[Review]

Role of the Androgen-Androgen Receptor Axis in the Treatment Resistance of Advanced Prostate Cancer: From Androgen-Dependent to Castration Resistant and Further

Naohiro FUJIMOTO*

Department of Urology, School of Medicine, University of Occupational and Environmental Health, Japan. Yahatanishi-ku, Kitakyushu 807-8555, Japan

Abstract **:** After the introduction of prostate-specific antigen (PSA) screening, prostate cancer diagnosis has shifted to early and curative stages, although 10-20% of patients still present with metastatic and incurable cancer. Prostate cancer is androgen-dependent, and most patients with prostate cancer initially respond to androgen deprivation therapy (ADT). After 1-2 years of the treatment, advanced prostate cancer eventually progresses to castration resistant prostate cancer (CRPC). A variety of mechanisms of progression from androgen-dependent prostate cancer to CRPC under ADT have been postulated, and the key pathway is re-activation of the androgen-androgen receptor (AR) axis, for example, caused by AR mutation/overexpression/splice variants, altered expression of AR cofactors, and increased production of androgens. Recently approved new agents, such as the hormonal agents abiraterone and enzalutamide and the chemotherapeutic agent cabazitaxel, have demonstrated survival benefit in men with CRPC. However, the prolongation of survival times provided with these agents is limited because of the treatment resistance. Androgen-AR axis still plays a pivotal role in the resistance to the new agents for CRPC. To improve the prognosis of patients with CRPC, intensive research to identify effective agents, treatment strategies, and useful predictive biomarkers to select the patients who can benefit from such treatments are required. Additional clinical data, with a better understanding of the biology of CRPC, may provide better CRPC treatment outcomes. This article reviews the underlying mechanisms of treatment resistance and future direction of CRPC treatments.

Keywords **:** prostate cancer, castration resistance, treatment resistance, androgen, androgen receptor.

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Introduction

Prostate cancer is the most commonly diagnosed cancer and the second leading cause of cancer-related deaths among men in the United States. In Japan, the number of patients with prostate cancer has been increasing. The National Cancer Center of Japan predicted that 98,400 men would be diagnosed with prostate cancer in 2015 accounting for the highest incidence of cancer among males [1].

After the introduction of prostate-specific antigen (PSA) screening, prostate cancer is being detected and treated at an early stage, although, 10−20% of patients still present with advanced stages at diagnosis. Androgen and its cognate receptor, androgen receptor (AR), are the pivotal and key factors for the development of not only normal prostate but also prostate cancer. Therefore, androgen deprivation therapy (ADT) is very effec-

*Corresponding Author: Naohiro FUJIMOTO, MD, PhD, Department of Urology, School of Medicine, University of Occupational and Environmental Health, Japan. Yahatanishi-ku, Kitakyushu 807-8555, Japan, Tel: +81-93-691-7446, Fax: +81-93-603-8724, e-mail: n-fuji@med.uoeh-u.ac.jp

tive for treating prostate cancer. For metastatic prostate cancer, ADT has been the mainstay of treatment since the pioneer work by Huggins and Hodges in 1941 [2]. Most patients with prostate cancer initially respond to ADT and ADT has yielded a median overall survival (OS) of longer than 40 months even in men with metastatic prostate cancer. However, the curative potential of ADT is very limited and virtually all patients progress to castration-resistant prostate cancer (CRPC) that is defined by rising PSA and/or clinical progression despite systemic androgen depletion. Despite the advances in the treatments with new agents, CRPC still remains incurable.

The discovery of the resistant mechanisms of prostate cancer to ADT has resulted in the development of effective therapeutic strategies for CRPC and recently developed, novel agents have demonstrated survival benefit [3]. However, treatment resistance to novel agents may eventually emerge. To explore the effective treatment strategies, an understanding of the treatment resistance is mandatory. Although a variety of mechanisms are involved, it is obvious that AR signaling remains a pivotal driver of prostate cancer progression before as well as after progression to CRPC. During the treatments, prostate cancer cells are under strong selective pressure to maintain AR activity. In this review, the resistant mechanisms of prostate cancer to ADT and novel agents, particularly AR-related mechanisms, are discussed.

1. Resistant mechanisms to primary androgen deprivation therapy (ADT)

Possible underlying mechanisms of prostate cancer progression under ADT are listed in Fig. 1.

