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REVIEW

Review of novel therapeutic medicines targeting androgen signaling in castration-resistant prostate cancer

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Abstract

Prostate cancer is the most common male malignant neoplasm. Androgens and the androgen receptor (AR) play a key role in the onset and progression of prostate cancer. The expression of the AR is still preserved in the majority of patients with castration-resistant prostate cancer (CRPC). CRPC is considered to be induced by the following mechanisms: (1) sustained AR activation by enhancing intracellular conversion of adrenal androgens to dehydrotestosterone *via* a *de novo* route; (2) AR hypersensitivity; (3) promiscuous activation of AR signaling; and (4) outlaw pathways. Recent advances in the treatment of CRPC include novel medicines targeting AR signaling pathways. In addition, functional molecular studies have shown that some of the AR-regulated genes and AR coregulators are prognostic markers and potential therapeutic targets for prostate cancer, particularly in the castration-resistant state. Therefore, identification of the AR signaling pathways responsible for establishment of CRPC is critical for developing new strategies for the treatment of CRPC.

Key words: Androgen receptor; Prostate cancer; Pyrrole-imidazole polyamide

Core tip: Prostate cancer is the most common male malignant neoplasm. Androgens and the androgen receptor (AR) play a key role in the onset and progression of prostate cancer. The expression of the AR is still preserved in the majority of patients with castration-resistant prostate cancer (CRPC). Therefore, identification of the AR signaling pathways responsible for establishment of CRPC is critical for developing new strategies for the treatment of CRPC.

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INTRODUCTION

Prostate cancer has been the most common male malignant neoplasm for more than 30 years and is the second leading cause of cancer-related death of men in the United States[1]. In Japan, partially because the diet seems to

be becoming Westernized, the incidence of prostate cancer has been increasing. The population of older males is also becoming larger and may also be a contributor.

Androgens and the androgen receptor (AR) play a key role in the onset and progression of prostate cancer. Functional ARs are expressed during various stages of prostate carcinogenesis, from prostate intraepithelial neoplasia to locally advanced primary tumors. Approximately 80%-90% of prostate cancers are androgen-dependent at the time of diagnosis[2-4].

Since the discovery that the progression of prostate cancer could be inhibited by castration in the 1940s[5,6], hormonal therapy that specifically inhibits AR activity by using a luteinizing hormone-releasing hormone analog/antagonist, with/without anti-androgens [androgen deprivation therapy (ADT)] has become the most effective and widely used palliative method for advanced and/or metastatic prostate cancer[7-9]. In the majority of patients, although ADT leads to a biochemical response for up to 3 years, prostate cancer eventually continues to progress through cell transformation. Previously, these conditions were known by various names over the years, including hormone-resistant prostate cancer and androgen-insensitive prostate cancer. However, most recent reports indicate that AR is still expressed in the majority of ADT resistant cases, and expression of AR target genes, such as prostate-specific antigen (PSA), remains persistently high despite serum testosterone in the castrated range after surgical castration or ADT[9-11]. This condition is called castration-resistant prostate cancer (CRPC)[12]. Patients with CRPC demonstrate poor prognosis associated with a deterioration in the quality of life, and few therapeutic options are currently available[13]. Therefore, it is important to understand the AR signaling pathway to develop an effective treatment for CRPC. In this review, we summarize the roles of the AR signaling pathway and novel therapeutic medicines that target this pathway in prostate cancer. We focus in particular on functional analyses of AR targets and indicate future directions for their therapeutic use.

AR STRUCTURE

The *AR* gene is a member of the steroid hormone receptor superfamily, which includes genes encoding receptors for estrogen, progesterone, glucocorticoids, mineralocorticoids, vitamin D, retinoic acid, and the retinoid X receptor. Similar to many other steroid receptors, the AR is characterized by a modular structure consisting of distinct functional domains: a poorly conserved N-terminal domain (NTD; 555 amino acids coded by exon 1), a highly conserved DNA-binding domain (DBD; 68-amino acid coded by exon 2 and 3), a hinge region, and a moderately conserved ligand binding domain (LBD; 295 amino acids coded by exons 4-8)[14]. The AR NTD contains the major transactivation function of the AR, which is known as activation function (AF)-1, and consists of two transcriptional activation units (TAU): TAU-1 and TAU-5[15]. AF-1 interacts with the LBD, the basal transcription factors transcription factor ⅡF (TFⅡF) and TFⅡH, members of the p160 family of nuclear receptor coactivator proteins and the general coactivator cAMP response-binding protein-binding protein[16-28]. These reports also indicate that AF-1 is one of the major domains responsible for mediating AR transcriptional activity.

