Chapter 20
The Role of Androgen Receptor in Prostate Cancer

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Contents

Androgen Receptor (AR): Description and Function

AR Gene and Protein Description

The androgen receptor (AR) is encoded by a 186,588 base-pair, 8-exon gene located on chromosome X (Xq11–12) and belongs to the steroid hormone nuclear receptor superfamily. AR expression is cell-dependent and regulated by androgen [1]. The AR gene encodes for a 919 amino acid nuclear receptor (~110 kDa) that acts as a

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hormone-dependent DNA-binding transcription factor. This modular protein is composed of four domains [2]: the N-terminal domain (NTD), the DNA-binding domain (DBD), the hinge region, and the C-terminal domain (CTD). The NTD contains residues involved in the recruitment of transcriptional co-regulators and is required for the activation of transcriptional activity. The autonomous transcriptional activation function (AF1) of the NTD is ligand-independent and required for maximal activity of AR [3]. The DBD is composed of two zinc-finger motifs involved in the recognition of specific DNA sequences, located in AR target genes [4, 5], known as androgen response elements (AREs: canonical consensus sequence = 5′-AGAACA-3′ in direct repeats or inverted repeats separated by a spacer of three base pairs for classical and selective AREs, respectively [6]). Noncanonical elements have also been described but are bound by AR with a lower affinity [7]. The DBD is separated from the CTD by the hinge region, a flexible region that includes the nuclear localization signal sequence (NLS). The CTD contains the ligand-binding domain (LBD), which is formed by 12 α[alpha]-helix arranged in a globular structure surrounding the hydrophobic ligand-binding cavity, and a second transcriptional activation function (AF2). The AF2 is ligand-dependent and has a synergistic effect with AF1 that results in full AR transactivation [8]. Despite a high similarity of sequence between members of the hormone nuclear receptor superfamily, some key residues in the AR AF2 core domain are essential for AR functionality and make it distinct from the other hormone nuclear receptors [9]. The CTD also contains the nuclear export signal (NES), which is used to export AR to the cytoplasm upon ligand withdrawal.

The Role of AR in Normal Development

AR is weakly expressed in numerous tissues and cells yet highly expressed in the adipocytes, liver, and prostate (http://biogps.org/#goto=genereport&id=367), directly linking its function to male dimorphism. Following androgen activation, AR participates widely in the male reproductive tract including gonadal development and maintenance [10]. During embryogenesis, AR signaling regulates the reproductive tract patterning by determining the Wolffian duct differentiation and inducing the development of the male reproductive tissues [11, 12]. In adults, AR remains essential for seminiferous tubule and prostate function in terms of epithelial and stromal compartment maintenance [13] and maintenance of paracrine factor-mediated secretory functions of the epithelial cells [14]. AR signaling is also involved in other physiological processes linked to sexual dimorphism, such as muscle development, lipid accumulation, and bone homeostasis [13].

AR Transcriptional Regulation

The activation of the AR signaling pathway depends on ligand binding to AR. In the absence of ligand, AR is localized in the cytoplasm and forms a complex with HSP90/HSP70-based multiprotein chaperone machinery, protecting it from

