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Targeting the Androgen Receptor and Overcoming Resistance in Prostate Cancer

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Abstract

Purpose of review: Prostate cancer is diagnosed in one out of every nine men and is the second leading cause of cancer death among men. While therapies targeting the androgen receptor are highly effective, development of resistance is universal and remains a major therapeutic challenge. Nonetheless, signaling via androgen receptor is frequently maintained despite standard androgen signaling inhibition. We review the current understanding of mechanisms of resistance as well as therapeutic approaches to improving treatment of prostate cancer via targeting of the androgen receptor.

Recent findings: Resistance to androgen-receptor-targeting therapies may be mediated by several mechanisms, including amplification, mutation, and alternative splicing of androgen receptor; intratumoral androgen synthesis; activation of alternative signaling pathways; and in a minority of cases, emergence of androgen-receptor-independent phenotypes. Recent trials demonstrate that intensification of androgen blockade in metastatic castration-sensitive prostate cancer can significantly improve survival. Similar strategies are being explored in earlier disease states. In addition, several other cellular signaling pathways have been identified as mechanisms of resistance, offering opportunities for co-targeted therapy. Finally, immune-based approaches are in development to complement androgen-receptor-targeted therapies.

Summary: Targeting the androgen receptor remains a critical focus in the treatment of prostate cancer.

Keywords

Prostate cancer; castration resistance; androgen receptor; androgen signaling inhibitors

Introduction

Prostate cancer (PCa) adapts to surgical or medical castration therapies (androgen deprivation therapy, ADT) that deplete testicular androgens by both increasing expression of androgen receptor (AR) and by increased intratumoral androgen synthesis. Therefore, although these tumors that relapse after castration are termed castration-resistant PCa

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Conflicts of Interest

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(CRPC), they are still largely AR- and androgen-dependent. Hence, they generally respond to agents that further decrease androgen levels by suppressing the synthesis of precursor steroids (CYP17A1 inhibitor abiraterone, ABI) or to direct AR antagonists such as enzalutamide (ENZ) or apalutamide (APA). Unfortunately, although at least transient responses can be obtained in the majority of patients, most men recur within 1-2 years. A major focus of PCa research is now on the mechanisms that are driving resistance to these newer androgen-signaling inhibitors (ASIs), and on therapeutic approaches that may enhance the efficacy of AR-targeted therapies.

Mechanisms Driving Resistance to AR-Targeted Therapies

The use of ASIs may be increasing the number of PCa that become AR-independent (see below), but persistent AR expression and activity in the majority of ABI/ENZ-resistant tumors suggests that AR is still important for tumor growth (Figure 1). Many of the mechanisms that contribute to AR activity in CRPC are also likely operative in ABI/ENZ resistance. One such mechanism is increased AR expression. Recent genomic sequencing studies have confirmed that the AR gene is amplified in over half of cases (1-5), although it is not yet clear whether the extent of AR gene amplification is further increased in response to ASIs. Significantly, recent studies have identified a potent amplified upstream AR enhancer that may be the major driver of increased AR expression (3, 6, 7).

Recurrent AR mutations that allow the AR to be activated by alternative ligands are also found in a subset of ABI-ENZ-resistant tumors. These include mutations in codons 875 and 878 that allow AR to be strongly activated by progesterone (which is upstream of CYP17A1 and markedly increased by ABI treatment), and a codon 702 mutation that allows activation by cortisol (1-5, 8). Codon 877mutation can allow activation by ENZ, but this has only rarely been detected in clinical samples, perhaps because a second mutation in codon 878 is required in order to obtain robust activation by ENZ (9).

