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REVIEW

Androgen Receptor Signalling in Prostate Cancer: Mechanisms of Resistance to Endocrine Therapies

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Abstract: Prostate cancer (PCa) is a major global health concern. It ranks as the fifth leading cause of cancer-related mortality worldwide. While localized PCa is often indolent, with a nearly 100% five-year survival rate, prognosis worsens significantly in metastatic disease, where survival drops to approximately 30%. Androgen deprivation therapy (ADT) is initially effective in suppressing tumor growth. However, resistance eventually develops, resulting in castration-resistant prostate cancer (CRPC). The androgen receptor (AR) plays a central role in both PCa progression and treatment resistance. It promotes tumor growth by mediating the effects of testosterone and 5α-dihydrotestosterone (DHT). Several mechanisms contribute to resistance. These include AR gene mutations that reduce ligand specificity or convert antagonists into agonists. AR overexpression can maintain activity even at low androgen levels. Splice variants such as AR-V7 can activate AR signaling despite androgen depletion. AR transcriptional activity is also modulated by coregulators. Coactivators (such as the SRC family) and corepressors (such as NCOR1/2) contribute to the persistence of AR signaling. Beyond AR-dependent mechanisms, CRPC may develop through AR-independent pathways. These include glucocorticoid receptor (GR) bypass signaling and lineage plasticity leading to neuroendocrine prostate cancer (NEPC). In addition, intratumoral steroidogenesis sustains AR activation despite systemic suppression of androgens. Together, these resistance mechanisms underscore the biological complexity of CRPC. They also highlight the urgent need for innovative therapeutic approaches. This manuscript reviews emerging molecular targets and resistance pathways to inform the development of next-generation treatments.

Keywords: prostate cancer, castration-resistant prostate cancer, CRPC, androgen receptor, AR, androgen deprivation therapy, ADT, therapeutic resistance

Introduction

Prostate cancer (PCa) is a major global health concern, ranking as the second most diagnosed cancer and the fifth leading cause of cancer-related mortality worldwide.[1] While localized PCa is often indolent, with a near 100% five-year survival rate, survival drops dramatically to 30% in metastatic cases.[2] Since the 1940s, PCa has been recognized as an androgen-dependent malignancy, with androgen deprivation therapy (ADT) representing the first example of targeted therapy though the inhibition of androgen receptor signalling.[3] The term ADT encompasses all hormonal therapies aimed at reducing androgen levels and/or blocking androgen receptor (AR) activity, serving as the mainstay treatment for locally advanced or metastatic disease. Although ADT is initially effective in nearly all patients, resistance inevitably develops,

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typically within 2–3 years, leading to the incurable and lethal form of the disease known as castration-resistant prostate cancer (CRPC). CRPC is characterized by disease progression despite low testosterone levels (< 50 ng/dL).[4,5]

In recent years, the treatment landscape of advanced PCa has evolved with the advent of next-generation AR-targeted agents such as enzalutamide, abiraterone, apalutamide, and darolutamide (Figure 1). These therapies have demonstrated significant survival benefits, especially in a combination setting with chemotherapies;[6,7] however, resistance still arises, underscoring the adaptability of AR signalling and the complexity of disease progression. Moreover, CRPC is increasingly recognized as a heterogeneous entity, with distinct molecular subtypes and varied clinical behavior, posing emerging therapeutic challenges.

AR continues to play a pivotal role not only in PCa development and progression, but also in therapeutic resistance. Understanding the mechanisms underlying AR-driven resistance is critical to improving patient outcomes, addressing current therapeutic limitations, and guiding future treatment strategies.

This narrative review aims to explore the key mechanisms through which AR signaling sustains tumor growth and mediates resistance to both conventional and next-generation androgen-targeted therapies in prostate cancer.

Androgen Receptor Expression, Structure and Signaling Pathway

Initially, CRPC was believed to be an AR-independent pathology due to the effectiveness of ADT in suppressing testosterone levels. However, it is now well established that AR expression is maintained in nearly all primary tumors, metastatic lesions, and castration-resistant tumors, regardless of disease stage or grade.[2,8] The persistence of AR expression in androgen-independent and CRPC cases underscores its continued significance as a therapeutic target, even in advanced disease stages. However, AR expression in the CRPC settings has been associated both with favorable and unfavorable risk.[2,9]

Androgens, such as dihydrotestosterone (DHT), bind to the AR, triggering a conformational change that causes the receptor to dissociate from heat shock proteins. This facilitates AR dimerization and translocation to the nucleus—a critical step in its function. Once inside the nucleus, AR acts as a transcription factor, regulating the expression of target genes, including androgen-responsive genes such as KLK3, the one related to prostate-specific antigen (PSA).[10]

The AR is a steroid receptor composed of three primary domains (Figure 2):