The DBD has important roles in mediating AR nuclear localization, homodimer formation, and specific DNA binding. The activated AR binds as a homodimer to specific DNA sequences called androgen response elements (AREs) located around the target genes[29]. These AREs can be classified into two types: canonical and non-canonical AREs[29]. Canonical AREs consist of an inverted repeat of hexameric half-sites (5'-TGTTCT-3') with a 3-bp spacer[30]. The non-canonical AREs have an atypical motif, and their binding specificity to steroid receptors is relatively weak, resulting in their need for coregulators[31,32]. Data indicate that some important androgen-regulated genes in prostate cancer are regulated by atypical AREs. The DBD contains two zinc finger domains. The first zinc finger contains a conserved P-box motif that binds the half site of the classical ARE. The second zinc finger contains a conserved D-box motif that functions to stabilize the DNA-receptor complex and to produce a receptor homodimer[33].

The LBD is located in the C-terminal region and comprises 12 helices. The LBD assists in the binding of dihydrotestosterone (DHT), which is the first step in the androgen signaling pathway. Like the AF-1 region in the NTD, the LBD contains an AF2 that interacts with coregulators [the steroid receptor coactivator (SRC)/p160 family] to bind to the NTD[34,35]. Because AF-2 shows a higher affinity for the NTD than the coactivator, interaction with the NTD is the primary role for AF-2 rather than direct transcriptional activation. The LBD plays a key role in current ADT for prostate cancer. Although anti-androgens used in ADT, such as bicalutamide, block the activity of AF-2 by binding to the LBD[36], point mutations in the AR in prostate cancer primarily occur in the regions of the LBD that include amino acids 670-676, 701-730, and 874-919, causing resistance to anti-androgens binding and proliferation in the presence of the anti-androgens[37-39].

THE AR SIGNALING PATHWAY

Androgens, the male sex steroids, regulate numerous physiological responses ranging from male sexual differentiation to the development of bone and muscle. The biological action of androgens is mediated through the AR. In prostate tissue, DHT is the primary ligand for the AR and is synthesized from testosterone by 5-reductase. The ligand-unbound AR is present primarily in the cytoplasm, where it interacts with heat shock proteins (Hsp)-90, -70, -56, cytoskeletal proteins, and other co-chaperones[40]. The AR-Hsp90 interaction is necessary to maintain the AR in a high-affinity ligand-binding confor-

mation, suggesting that Hsp90 plays a key role in the activation of agonist-bound AR regulation of nuclear transfer, nuclear matrix binding, and transcriptional activity. Following DHT binding to the AR, the AR translocates into the nucleus, and binds to the ARE in the promoter and enhancer regions of target genes. For example, PSA is a typical product of the AR-dependent gene and an important biomarker for prostate cancer.

The AR transcriptional complex is completed by recruitment of coregulators, which ultimately results in regulation of gene expression[36]. After the discovery of SRC-1, more than 200 nuclear receptor coregulators have been identified[41,42]. Coregulators were previously classified as either enhancing (coactivators) or repressing (corepressors) AR activity, and the requirements for coregulators vary among genes[43].

The AR is also regulated by post-translational modifications generated by signal transduction pathways. These modifications can be further divided into two categories: (1) reversible modifications of specific amino acid residues of target proteins (phosphorylation and acetylation); and (2) modifications involving addition of other proteins or polypeptides (ubiquitination and sumoylation). These changes have the potential to affect AR stability, subcellular localization, and interaction with other proteins, including coregulators.

MECHANISMS OF CASTRATION RESISTANCE

Castration resistance has been reported to be induced by: (1) sustained AR activation by enhancing intracellular conversion of adrenal androgens to DHT *via* a *de novo* route[44]; (2) AR hypersensitivity[45]; (3) promiscuous activation of AR signaling; and (4) outlaw pathways[9]. AR hypersensitivity results in the facilitation of a susceptibility to androgen by variation of a coregulator or cytokine activity and overexpression of the AR. In addition, Cai *et al*[46] reported that prostate cancer cells incubated with levels of androgen comparable to those seen in castration decreased AR-induced lysine-specific demethylase 1 levels, which negatively regulates AR signaling, resulting in an increase in the expression of AR and of multiple genes that contribute to increased androgen synthesis and sensitivity in CRPC[46].