One basis of increased intratumoral androgen synthesis is a common polymorphism that increases the stability of HSD3B1, which converts DHEA to androstenedione (10-12). This HSD3B1 variant can also increase the metabolism of ABI to an AR agonist, which may contribute to ABI resistance (13). More generally, persistent/increased intratumoral androgens could contribute to ENZ resistance as it is a competitive antagonist, and there is no clear evidence that ENZ gains partial agonist activity. Similarly, persistent androgen synthesis may contribute to ABI resistance (14, 15). However, several studies that have attempted to further decrease androgen levels, including ABI dose escalation (16), adding dutasteride to ABI (17), adding ABI to ENZ at time of ENZ resistance (18), or treatment with an AKR1C3 inhibitor (19), have not yet yielded evidence of efficacy. Nonetheless, it remains unclear whether AR activity in ABI/ENZ-resistant tumors is mediated by an unliganded or ENZ-liganded AR, by alternative ligands, or by low levels of androgen-liganded AR (which may be hyperactive due to posttranslational modifications, alterations in coactivator proteins, or in chromatin structure).

A further mechanism that can drive resistance to current AR-directed therapies, which all target the AR ligand binding domain (LBD), is expression of AR splice variants that contain

the transcriptionally active N-terminal domain (NTD) and DNA binding domain (DBD), but delete the LBD (20). Low levels of transcripts predicted to encode multiple such isoforms have been identified, but the major transcripts (which have been confirmed to encode proteins) are AR-V7 (which is most common) and ARv567es. Previous studies have shown that AR-V7 expression increases with progression to CRPC, and a series of recent studies found that AR-V7 expression in circulating tumor cells (CTCs) is associated with ABI/ENZ resistance (21-23). However, increased AR-V7 is associated with increased full length AR (AR-FL), and it remains unclear whether AR-V7 is a biomarker or also a driver (dependent or independent of AR-FL) of resistance. A recent study using a validated AR-V7-specific antibody has established that AR-V7 is very rarely expressed in primary PCa, but is expressed in ~75% of CRPC prior to ABI/ENZ therapy, and is further increased in ABI/ENZ resistance (24). Although all tumors that were AR-V7 negative responded to ABI or ENZ, 54% of the AR-V7 positive tumors also responded. Therefore, while AR-V7 detection in CTCs may be more predictive than in tissue, AR-V7 expression clearly does not preclude responses to ASIs, and its role as a biomarker remains to be clarified (25, 26).

The extent to which AR-V7 (or AR-FL) is driving ABI/ENZ resistance will not be clear until effective inhibitors are available. In addition to APA, there are several other new agents in clinical trials that target CYP17A1 and/or AR (including orteronel, seviteronel, and darolutamide), but there is no clear mechanistic basis by which they might be substantially better that ABI or ENZ. In contrast, several groups are developing novel agents that bind the AR LBD and target it to a ubiquitin ligase to drive AR degradation (27), with one such agent poised to enter clinical trials (ARV-110, Arvinas). To the extent that ABI/ENZ-resistant tumors are being driven by AR-FL (either as homodimers or possibly heterodimers with AR-V7), these agents may be very effective. There are also many efforts to develop agents targeting the AR NTD or DBD, which should be effective against AR-V7 and other splice variants, but this has proven very challenging (28-31).

While AR activity persists in most ABI/ENZ-resistant tumors, it is generally decreased, and additional mechanisms are likely decreasing AR dependence. One such mechanism is increased expression of glucocorticoid receptor, which can drive the expression of multiple pro-growth/survival genes, with some also being AR targets (32-35). Recent sequencing efforts have expanded the number of identified recurrently mutated genes in PCa, and shown that most (with the striking exception of *SPOP*) are more frequently mutated in metastatic CRPC (mCRPC) versus primary PCa (1-5). Significantly, with the exception of *APC*, all were enriched in mCRPC relative to metastatic castration-sensitive PCa (mCSPC), suggesting a role in progression to castration resistance. In addition to AR, the genes more frequently altered in mCRPC include *RB1*, *BRCA2*, *CCND1*, *KMT2D*, *KMT2C*, *FOXA1*, and *MYC*. These alterations may have direct or indirect effects on AR, and enhance tumor growth by AR-independent mechanisms.