1) androgen receptor (AR)-related mechanisms

a) Increased intra-cellular androgens

In men approximately 80% of androgen is produced by the testes. Surgical or medical castration by lutenizing hormone-releasing hormone (LH-RH) agonists or antagonists effectively inhibits circulating androgens. However, intraprostatic dihydrotestosterone (DHT) level, which is a more potent androgen than testosterone, decreases only by 40% [4]. In addition, CRPC tissues overexpress androgen-synthetic enzymes and have higher intra-tumoral androgens levels than those in androgen-sensitive tumor by active conversion of circulating adrenal androgens and *de novo* androgen synthesis [5, 6]. These androgens activate AR, resulting in progression of prostate cancer under castration.

Androgens and cholesterol, a precursor of androgens, are actively transported into the cells by membrane-transporting peptides such as organic anion-transporting polypeptides (OATPs). The single nucleotide polymorphisms (SNPs) of *SLCO* genes, which encode OATP, alter cellular uptake of androgens [7, 8]. The active form of *SLCO2B1* is associated with prostate cancer progression under ADT [9]. Patients with prostate cancer with

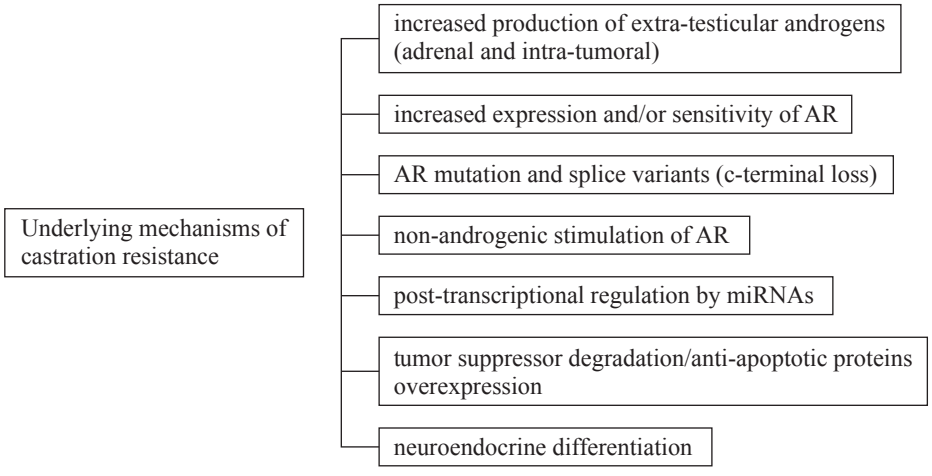

Fig. 1. The putative underlying mechanisms of resistance to androgen deprivation therapy.
AR: androgen receptor, miRNAs: microRNAs.

the active form of *SRD5A2*, encoding 5α-reductase type 2 that converts testosterone to the more potent androgen DHT, have worse survival when treated with ADT [10]. Increased intra-cellular androgen activates AR in cancer cells and aids in the survival of cancer cells under ADT.

b) Increased expression of AR

AR gene amplification and/or protein overexpression are commonly observed in CRPC tissues [11]. Unlike normal cells, AR-overexpressed cells have the ability to respond to very low androgen levels. In addition, overexpression of AR can convert an antiandrogen, bicalutamide, from an antagonist to an agonist [12].

c) AR mutation and splice variants

Mutations are frequently observed in the AR gene. Mutations in the hinge and the ligand-binding domain (LBD) confer increased transcriptional activity and reduced ligand specificity. Other steroid hormones, such as estrogens, progesterone, or glucocorticoid, can activate the mutated ARs [13−17]. Specific point mutations in LBD of AR convert AR antagonists into agonists. For example, antiandrogen flutamide and bicalutamide activate ARs with mutation at codons 877 (T877A) [15, 17] and 741 (W741C) [18], respectively. In general, prostate cancers expressing AR mutations are activated by the therapeutic agents. In other words, these AR mutations occur under the pressure of the treatments [19].

