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REVIEW

# Recent advances on the progressive mechanism and therapy in castration-resistant prostate cancer

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**Background:** Although there have been great advances in mechanisms and therapeutic methods of prostate cancer, the mortality rate of prostate cancer remains high. The castration-resistant prostate cancer (CRPC), which develops from hormone-sensitive prostate cancer, foreshadows a more dismal outcome. Concomitant with the researches in the mechanism of CRPC and therapy for CRPC, more and more landmark progress has been made in recent years.

**Methods:** A number of clinical and experimental studies were reviewed to indicate the novel advancement in the progressive mechanism and therapy of CRPC.

**Results:** The androgen receptor (*AR*) is still a vital driver in the progression of CRPC, while other multiple mechanisms also contribute to this progression, such as tumor immunity, cancer stem cells, epithelial–mesenchymal transition and DNA repair disorder. In terms of the therapeutic methods of CRPC, chemotherapy with drugs, such as docetaxel, has been the first-line therapy for CRPC for many years. Besides, newer agents, which target some of the above mechanisms, show additional overall survival benefits for CRPC patients. These therapies include drugs targeting the androgen axis pathway (androgen synthesis, androgen receptor splice variants, coactivators of AR and so on), *PI3K-AKT* pathway, *WNT* pathway, DNA repair, rearrangement of *ETS* gene, novel chemotherapy and immunotherapy, bone metastasis therapy and so on. Understanding these novel findings on the mechanisms of CRPC and the latest potential CRPC therapies will direct us for further exploration of CRPC.

**Conclusion:** Through comprehensive consideration, the predominant mechanism of CRPC might be the AR signal axis concomitant with tumor microenvironment, stress, immunity, tumor microenvironment and so on. For CRPC therapy, targeting the AR axis pathway and chemotherapy are the first-line treatments at present. However, with the advancements in CRPC therapy made by the researchers, other novel potential methods will occupy more and more important position in the treatment of CRPC, especially the therapies targeting the tumor microenviroment, tumor immunity and DNA repair and so on.

**Keywords:** CRPC, androgen receptor, tumor immunity, mechanism, therapy

## Introduction

Prostate cancer, which has the highest incidence among male malignancies in European and American countries, seriously threatens human health and affects the patients' life quality.[1] According to the statistics, the incidence and mortality rates of prostate cancer have been increasing every year with the rapid increase in Chinese aging society. Specifically, the castration-resistant prostate cancer (CRPC), which develops from hormone-sensitive prostate cancer, has a much higher mortality rate compared with prostate cancer.[2]

The clinical prognosis of CRPC patients is still unsatisfactory despite the fact that several important mechanisms and therapy advancements of CRPC have been reported.

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New drugs such as docetaxel, abiraterone and enzalutamide that could delay, to a certain extent, the development of CRPC are still the main therapy agents for CRPC in clinical practice.[3] In recent years, numerous progressive mechanisms and therapeutic targets of CRPC have been found due to the efforts of the researchers. In this paper, we will review the novel research advancements of the progressive mechanisms and therapy in CRPC.

## The progressive mechanisms of CRPC

At present, gene alteration in the androgen axis and the kinase-dependent signal pathways are the most important mechanisms of CRPC genesis and development. However, accumulated evidences have indicated that tumor immunity, cancer stem cells (CSCs), epithelial–mesenchymal transition (EMT), DNA repairing disorder and other mechanisms might also participate in the progress of CRPC (Figure 1).

### De novo synthesis of androgen

The levels of intratumoral androgen in some CRPC patients were higher than in the primary prostate cancer patients, although serum testosterone (T) was at the castration level (<1.7 nmol/L) in these CRPC patients.[4] According to the recent research, the mechanisms of de novo synthesis of androgen are discussed next.