A subset of PCa that recurs after castration, and particularly after treatment with ASIs, has low or absent AR expression and activity, may have neuroendocrine features including small cell histology and expression of genes such as *SYP* and *CHGA*, and is associated with genomic losses of *RB1* and *TP53* (36, 37) (Figure 1). A recent analysis of metastatic PCa biopsies, primarily from men progressing on ABI/ENZ, supports an association between

small cell histology, decreased AR expression/activity, neuroendocrine markers, and *RB1* loss, but show that these subsets are only partially overlapping (38). A second recent study examined tumors obtained through rapid autopsies from 2012-2016, versus a cohort prior to the introduction of ASIs (from 1998-2011), and found a doubling (6.3% to 13.3%) in the fraction of patients with neuroendocrine PCa (negative for AR/PSA and positive for SYP/CHGA) in the 2012-2016 cohort, and in addition these tumors were enriched for *RB1* loss (39). However, this study also found an increase in tumors that were AR- and SYP/CHGA-negative (from 5.4% to 23.3% in the latter period). Together these and other studies indicate that up to ~30% of late-stage ASI-resistant tumors may have minimal or no AR dependence, that ~15% may have neuroendocrine features, and that this latter group is enriched for *RB1* loss. However, the precise role of *RB1* or *TP53* loss, and of additional transcription modulators, in neuroendocrine differentiation is not yet clear (40-47). Unfortunately, therapies that can effectively target *RB1* and/or *TP53* loss are lacking, and it is not clear whether there are exploitable vulnerabilities conferred by neuroendocrine differentiation (48).

Therapeutic Approaches to Enhance Efficacy of AR-Targeted Therapies

Novel strategies for targeting AR include intensified androgen blockade in earlier disease settings, co-targeting other pathways, bipolar androgen therapy, and immuno-oncology approaches (Figure 2).

Intensified Androgen Blockade Earlier in the Disease

The addition of ABI to ADT for mCSPC improves overall survival (OS) (49, 50). An ongoing trial (NCT01957436) will test whether this strategy should be further intensified with the addition of docetaxel to ADT and ABI. Another trial (NCT01809691) will evaluate the effectiveness of orteronel in mCSPC. The addition of ABI even earlier may also be effective, such as in the pre-metastatic setting (50), although longer-term follow-up is needed.

The addition of AR antagonists for mCSPC (with or without docetaxel) is also under study in ongoing trials, including ENZ (NCT02446405, NCT02677896), APA (NCT02489318), and darolutamide (NCT02799602). Of note, a trial of combined docetaxel and APA in mCRPC (NCT03093272) is on hold due to concerns regarding pneumonitis, raising the possibility of unexpected toxicity. Finally, although adding ABI to ENZ at time of ENZ-resistance was not effective in mCRPC (18), the up-front combination of ABI and ENZ is being tested in mCSPC (NCT00268476).

Although the use and timing of ADT for “pre-metastatic” biochemically recurrent PCa (BCR) is controversial, intensified AR blockade is effective in nonmetastatic CRPC (nmCRPC) patients experiencing biochemical progression, particularly those with shorter PSA doubling times, as the addition of APA or ENZ to ADT improved metastasis-free survival versus ongoing ADT alone (51, 52). Metastasis-free survival was used as a surrogate for OS in these nmCRPC trials, but OS data are not yet mature. It is not certain that this strategy will be superior to starting these agents after development of metastatic

disease. In addition, up-front ABI with ADT for localized or BCR CSPC may be an alternative strategy (50), but longer follow-up is needed to assess effects on OS.

Recent studies have examined neoadjuvant intensive androgen blockade in men with high-risk localized PCa (53-56). While this reduces disease in the primary site, further follow-up will be needed to determine whether this translates into improved disease-free survival or OS, and whether recurrent disease is more aggressive. A similar strategy is being tested in very high-risk localized and oligometastatic PCa (NCT03436654). Molecular analysis of residual tumor in these cases may reveal mechanisms of resistance that can be used to guide adjuvant therapies or strategies for overcoming resistance in more advanced disease (57). Intensified androgen blockade is also under investigation in combination with primary radiation therapy for localized PCa (NCT02446444).