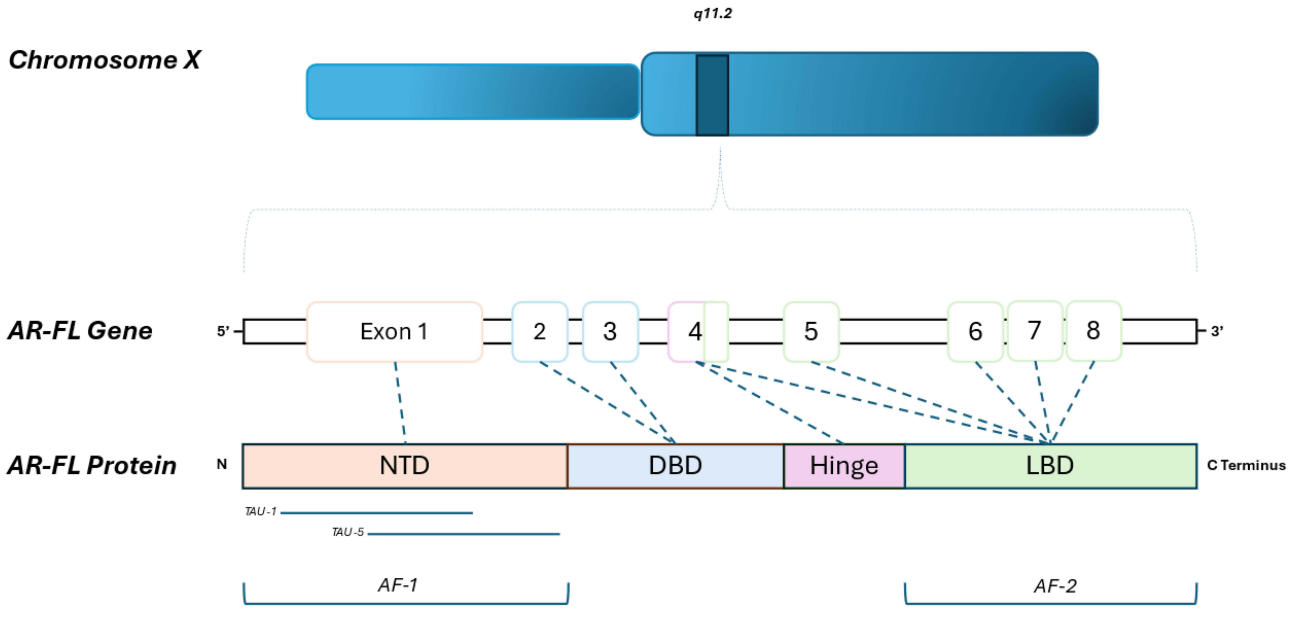

Figure 1 Timeline of key translational discoveries and therapeutic innovations in the treatment of PCa.
Abbreviations: ADT, androgen deprivation therapy; AR, androgen receptor; CRPC, castration-resistant prostate cancer; DHT, dihydrotestosterone; FDA, US Food and Drug Administration; GnRH, gonadotropin-releasing hormone; mCSPC, metastatic castration-sensitive prostate cancer; PCa, prostate cancer; PSA, prostate-specific antigen.