#### Cytochrome P450 family-induced synthesis

The synthesis of T and dihydrotestosterone depends on the cytochrome P450 (CYP) family. CYP17, a member of the CYP family, has been proved to play a vital role in CRPC. Abiraterone acetate, one of the most common medicines for CRPC, is a kind of inhibitor of CYP17 and has been proved to improve the prognosis of CRPC patients.[5]

#### The synthesis of intratumoral androgen

According to previous researches, the levels of T and dihydrotestosterone are mainly dependent on the synthesis of intratumoral androgen, which is based on the conversion of dehydroepiandrosterone in the prostate cancer tissues after androgen deprivation therapy (ADT). This kind of intratumoral androgen synthesis mostly relies on some steroidogenic enzymes such as hydroxysteroid dehydrogenase (HSD)17β, HSD3β and steroid-5α-reductase.[6]

The activities of steroidogenic enzymes are also correlated with the expression of some other cytokines. Transforming growth factor beta could regulate the synthesis of the intratumoral androgen by upregulating HSD3β and downregulating HSD17β; insulin-like growth factor (IGF)-β could promote the synthesis of intratumoral androgen by increasing the expression of CYP17, AKR1C3 and HSD17β, so as to improve the development of CRPC.[7] Moreover, activin A, interleukin (IL)-6 and IGF2 could also regulate the activities of the steroidogenic enzymes.[8–10]

Recently, it was indicated that arachidonic acid could induce the synthesis of StAR, which is bound to hormone-sensitive lipase and transforms the free cholesterol into androgen in the steroid synthesis-related cells.[11]

#### Elevation of the expression level of androgen metabolism–related genes

The upregulation of the expression level of the androgen metabolism–related genes, such as *HSD3β2*, *AKR1C3*,

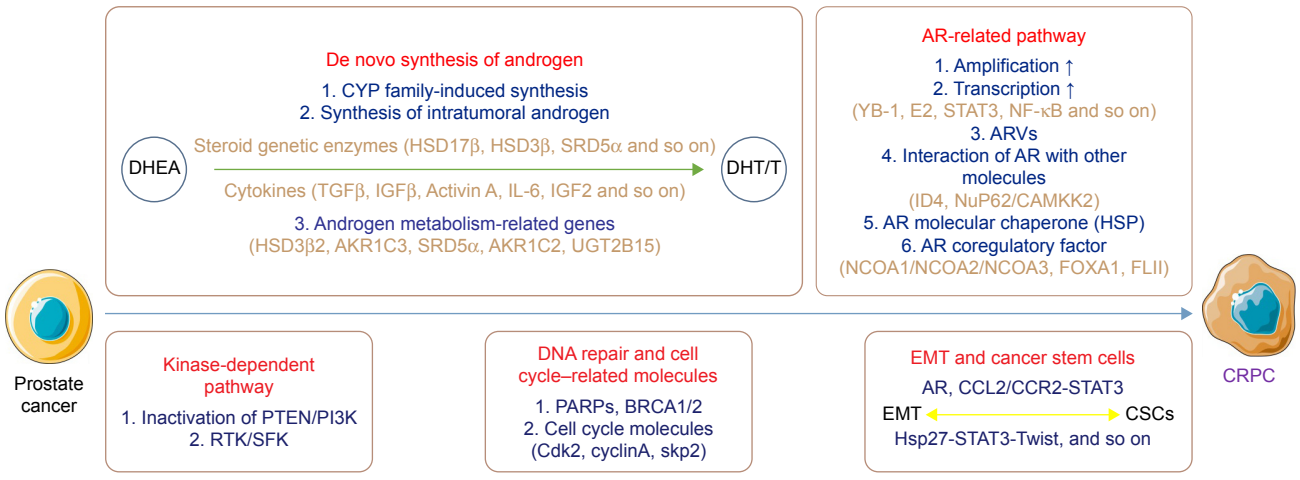


**Figure 1** Main progressive mechanisms of CRPC.
**Abbreviations:** AR, androgen receptor; ARVs, AR splice variants; CRPC, castration-resistant prostate cancer; CSCs, cancer stem cells; CYP, cytochrome P450; DHEA, dehydroepiandrosterone; DHT, dihydrotestosterone; EMT, epithelial–mesenchymal transition; HSP, heat shock protein; T, testosterone; HSP, heat shock protein.