degradation [15]. Barring 10% that is produced in the adrenal cortex, the vast majority of circulating androgen is testosterone produced by the testes. Circulating testosterone enters prostate epithelial cells and is rapidly converted to the potent AR ligand 5α[alpha]-dihydrotestosterone (5α[alpha]-DHT) by the enzyme 5α[alpha]-reductase to DHT (dihydrotestosterone or androstanolone) [16]. DHT binds the LBD of AR with a twofold higher affinity and a fivefold decreased dissociation rate compared to its precursor [17]. Binding of DHT to the LBD of AR induces conformational changes resulting in AR dissociation from the HSP90/HSP70 complex and the exposition of the AF2 domain and the NLS. AR is then shuttled to the nucleus via the microtubule network [18, 19]. The AR NLS interaction with importin-α[alpha] and importin-β[beta] mediates the translocation of AR across the nuclear membrane [20]. Upon entry into the nucleus, AR homodimerizes and binds to AREs associated with AR target genes. These sequences are found in both proximal promoters and distal enhancers, up to several thousand base pairs upstream or downstream of the transcription start site [21]. The AR cistrome has been defined by multiple research groups in cell lines, such as LNCaP [22–24] and VCaP cells [25], in transgenic mouse models [26], and in human clinical samples of prostate cancer tissues [27] including castrate-resistant prostate cancer [28]. These studies clearly demonstrated that the AR cistrome is reprogrammed in human prostate tumorigenesis [27, 28]. AR binding to AREs leads to recruitment of co-regulators (replacement of transcriptional corepressors with coactivators), general transcription factors, and RNA polymerase II to induce transcription activation. Two well-described AR target genes and indicators of androgen signaling pathway activation are prostate-specific antigen (PSA) and transmembrane protease, serine 2 (TMPRSS2). A noncanonical pathway of androgen signaling, independent of androgen binding and involving cofactors or crosstalk with other intracellular signaling pathways, has also been characterized.

AR Signaling Regulation

AR Co-regulators and Cofactors

AR activity is modulated through an interaction with specific cofactors. Depriest et al. recently generated a database referencing 274 AR-associated co-regulator genes [29]. According to Heemers and Tindall [30], AR-interacting proteins can be classified into three main groups: (1) general transcription factors, comprising the classical transcriptional machinery, (2) co-regulators that shift the balance toward expression or repression of the transcriptional activity, and (3) specific transcription factors.

The first class includes TFIID/B/F proteins, required for the recruitment of RNA polymerase II, and TFIIE/H. Of these, AR directly interacts with TFIIF, TFIIH, and polymerase II through its RPB2 subunit.

The second class of cofactors is composed of more than 160 proteins [30] including components of the chromatin remodeling complex (e.g., ARIP4 [31], BAF57 [32], the SWI3-related gene product SRG3 [33], and SRCAP [34]) and histone modifiers (e.g., members of the p160 SRC gene family [35, 36]). P300 [37] and CREB-binding

protein (CBP) also directly acetylate AR through their acetyltransferase activity. This acetylation allows for the recruitment of other coactivators to serve as molecular bridges between AR and the transcriptional machinery [37]. Histone modifiers either promote (e.g., demethylases such as LSD1 and JMJD2C [38, 39]) or repress (e.g., deacetylases such as SIRT1 [40]) AR-mediated transcriptional activity. AR also interacts with ubiquitination/proteasome and SUMOylation pathway components, proteins involved in splicing and RNA metabolism, DNA repair proteins, chaperones, cell cycle proteins, signal integrators, and apoptosis regulators [30, 41].

The third category of AR-interacting proteins [30] regulates AR signaling by defining the temporal, spatial, and functional binding pattern of AR [42]. This class of cofactors acts by modifying the interaction of AR with DNA [43], titrating other co-regulators [44], or recruiting AR on non- or partial AREs [42]. For example, DNA motifs recognized by the three transcription factors FoxA1, GATA2, and Oct1 are enriched at AR half-site motifs [42]. FoxA1 is a known pioneering factor that is essential for maximal prostatic gene activation [45] by facilitating AR binding on FoxA1-dependent AR binding sites. More recently, FoxA1 has been shown to regulate AR function by masking AR binding sites, which become functional upon FoxA1 depletion [23]. While FoxA1-AR interaction is not affected by ligand binding, AR interacts with GATA2 and Oct1 in a hormone-dependent manner. These collaborating partners have distinct functional roles in androgen-dependent gene transcription and cell proliferation [42].

These observations highlight the balance between coactivators and corepressors of AR and their importance on its activity. AR cofactors are differentially expressed in prostate cancer and have the potential to drive disease progression.

AR Protein Posttranslational Modifications and Signaling Crosstalk

Although androgen binding is the primary means for AR activation, protein posttranslational modifications also influence AR activity. AR, at the protein level, can be altered by up to five well-described modifications (phosphorylation, acetylation (discussed above), SUMOylation, methylation, and ubiquitination) on a subset of 23 different amino acids [46].