Promiscuous activation of the AR signaling pathway occurs in cases of AR structural change and when the AR combines with ligands other than androgen. This phenomenon induces the anti-androgen withdrawal syndrome, *i.e.*, anti-androgen itself serves as an accelerator of progression. Outlaw pathways include AR structural changes when androgen is absent or when cytokines other than androgen bind to the AR to activate a signaling pathway, resulting in a facilitation of an androgenic response in gene expression. The extragonadal androgen synthesized in adrenal or prostate cancer cells plays a key role in the occurrence of sustained AR activation. Androgen is a metabolite of cholesterol in the testis and adrenal gland. Most of its synthetases belong to the cytochrome P450 (CYP) family. CYP17 in particular has both 17-hydroxylase and 17,20-lyase activity that plays an important role in the synthesis of adrenal androgen. Castration does not influence the synthesis of adrenal androgen. Adrenal androgen is converted into DHT by 5-reductase in prostate cancer cells. The affinity of DHT for the ligand-binding domain on the AR is higher than testosterone as a main ligand in prostate cells. Furthermore, the CRPC cells contain increased CYP17 activity with a new metabolic pathway that converts cholesterol to androgen. Thus, the expression of androgen-dependent genes is achieved by a very small amount of testosterone under castration[47].

NEW THERAPEUTIC DRUGS TARGETING THE AR SIGNALING PATHWAY

Standard therapeutic strategies for prostate cancers have recently been changed to utilize newly developed medicines for CRPCs. As described above, because androgens and the ARs remaining in CRPC cells are important for cancer progression, novel medicines should be designed to target the androgen synthesis pathway or the AR signaling pathway (Figure 1). Here, we introduce these new medicines, including compounds currently being developed in Japan.

Abiraterone

Abiraterone is a dual inhibitor of the 17-hydroxylase and 17,20-lyase expressed in testicular, adrenal, and prostatic tumor tissues. Ketoconazole, an azole antifungal medicine that has a similar target as abiraterone, initially showed a preferable outcome in patients with CRPC[48]. Ketoconazole inhibits both testicular and adrenal androgen biosynthesis by targeting cytochrome P450 isozyme 3A4 and 17,20-lyase. However ketoconazole results in severe toxicities because it has low specificity for the CYP17 family. Based on these pieces of evidence, abiraterone was selected for development at the Institute of Cancer Research in the UK as a selective inhibitor of CYP17. The multicenter phase Ⅲ randomized placebo-controlled trial COU-AA-301 evaluated the efficacy of abiraterone compared with docetaxel for men with progressive CRPC[49]. The overall survival in the abiraterone arm was significantly longer than in the docetaxel arm (14.8 *vs* 10.9 mo). However, abiraterone induces hyperaldosteronism by reduction of glucocorticoid following secondary adrenocorticotropic hormone overexpression. Although steroids are useful to protect against such adverse effects, the combination of steroids with abiraterone could limit its use for patients with early-stage disease and longer life expectancies.

TAK-700

TAK-700 is a next-generation CYP17 inhibitor that requires no steroid administration. Because TAK-700 selectively targets 17,20-lyase, and inhibition of 17α-hydroxylase