*SRD5α*, *AKR1C2* and *UGT2B15*, also plays an important role in the development of CRPC.[12]

### The regulatory effect of tumor microenvironment in CRPC

Recent studies have demonstrated that the synthesis of intratumoral androgen is related to the tumor microenvironment to a certain extent. The expression levels of steroidogenesis enzymes in the stromal cells are much higher in the CRPC cells. Meanwhile, the activity of prostate specific antigen (PSA) promoter, which is induced by dehydroepiandrosterone through androgen receptor (AR) activation in CRPC cells, could also be enhanced by prostate stromal cells.[13] Besides, the anti-angiogenesis effect induced by vascular endothelial growth factor also plays a vital role in the progress of CRPC, while the vascular endothelial growth factor–targeted therapy was suggested to be useful for CRPC according to a study.[14]

## The adaptive variation of AR-related pathway

During the progress of CRPC, the adaptive variation of AR-related pathway plays a vital role and the variation mainly focuses on the following parts.

### The amplification of AR gene

The depletion of AR ligands could lead to the amplification of AR gene via feedback regulation.[15] The overexpression and the importance of AR signaling in androgen-independent prostate cancer have been proved by reports.[16,17] The amplification of AR gene could directly increase the expression level of AR and accelerate the development of CRPC. According to studies, glucocorticoid receptor could regulate some of AR targets in CRPC cells, and endostatin could inhibit glucocorticoid receptor–induced resistance upon AR antagonism.[18,19]

### The transcription activity of AR gene

The regulation of AR transcription via cytokine plays an important role in the development of CRPC. YB-1 protein could combine with the Y-box domain in AR promoter and regulate the transcription of AR gene.[20] The estrogen E2 could enhance the expression of SOX4, which is a member of the AR transcription factors in CRPC cells.[21] Besides, STAT3, NF-κB and NF-κB/p52 could also activate the transcription of AR and increase its expression level through different pathways.[22–24]

### The mutation of AR gene

The mutation of ligand-binding domain (LBD) or co-effective areas in AR gene could decrease the specificity of the combination between AR and its ligands, while the mutation of F876L region in AR gene has been demonstrated to be correlated with enzalutamide resistance in CRPC.[25] Furthermore, the generation of AR splice variants (ARVs) is reported to play an important role in the development of CRPC, especially the AR-V7, which is transferred from AR due to a deficiency of LBD ligand. The expression of AR-V7 could activate the androgen synthesis–related genes and promote the progression of CRPC.[26]

### The interactions between AR and other molecules

Besides the above signal pathways, the activity of AR is also correlated with some other molecules. The inactivation of inhibitor of differentiation 4 could activate the AR and promote CRPC.[27] Nucleoporin62 and calcium/calmodulin-dependent protein kinase kinase 2 could impact the activity and development of CRPC.[28]

## The regulator effect of AR molecular chaperone

As a molecular chaperone of AR, the expression of heat shock proteins (HSPs), especially HSP27 and HSP90, could be induced by ADT. It was reported that the activation of HSP27 and HSP90 might contribute to the resistance of ADT.[29]

## The modulation of AR co-regulatory factor

The implementation of AR function was also associated with some co-regulatory factors. The nuclear receptor coactivators (NCOAs)1, NCOA2 and NCOA3, which are the members of non-receptor tyrosine kinase (SRC) family and coactivators of AR, have attracted special attention of the researchers.[30] Meanwhile, forkhead box A1 (FOXA1), another cofactor, could modulate the transcription of AR and regulate the development of CRPC via GAT 3A2 gene.[31]

A recent study demonstrated that the Flightless I Homolog, FLII, could activate as a kind of transcriptional co-regulatory factor of AR and suppress the development of CRPC by regulating the cellular localization of AR in prostate cancer cells and inhibiting the expression of AR. This study revealed that FLII might be an important therapy target of CRPC.[32]

## The regulator effect of kinase-dependent pathway

The kinase-dependent signal pathway, which is modulated by AR axis during ADT, also plays a vital role in the development of CRPC. The inactivation of PTEN gene in CRPC patients could activate PI3K resulting in AR activation.[33]