AR phosphorylation occurs at serine 16, 81, 256, 308, and 424 in the presence of androgen, but the impact of phosphorylation at any one of these sites in terms of AR activity remains unclear. For example, stress-induced JNK1 phosphorylation on serine 650 regulates nuclear export of AR, antagonizing AR-mediated transcription [47]. AR phosphorylation at specific tyrosines results from specific growth factor signaling. Growth factors such as IGF-I (insulin-like growth factor-I), KGF (keratinocyte growth factor), and EGF (epidermal growth factor) are able to activate androgen signaling through AR phosphorylation, leading to an increase of PSA level. This activation is inhibited by the AR antagonist Casodex, highlighting the specificity of the mechanism for AR [48]. EGF, for example, induces the activity of Src and Ack1 kinases, which, in turn, phosphorylate AR at tyrosines 534 and 267, respectively. Phosphorylation at these sites increases AR transcriptional activity by

enhancing its nuclear translocation and DNA binding. EGF can also modify AR activity by inducing IL-6 upregulation in prostate cancer cells.

AR SUMOylation, occurring at regulatory amino acid SUMO acceptor motifs at lysines 386 and 520, results in an inhibition of both the ligand-activated and the basal ligand-independent activity of AR [49]. AR is also regulated by mono- and polyubiquitination, which impact the stability and turnover of the protein or its activity, depending on the topology of the polyubiquitin chains [28, 50, 51]. The position of the lysine residue used for ubiquitin chain branching dictates the fate of the substrate. For example, the polyubiquitination of AR mediated by MDM2 induces AR degradation by the 26S proteasome [51], while the one driven by RNF6 promotes AR transcriptional activity [50].

AR Involvement in Primary Prostate Cancer

After skin cancer, prostate cancer is the most common and the third most lethal form of cancer in men in the United States, with 161,360 estimated new cases in 2017 [52]. Over 50 years ago, Huggins' work [53, 54] demonstrated a direct relation between androgen and prostate cancer, reporting a regression of prostate cancer after orchiectomy. High levels of AR in prostate cancer luminal epithelial cells are associated with a high tumor grade, deregulation of cell-cycle genes [55–57], inhibition of apoptosis [58], increased angiogenesis [59], and crosstalk with PI3K-AKT-PTEN, RAF, Wnt, and DNA repair signaling pathways [60]. AR has also been implicated in the development of chromosomal rearrangements, such as the TMPRSS2-ERG gene fusion, detected in around 50% of prostate cancer patients [61–63]. Clinically, androgen signaling is monitored using the prostate-specific antigen (PSA) level, encoded by the AR target gene *KLK3* [64]. The level of circulating PSA is measured to track prostate cancer progression and disease recurrence in the context of androgen deprivation therapy (ADT) [64–66], which is the first line of treatment for advanced prostate cancers. Current ADT approaches are aimed at chemically lowering circulating testosterone levels by the administration of luteinizing hormone-releasing hormone (LHRH) analogs. Since these approaches target only 90% of androgen production (not from the adrenal glands), they are often used in combination with the classic antiandrogen compounds (e.g., flutamide, bicalutamide, and nilutamide). Despite encouraging initial response following ADT, relapse occurs for almost all cases within several months and leads to a more aggressive form of prostate cancer defined as castration-resistant prostate cancer (CRPC).

Mechanisms of AR Reactivation Associated with CRPC

There are several mechanisms of resistance associated with the onset of metastatic CRPC (mCRPC) tumors, among which include AR-related alterations (e.g., *AR* gene amplification or mutations [60, 67, 68], alternative splicing of *AR* mRNA [69–72], and posttranslational modifications of AR protein (Fig. 20.1)), crosstalk with other