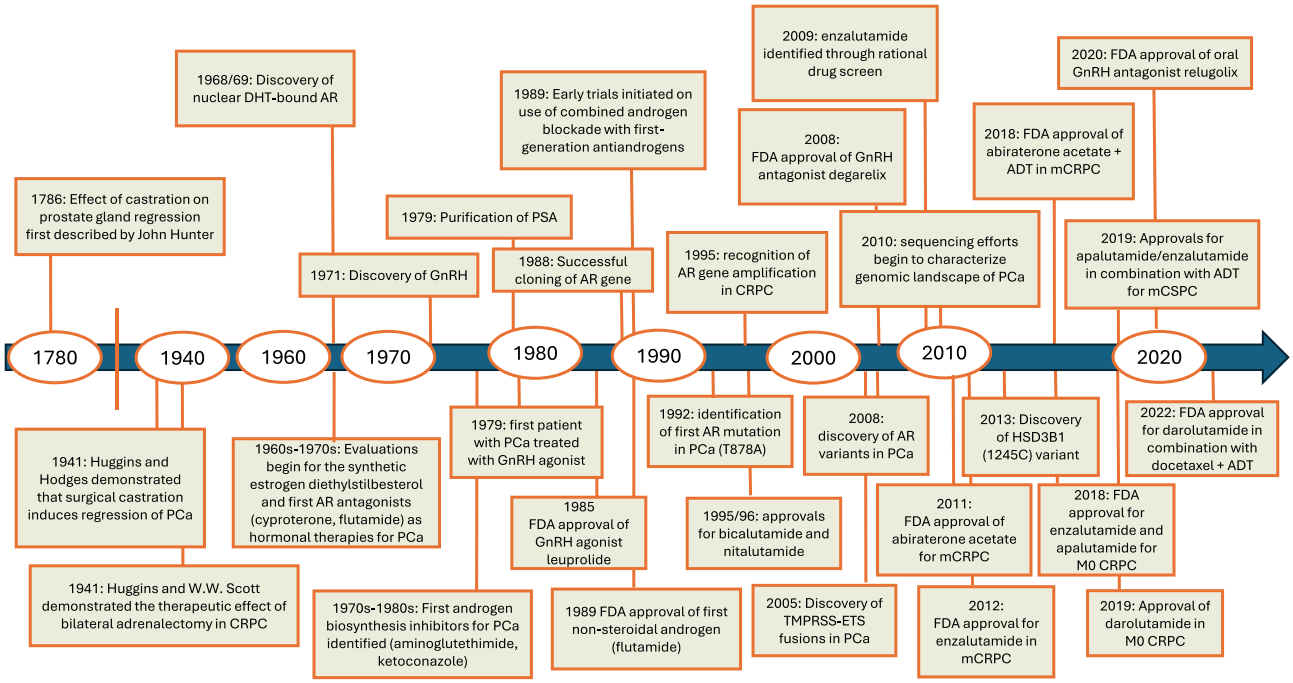

Figure 2 AR Gene and Protein structure.
Abbreviations: AF-1, activation function 1; AF-2, activation function 2; AR-FL, androgen receptor full length; DBD, DNA-binding domain; LBD, ligand-binding domain; NTD, N-terminal transactivation domain; TAU-1, transactivation unit 1; TAU-5, transactivation unit 5.

- N-terminal domain (NTD): contains 555 amino acids and polymorphic polyglutamine repeats that influence AR activity. Shorter repeats enhance transcriptional activity, while longer repeats reduce it.
- DNA-binding domain (DBD): responsible for recognizing androgen response elements, ensuring specificity in gene regulation.
- Ligand-binding domain (LBD): located at the C-terminus, this domain binds androgens like testosterone, inducing structural changes that activate AR.[11–13]

AR expression patterns vary across different cellular compartments of the prostate and play a crucial role in cancer biology. During normal prostate development, AR is absent in epithelial cells but highly expressed in stromal cells.[14] However, as prostate cancer progresses, AR expression in stromal cells significantly declines. Notably, AR stromal expression decreases linearly from low-grade to high-grade PCa, where it is almost entirely absent. While AR depletion is also observed in the epithelial compartment, it is less pronounced than in stromal cells.[15] Metastatic PCa lesions exhibit further reductions in AR stromal expression compared to primary tumors, and this decline is even more pronounced in CRPC compared to hormone-sensitive PCa.[16]

AR is not exclusively expressed in prostate cells; indeed, it is present in multiple tissues in both males and females, where it mediates vital regulatory functions. For example, AR plays a key role in bone mass acquisition and maintenance, muscle growth and development, and neuronal health and function.[17–19]

Altogether, these findings reinforce the centrality of AR signaling in prostate cancer pathogenesis, including in castration-resistant states. Despite initial assumptions of AR-independence in CRPC, AR expression persists across disease stages and anatomical sites, highlighting its enduring role as a therapeutic target. The receptor's domain architecture underpins its complex functional regulation, while its differential expression across stromal and epithelial compartments reflects dynamic changes during tumor progression. Beyond the prostate, AR maintains physiological relevance in diverse tissues, implicating its broader systemic role. These biological insights establish a foundation for understanding resistance mechanisms and for refining AR-targeted therapeutic strategies in advanced prostate cancer.

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Mechanisms of Resistance to Androgen Deprivation Therapy

The transition from hormone-sensitive PCa to CRPC is driven by multiple resistance pathways, allowing tumors to continue growing despite low androgen levels. These mechanisms can be broadly categorized into two alterations:

- AR-dependent, such as AR gene mutations, AR overexpression, and AR splicing, and
- AR-independent mechanisms (Table 1).

Androgen Receptor Dependent Mechanisms: Androgen Receptor Gene Mutations

AR gene mutations are detected in up to 60% of metastatic PCa cases.[20–22] Patients with metastatic PCa who receive AR antagonists exhibit a higher incidence of AR mutations compared to those treated with ADT alone.[23] While AR mutations are relatively rare in primary PCa, they can be present before ADT initiation or arise during treatment. In such cases, therapy-driven selection of these mutations may contribute to resistance.[24]

AR mutations primarily fall into two categories: i) mutations that convert AR antagonists into agonists, leading to unintended AR activation; and ii) mutations that broaden the receptor's ligand specificity, creating a "promiscuous AR" capable of binding to non-canonical steroids.