In recent years, it was reported that the receptor tyrosine kinases and SRC family kinases could regulate the AR signal and the development of CRPC by inducing the phosphorylation of AR and inhibiting the expressions of co-regulatory factors of AR.[34]

## Modulation of DNA repair genes and cell cycle–related molecules

Mutation of DNA repair genes might play a vital role in CRPC.[35] Poly (ADP-ribose) polymerase, which is a kind of DNA repair enzyme, could maintain the function of AR.[36] Meanwhile, the mutation of BRCA1/2 gene, which is a member of DNA repair gene, was closely correlated with the development of CRPC.[37] Furthermore, the androgen could inhibit the proliferation of AR-positive CRPC cells through the suppression of Cdk2, CyclinA and Skp2, which are typical members of cell cycle–related cytokines.[38]

## The regulation of EMT and CSCs

In recent years, the importance of EMT and CSCs in the progressive CRPC has been demonstrated by various studies. The expression levels of E-cadherin, N-cadherin, Snail, Twist and other EMT markers are altered significantly during ADT. According to previous studies, ADT could trigger the appearance of EMT, which could further accelerate the development of CRPC.

CSC, a kind of potential malignant epithelial stem cell, might effect as an important regulatory target in CRPC. Some representative markers such as Nkx3.1, CD166, $PSA^{-/LO}$, Nanog, Bmi-1 and SOX2 are shown to be correlated with the progress of CRPC on the grounds of recent studies.[39,40]

Furthermore, according to a recent study, the interaction between EMT and CSCs might also play a vital role in the recurrence and drug resistance of CRPC through AR, CCL2/CCR2-STAT3, Hsp27-STAT3-Twist and other pathways.[41,42]

## The regulation of inflammation cytokines

The roles of inflammation factors in prostate cancer were proved by accumulating evidences during recent years (Table 1). IL-6 could induce the drug resistance of prostate cancer by activating SRC-1, regulating the expression of genes GRB2, SHC and JAK-1 and inhibiting the apoptosis of CRPC cells.[43] IL-4, another important inflammation factor, could affect the coactivators of AR, such as CBP/P300 and NF-κB, and regulate the development of CRPC.[44] IL-8, which could interact with NF-κB, is overexpressed in CRPC and could promote the angiogenesis and metastasis of CRPC through the SRC and FAK pathway.[45] Furthermore, CXCR4, CXCR2/CXCR3, CXCR6 and CXCR7, which belong to the CXCR family, also play an important role in the development of CRPC via inflammation pathways according to recent studies.[46–50] The roles of inflammation factors in cancers have been a hot issue in recent years, and a deeper and broader discussion is expected in future.

## The regulation of ncRNAs in CRPC

The ncRNAs serve as a transcription regulator in CRPC (Table 2). It was known that miRNA could modulate the development of CRPC by regulating the cell cycle, cell differentiation and cell proliferation.[51] Among the miRNAs, miR-1 and miR-206 could regulate the expression levels of glucose metabolism-related genes such as G6PD, TKT, PGD and GPD2 to affect the development of CRPC. Meanwhile, miR-185, miR-342, miR-17/92 and miR101 could regulate the development of CRPC through influencing SREBP, PPARA, COX-2 and other lipid metabolism-related pathways.[52,53] Besides, miR-32, miR-148a, miR-99a, miR-2 and miR-221 also play an important role in CRPC via AR signals.[54]

According to studies, lncRNAs such as PRNCR1, PCGEM1 and CTBP-AS could promote the development of prostate cancer by activating and promoting the transcription of AR.[55] lncRNA-p21 could promote the survival of prostate cancer cells through the Warburg effect and hypoxia-inducible