Therapies Targeting AR in Combination with other Pathways

The addition of docetaxel to ADT improved OS in mCSPC (58, 59), although the benefit is limited to patients with greater disease volume (60). Since intensified AR blockade appears to be effective even in low-volume mCSPC, an important question is whether patients who present with high-volume mCSPC are a molecularly distinct subset (rather than just patients who present later in their disease course), and whether there are biomarkers that might identify this subset. Disease volume may correlate with loss of tumor suppressor genes (61), but precise biomarkers and mechanisms of taxane sensitization are unclear. Currently, clinicians may offer ADT plus docetaxel or ABI to patients with high-volume mCSPC, and ADT plus ABI to patients with low-volume disease, understanding that both agents are likely to be used at some point in the disease course.

There is substantial cross-talk between AR signaling and multiple other pathways that might be exploited by combination therapies. DNA-damage repair (DDR) defects in ~20% of mCRPC can sensitize patients to platinum or PARP inhibitor therapy (62, 63). Monotherapy with PARP inhibitors (plus ongoing ADT) is increasingly becoming standard-of-care in DDR-deficient tumors, although better predictive biomarkers are imperative. ADT may also directly or indirectly (through G0/G1 arrest) impair DDR and/or impart PARP-dependence (64-69). One study tested the hypothesis that AR/PARP co-targeting with ABI and veliparib would improve outcomes (70). Surprisingly, adding veliparib did not improve responses over ABI alone, even in the DDR-deficient subset. In contrast, DDR alterations seemed to predict for better response to ABI with/without PARP inhibition, although this is not a consistent finding (71). Moreover, adding olaparib to ABI did improve responses in another phase 2 study (72).

PTEN loss and PI3K/AKT pathway activation are common in mCRPC and (depending on the model) can enhance or repress AR expression/activity. Unfortunately, PI3K inhibition alone has had little clinical efficacy, possibly due to dose-limiting on-target toxicity that might be addressed with isoform-specific inhibitors. Promising results were seen in the first-line mCRPC setting with ABI plus an AKT inhibitor (ipatasertib), suggesting earlier use of combination therapies in selected patients may be effective (73). There are a series of CDK4/6 inhibitor trials in mCRPC, including one of abemaciclib combined with ABI (NCT03706365), although by analogy with results in breast cancer, these agents might be

most effective if used earlier in CSPC together with aggressive androgen blockade. Additional compelling therapeutic targets in mCRPC that may interact with AR include BRD4 (74-79) and EZH2 (80, 81). The latter may also contribute to neuroendocrine differentiation (40, 82, 83), and EZH2 inhibition is being tested in ASI-exposed patients in combination with a second ASI (NCT03480646).

Bipolar Androgen Therapy (BAT)

The adaptive overexpression of AR in mCRPC may present a therapeutic vulnerability, as supraphysiological testosterone can cause growth arrest and death in PCa models with AR overexpression through transient DNA damage, downregulation of MYC, or enhanced expression of genes driving differentiation. Thus, alternating high and low testosterone ("BAT") may offer a therapeutic strategy in mCRPC, and PSA responses to BAT and ENZ re-challenge have been demonstrated (84). DDR alterations may especially sensitize PCa to BAT (85).