One of the major effects of common LBD mutations is antagonist-agonist switching, which explains the withdrawal syndrome observed in up to 15–30% of patients after discontinuation of first-generation AR antagonists.[25] Among these mutations, for example, T878A mutation has been reported to confer agonist properties to flutamide and nilutamide.[26] F877L mutation has been shown to transform enzalutamide and apalutamide into AR agonists in animal models and in metastatic CRPC patients resistant to apalutamide or enzalutamide.[27,28] This is particularly significant because F877L frequently coexists with T878A, especially following prolonged exposure to enzalutamide. While enzalutamide alone acts as a weak partial agonist for AR-F877L, its agonistic effect is significantly enhanced in the AR-F877L/T878A double mutation.[26,29] Conversely, darolutamide appears to retain its antagonistic properties against several clinically relevant AR mutations, including F877L, W742L, and T878A. Additionally, it functions as a full antagonist against

Table 1 Main Mechanisms of Androgen Receptor Pathway Dysregulation

Mechanism		How it Works
AR dysregulation	Mutations	Ligand-binding domain mutation (eg T878A, F877L) lead to AR ligand promiscuity or antagonist-agonist conversion.
	Overexpression	Often mediated by AR gene amplification or transcriptional activation or oncogene signalling (eg cMYC) enabling tumor growth despite androgen deprivation.
	Splice variants	Variants of gene that lack the ligand-binding domain (eg AR-V7, Arv567es) but retain transcriptional activity leading to resistance to some therapies like taxanes and antiandrogens.
AR-independent pathways	Glucocorticoid receptor compensation	Blockage of AR upregulates GR expression, leading to activation of similar AR-related genes enabling the resistance to AR-targeted therapies.
	Lineage Switching	During PCa progression, under pressure of ADT, cancer cells may acquire neuroendocrine features, resulting in a more aggressive, treatment-resistant PCa.
Intratumoral steroidogenesis		Castration resistance persists due to intratumoral androgen production via adrenal precursor steroids and the 5α-androstanedione pathway, bypassing testosterone. CYP17A1 inhibitors like abiraterone block androgen synthesis but may lead to precursor accumulation, activating AR.
Coregulators dysregulation	Coactivators	Steroid receptor coactivators and pioneer factors like FOXA1, HOXB13, GATA2 enhance AR signaling in CRPCa, promoting tumor progression in low-androgen environments.
	Corepressors	Loss or mutation of AR corepressors like SPOP, enhance AR signalling in CRPCa by deleting AR inhibition.

Abbreviations: AR, androgen receptor; GR, glucocorticoid receptor; PCa, prostate cancer; CRPCa, castration resistant prostate cancer; ADT, androgen deprivation therapy.

W741L and T877A, which are linked to bicalutamide resistance, and against F877L, which mediates enzalutamide and apalutamide resistance. In an in vitro study evaluating the response of AR antagonists to 68 different AR mutations in CRPC patients, darolutamide maintained efficacy against all full-length AR gain-of-function mutations, except AR-A587V.[30] In contrast, enzalutamide caused full or partial activation of eight different AR mutants. However, the clinical significance of the advantage of darolutamide remains uncertain due to the presence of multiple genetic alterations in tumors, the poor in vivo bioavailability of darolutamide, the cross-resistance mechanisms involving the Aldo-Keto Reductase 1C3 AKR1C3/AR-V7 pathway.[30,31] AKR1C3 is a key enzyme in intratumoral androgen biosynthesis, catalyzing the conversion of androstenedione to testosterone and estrone to estradiol. It is consistently overexpressed in CRPC, enabling local androgen production that sustains AR signaling despite castrate systemic levels. AKR1C3 activity compensates for upstream blockade, such as CYP17A1 inhibition by abiraterone, allowing tumors to bypass pharmacologic suppression of adrenal precursors. Elevated AKR1C3 also contributes to resistance to enzalutamide by restoring intratumoral testosterone levels. Beyond steroid metabolism, AKR1C3 reduces prostaglandin D2 to 9α,11β-PGF2α, promoting tumor proliferation via non-AR pathways. Its pleiotropic role highlights its relevance as both a therapeutic target and biomarker of resistance. Selective AKR1C3 inhibitors (eg, ASP9521, BAY1128688) have shown preclinical efficacy, though translation to clinical use is ongoing.[31,32]