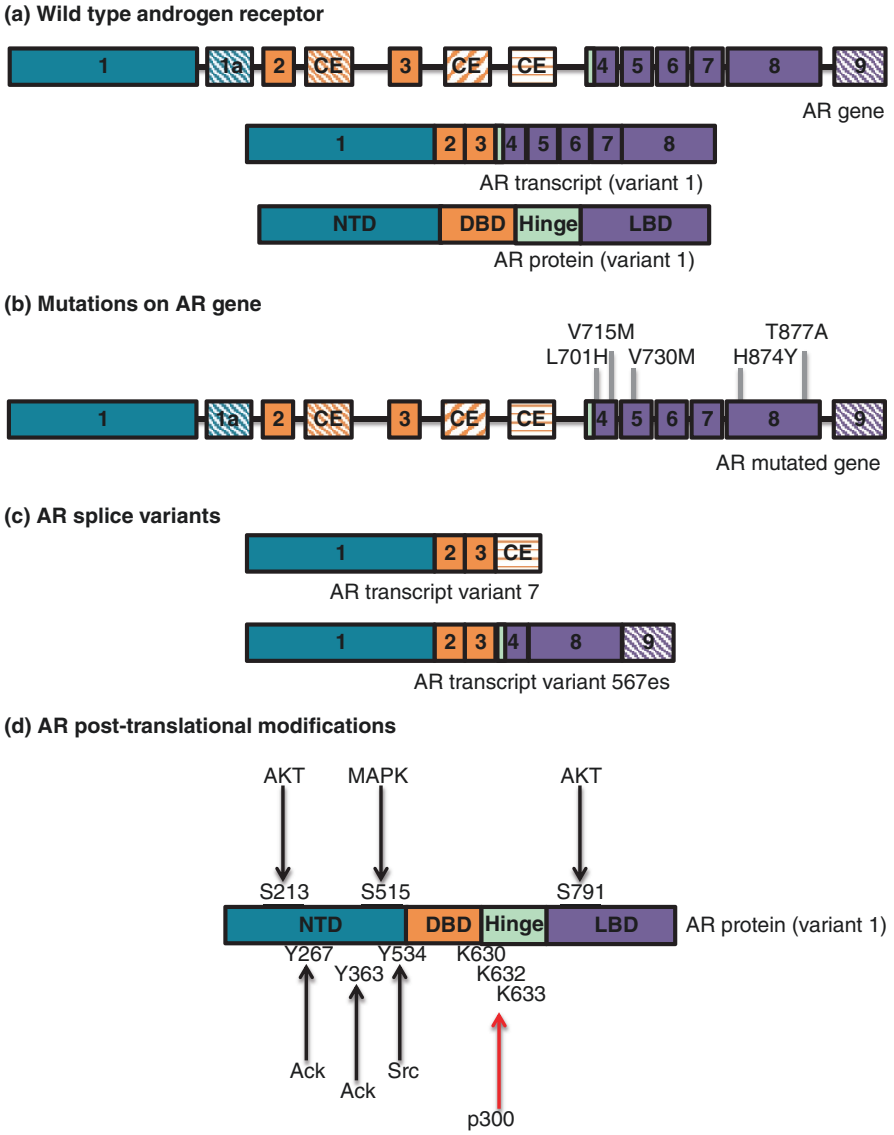

Fig. 20.1 AR modifications associated with castrate-resistant prostate cancer development. (**a**) Wild-type AR gene, RNA, and protein. (**b**–**d**) Alterations to the AR gene DNA, mRNA, or protein-associated androgen deprivation therapy resistance. These alterations result in constitutive activation of AR, due to mutation in the LBD (**b**) or splicing variant (**c**). (**d**) The most common posttranslational modifications of AR that enhance its transcriptional activity and that are driven by one of the AR cofactors (e.g., p300) or crosstalk with other signaling pathways (e.g., AKT, MAPK, Ack, and Src). *Black arrows* represent phosphorylation, while the *red arrow* represents acetylation. CE = cryptic exon, NTD = N-terminal domain, DBD = DNA-binding domain, hinge = hinge domain, LBD = ligand-binding domain

