT reaction and is necessary for proper development of the male phenotype (Wilson 2001). A loss-of-function mutation in SRD5A2 causes 5α-reductase deficiency, manifesting in pseudohermaphroditism and failure to develop a normal prostate (Imperato-McGinley et al. 1974; Andersson et al. 1991). The requirement for DHT in prostatic growth has also been confirmed through the development of 5α-reductase inhibitors as an effective treatment for benign prostatic hyperplasia (BPH) (Rittmaster 1997; Steers 2001; Marks 2004). Recognizing the potential complement of enzymes that can participate in androgen biosynthesis is essential, because prostate cancers may frequently commandeer this enzymatic machinery to sustain steroidogenesis and fuel tumor growth, particularly following ADT (Stanbrough et al. 2006; Montgomery et al. 2008; Knudsen 2014).

PRERECEPTOR MODULATION OF AR SIGNALING

Androgen synthesis is tightly governed by the hypothalamic–pituitary–gonadal axis. Pulsatile release of hypothalamic gonadotropin-releasing hormone (GnRH) stimulates luteinizing hormone (LH) secretion from the anterior pituitary gland, which signals for the production of testosterone in the testes. Testosterone subsequently exerts negative feedback on the hypothalamus and pituitary gland. The pulsatile nature of GnRH is necessary to sustain continued LH secretion; persistent GnRH stimulation leads to ensuing desensitization, which is the rationale behind administering long-acting GnRH agonists for ADT. Following an initial flare, serum testosterone concentrations are effectively suppressed by GnRH agonists to medically castrate levels of $<$50 ng/dL (Nishiyama 2014).

Although testosterone is a physiologic AR ligand sharing a similarly high equilibrium affinity as DHT (Wilson and French 1976), DHT is the principal androgen found within the prostatic cell nucleus (Bruchovsky and Wilson 1968) and is approximately 10-fold more potent

in the stimulation of AR target genes (Deslypere et al. 1992). This difference is thought to be attributed to the greater hydrophobicity of DHT, which stabilizes the ligand–receptor state through intermolecular interactions and decreases the ligand dissociation rate (Zhou et al. 1995; Askew et al. 2007). Therefore, the principal effect achieved through testosterone depletion is likely attributed to the intraprostatic reduction in DHT. However, despite castrate concentrations of testosterone and an observed tumor response in 80%–90% of patients, incomplete depletion of prostate cancer tissue androgens occurs following ADT. Residual concentrations of intratumoral DHT can remain at 10%–40% of pretreatment levels (Forti et al. 1989; Labrie et al. 1993; Page et al. 2006), even before the development of CRPC (Nishiyama et al. 2004). This is substantial because this concentration range of typically 1 nM remains sufficient to permit AR signaling, AR target gene expression, and tumor growth both in vitro and in vivo (Gregory et al. 1998, 2001; Mohler et al. 2004; Mostaghel et al. 2007). Multiple studies have now corroborated the presence of residual androgens in recurrent tumors after castration (Geller et al. 1978; Titus et al. 2005; Montgomery et al. 2008), together signifying that the persistence of AR signaling likely promotes the emergence of CRPC. This is perhaps unsurprising, given that the onset of CRPC is predictably and near universally accompanied by an increase in PSA, a widely used clinical biomarker expressed by an AR-responsive gene (Ryan et al. 2006). Furthermore, recent therapeutic advances in the Food and Drug Administration (FDA) approval of novel, life-prolonging AR-directed therapies, such as the potent second-generation competitive AR antagonist enzalutamide (Scher et al. 2012; Beer et al. 2014) and the androgen synthesis inhibitor abiraterone acetate (de Bono et al. 2011; Ryan et al. 2015), have provided the highest level of clinical evidence for this evolving paradigm. A number of similar agents are currently under clinical investigation, which could soon add to a growing arsenal of therapeutic options for men with metastatic CRPC (Dellis and Papatsoris 2016).

INTRACRINE ANDROGEN BIOSYNTHESIS IN PROSTATE CANCER

A variety of mechanisms may explain the restoration of competent AR signaling in CRPC. These include AR overexpression and amplification, intracrine androgen synthesis, acquisition of constitutively active AR splice variants, and gain-of-function mutations, deregulated AR coactivators/corepressors that sensitize AR in response to ligand binding, and ligand-independent signaling and redundant downstream cross talk (Sharifi 2013; Ferraldeschi et al. 2015). Of note, these postulated mechanisms are not necessarily mutually exclusive and may arise together under the selective pressure of ADT. Importantly, the persistence of physiologically significant intratumoral androgens despite castration indicates that prereceptor regulation remains central to many of these mechanisms to further fuel tumor growth (Zhang et al. 2016). To support this are observations that castrate tumors often up-regulate key steroidogenic enzymes to utilize alternative sources of androgen synthesis (Holzbeierlein et al. 2004; Stanbrough et al. 2006; Montgomery et al. 2008).