Single-nucleotide point mutations, primarily occurring in the ligand-binding domain of the AR gene result in missense mutations. These mutations have been reported in up to 15–20% of CRPC cases.[33–35] These mutations reduce ligand specificity and increase AR transactivation, enabling the receptor to respond to alternative ligands even in a castrate setting. This not only sustains AR signaling but may also alter receptor behavior, activating a distinct set of genes that promote prostate cancer cell proliferation.[36] Studies of circulating tumor cell (CTC) DNA have identified a median of six AR mutations per patient, with the most prevalent being L702H, T878A, H875Y, W742C, and W743L.[37] These mutations were originally discovered in response to first-generation antiandrogens, flutamide and bicalutamide.[38] T877A, H875Y, L701H, and L702H mutations cause AR activation by glucocorticoids.[39] T878A mutation is a prototypical promiscuous AR mutation, allowing activation by progesterone, estrogens, and glucocorticoids.[40] Additionally, evidence suggests that T878A and similar mutations can recruit different coactivators depending on the ligand involved, further altering AR activity.[41] Approximately 30% of metastatic CRPC cases harbor the F877L mutation,[35] which enables AR activation by alternative ligands such as progesterone, dehydroepiandrosterone (DHEA), and androstenediol.[42,43] Abiraterone inhibits CYP17A1, blocking androgen biosynthesis in the testes, adrenals, and tumor microenvironment, thereby reducing ligand availability for androgen receptor (AR) activation. Galeterone extends this mechanism by combining CYP17A1 inhibition with direct AR antagonism and AR degradation, offering a multifaceted approach to suppress AR signaling, including in resistant prostate cancer phenotypes. Notably, while both agents can fully antagonize AR-F877L, some mutations—including F877L, L702H, and T878A—may still lead to abiraterone resistance.[44] Mutations in the AR-N terminal domain (NTD) account for approximately one-third of all AR mutations and primarily lead to increased AR transactivation activity, enhanced coactivator recruitment, changes in the interaction between the N and C termini, increased response to 5α-dihydrotestosterone, and greater AR protein stability and nuclear retention.[45]

In summary, AR gene mutations represent a critical mechanism of resistance in metastatic CRPC, particularly under the selective pressure of AR-targeted therapies. These mutations may either broaden ligand specificity or convert antagonists into agonists, sustaining AR signaling despite androgen deprivation. Notable mutations, including T878A and F877L, are frequently detected and can drive resistance to first- and second-generation antiandrogens. While newer agents such as darolutamide exhibit antagonistic activity across a broad spectrum of AR mutants, their clinical benefit remains uncertain due to pharmacokinetic limitations and the complexity of co-occurring resistance pathways. Understanding the mutational landscape of the AR is therefore essential to optimize therapeutic strategies and guide the development of next-generation AR inhibitors.

Androgen Receptor Dependent Mechanisms: Androgen Receptor Overexpression

Beyond genetic mutations, AR overexpression is another key mechanism of resistance, enhancing the receptor's sensitivity to minimal androgen levels. This allows PCa cells to sustain growth in low-androgen environments, promoting tumor survival during ADT. It remains unclear whether increased AR gene expression necessarily correlates with increased AR protein expression and AR target gene activation.[46]

The amplified AR regions typically include the AR gene locus and/or upstream enhancer regions near the transcription start site, the most common site of amplification. Recent research suggests that non-coding regions of the genome play a role in AR overexpression. Cell-free DNA sequencing of metastatic CRPC patients has frequently identified structural rearrangements and duplications in the AR upstream enhancer region, a hallmark of CRPC. Additionally, CDK12 mutations—which impair DNA repair and promote genomic instability—may contribute to AR amplification. CDK12 loss is linked to faster metastasis and reduced efficacy of androgen antagonists.[47–49]

AR overexpression is one of the most common alterations in CRPC, frequently mediated by AR gene amplification. Multiple studies have demonstrated that CRPC patients with AR gene amplification experience significantly shorter progression-free survival (PFS) than those without amplification.[50] However, some metastatic CRPC patients with AKT1/PIK3CA mutations exhibit fewer AR amplifications, suggesting that PIK3CA mutations may influence AR signaling.[51,52] In pre-treated CRPC tumors, AR amplification is observed in 17–57% of cases, whereas treatment-naïve tumors rarely exhibit AR copy number alterations.[20,22,24] Interestingly, AR overexpression occurs more frequently in patients who progress on enzalutamide compared to abiraterone or other agents (53% vs 17% or 21%; $p = 0.02$).[26] Recent studies by Spratt et al suggest that radiotherapy can activate AR gene expression, leading to enhanced cancer cell survival in vitro and accelerated disease progression in vivo.[53]

AR overexpression is being also explored as a potential biomarker for predicting low response rates to ^{177}Lu-PSMA -617 treatment.[54] While AR inhibition increases PSMA expression, leading to higher uptake of PSMA-targeted drugs (eg, ^{177}Lu-PSMA-617) and improved PET scan visibility, AR amplification reduces expression of the PSMA gene (FOLH1), lowering PSMA levels and impairing treatment efficacy. According to Sun et al, patients with AR amplification are 2.4 times less likely to achieve PSA responses following PSMA-ligand therapy.[55] In this context, 80% of patients with AR overexpression showed early disease progression, compared to only 20% with normal AR levels. Indeed, PFS was significantly shorter in AR-amplified patients (4.7 months vs 9.4 months; $p = 0.020$) and overall survival (OS) was also reduced (7.4 months vs 19.1 months; $p = 0.020$) compared to AR-non-amplified patients treated with ^{177}Lu-PSMA-617.[55]

AR expression can increase independent of gene amplification, for example through transcriptional upregulation. A key mechanism of ADT-induced AR upregulation has been identified, ie ligand-bound AR binds to a regulatory region in its second intron, suppressing its own expression; AR-targeted therapies disrupt this suppression, leading to increased AR transcription.[56]