cancer-promoting signaling pathways, genomic alterations involving cofactors/co-regulators and other AR signaling proteins, and intraprostatic generation of androgen [73, 74]. These findings have led to the development of second-generation antiandrogens, which are improved AR antagonists (e.g., enzalutamide) or inhibitors targeting the biosynthesis of AR (e.g., abiraterone acetate). Enzalutamide (MDV3100) is a targeted AR inhibitor that competitively binds to the LBD of the androgen receptor and inhibits androgen-receptor translocation to the cell nucleus, recruitment of AR cofactors, and AR binding to DNA [75, 76]. The 17α[alpha]-hydroxylase/C17,20-lyase (CYP17) inhibitor abiraterone acetate acts as an antagonist to AR and inhibits 3β[beta]-hydroxysteroid dehydrogenase blocking androgen synthesis in the adrenal glands, testes, and within the prostate tumor [77, 78]. Despite improved response rates and overall survival with these molecules [79], almost all metastatic CRPC patients develop resistance to these agents as well. Recent genomic sequencing studies of large cohorts with resistance to these molecules have recently been reported and show further AR signaling reactivation alterations [60]. Below, we discuss the mechanisms, linked to AR or AR signaling, known to be involved in the resistance of mCRPC to second-generation ADT.

AR Gene Amplification

Early studies using both targeted or genome-wide approaches of hormone-naïve versus hormone-refractory primary prostate cancers led to the finding of an acquired increased copy number (up to 60 copies per cell) at chromosome Xq11–13 including the genomic loci of AR in roughly 30% of recurrent tumors [80–82]. Other studies have also reported an AR amplification in more than 50% of circulating tumor cells (CTC) from metastasized CRPC [83, 84]. This observation is consistent with the frequency of AR amplification found in recent genome sequencing studies [60, 85]. AR amplification drives its overexpression and increases the likelihood of androgen-AR interaction, thus reactivating the AR signaling pathway.

AR and AR-Associated Gene Mutations

AR mutations in the context of CRPC were first described roughly 20 years ago [67, 68] and have since been characterized in around 20% of CRPC [86]. Numerous AR mutations have been described in prostate cancer, approximately 45% of which are somatic single-base substitution occurring in the LBD [87]. Several mutations in this region affect the ligand specificity of AR, allowing its activation by non-androgenic steroids or antiandrogens [88]. Recent genomic sequencing analyses of metastatic prostate cancers have shed a considerable amount of light regarding mutations to AR and AR signaling genes such as NCOR1, NCOR2, FOXA1, and NKX3.1 [85, 86, 89–91]. The most recent study, based on a large sequenced CRPC patient cohort treated with the most up-to-date standard-of-care antiandrogen

therapy (abiraterone or enzalutamide) or through a cohort of prospective clinical trials (n = 150), found that upward of 70% of cases harbored AR pathway aberrations [60]. The majority (63%) of alterations impacted AR directly, through amplifications and mutations including hotspot mutations that confer agonism to AR antagonists such as flutamide (T878A) and bicalutamide (W742C) [92]. This agonism to enzalutamide has also been described with the F876L mutation [93] as well as to glucocorticoids in case of L702H mutation. In addition to AR mutations itself, Robinson et al. also observed alterations in AR pathway members such as NCOR1, NCOR2, and FOXA1 [51] and AR-associated genes such as deletion of ZBTB16 [94, 95] and SPOP mutations [89, 96].