Several possibilities exist for the origin of these intratumoral androgens. The first is the de novo pathway, which begins with cholesterol and requires multiple steps in the synthesis of DHT. This may occur either via the canonical route as described in normal physiology (Sharifi and Auchus 2012), or alternatively via a "backdoor" pathway, which involves intratumoral CYP17A1 activity to convert pregnanes to androgens that are then 5α- and 3-keto-reduced, with eventual terminal conversion to DHT (Fig. 1) (Fiandalo et al. 2014). Whether tumors express the complete repertoire of steroidogenic enzymes required to generate androgens from cholesterol remains to be fully elucidated (Hofland et al. 2010). On the other hand, circulating adrenal androgens, which are abundant in the form of DHEA and a larger depot of sulfated DHEA-S, are readily interconverted to DHT via an abbreviated series of steps (Mostaghel 2013). DHT concentrations in prostatic tissues of castrate men positively correlate with serum DHEA/DHEA-S levels (Page et al. 2006) and

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treatment with abiraterone acetate markedly reduces serum DHEA concentrations (Attard et al. 2012; Taplin et al. 2014; Mostaghel 2014a), while aptly suppressing intraprostatic androgen levels (Mostaghel et al. 2014). To generate downstream testosterone and DHT, DHEA must first undergo oxidation of its 3β-hydroxyl group and Δ^5 to Δ^4 isomerization to form androstenedione (AD). This rate-limiting step is catalyzed by 3β-HSD, for which there are two human isoenzymes: 3β-HSD1 and 3β-HSD2. In peripheral tissues, including the prostate, 3β-HSD1 predominates, whereas 3β-HSD2 is expressed preferentially in the adrenal glands and gonads (Simard et al. 2005). Given its unique position within the steroidogenic pathway, 3β-HSD1 is likely a critical enzymatic gatekeeper that confers on tumors the ability to harness adrenal androgens (Evaul et al. 2010). In fact, a gain-of-function missense in 3β-HSD1 has recently been described, which remarkably augments the capacity of this enzyme to drive conversion of DHEA→AD, thereby permitting more efficient DHT synthesis (Chang et al. 2013). This missense arises from a single nucleotide polymorphism (SNP) at position 1245 (A→C), substituting an asparagine for threonine at amino acid position 367. The functional consequence of this alteration, which can occur as either a somatic mutation or germline variant, is an enzyme protein product that is rendered resistant to ubiquitin-mediated degradation, resulting in intracellular accumulation. Notably, it appears that ADT may select for this particular mutation; CRPC tumors from patients who are germline heterozygous variants will not infrequently show loss of heterozygosity or acquire a second variant allele by way of a somatic mutation (Chang et al. 2013). This leads to markedly stable enzyme expression, detailing yet another adaptive mechanism through which tumors may subvert androgen deprivation. Furthermore, inheritance of the gain-of-function *HSD3B1*(1245C) SNP is associated with rapid resistance and poorer survival after ADT in patients with prostate cancer (Hearn et al. 2016).

The subsequent conversion from AD to DHT requires two additional reactions. In the canonical pathway, AD first forms testosterone through reduction of its 17-keto moiety mediated by 17β-HSD, before 5α-reduction to DHT by SRD5A (Fig. 1). In contrast, an alternative pathway has been described, in which AD can bypass testosterone as an obligate precursor, instead undergoing 5α-reduction to an intermediate 5α-androstanedione (5α-dione), followed by 17-keto reduction to DHT (Chang et al. 2011). In fact, this "5α-dione pathway" appears to be the favored directionality of adrenal androgen flux in virtually all prostate cancer cell lines as well as in sampled metastatic CRPC biopsies from patients (Chang et al. 2011). Furthermore, in contrast to the robust flux of AD→5α-dione, the comparable reaction of testosterone→DHT is relatively inefficient. This paradoxical shift in the preferred precursor for 5α-reduction from testosterone to AD in CRPC tissues may be explained by the differential expression of 5α-reductase isoenzymes in tumors. Expression studies have repeatedly revealed that the transition from benign tissue to high-grade prostate cancers and CRPC is associated with stepwise up-regulation of SRD5A1 and subtotal loss SRD5A2 (Thomas et al. 2008). Given that the optimal substrate for SRD5A1 is AD rather than testosterone (Thigpen et al. 1993), this genotypic switch may specifically herald an acquired ability of tumors to efficiently harness adrenal androgens to circumvent testosterone depletion. Genetic silencing of SRD5A1 in cell lines effectively abolishes the conversion of adrenal androgens to DHT (Chang et al. 2011).