Furthermore, AR transcription can be indirectly activated via oncogenic signaling. For example, c-MYC overexpression or other oncogenic pathways can increase AR transcription, leading to tumor progression despite minimal androgen stimulation Additionally, in vitro studies by Chen et al demonstrated that bicalutamide can act as an AR agonist in the presence of high AR mRNA levels, likely due to altered coactivator and corepressor recruitment at AR target gene promoters.[57]

In conclusion, AR overexpression—driven by gene amplification, structural rearrangements, or transcriptional dysregulation—constitutes a major mechanism of resistance in CRPC. This phenomenon enables sustained AR signaling under castrate androgen levels and is associated with poor clinical outcomes, including shorter PFS and reduced response to therapies such as enzalutamide and ^{177}Lu-PSMA-617. Mechanistically, AR overexpression can arise from enhancer amplification, CDK12 loss, or oncogenic pathway activation, independent of gene copy number alterations. These insights underscore the complexity of AR regulation in advanced prostate cancer and highlight the potential of AR overexpression as both a prognostic marker and a therapeutic challenge in the era of precision oncology.

Androgen Receptor Dependent Mechanisms: Androgen Receptor Splicing

In addition to full-length AR (AR-FL), several splice variants (AR-Vs) have been identified, with AR-V7 and ARv567es being the most common. AR-Vs arise due to aberrant splicing, where some of the eight exons are skipped, resulting in altered amino acid sequences. c-MYC, a well-known oncogene, plays a role in regulating the expression and activity of both AR-FL and AR-Vs.[58,59]

Some AR-Vs lack the LBD but retain the DBD, allowing them to activate gene transcription independently of androgens.[60] The presence of AR-Vs has been associated with a more aggressive disease phenotype, particularly in CRPC.

AR-V7 is commonly overexpressed in CRPC compared to hormone-sensitive PCa and is associated with poor prognosis, including an increased risk of biochemical recurrence after radical prostatectomy and shorter overall survival

(OS) in CRPC patients.[61,62] AR-V7 expression increases significantly following ADT, particularly after treatment with abiraterone or enzalutamide.[63] It is strongly linked to the upregulation of 59 genes that drive CRPC progression, including the coregulator HOXB13.[63]

AR-V7 and ARv567es have distinct transcriptional profiles compared to AR-FL. AR-V7 affects the expression of genes related to cell cycle progression, such as UBE2C.[64] In addition, the absence of a hinge region in AR-V7—a crucial site for microtubule binding—is thought to promote antiandrogen resistance, particularly to taxane-based chemotherapeutics. AR-V7-positive patients show higher resistance to taxanes, whereas those negative for AR-V7 but positive for ARv567es demonstrate greater sensitivity to these drugs.[65] In circulating tumor cells (CTC) analysis undergoing taxane chemotherapy, AR-V7-positive patients exhibited minimal reductions in nuclear AR levels during treatment, while AR-V7-negative, but ARv567es-positive patients showed a more pronounced decrease, suggesting that AR-V7 plays a more dominant role in taxane resistance.[65] Furthermore, AR-V7 has a unique gene regulatory pattern, distinct from AR-FL. While antiandrogens block AR-FL via the LBD, this inhibition enhances AR-V expression, contributing to CRPC resistance.[64,66] Indeed, apalutamide and darolutamide are designed to target AR-FL, but they do not appear to affect AR-V7 activity. One key resistance mechanism involves AKR1C3, an enzyme that converts weak androgens into testosterone and DHT.[31,32] AKR1C3 also stabilizes both AR-FL and AR-V7, leading to increased c-MYC levels and activation of AR target genes. Inhibition of AKR1C3 reduces both AR-V7 and c-MYC levels, restoring sensitivity to enzalutamide, abiraterone, apalutamide, and darolutamide.[31,32]

Finally, AR splice variants—particularly AR-V7 and ARv567es—represent a pivotal mechanism of therapeutic resistance in CRPC, enabling ligand-independent AR signaling. These variants, especially AR-V7, are linked to aggressive disease features, reduced taxane sensitivity, and resistance to AR-targeted agents such as abiraterone and enzalutamide. Their distinct transcriptional activity and the lack of a ligand-binding domain render conventional antiandrogens ineffective. Moreover, the involvement of AKR1C3 in stabilizing both AR-FL and AR-V7 and promoting c-MYC expression highlights a promising target for overcoming resistance. The detection and modulation of AR-Vs are therefore crucial components in the management and therapeutic personalization of advanced prostate cancer.