AR Splice Variants

More than 20 different AR variants have been described in preclinical or clinical CRPC samples ([60, 69–72], reviewed by Lu C. and Luo J. [97] and more recently by Wadosky and Koochekpour [98]). The AR variants are generated from multiple alternative splicing events (e.g., aberrant splicing, inclusion of an alternative exon, or insertion of cryptic exons) of the *AR* mRNA. Structural alterations in the *AR* gene resulting in AR variant expression have also been described [99, 100]. Insertions of cryptic exons downstream of the sequences encoding the DBD or deletions of the exons encoding the LBD result in a truncated AR protein devoid of the functional LBD. AR splice variants that lack the LBD (encoded by exons 5–6-7–8) generate constitutively active forms of AR [70, 71]. The activity of these AR variants is no longer regulated by androgens. They are thus resistant to antiandrogen therapies and constitutively activate the AR signaling pathway [71, 72]. Moreover, while AR is translocated to the nucleus via microtubule transport, AR-V7 (the most characterized AR variant lacking the LBD) exploits another way to its translocation that is still under investigation [101]. AR-V7 and AR-v567es are the most commonly detected AR variants in prostate cancer and thus, the most studied to date (Fig. 20.1). A genome-wide occupancy study using ChIP-seq found that AR variants bind DNA as dimers and display a binding preference for the same canonical high-affinity AREs that are engaged by AR-FL, albeit with lower affinity [102]. While initially described as heterodimers with AR full length (AR-FL), the variants have since been implicated in homodimerization and driving AR signaling independently of AR-FL [102–105]. Based on nuclear AR expression using N- and C-terminal-specific AR antibodies, Zhang et al. found an increase in the prevalence of AR variants in CRPC clinical samples compared to primary prostate cancer [106]. Another study of 13 CRPC bone metastasis samples found that the level of AR variant protein constituted 32% (range 0–95%) of the AR full length. Meanwhile, the RNA level was relatively weak compared to the full length, suggesting that AR variants could be posttranscriptionally stabilized in CRPC [107]. AR-FL, AR-V1, and AR-V7 transcripts were detected in most of the nonmalignant primary tumors and metastatic samples examined, while the AR-V567es transcript was detected in only 7 (23%) CRPC bone

metastases. The expression of these variants is also associated with a poor prognosis of patients, most likely due to their constitutive activation [107]. AR variants drive androgen-independent cell proliferation in a manner that is resistant to antiandrogens, including enzalutamide [108], and are widely expressed in the context of metastatic CRPC (SU2C cohort) and to a lower extent in pre-abiraterone/enzalutamide primary prostate cancer (TCGA cohort [60]). While controversial [109], AR-V7 expression has been associated with abiraterone and enzalutamide resistance [110–113]. More recently AR-V9 has also been associated with abiraterone resistance [114]. AR variants are hypothesized to induce epithelial-to-mesenchymal transition and stem cell phenotypes [115], but a further validation of this notion is needed.

AR Signaling and Crosstalk with Other Signaling Pathways Associated with CRPC

Many signaling pathways interacting with AR have been observed as altered or dysregulated in prostate cancer cells. For example, (1) the loss of PTEN and subsequent activation of PI3K/AKT are critical event in human prostate cancer [116, 117], (2) increased expression of EGFR correlates with the evolution of prostate cancer [118], (3) elevated circulating IL-6 and IL-8 levels have been observed and associated with advanced prostate cancer cases [119–123], and (4) members of SRC family have been described as increased in prostate cancer, even at higher levels in CRPC [124, 125].

Some of them have been shown to enhance AR signaling in the context of CRPC that arises either as a feedback following androgen withdrawal and/or compensation from growth factors and other signaling ligands. The expressions of several peptide growth factors, such as EGF/TGFα[alpha] and IGF-1, have been shown to be increased during progression to CRPC [118, 123, 126] and either induce AR transcriptional activity irrespective of androgen stimulation or sensitize AR to low concentrations of androgens (Fig. 20.2) [48, 127, 128]. More recently, another growth factor, CXCL12, has been characterized as androgen-independent AR activator in prostate cells [129]. Interleukins are also able to induce androgen-independent AR activity. IL-6 (interleukin-6), a multifunctional cytokine produced by prostate cells, binds to its specific receptor and induces a signaling cascade including JAK, STAT3, and p300. The N-terminal domain of AR directly interacts with STAT3, after IL-6 induction through phosphorylation of mitogen-activated protein kinase (MAPK) pathway [130]. This interaction leads to the activation of the AR NTD. IL-8 is also able to increase AR expression and promote its activity in an androgen-independent manner [131]. In addition, several protein kinases (e.g., MAPK, Akt/PKB, PKA, and PKC) and non-receptor tyrosine kinases (ERBB2/HER-2/neu, Src, FAK, and Etk/BMX) modulate AR activity by direct phosphorylation of serine/threonine or tyrosine residues, respectively, on AR or one of its cofactors (e.g., TIF2 and SRC1) [127, 128, 132]. The ERBB2/HER-2/neu tyrosine kinase modulates AR signaling [133], through MAP kinase pathway [134] or AKT pathway [135] or when associated with ERBB3 through