Because 3β-HSD1, 17β-HSD, and SRD5A are all required for the generation of DHT from adrenal androgens, pharmacologic inhibition of these enzyme targets has been an active area of clinical interest. Two 5α-reductase inhibitors are currently available: finasteride, primarily an SRD5A2 inhibitor, and dutasteride, a dual SRD5A1/SRD5A2 inhibitor (Schmidt and Tindall 2011). These agents have been tested in a variety of settings, including in the prevention of prostate cancer (Azzouni and Mohler 2012; Fleshner et al. 2012; Schröder et al. 2013) and as an adjuvant therapy to additionally suppress residual androgens following ADT (Xu et al.

2006; Shah et al. 2009). One challenge to SRD5A inhibition is a concomitant rise in upstream testosterone following blockade, which may rescue AR activity and obscure potential therapeutic efficacy (Rittmaster et al. 2008; Chang et al. 2011).

Inhibition of the 17β-HSD family enzymes instead may potentially overcome this issue. 17β-HSD5 (aldo-keto reductase 1C3 [AKR1C3]) is one particular member of this family, which shows a reductive preference for the conversion of AD→testosterone and is broadly implicated in prostate cancer (Adeniji et al. 2013). Expression levels of AKR1C3 are associated with the highest increase in CRPC relative to primary cancer among profiled steroidogenic enzymes; in one study, 58% of CRPC samples were positively stained for AKR1C3 compared with only 5.6% of primary cancers (Stanbrough et al. 2006). The design of effective AKR1C3 inhibitors is an ongoing area of investigation. Importantly, inhibitors must show enzyme specificity given multiple closely related aldo-keto reductase isoforms, some of which drive other reactions (Byrns et al. 2011; Adeniji et al. 2013).

Further upstream inhibition of 3β-HSD isoenzymes presents as another potentially viable opportunity for additional androgen suppression. In preclinical models, treatment with abiraterone acetate notably reduces activity of not only CYP17A1 but also 3β-HSD (Evaul et al. 2010). Interestingly, the Δ^5, 3β-hydroxyl steroidal structure of abiraterone is amenable to direct enzymatic conversion by 3β-HSD to a Δ^4, 3-keto congener (D4A), which is an active inhibitor of multiple steroidogenic enzymes, including 3β-HSD, CYP17A1, and SRD5A (Li et al. 2015). Furthermore, D4A antagonizes AR at levels comparable to enzalutamide (Li et al. 2015). A subsequent metabolite of D4A also shows AR agonist activity; the contributory effect of these derivative compounds therefore suggests that pharmacologic blockade of particular metabolic pathways could be a feasible method to limit the production of AR-promoting metabolites, thereby refining the antitumor properties of abiraterone (Li et al. 2016). Given the appreciable role of residual androgen production in driving progression to CRPC, identifying opportunities for intensive and directed suppression of intracrine androgen synthesis remain paramount.

ANDROGEN RECEPTOR STRUCTURE/FUNCTION

The AR is a ligand-dependent nuclear transcription factor (TF) and member of the steroid hormone receptor superfamily (Nuclear Receptors Nomenclature Committee 1999). The gene for AR is located on the X chromosome (q11-12) and expresses a 110-kDa protein that is 919 amino acids in length, encoded by eight exons (Chang et al. 1988; Lubahn et al. 1989; Tilley et al. 1989). Common in resemblance to other nuclear hormone receptors, the structure of AR is comprised of four separate functionally distinct domains: an amino-terminal domain (NTD), a carboxy-terminal ligand-binding domain (LBD), a DNA-binding domain (DBD), and a flexible hinge region, which joins the LBD and the DBD (Fig. 2) (Gelmann 2002; Claessens et al. 2008).