Compared with androgen-sensitive cancer, truncated AR splice variants (ARVs) increase in CRPC. Most frequently detected ARVs are AR-V7 [20] and ARv456es [21]. These ARVs lack LBD that is the target of current antiandrogens and are thus constitutively active. Thus, these ARVs promote prostate cancer progression even without any androgens. ARVs can also facilitate nuclear localization of full-length AR and its activation of its target genes [20, 21].

d) Altered expression of AR coregulators

The nuclear receptors, including AR, require coregulators for efficient transcriptional regulation [22]. AR coactivators and corepressors can enhance and repress the AR transactivation, respectively. In the presence of AR coactivators, AR can exert enough transcriptional activity even at very low androgen levels [23]. Prostate cancer cells express AR coactivators and expression levels of AR coactivators increase in CRPC [24−26]. Therefore, prostate cancer cells can become androgen-hypersensitive during the process of progression.

e) Non-androgenic activation of AR

Androgens, as well as growth factors and cytokines, activate AR. For example, epidermal, keratinocyte and insulin-like growth factors, interleukin 6 protein kinase A and C: mitogen-activated protein kinase and Her2/neu can activate AR [27]. These signaling pathways and their interaction with AR play a role in prostate cancer progression.

f) AR regulation by microRNAs (miRNAs)

Recent studies have indicated that non-coding RNAs are differentially expressed in each stage of prostate cancer. miRNAs regulate gene expression at post-transcriptional or translational levels and reactivate AR [28, 29]. The regulation of AR by non-coding RNAs may confer the treatment-resistance to prostate cancer cells.

2) AR-unrelated mechanisms

Mechanisms unrelated to AR also play a role in the progression of prostate cancer. Tumor suppressor degradation/anti-apoptotic proteins overexpression, and neuroendocrine differentiation are associated with the resistance to ADT [30].

2. Treatments for CRPC

Several drugs, such as estramustine phosphate and glucocorticoids, have been used for treatment in patients with CRPC. These treatments have demonstrated various clinical benefits, namely PSA reduction, radiological response, pain relief, and improvement in the quality of life. However, none of them showed the survival benefit. In 2004, TAX327 [31] and southwest oncology group (SWOG) 9916 [32], the large-scale phase 3 clinical trials, demonstrated for the first time a survival advantage for CRPC treated with docetaxel (DTX). Although DTX has become a standard treatment for CRPC, the difference in OS between DTX and placebo groups was less than 3 months. Abiraterone

acetate (AA) [33, 34], enzalutamide (EZL) [35, 36], sipuleucel-T [37], cabazitaxel (CBZ) [38], and radium 223 [39] have recently emerged as novel therapies for treating CRPC. Phase 3 clinical trials evaluating the efficacy of these five agents, with different mechanisms of action, demonstrated that they all improved OS.

In 2014, the androgen and AR targeting agents, AA and EZL, and the chemotherapeutic agent, CBZ, were approved as therapeutic agents for CRPC in Japan. AA inhibits androgen synthesis in the adrenal gland, testes, and within the prostate cancer tissue by inhibiting CYP17A1 and 17α-hydroxylase/C17,20 lyase, which are critical enzymes for androgen biosynthesis. Because androgen levels are maintained by overexpression of androgen synthesis enzymes in the CRPC tissues [5, 6], further suppression of androgen production in patients with CRPC receiving ADT by administering AA is anticipated to result in a clinical benefit [33, 34, 40]. A large-scale, phase 3 clinical trial demonstrated that AA treatment provided a survival benefit in the post- and pre-DTX setting. AA combined with prednisone in men with metastatic CRPC, who received DTX (COU-AA 301 trial) prolonged the OS compared with that in men in the control group (median OS 15.8 vs 11.2 months: $P < 0.0001$) and the PSA response rate and progression-free survival (PFS) were all favored in the AA over the placebo group [33, 41]. In the pre-DTX setting (COU-AA 302), OS was significantly longer in the AA group than in the control group (median 37.4 vs 30.3 months: $P = 0.0033$) [34]. EZL was selected based on its activity in AR-overexpressing cells and as it was a more potent antiandrogen than the first generation antiandrogen, bicalutamide. EZL has a higher affinity for AR than bicalutamide and has a distinct mechanism of action. For example, EZL inhibits AR nuclear translocation, recruitment of AR coactivators to the receptor, and AR binding to its regulatory target genes [42]. EZL treatment induces a shift from nuclear to cytoplasmic AR subcellular localization [43]. The phase 3 clinical trial in men with CRPC in the post DTX-setting (AFFIRM trial) showed superiority for EZL vs placebo (media OS 18.4 vs 13.6 months: $P < 0.001$). Compared with the placebo group, PSA and radiologic objective response, quality of life response, PFS, and time to first skeletal-related event all favored in the EZL group [35, 44]. PREVAIL study that compared the effects of EZL and placebo in patients with DTX-naïve CRPC also demonstrated the superiority of EZL vs placebo. Estimated median OS was 32.4 and 30.2 months in the EZL and placebo groups, respectively, with EZL treatment decreasing the risk of death by 29% hazard ratio (HR): 0.71: $P < 0.001$) [36]. These favorable results suggest that androgen-AR axis-targeting agents are effective and that CRPC still remains in part an androgen-driven cancer after progression on castration and/or chemotherapy.