**Table 1** The regulation of inflammation factors in CRPC

| Cytokines | Signaling pathways | Target genes | Possible effect on cancer cells | References |
|---|---|---|---|---|
| IL-6 | Coactivator of AR | SRC-1/GRB2, SHC, JAK-1 | Inhibits apoptosis of the CRPC cells | 39 |
| IL-4 | Coactivator of AR | CBP/P300, NF-κB | Induces AR activation | 40 |
| IL-8 | Kinase-dependent pathway | NF-κB, SRC, FAK | Promotes angiogenesis and metastasis of CRPC | 41 |
| CXCR4 | IL-8 receptor | CXCL12/SDF-1 | Promotes proliferation, differentiation and metastasis | 42 |
| CXCR2/CXCR3 | / | / | Promotes proliferation and angiogenesis | 43 |
| CXCL16/CXCR6 | Akt pathway | IL-8, VEGF | Promotes selective metastasis to bone | 44 |
| CXCR7 | Akt pathway | IL-8/VEGF, EGFR | Promotes proliferation and metastasis | 45, 46 |

**Note:** "/" indicates unknown.
**Abbreviations:** AR, androgen receptor; CRPC, castration-resistant prostate cancer; IL, interleukin.

**Table 2** The regulation of ncRNA in CRPC

| ncRNA | Names | Target gene | Possible effect on cancer cells | References |
|---|---|---|---|---|
| miRNA | miR-1 and miR-206 | G6PD, TKT, PGD and GPD2 | Regulates glucose metabolism | 48 |
| | miR-185, miR-342, miR-17/92 and miR101 | SREBP, PPARA and COX-2 | Regulates lipid metabolism | 49 |
| | miR-32, miR-148a, miR-99a, miR-2 and miR-221 | AR | Activates AR signals | 50 |
| lncRNA | PRNCR1, PCGEM1 and CTBP-AS | AR | Activates AR and promotes the transcription of AR | 51 |
| | lncRNA-p21 | Warburg effect-related genes | Regulates the Warburg effect and HIF pathway | 52 |
| | HOTAIR | AR | Promotes the proliferation, invasion and metastasis of CRPC | 53 |
| | PCAT1 and ANRIL | PRC/AR | Modulates the expression of AR | 54, 55 |

**Abbreviations:** AR, androgen receptor; CRPC, castration-resistant prostate cancer; HIF, hypoxia-inducible factor; PRC, PGC-1-related coactivator.

factor pathway.[56] In addition, HOTAIR, which is a member of lncRNA, could promote the proliferation, invasion and metastasis of CRPC via the modulation of epigenetics and transcription of AR.[57] Similarly, the lncRNAs PCAT1 and ANRIL could modulate the expression of AR through interacting with the PGC-1-related coactivator family.[58,59]

## The transformation of prostate cancer into neuroendocrine prostate cancer

Neuroendocrine prostate cancer (NEPC) is insensitive to the ADT. According to recent studies, the loss of RB1 and TP53 and the increase in MYCN and AURKA might be the reasons for the formation of NEPC.[60] As a result, these genes related with the formation of NEPC are considered as a potential therapy target of NEPC.

# The new advancement of CRPC therapy

Drugs targeting the androgen axis, cytotoxic drugs, immune drugs and drugs targeting bone metastasis (zoledronic acid, $^{233}$Ra and denosumab) are the main choices for clinical doctors for CRPC therapy.[61,62] Moreover, the drugs targeting PI3K-AKT, WNT, DNA repair and other molecular signaling pathways were demonstrated to be essential in CRPC therapy, while the advances in prostate cancer immunity researches also indicated that immunotherapy might be indispensable in CRPC therapy in the future[63,64] (Table 3).

## Targeting the androgen axis pathway

As a nuclear receptor related to steroidogenesis, AR is constituted by DNA-binding domain (DBD), LBD, N-terminal domain (NTD) and hinge region. The alteration in any component of AR structure might change the activity of AR and influence the development of CRPC.[65] As a result, targeting the structural domain of AR is also a hotspot in CRPC.

### Inhibition of androgen synthesis

The inhibitors of the key enzymes in androgen synthesis were indicated to have a satisfactory effect in clinical trials. The therapeutic effect of the combination of abiraterone acetate and prednisone for CRPC has been proved in clinical practice.[66,67] Besides, VT-464, acting on CYP17, could suppress the proliferation of tumor and decrease the PSA level through inhibition of AR-axis.[68] However, according to a clinical trial, TAK-700 (Orteronel), which also acts on CYP17, showed no significant effect on the overall survival time of CRPC patients.[69]

Although many new drugs might be effective for CRPC, administration of drugs that act upon the AR axis would still be the most essential and important method in CRPC clinical therapy for some time.