The main native agonists for AR under normal physiologic conditions are testosterone and DHT. When unoccupied by ligand, AR resides primarily in the cytoplasm, anchored to cytoskeletal elements, and associated in a complex with heat shock proteins (HSP-90, HSP-70, HSP-56) and other chaperone proteins to protect the receptor against degradation (Smith and Toft 2008). Binding of ligand to the cognate receptor causes dissociation from this complex and initiates a sequence of molecular events that eventually leads to AR nuclear translocation and activation of AR target genes (Fig. 3). The LBD is vital to directing this response; this is well illustrated by the fact that a deletion of the LBD renders AR completely unresponsive to androgens (Jenster et al. 1991). Furthermore, the LBD is the target for the most competitive AR antagonists, including enzalutamide (Knudsen and Scher 2009), and is the most frequent site of gain-of-function point mutations (Buchanan et al. 2001). Although AR mutations are relatively infrequent in early-stage hormone-naïve prostate cancers, they are detected in approximately 10%–30% of patients previously treated

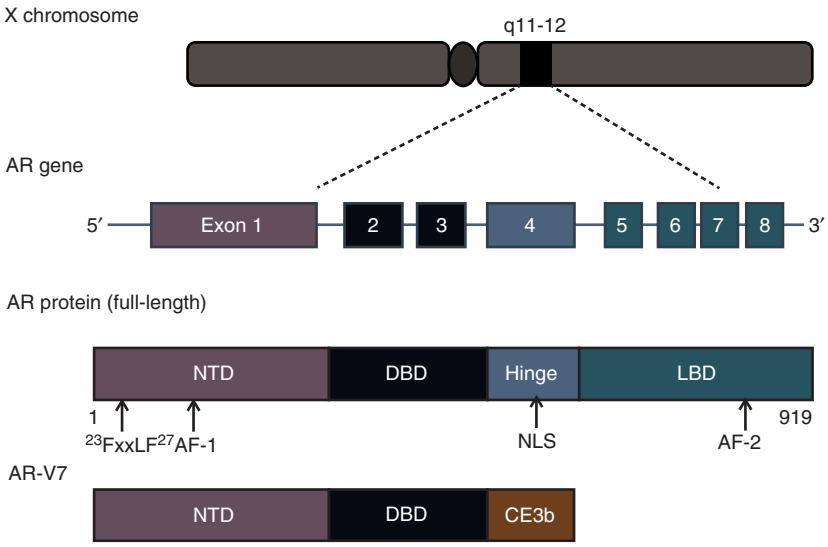

Figure 2. The androgen receptor (AR) gene locus and structure of the AR (full-length and AR-V7). The transcript for wild-type AR full-length (FL) includes eight exons, which correspond to the four respective domains of the AR protein (as depicted by color scheme). AR-V7 includes a cryptic exon region (CE3b) at the carboxyl terminus. NTD, Amino-terminal domain; DBD, DNA-binding domain; LBD, ligand-binding domain; NLS, nuclear localization signal.

with first-generation competitive AR antagonists (Taplin et al. 1995, 2003; Wallén et al. 1999). Acquisition of AR mutations can enhance receptor promiscuity, broadening the range of potential endogenous steroid ligands (Culig et al. 1993; Mostaghel 2014b) or imparting the reversal of AR antagonists to agonists (Veldscholte et al. 1992; Culig et al. 1999; Taplin et al. 1999). The latter is the presumed mechanism by which tumors may regress following the withdrawal of AR antagonist therapy (Scher and Kelly 1993; Hara et al. 2003). Furthermore, this mechanism may explain why tumors refractory to select AR antagonists can show continued susceptibility to alternative agents (Tran et al. 2009; Balbas et al. 2013).

Ligand binding causes a critical conformational change in AR, which not only facilitates the nuclear targeting of AR but also exposes transcriptional activation function 2 (AF-2), a functionally significant hydrophobic binding surface-spanning helices 3, 4, and 12 within the LBD. Through recognition of FxxLF motifs embedded in the NTD (He et al. 2000), AF-2 mediates protein–protein interactions between the carboxyl and amino termini that are necessary for receptor homodimerization, stabilization of the ligand within the ligand-binding pocket, and optimization of AR activity (Doesburg et al. 1997; Berrevoets et al. 1998). AF-2 also enables the recruitment of specific AR cofactors, which bear FxxLF and LxxLL motifs to modulate receptor function (Heery et al. 1997; He et al. 2002). Nuclear translocation is mediated by a bipartite nuclear localization signal (NLS) located within the hinge region, which interacts with cytoskeletal proteins (Ozanne et al. 2000; Thadani-Mulero et al. 2012) to orchestrate the transport of AR via importin-α across the nuclear membrane (Kaku et al. 2008; Ni et al. 2013). Once in the nucleus, AR generally persists in a homodimer localizing to specific recognition sequences designated as androgen response elements (AREs) found within the promoter and enhancer regions of AR target genes (Claessens et al. 2001). Following localization, coregulators, general TFs, and RNA polymerase II are successively recruited to AR to direct the organization of the preinitiation transcriptional complex (Heemers and Tindall 2009).