AR-Targeted Therapy and Immuno-Oncology

The impact of AR-targeted therapy on the immune milieu of PCa is complex and may include both pro- and anti-inflammatory effects. The dendritic cell vaccine sipuleucel-T conferred a survival benefit in the pre-ASI era, and trials are looking at combining ASIs with sipuleucel-T (NCT01981122, NCT01487863), and ADT with novel vaccines (NCT02649855, NCT02107391, NCT01696877, NCT01436968, NCT01496131) or ASI with novel vaccines (NCT01875250). Inhibition of CTLA-4 and PD-1/PD-L1 had disappointing results in advanced mCRPC, but more recent data suggest that there may be a subset of PCa that is responsive to this strategy (86, 87). Responses were seen with the addition of PD-1 inhibition in the setting of ENZ resistance (88), although one response was likely explained by microsatellite instability (89). PD-L1 expression appears to be higher in mCRPC versus primary PCa and more prevalent than previously appreciated (90, 91), but this may not predict responses. Moreover, castration may increase immune-suppressive cells in the tumor microenvironment (92), prompting trials of vaccines and checkpoint inhibitors in pre-castration/pre-ASI BCR (NCT02649439, NCT03637543). Of note, myeloid-derived suppressor cells may also drive development of CRPC, potentially targetable with IL-23 blockade (93).

Conclusion

The earlier use of intensive androgen blockade appears promising. AR appears to remain a therapeutic target in many men who progress to ABI/ENZ resistance, but the basis for its persistent activity is unclear and novel agents that directly or indirectly ablate AR activity are needed. ASIs are increasing the fraction of AR-independent tumors, a subset of which have neuroendocrine features, but loss of *RB1* and *TP53* in many of these tumors presents a major therapeutic challenge.

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Key Points

- Androgen receptor-mediated signaling remains a key driver of prostate cancer even after resistance to androgen receptor-targeted therapies.
- Several recently identified mechanisms may preserve androgen receptor signaling in the treatment-resistant setting.
- One potential approach is the use of intensive androgen blockade using androgen-signaling inhibitors in addition to conventional androgen deprivation therapy in earlier disease settings.
- Potential methods of treating castration-resistant disease include co-targeting of alternative pathways including DNA damage repair, PI3K/AKT, and epigenetic modifiers; bipolar androgen therapy; and a variety of immunomodulatory approaches in combination with androgen receptor-targeted therapy.