Androgen Receptor Independent Mechanisms: Role of Coregulators

The transcriptional function of the AR is finely regulated by a diverse group of over 150 coregulators, which can either promote (coactivators) or inhibit (corepressors) AR activity. These coregulators influence multiple processes, including RNA splicing, the assembly of transcriptional machinery, and post-translational modifications such as phosphorylation, methylation, or ubiquitination of other proteins within the transcription complex. Enhanced activity of coactivators, along with a diminished influence of corepressors, drives the progression of prostate cancer toward castration resistance.[67]

Coactivators

Steroid receptor coactivators (SRC-1, SRC-2, and SRC-3) play critical roles in abnormal AR signaling observed in CRPC cancer. All three SRCs often exhibit elevated expression levels even in early-stage prostate cancer, correlating strongly with disease progression and poor clinical outcomes.[68,69] This upregulation becomes even more pronounced in CRPC, enhancing AR signalling in low-androgen environments and supporting AR activation by alternative ligands. The clinical significance of SRCs is underscored by studies showing that SRC-2 overexpression in mouse prostate epithelium leads to prostate cancer development, while its depletion can effectively prevent CRPC.[70,71]

Other critical coregulators, termed pioneer factors—such as FOXA1, HOXB13, and GATA2—also play pivotal roles in prostate cancer progression.

FOXA1 regulates androgen-independent gene expression by functioning as an "opener" of condensed chromatin, thereby facilitating AR binding and enhancing transcriptional activity.[66] Although FOXA1 amplification is detectable in primary tumors, it is notably more common in metastatic CRPC and it is associated with poor outcomes and increased AR expression.[34,72] However, some studies suggest that the loss of FOXA1 might paradoxically enable androgen-independent AR binding to non-canonical chromatin sites, further enhancing AR signaling in CRPC. Thus, stable FOXA1 expression and activity may be crucial for maintaining prostate health.[73,74]

GATA2, another essential pioneer factor in AR signaling, plays a complex role in regulating AR function. It promotes the expression of both AR and AR splice variants; it is essential for AR's transcriptional activity; and it enhances the interaction between AR and chromatin.[75] Due to its oncogenic functions, GATA2 is frequently overexpressed in CRPC, and it is associated with poor prognosis. GATA2 also interacts closely and bidirectionally with FOXA1. While targeting FOXA1 is challenging due to its dual role in prostate cancer, inhibiting GATA2 may represent a more feasible therapeutic strategy, given its crucial role in driving CRPC growth.[76]

CBP and p300, two critical histone acetyltransferases, are also instrumental in AR activation. Disruption of p300/CBP function reduces AR transcriptional activity and inhibits tumor cell proliferation in prostate cancer models.[77]

To sum up, steroid receptor coactivators (SRCs), pioneer factors such as FOXA1, HOXB13, and GATA2, and chromatin modifiers like p300/CBP play essential roles in sustaining aberrant AR signaling in CRPC. Their overexpression or functional alterations contribute to enhanced AR transcriptional activity, androgen independence, and disease progression. In particular, SRC-2 and GATA2 have emerged as critical drivers of tumor growth and resistance, with evidence supporting their potential as therapeutic targets. The dynamic and context-dependent roles of FOXA1 highlight the complexity of AR co-regulation, suggesting that selectively modulating coregulator function may represent a promising avenue for disrupting AR-driven oncogenic programs in advanced prostate cancer.

Corepressors

Alterations in AR corepressors significantly contribute to CRPC development. For instance, loss-of-function mutations or deletions in nuclear receptor corepressors NCOR1 and NCOR2 are common in both primary prostate cancer and CRPC.[20,22] NCORs normally inhibit AR activity by competing with coactivators such as p300 and SRC-1 for binding to ligand-activated AR. Consequently, loss of NCOR function results in enhanced AR signaling in cancer cells.

Another critical corepressor, SPOP, functions as a tumor suppressor by promoting the degradation of AR and SRC-3, thereby reducing AR's transcriptional activity.[78] Mutations in SPOP impair its ability to interact with AR or SRC-3, leading to stabilization of these proteins. Notably, the SPOP-binding motif resides within the AR hinge domain; thus, AR splice variants lacking this region (such as AR-V2, AR-V5, AR-V7, and AR-V4) escape SPOP-mediated degradation, promoting CRPC progression.[79]

In conclusion, disruptions in AR corepressor function play a substantial role in facilitating CRPC progression by removing key inhibitory controls on AR signaling. Loss-of-function mutations or deletions in NCOR1 and NCOR2 diminish their competitive antagonism toward coactivators, thereby amplifying AR transcriptional activity. Similarly, mutations in the tumor suppressor SPOP lead to the accumulation of AR and coactivators such as SRC-3, further driving resistance. Importantly, AR splice variants lacking the SPOP-binding hinge domain evade this regulatory degradation, underscoring a mechanistic link between corepressor loss and the persistence of AR activity in advanced disease. These insights position AR corepressors as both mechanistic contributors to resistance and potential targets for therapeutic intervention in CRPC.