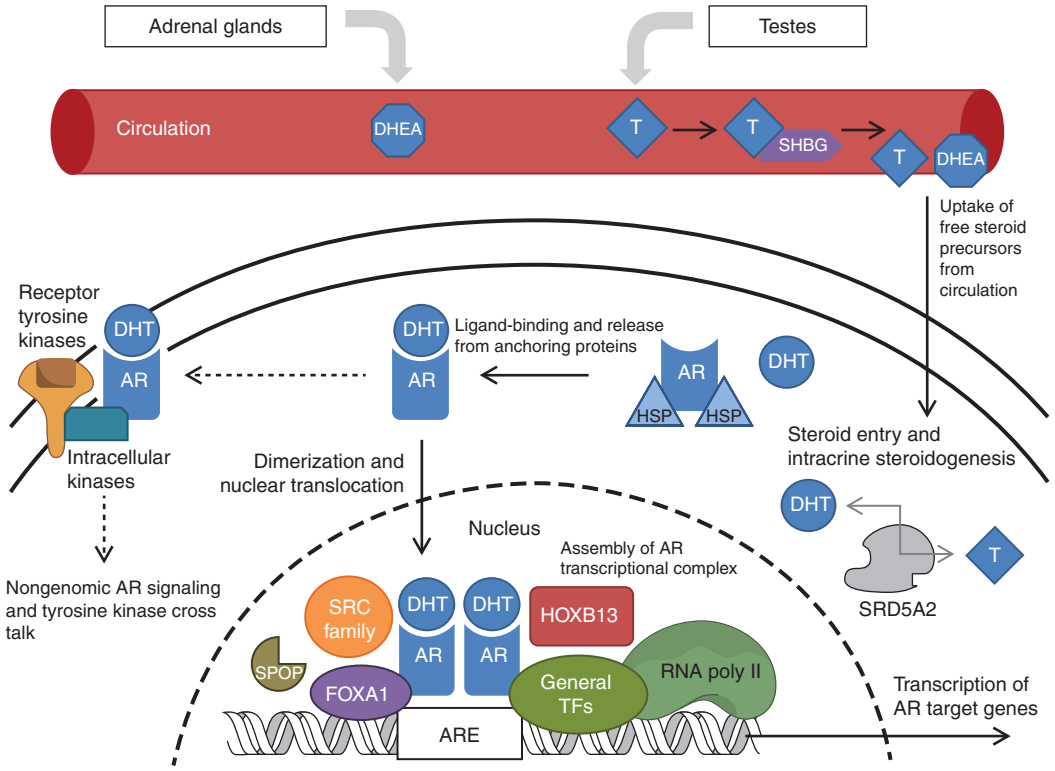

Figure 3. Prereceptor and receptor-level modulation of androgen receptor (AR) action within the prostate cancer cell. Examples of transcriptional coregulators discussed within the text are depicted but are a limited representation of all potential participating proteins. DHEA, dehydroepiandrosterone; SHBG, sex hormone–binding globulin; T, testosterone; DHT, dihydrotestosterone; HSP, heat shock protein; TF, transcription factor; ARE, androgen response element.

The DBD of AR is highly conserved and contains two zinc finger domains, through which specificity for DNA binding is determined (Umesono and Evans 1989; Shaffer et al. 2004). The first zinc finger is responsible for interacting with nucleotides within the major groove of DNA, thereby tethering the receptor for the assembly of a transcriptional complex around AR, whereas the second zinc finger coordinates homodimer formation (Shaffer et al. 2004). Notably, a specific sequence of three amino acid residues (Gly-Ser-Val) within the first zinc finger, known as the P(roximal)-box, is conserved across other steroid receptors, including glucocorticoid receptor (GR), progesterone receptor (PR), and mineralocorticoid receptor (MR) (Umesono and Evans 1989). This homology enables other steroid receptors to recognize response elements in common with AR, which bears potentially significant clinical implications. Recent investigation into post-enzalutamide resistance in CRPC has revealed that GR up-regulation may reinstate oncogenic programming through the expression of overlapping, albeit not identical, AR-regulated genes (Arora et al. 2013; Sahu et al. 2013). Around 30% of prostate cancers express GR, with this proportion increased under androgen-deprived conditions (Szmulewitz et al. 2012). In preclinical models, treatment with enzalutamide up-regulates GR expression, which is increased considerably more so following the emergence of enzalutamide resistance. Furthermore, dexamethasone can induce enzalutamide resistance in prostate cancer cell lines, which is subsequently reversed by a glucocorticoid antagonist