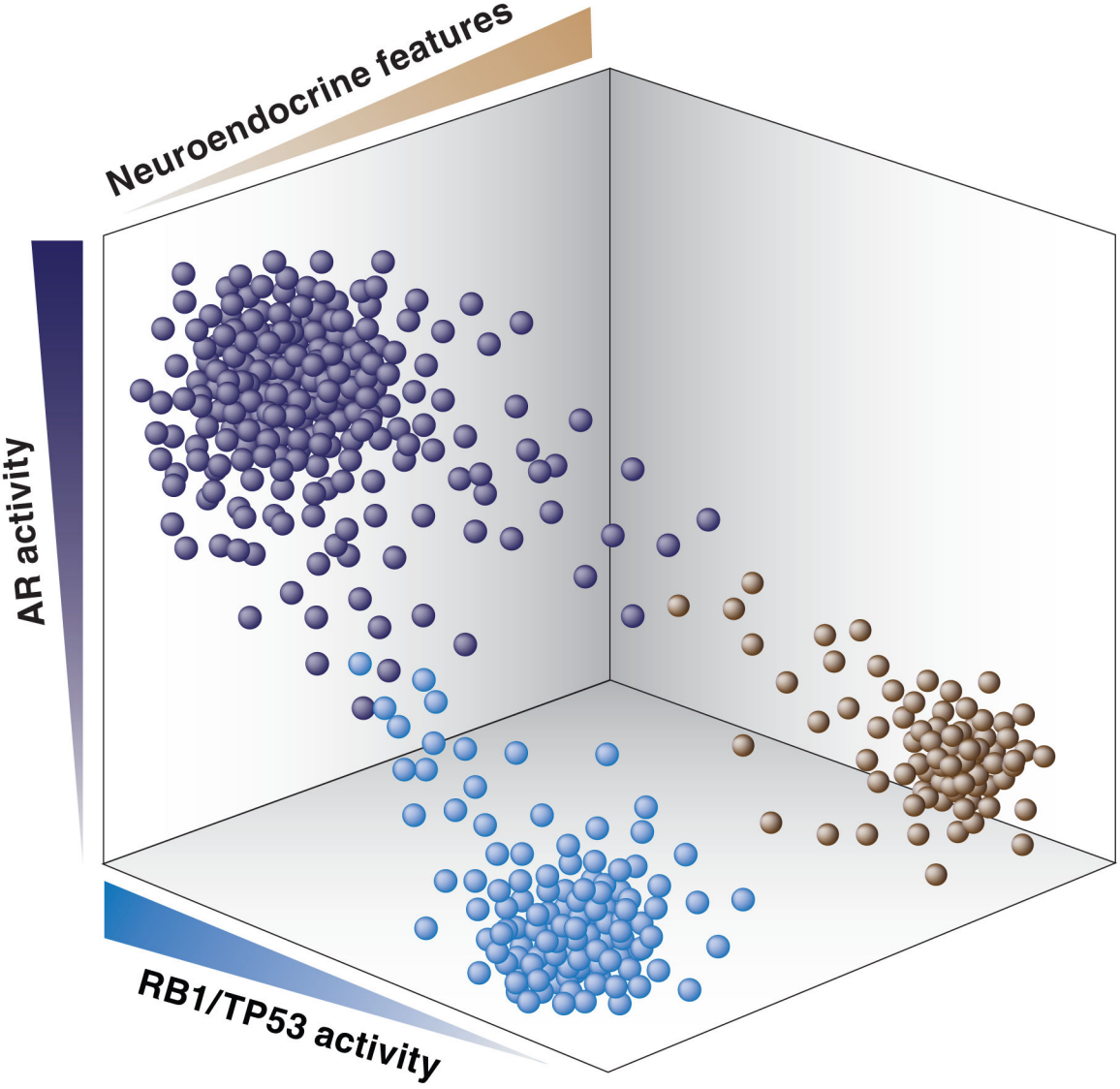

Figure 1. Landscape of AR activity, RB1/TP53 activity, and neuroendocrine features in advanced PCa.

Each dot reflects hypothetical level of AR activity, RB1/TP53 activity, and neuroendocrine differentiation in an individual advanced tumor that is resistant to AR targeted therapies.

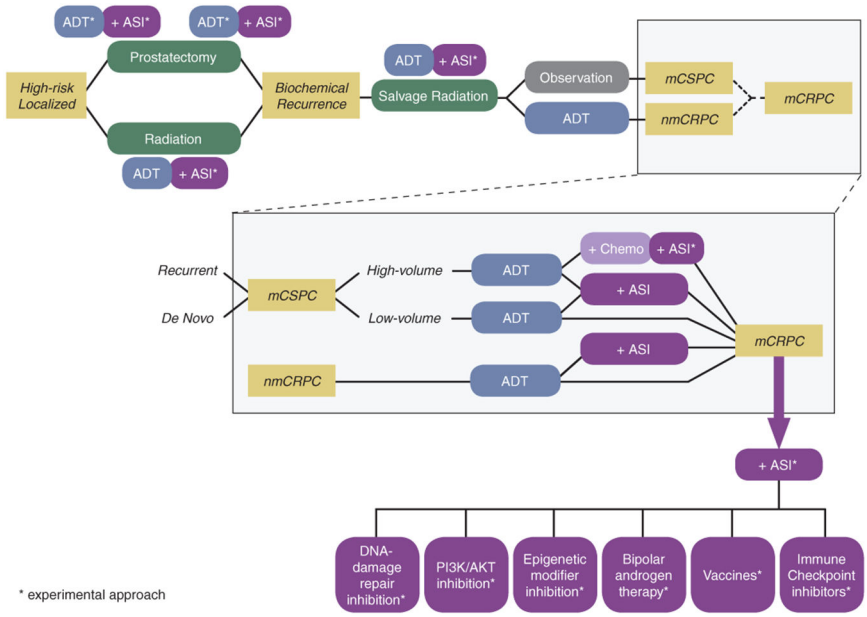

Figure 2.
Standard and experimental approaches to target AR across the spectrum of PCa.