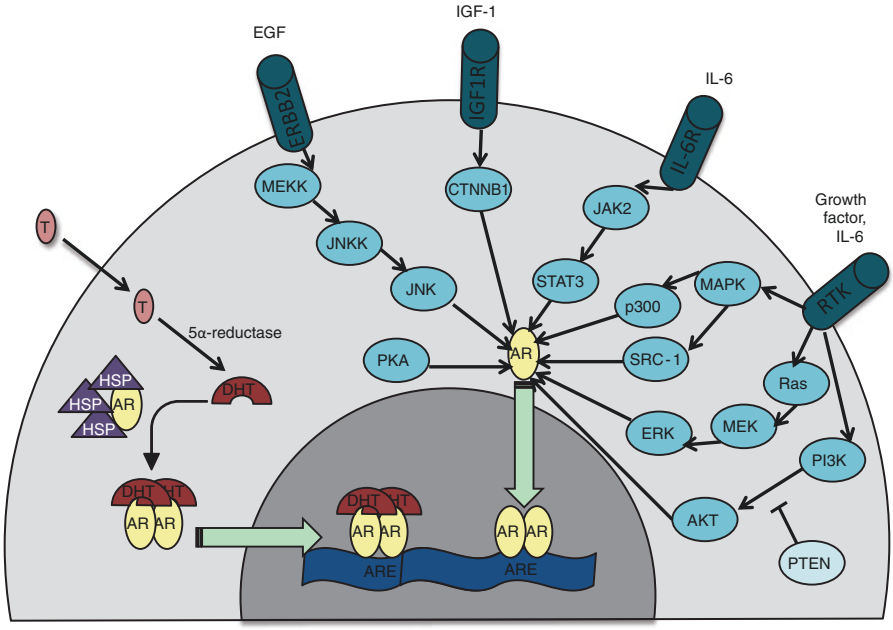

Fig. 20.2 Androgen-dependent and independent AR activation. AR can induce androgen-signaling pathway upon androgen binding (on the *left*) or activation through interaction with other signaling pathways (on the *right*)

a mechanism that remains to be elucidated [136]. As mentioned above, some specific AR polyubiquitinations serve as negative regulators of AR by enhancing its degradation [51]. This degradation is inhibited by HER2/ERBB3/PI3-kinase pathway in the context of hormone-refractory prostate cancer, providing a mechanism of enhanced AR stability as an additional mechanism of resistance [136]. PKA (protein kinase A), whose activity is dependent on the cellular level of cAMP, activates AR in the absence of androgen (Fig. 20.2) [137, 138]. There is a well-described and dynamic interplay between PI3K/AKT/mTOR and AR signaling axes during prostate cancer progression as well as a mechanism of ADT resistance. In the presence of androgen, AKT phosphorylates AR on Ser 213 and Ser 791, inducing a modification in AR signaling [139–141]. However, activation of the PI3K/AKT/mTOR pathway resulting from PTEN loss is associated with androgen insensitivity and the development of CRPC [142]. To address the mechanism underlying this finding, two independent groups found that the loss of PTEN in prostates results in a decrease in transcription of AR target genes through derepression of negative regulators of AR activity, EGR1, and c-Jun [143, 144]. In addition, loss of AR signaling either through genetic or pharmacological manipulation with enzalutamide leads to a reduction of FKBP5, an AR target gene. Low FKBP5 levels lower the AKT phosphatase and negative regulator PHLPP protein levels. In addition, mTOR inhibition in the background of PTEN loss leads to an increase in AR levels through upregulation of HER3, which increases

AR stability. Altogether, these data show how PI3K/AKT/mTOR pathway activity in the context of CRPC alters the need of the restricted levels of circulating androgens.

Moreover, an increase of AR acetylation enhances the binding of p300 on AR, reducing N-CoR/HDAC/Smad3 corepressor binding. This effect leads to a modulation of the transcriptional activation on AR-responsive genes, resulting in an aberrant cell growth in prostate cancer stable cells [37].