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or genetic silencing of GR expression. This newfound reliance on GR, however, presents an inherent challenge for any additional signaling inhibition because, unlike AR, GR signaling is essential for life (Nicolaides et al. 2010). A satisfactory approach to GR pathway blockade may therefore necessitate the identification of suitable downstream targets for inhibition that will not elicit intolerable or life-threatening toxicities (Sharifi 2014; Li et al. 2017).

The NTD contains transcriptional activation function-1 (AF-1), which commands transcriptional activity and is basally suppressed by the LBD (Jenster et al. 1991; Simental et al. 1991). In recent years, a number of truncated AR splice variants (AR-Vs) have been identified and implicated in CRPC (Dehm et al. 2008; Guo et al. 2009; Hu et al. 2009; Sun et al. 2010); these variants all harbor an intact NTD and DBD but reveal notable loss of the carboxy-terminal LBD, leading to the uncoupling of transcriptional control from ligand-dependent induction. It is thought that AR-Vs may emerge through aberrant alternative splicing (Liu et al. 2014) or AR gene rearrangements (Li et al. 2011, 2012) to escape antiandrogen therapies that target the LBD. Although more than 20 AR-Vs have now been confirmed in prostate cancer specimens (Robinson et al. 2015), which show different levels of transcriptional activity and expression (Ware et al. 2014; Lu et al. 2015), AR-V7 is the most commonly detected variant in CRPC (Ware et al. 2014). Truncation of AR-V7 occurs after exon 3 and includes a cryptic exon 3b from an intron into the expressed protein (Fig. 2). AR-V7 is constitutively active, and mRNA levels in circulating tumor cells (CTCs) have been recently found to correlate strikingly with resistance to enzalutamide and abiraterone, suggesting that AR-Vs may serve as a promising biomarker for therapeutic response (Antonarakis et al. 2014). Several preclinical models in which AR-V7 is either expressed endogenously with full-length AR (AR-FL) or exogenously in AR-FL-negative cells show an abrogated androgen requirement and resistance to antiandrogens in the presence of AR-V7 (Hu et al. 2009; Mostaghel et al. 2011; Li et al. 2013; Cao et al. 2014). Furthermore, exposure to ADT and AR-directed therapies may reciprocally induce AR-V7 expression (Watson et al. 2010; Mostaghel et al. 2011). Although it was originally suggested that AR-V7 primarily heterodimerizes with AR-FL to mediate target gene transcription (Watson et al. 2010; Cao et al. 2014), AR-V7 may also alternatively homodimerize to drive AR signaling independently of AR-FL (Chan et al. 2015; Xu et al. 2015). However, in comparison to AR-FL, AR-V levels are generally low (Watson et al. 2010), particularly in tumors treated with new generation hormonal therapies, and expression of AR-FL nearly always co-occurs with the presence of AR-Vs (Lu et al. 2015). Thus, whether AR-Vs are a self-sufficient substitute for AR-FL and whether differential changes in oncogenic transcriptional programming can occur in the presence of AR-Vs remains a topic of interest for further investigation (Lu et al. 2015).

Advances in our knowledge on AR-Vs in prostate cancer progression and the dynamic structure–function relationships of the different AR domains have unveiled alternative approaches to achieve therapeutic inhibition of AR signaling. Among these are AR-directed agents that do not target the LBD. EPI-506 is an NTD inhibitor that can bind both AR-Vs and AR-FL and is currently under evaluation in phase I clinical trials (NCT02606123) (Maughan and Antonarakis 2015). Other potentially attractive therapeutic targets include the DBD (Dalal et al. 2014) and sites of AR cofactor interaction (Ravindranathan et al. 2013). In summary, our progressive understanding of the potential molecular mechanisms through which AR may drive transcriptional programming continues to guide the development of novel strategies to disrupt AR signaling.