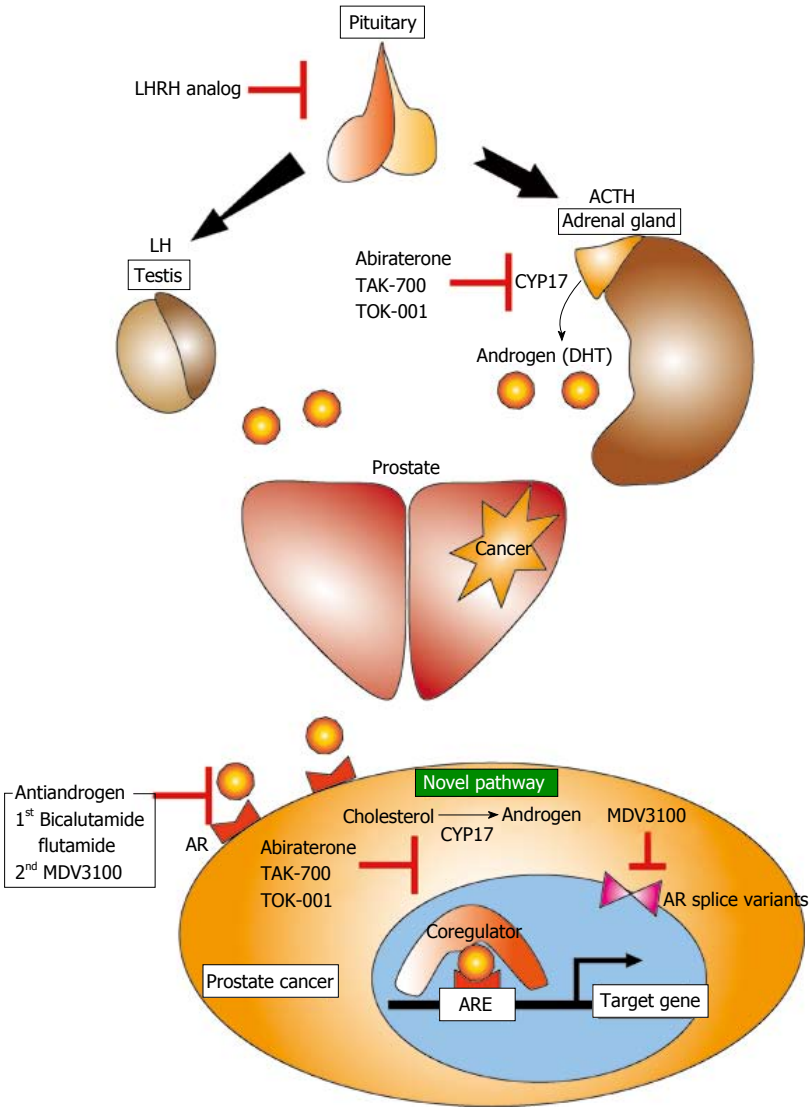

Figure 1 Schematic view of the therapeutic medicines targeting androgen receptor signaling pathways. ACTH: Adrenocorticotropic hormone; AR: Androgen receptor; ARE: Androgen response element; LH: Luteinizing hormone; LHRH: Luteinizing hormone-releasing hormone; DHT: Dihydrotestosterone; CYP: Cytochrome P450.

and reduction of glucocorticoids were smaller than those seen in patients treated with abiraterone[47,50]. A phase Ⅲ clinical trial of TAK-700 for metastatic CRPC (Evaluation of the Lyase inhibitor orteronel in Metastatic Prostate Cancer 5) is ongoing. The results of the interim analysis show that although overall survival was not significantly improved as a primary endpoint, progression-free survival was improved in the TAK-700 arm compared with the placebo arm (HR = 0.755).

TOK-001

The chemical composition of TOK-001 is similar to that of abiraterone. In addition to 17-hydroxylase inhibitory activity, TOK-001 also has AR antagonistic action[51-53]. Phase Ⅰ / Ⅱ clinical trials for CRPC are ongoing.

MDV3100

MDV3100 binds to the AR directly and targets multiple steps in the AR signaling pathway, including translocation to the nucleus and binding of the AR to the ARE and coregulators. Because MDV3100 differs from an agonistic anti-androgen, this compound does not induce anti-androgen withdrawal syndrome. MDV3100 induces the same action as the structural variant AR, which causes castration resistance; therefore, it is considered to be a second generation anti-androgenic agent[54]. In a phase Ⅲ double-blind, placebo-controlled trial (AFFIRM Clinical Trials), MDV3100 was superior in the proportion of patients with a reduction in PSA level by 50% or more, the quality-of-life response rate, progression-free survival, and overall survival of men with metastatic CRPC after chemotherapy[55]. Based on these results, MDV3100 obtained approval for treatment of metastatic prostate cancer in Europe. In addition, recent clinical trial (PREVAIL Clinical Trials) showed that MDV3100 significantly decreased the risk of radiographic progression and prolonged overall survival in men with metastatic CRPC who have not received chemotherapy[56].