Androgen Receptor Independent Mechanisms: Role of Glucocorticoid Receptor

AR-independent resistance mechanisms also include bypass signaling pathways, in which alternative routes drive the expression of AR-related genes without directly activating AR signaling. The glucocorticoid receptor (GR) has emerged as a critical mediator of this process. Indeed, GR and AR share several transcriptional targets, and GR expression is notably high in prostate cancer cell lines lacking AR expression, suggesting GR can complement or substitute certain AR functions.[80] In patients undergoing androgen deprivation therapy (ADT), increased GR expression has been observed as a potential compensatory mechanism to bypass AR blockade, activating similar downstream target genes. Evidence points to a negative feedback loop: ADT-mediated repression of AR leads to enhanced GR expression. These findings highlight GR's significant role in promoting resistance through AR signaling bypass, emphasizing the need to better understand GR's function in castration-resistant prostate cancer (CRPC) and develop new therapeutic strategies targeting this pathway.[81,82]

To sum up, bypass signaling via the glucocorticoid receptor (GR) enables continued expression of AR-regulated genes despite AR inhibition. GR upregulation, particularly after ADT, represents a key escape mechanism in CRPC, reinforcing the need for targeted approaches to block GR-mediated resistance.

Androgen Receptor Independent Mechanisms: Lineage Switching

Lineage switching represents another AR-independent resistance mechanism, whereby prostate cancer cells under selective pressure from androgen receptor signalling inhibitors (ARSI) differentiate into alternative, treatment-resistant phenotypes, such as neuroendocrine prostate cancer (NEPC). Neuroendocrine differentiation is well documented in metastatic prostate cancer, occurring in approximately 25% of metastatic cases.[83–85]

Genetically engineered mouse models demonstrate that loss of tumor suppressors p53 and Rb is critical for spontaneous development of a neuroendocrine phenotype, closely mimicking human prostate cancer progression. Furthermore, ADT is thought to significantly contribute to this neuroendocrine transition, resulting in an aggressive, therapy-resistant prostate cancer subtype.[86]

In summary, lineage switching—particularly toward a neuroendocrine phenotype—represents a key AR-independent resistance mechanism in CRPC. Driven by selective pressure from AR-targeted therapies and loss of tumor suppressors like p53 and Rb, this transition results in an aggressive, treatment-resistant subtype observed in a substantial proportion of metastatic cases.

Androgen Receptor Independent Mechanisms: Steroidogenesis

Castration resistance can persist even under conditions of low circulating androgens. Intratumoral androgen levels in CRPC models are often elevated, indicating continued androgen production through alternative pathways involving the adrenal glands and prostate cancer cells themselves. Tumor cells frequently overexpress enzymes responsible for androgen synthesis, thus maintaining AR activation despite castration.

Initially, ADT induces gonadal testosterone depletion, thereby limiting the substrate available for conversion to dihydrotestosterone (DHT) by 5α-reductase. However, during disease progression, DHT synthesis predominantly originates from adrenal 19-carbon precursor steroids, which depend on the enzyme CYP17A1. Traditionally, the conversion from adrenal precursors to DHT was believed to require 5α-reduction of testosterone. However, recent data suggest an alternative pathway: androstenedione is converted by 5α-reductase into 5α-androstanedione, followed by further conversion into DHT.[87] Notably, this intracrine steroidogenesis is not restricted to the primary tumor but also occurs in distant metastatic sites.

Abiraterone, an inhibitor of CYP17A1, effectively blocks androgen synthesis in both adrenal glands and prostate tumors. Nonetheless, recent studies have shown that prostate cancer cell lines treated with abiraterone can accumulate steroidogenic precursors, which may activate AR without the CYP17A1-dependent conversion to testosterone, enabling continued tumor growth.[88] Interestingly, the potent AR antagonist RD162 has been demonstrated to inhibit this proliferation. This finding supports a therapeutic strategy combining CYP17A1 inhibitors like abiraterone with potent antiandrogens to prevent AR activation driven by steroid precursors.[89]

Altogether, intratumoral androgen biosynthesis enables persistent AR activation in CRPC, even under castrate conditions. Prostate cancer cells harness adrenal precursors and alternative steroidogenic pathways to produce DHT locally, including at metastatic sites. Although CYP17A1 inhibitors like abiraterone suppress androgen synthesis, residual steroid precursors may still activate AR, supporting the therapeutic potential of combining synthesis inhibitors with next-generation AR antagonists.

Conclusion

AR signaling plays a central role in the development and progression of CRPC. Multiple mechanisms contribute to resistance against ADT, including AR mutations, AR overexpression, splice variants, and alterations in co-regulatory pathways. While strong evidence links these mechanisms to CRPC progression, the clinical utility of AR splice variants and other AR-related biomarkers as tools for prognosis and therapeutic guidance remains controversial. Thus, although a deeper understanding of AR signaling is critical for enhancing therapeutic strategies in CRPC, translating these findings into clinical practice will require further validation to confirm their predictive value and ensure clinical applicability. Future research should focus on integrating molecular insights into prospective clinical trials to determine how AR-related biomarkers can inform personalized treatment approaches and improve patient outcomes.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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