CBZ is a new generation taxane developed to overcome resistance to DTX. CBZ has less affinity to P-glycoprotein, the cellular drug efflux system, than DTX, resulting in being active in DTX-resistant cells [45]. In the TROPIC study, a phase 3 clinical trial, CBZ demonstrated a survival benefit of CBZ in men with CRPC who had progressed during or after treatment with a regimen that included DTX. CBZ resulted in longer median OS than the placebo (15.1 and 12.7 months: $P < 0.001$). PFS and time to progression also favored in CBZ [38].

3. Resistance to new agents

Although AA, EZL, and CBZ showed survival benefit in patients with CRPC, prolongations of OS obtained by these agents were only several months. Resistance to novel agents eventually occurs during the treatment and prostate cancer progresses in almost all patients. Identifying the resistant mechanisms is necessary for developing more effective treatment strategies. Accumulating evidence indicates that androgen-AR axis still plays an important role in resistance to the new hormonal agents, AA and EZL (Fig. 2).

A strong inhibition of androgen may induce AR overexpression and ARVs. AA increases AR expression [46] and induces ARVs, such as ARV7 [47, 48]. Because ARVs lacking LBD are active in the absence of any androgen, AA is not effective. Although AA itself does not activate wild-type and mutated AR, double mutations in AR (T877A + L701H) can be activated by glucocorticoids which is required to combine with AA [14, 49, 50]. AA induces mutation in a catalytic enzyme in steroidogenesis, 3β-hydroxysteroid dehydrogenase 1 (3β-HSD1), which converts dehydroepiandrosterone to DHT. AA-induced mutation of 3β-HSD1 (N367T) con-

fers enzyme resistance to ubiquitination and degradation, resulting in intracellular accumulation of 3β-HSD1 and increased DHT synthesis [51]. AA also increases intratumoral CYP17A1 mRNA [52].

EZL induces AR expression [46] and increases androgen levels in the serum and bone marrow [43]. EZL induces AR mutation (F876N), which is in turn activated by EZL [53, 54]. ARVs are also induced by EZL. Patients with ARV7 showed significantly unfavorable responses to EZL as well as to AA [47]. EZL may also induce overexpression of the glucocorticoid receptor (GR) in prostate cancer cells, and GR overexpression activates AR target genes [55]. Upregulation of clusterin [56], protein kinase C (PKC) phosphorylation/Twist1 [57], Y-box binding protein 1 (YB-1) activation and Her2 [58], and phosphatidylinositol-3 kinase- (PI3k-AKT) pathways [59] have also been suggested as mechanisms of EZL resistance.

Many kinds of new agents are being developed and over 150 clinical trials enrolling patients with CRPC are currently being conducted. ARN-509 is a more potent antiandrogen than EZL and shows activity in AR-overexpressing cells [60] and AA-pretreated patients with mCRPC [61]. EPI-001 and its derivative EPI-506 and Galeterone (TOK001) target the N-terminal domain of AR and can inactivate ARV7 and ARv567es as well as full-length AR and inhibit the growth of prostate cancer cells [62−64]. Therefore, these agents may be effective in patients with ARV-expressing CRPC. These novel treatments may overcome the treatment resistance and improve the prognosis of men with CRPC.

Although identification of predictive biomarkers is mandatory to select the right therapy for the right patient, it remains elusive. Tumor biopsy provides useful information, but the procedure is invasive and risky and some lesions are technically difficult to access. In addition, biopsy lesion may not represent the main character of the cancer. Recently, liquid biopsy, either using circulating tumor cell or cell-free DNA, has been developed. Information about the status of AR or androgen-synthetic enzyme obtained by these less invasive methods can predict treatment results in patients with CRPC [47, 65].