The activity of the glucocorticoid receptor (GR) has also been described as a potential mechanism of resistance to enzalutamide and ARN-509 in a preclinical model and has been confirmed in patient samples [145]. Glucocorticoids administrated at a low dose inhibit adrenocorticotropic hormone (ACTH) production by the pituitary and initially result in reduced androgen levels. However, a high expression of GR by the prostate cancer will result in GR activation in tumor cells. In this context, a more efficient strategy could be to combine AR and GR inhibition. This is currently being explored in an early phase clinical trial combining enzalutamide and mifepristone (NCT02012296).

Next Generation of AR-Targeted Therapies

Even in the face of potent second-line AR antagonists (enzalutamide) or CYP17 inhibitors (abiraterone), metastatic CRPC tumors continue to evolve different mechanisms to reactivate AR signaling, which has spurned the development of further agents targeting the AR signaling axis. New inhibitors have emerged that efficiently block both AR full length and variant action by targeting the N-terminal domain of AR [146, 147] or inducing degradation of AR mRNA [148] or protein [149–151]. None of them have been fully tested on patients and FDA-approved. One of the two most promising compounds is EPI-506 (binds the NTD of AR), which is currently in phase I/II clinical trial (NCT02606123). While the patients will not be selected based on AR-V7 status, responses to treatment will be stratified based on AR-V7 expression in CTCs. The second promising compound is the FDA-approved niclosamide, which promotes AR-V7 degradation and potentially restores the sensitivity of the tumors to second-generation ADT [152–154]. Two clinical trials are currently ongoing to assess the efficiency of niclosamide in combination with enzalutamide (NCT02532114) or abiraterone (NCT02807805).

The concept of bipolar androgen therapy is also emerging. This is based on the observation that the growth of AR-positive human CRPC cell lines is inhibited by supraphysiologic levels of androgens [155–157]. This has recently been the subject of a pilot clinical trial [158]. These newer strategies may also prove beneficial in combination with inhibitors targeting key crosstalk pathways (e.g., PI3K/AKT/mTOR or ERBB2/Her2/neu) or microtubule-targeting agents (e.g., taxanes). One consequence of taxane treatment is the inhibition of AR nuclear trafficking [18, 19, 159, 160]. This mechanism predicts synergy between effective AR-targeted therapy and taxanes, clinically validated by the unprecedented survival results for men with advanced, hormone-naïve prostate cancer in CHAARTED and STAMPEDE clinical trials (Sweeney ASCO 2014; James ASCO 2015 [161–163]).

Conclusion

Androgen signaling is a cellular pathway activated upon androgen binding to its specific receptor AR, leading to the transcriptional activation of androgen-responsive genes. Regulation of this pathway occurs through the action of numerous co-regulators of AR and is influenced by crosstalk from other signaling pathways in the cell and the microenvironment. Activation of AR is essential for the male dimorphism and also determinant for the development and maintenance of the prostate. Androgen signaling is also essential for the maintenance and progression of prostate cancer, making chemical castration, in the case of non-organ confined disease, the first line of intervention. While the involvement of androgen receptor in prostate cancer progression is established, the therapeutic strategy targeting androgen signaling-driven prostate cancer still needs to be improved for the incurable forms of the disease.

Despite continued hormonal therapy, including the most robust and potent second-line antiandrogens (e.g., enzalutamide) or CYP17 inhibitors (e.g., abiraterone), metastatic CRPC tumors evolve complex and ever-adapting mechanisms to reactivate AR signaling or other mechanisms that render the tumor cells indifferent to AR signaling. Recent evidence shows that neuroendocrine prostate cancer can arise in later stages of prostate cancer progression from a pre-existing adenocarcinoma during the course of treatment resistance to AR-directed therapies [164]. This is as an adaptive resistance mechanism.

The complexity and variability of mechanisms of resistance that have been described to date emphasize the growing need for better model systems that recapitulate clinically relevant mechanisms and a precision strategy adapted to each patient. The synergistic effect observed in recent combinatory treatments also highlights the important question of the timing, order, and/or combination of drugs in future strategies.

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