DEVELOPMENT OF THERAPEUTIC DRUGS THAT TARGET THE ANDROGEN RESPONSIVE GENES

The goal of the AR signaling pathway is the transcriptional activation of target genes (androgen-responsive genes). The overexpression of the androgen-responsive genes is the main cause of cancer progression regardless of the presence or absence of castration resistance. We have reported the results of the functional analysis of novel androgen responsive genes and AR coregulators that influence the progression of prostate cancer[57-62]. Here, we introduce a part of these studies, including therapeutic medicines.

ADP ribosylation factor GTPase-activating protein 3

ADP ribosylation factor GTPase-activating protein 3 (*ARFGAP3*) is a novel androgen-regulated gene that is considered to be associated with regulation of the vesicular transport of the Golgi apparatus. In androgen-sensitive prostate cancer LNCaP cells, we observed induction of ARFGAP3 expression at the mRNA and protein levels in response to stimulation with 100 nmol/L DHT[59]. In functional analyses using LNCaP cells, the increased expression of ARFGAP3 was associated with cell growth, the G1/S cell cycle progression and cell migration. In addition, we found that ARFGAP3 interacted with paxillin as an AR coactivator, and enhanced migration activity and AR activity in LNCaP cells[59]. These findings suggest that *ARFGAP3* is a novel androgen-regulated gene that can promote prostate cancer cell proliferation and migration in collaboration with paxillin.

Octamer transcription factor 1

Octamer transcription factor 1 (Oct1) is a ubiquitous member of the Pit-Oct-Unc-homeodomain family. Although Oct1 does not demonstrate androgenic responsiveness, it works as a coregulator of the AR, binding to neighbors of the ARE and regulating AR activity[29]. We found that Oct1 is expressed in the nuclei of LNCaP cells using immunocytochemistry. SiRNA silencing of Oct1 inhibited the proliferation in LNCaP cells[60]. In addition, using surgical specimens, we found a positive correlation between Oct1 immunoreactivity in samples with a high Gleason score and AR immunoreactivity. Moreover, patients with high immunoreactivities of both Oct1 and AR exhibited poorer cancer-specific survival[60]. These results demonstrate that Oct1 may be a prognostic factor for prostate cancer and a contributing factor for increased AR sensitivity and castration resistance.

Pyrrole-imidazole polyamides

Pyrrole-imidazole (PI) polyamides are small synthetic molecules that recognize and attach to the minor groove of DNA to inhibit DNA-transcription factor interactions with high affinity and sequence specificity[63-65]. DNA recognition by PI polyamides depends on a code of side-by-side pairing of pyrrole and imidazole in the hairpin structure. Various types of sequence-specific PI polyamides have recently been developed to control gene expression[66-69]. One of the most important advantages of PI polyamide is their resistance to biological degradation by nucleases and proteases compared to nucleic acid medicines, including siRNA. In addition, PI polyamides could be efficiently delivered to cell nuclei without any specific drug delivery system. Another important advantage is the safety of PI polyamides when they are injected intravenously or *via* peritoneal to mice or rats[66,67]. PI polyamide that recognizes AREs suppresses DHT-dependent gene expression in LNCaP cells[70]. In addition, this polyamide was reported to inhibit the binding of RNA polymerase Ⅱ to the transcription start site of AR-driving genes[71]. These reports indicate that PI polyamides could be a powerful tool in the development of molecularly targeted therapeutics for androgen responsive genes/AR coregulators in prostate cancer.

CONCLUSION

The clinical challenges in prostate cancer are currently focused on controlling the action of the AR, which plays an important role in the development of hormone therapy naïve prostate cancer and also CRPC. Recent evidence shows that CRPC cells are still dependent on AR activity after ADT. Selective inhibition of the AR signaling pathway by typical ADT induced a bypass mechanism to activate the AR in low dose or in the absence of DHT, and thereby restore AR-dependent cellular proliferation. Thus, blocking the AR with second-generation AR antagonists has the potential to treat CRPC because of stronger and more durable inhibition of transcriptional activity than previous compounds. Various functional studies, including our reports, have cited androgen-regulated genes and AR collaborating factors, such as Oct1, as preferable candidates for biomarkers and therapeutic targets for CRPC. We believe future investigations of the AR signaling pathway and novel therapeutics targeting this pathway are mainstays for considering new strategies to treat CRPC.

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