Conclusion

The use of novel agents for prostate cancer has improved clinical outcomes. However, resistance to these agents is inevitable and CRPC is still incurable. Combination of currently available drugs and the development

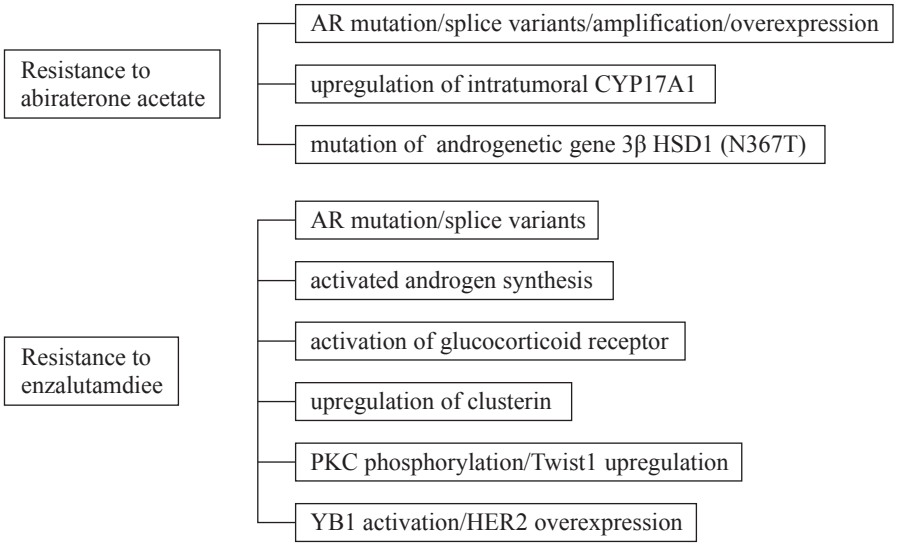

Fig. 2. The putative underlying mechanisms of resistance to abiraterone and enzalutamide. AR: androgen receptor, 3βHSD1: 3β-Hydroxysteroid dehydrogenase 1, PKC: protein kinase C, YB1: Y-box binding protein 1.

of effective agents that overcome evolving treatment resistance may improve survival. It is anticipated that continued intensive researches exploring novel treatment strategies and predictive biomarkers to identify patients who would benefit from each treatment will open a new window for the new future of CRPC treatment.

Conflict of Interest

The author has no conflicts of interest to declare.

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前立腺癌進展におけるアンドロゲン–アンドロゲン受容体の役割

藤本　直浩

産業医科大学　医学部　泌尿器科学講座

要　　旨：Prostate-specific antigen（PSA）スクリーニングの導入により, 前立腺癌は早期に発見されるようになったが, 10から20%は診断時にすでに進行癌である．前立腺癌はアンドロゲン感受性癌であり, 多くの患者において初期治療としてのアンドロゲン除去療法（ADT）が有効である．しかし, 1〜2年で多くの進行癌患者は去勢抵抗性前立腺癌（CRPC）となる．アンドロゲン依存性癌からCRPCに進行する機序としては多くの機序が報告されているが, アンドロゲン–アンドロゲン受容体（AR）の経路がもっとも重要である．これにはARの遺伝子変異, 発現増強, 変異型ARの出現, AR共役因子の発現増強, アンドロゲンの産生増加などがある．ホルモン剤であるアビラテロン, エンザルタミド, 抗癌剤であるカバジタキセルなどのCRPCに対する新規薬剤が開発され, 臨床試験においてCRPC患者の生存期間の延長が示された．しかし, そのような新規薬剤に対しても前立腺癌は抵抗性を獲得して進行し, これらの新規薬剤による生存の延長期間は限られている．アンドロゲン–AR経路は新規薬剤に対する抵抗性においても中心的な役割を担っている．CRPC患者の予後を改善するためには, 有効な薬剤および治療法の開発, さらにそれぞれの患者に対してもっとも適切な治療法を選択するためのバイオマーカーの開発などの精力的な研究が必要である．CRPCの生物学的特徴を理解したうえでの臨床試験の蓄積により予後の改善が可能であろうと期待される．本総説では, 前立腺癌の治療抵抗性とCRPC治療の今後について述べる．

キーワード：前立腺癌, 去勢抵抗性, 治療抵抗性, アンドロゲン, アンドロゲン受容体.

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