ANDROGEN RECEPTOR COREGULATORS

Approximately 300 AR coregulators have now been identified (Heemers and Tindall 2007; DePriest et al. 2016), which can coactivate or corepress AR transactivation and are increasingly recognized to do so in a target-gene-specific manner (Marshall et al. 2003; Agoulnik and Weigel 2009; Heemers et al. 2009; Ianculescu

et al. 2012). Within a large class of proteins with diverse cellular functions and characteristics, these coregulators commonly associate with AR to ensure effective transcription of target genes (Fig. 3) (Heemers and Tindall 2007). Coregulators can alter transcriptional activity through modulation of a variety of processes, including (1) AR stabilization, homodimerization, and nuclear translocation, (2) chromatin remodeling and DNA occupancy, (3) recruitment of general TFs, and (4) priming and assembly of the preinitiation transcriptional complex (Heemers and Tindall 2007; Shiota et al. 2011). Among the prototypical and most well-studied coregulators is the p160 coactivator family, comprised of three protein members: SRC1, SRC2 (TIF2), and SRC3. These proteins specifically bind to the AR NTD, influencing transactivation through direct histone acetyltransferase activity, as well as through indirect recruitment of secondary coactivators to induce chromatin remodeling (Chakravarti et al. 1996). A common attribute among many coregulators is the ability to enzymatically modify AR and other components within the local molecular environment, such as histones, transcriptional proteins, and other coregulators, through acetylation, methylation, phosphorylation, SUMOylation, and ubiquitination (Heemers and Tindall 2007, 2009). This, in turn, initiates cellular processes such as proliferation and invasion, driving tumor progression. An example of this relationship is underscored by speckle-type POZ protein (SPOP) missense mutations in prostate cancer (Berger et al. 2011; Barbieri et al. 2012; Grasso et al. 2012). SPOP, which is an E3 ubiquitin ligase normally involved in the degradation and turnover of AR as well as SRC3, may incur mutations that lead to increased AR protein levels and liberation of AR-mediated gene transcription (An et al. 2014; Geng et al. 2014). Interestingly, AR-Vs that lack the hinge region required for interaction with SPOP are resistant to degradation (An et al. 2014). SPOP mutations are common, occurring in up to 11%–13% of primary prostate cancers, and represent a distinct molecular subtype of disease (The Cancer Genome Atlas Research Network 2015).

Androgens have been shown to regulate the expression of ~30% of coregulators (Heemers et al. 2009, 2010). This response is variable across coregulators and is highly specific to particular AR target genes (Heemers et al. 2009). Furthermore, overexpression of coactivators is associated with increased clinical aggressiveness (Gnanapragasam et al. 2001; Debes et al. 2003; Zhou et al. 2005). The recent development of peptidomimetics (Ravindranathan et al. 2013) and small molecule inhibitors (Wang et al. 2011b, 2014; Asangani et al. 2014), which target these various coregulators offers a promising approach that may yield a new class of therapeutic agents for CRPC. Prototypical examples include SRC-3 and SRC-1 inhibitors (Wang et al. 2011b, 2014), as well as bromodomain and extraterminal (BET) inhibitors, which disrupt target gene activation by preventing the binding of BET subfamily proteins to acetylated chromatin (Asangani et al. 2014, 2016). In addition, the use of innovative molecular screening approaches such as "Chem-seq"—in which biotin-tagged small molecules are captured by ChIP to link candidate compounds to regulated target genes—may increasingly reveal suitable agents to disrupt the transcriptional program of prostate cancer. Overall, efforts to elucidate key AR coregulators have shown an impressive number of potentially actionable proteins involved in the intricate, selective, and dynamic interplay with AR to promote AR signaling (DePriest et al. 2016).

ANDROGEN RECEPTOR ACTION

The classical model of genomic AR signaling involves the recruitment of the ligand-bound steroid receptor to AR-binding sites to activate the AR transcriptome (Nelson et al. 2002; Dehm and Tindall 2006). A compelling link that underpins AR signaling to prostate tumorigenesis is well illustrated through the occurrence of chromosomal rearrangements that generate novel fusions between the androgen-regulatory elements of TMPRSS2 and ETS family of oncogenes (ERG, ETV1) (Tomlins et al. 2005). TMPRSS2-ERG fusions are the most common molecular alteration in prostate cancer, occur-

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ring in 40%–50% of tumors (Tomlins et al. 2009; The Cancer Genome Atlas Research Network 2015). These fusions are also recognized in isolated high-grade prostatic intraepithelial neoplasia (HGPIN) lesions (Park et al. 2014), lesions associated with cancer (Perner et al. 2007), as well as benign prostatic epithelial cells after extended exposure to DHT (Berger et al. 2011), suggesting that the acquisition of TMPRSS2-ETS fusions is likely an early carcinogenic event. Moreover, some evidence suggests that androgens themselves can provoke nonrandom fusion events (Lin et al. 2009; Mani et al. 2009). However, other instigators such as activation of the PI3K/Akt pathway may be required in the presence of fusions to fully induce malignant transformation (Carver et al. 2009; King et al. 2009).

The collective AR cistrome appears to undergo extensive reprogramming with malignant transformation and disease progression (Wang et al. 2009; Sharma et al. 2013; Pomerantz et al. 2015a). Large-scale bioinformatics and systems-based initiatives to characterize the genomic regions of global AR occupancy have revealed an incredible degree of complexity and variation to AR-responsive gene regulation (Sharma et al. 2013; Mills 2014). In fact, the interfacing of TF networks may critically dictate a particular AR-binding profile, which is distinctly different between normal and tumor tissue (Pomerantz et al. 2015b) and may be perturbed by the presence of external signaling factors such as inflammatory cytokines (Sharma et al. 2013). Considerable differences also exist between the AR-binding profile of cell lines and that of primary tissue, indicating that a set of genes might be selectively activated through in vivo signaling (Sharma et al. 2013). Among TFs most enriched at AR-binding sites is forkhead box A1 (FOXA1), a pioneer factor that globally facilitates AR action through interaction with AR at the DBD. FOXA1-binding sites are typically found in close proximity to AR-binding sites, with a large amount of overlap between their respective cistromes (Zhao et al. 2014). In experiments, FOXA1 may either augment or antagonize AR signaling depending on the setting (Wang et al. 2011a). Homeobox B13 (HOXB13), a highly lineage-specific factor, which is itself regulated by FOXA1 (McMullin et al. 2010), has also emerged through recognition of its role in hereditable prostate cancer disposition and disease progression (Ewing et al. 2012; Decker and Ostrander 2014). Together, FOXA1 and HOXB13 have been shown to be sufficient in reprogramming the AR cistrome in an immortalized prostate cell line to resemble that of malignancy (Pomerantz et al. 2015a). These findings have highlighted the dynamic and contextually dependent nature of AR binding (Heemers and Tindall 2009).

AR PATHWAY CROSS TALK AND LIGAND-INDEPENDENT ACTIVATION

Evidence also indicates that various growth factor, cytokine, and nonreceptor tyrosine kinase pathways are activated in prostate cancer (Lamont and Tindall 2011). A number of cell surface receptors including epidermal growth factor receptor (EGFR), interleukin (IL)-6 and IL-8 receptors, insulin-like growth factor 1 (IGF-1) receptor, and Her2/neu have been implicated in cross talk with AR to drive ligand-independent signaling or to sensitize AR to subphysiologic androgen concentrations (Mellinghoff et al. 2004; Guo et al. 2006; Ponguta et al. 2008; Dutt and Gao 2009). Intracellular kinases such as mitogen-activated protein kinase (MAPK), as well as its effectors Src and ERK1/2, and PI3K/Akt have also been shown to drive prostate cancer progression (Guo et al. 2006). Many of these proteins are downstream elements of nongenomic AR signaling, which can mediate a proliferation response typically within minutes of ligand stimulation (Lösel and Wehling 2003; Liao et al. 2013) via cytoplasmic and lipid raft–associated AR (Pedram et al. 2007). Although sizable preclinical data exist to suggest a therapeutic benefit with pharmacologically inhibiting these pathways, clinical results have been mostly disappointing to date (Ziada et al. 2004; de Bono et al. 2007; Araujo et al. 2013). Overall, these signaling molecules may represent a larger coordinated and possibly redundant network of signal transduction path-

ways that act in concert with AR signaling to promote key neoplastic processes.

CONCLUDING REMARKS

Since the work of Huggins and Hodges, major advances have contributed to our understanding of the AR signaling axis in the pathogenesis of prostate cancer. With this also comes a greater appreciation for the complexity of prereceptor and postreceptor AR regulation. Major milestones were achieved with the introduction of abiraterone and enzalutamide in the treatment of CRPC, which has resulted in a significant paradigm shift and renewed interest in intratumoral androgen suppression. However, onset of resistance to these second-generation agents has also galvanized new directions to investigate the mechanisms that may promote this escape. Evolving molecular approaches have revealed key insights into the structural basis of AR function and the dynamic, context-dependent nature of AR transcriptional control. The hope is that these ongoing efforts will translate into greater precision in AR targeting and novel therapeutic options in the near future for men with prostate cancer.

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