### Targeting HSP protein

HSP protein is a very important target in CRPC therapy as mentioned before.[29] The application of inhibitors targeting the HSP90 protein has been considered as a novel therapeutic strategy for CRPC patients with mutant AR.[70] Knockdown of TCTP that interacts with HSP27 could suppress the survival and proliferation of CRPC cells.[71] In recent years, some preclinical studies have indicated that silencing HSP27 or HSP90 could sensitize the prostate cancer cells to chemotherapy and radiation treatments, and several HSP protein inhibitors (tanespimycin, ganetespib, OGX-427) could delay castration resistance or prolong survival in CRPC.[72–75] Thus, the combination of HSP blockage and other chemotherapy drugs could be a potential therapeutic strategy in patients with metastasis (m)CRPC.

### Targeting the AR-LBD or ARVs

Enzalutamide and ARN-509 (apalutamide) show a great affinity for AR and are effective in CRPC that is resistant to

**Table 3** Novel potential targets of CRPC therapy

| Possible targeting pathways | Targeting genes | Potential treatments | References |
|---|---|---|---|
| Androgen axis pathway | | | |
| Inhibition of androgen synthesis | CYP17 | VT-464, TAK-700 | 64, 65 |
| Targeting HSP protein | HSP90/TCTP | Knockdown | 66 |
| ARVs | ARVs, calpain | ARN-509, niclosamide, ASC-J9, CUDC-101/TAS3681 | 29, 69–73 |
| AR-NTD | AR-NTD | EPI-001 | 75 |
| Antagonist of AR | AR | CB | 77 |
| Coactivators of AR | SRC | Dasatinib, saracatinib | 78 |
| Inhibitors of AR expression | AR | ENZ-4716 | 79 |
| PI3K-AKT pathways | PI3K-AKT | BEZ235, GDC0068 | 80 |
| WNT pathways | PORCN | | 81 |
| Targeting DNA repair | PARP | AZD-2281 | 82 |
| Targeting the rearrangement of ETS gene | TMPRSS2-ERG, FLI1 | DB1255, PLA2G7, YK-4-279 | 82, 84 |
| Chemotherapy | MMP2/9, WNT/β-actin | Saikosaponin-d, PEDF | 87, 88 |
| Immunotherapy | | | |
| Vaccines | Peptide vaccine | PROSTVAC-VF | 90 |
| | Nucleic acid vaccine | PTVG-HP | 91 |
| | Whole-cell vaccine | GVAX | 82 |
| | Dendritic cell vaccine | Sipulencel-T | 92 |
| Immune checkpoints | CTLA-4 | Ipilimumab | 94 |
| | PD-1 | Nivolumab, pembrotizumab | 95 |
| MDSC | MDSC | Tasquinimod, lenalidomide | 96 |
| PSMA | PSMA | J591 | 97 |
| Bone metastasis | | | |
| Chemotherapy | Osteoclast, RANKL | Bisphosphonates, denosumab | 98 |
| Radiotherapy | DNA of cancer cells | Radium-223 | 99 |
| | ACK1/AR | AIM-100 | 100 |
| Other potential drugs | | | |
| Inhibitors of tyrosine kinase | IGF-1R | Figitumumab, cabozantinib | 101, 102 |
| Inhibitors of BET protein | BRD4 | GSK525762, OTX015 | 103, 104 |
| Inhibitors for NOTCH pathway | NOTCH | RO4929097 | 105 |
| Apoptosis and cell cycle pathway | Cell cycle | Escin | 107 |

**Abbreviations:** AR, androgen receptor; ARVs, AR splice variants; CRPC, castration-resistant prostate cancer; CTLA-4, cytotoxic T-lymphocyte-associated antigen-4; MDSC, myeloid-derived suppressor cell; NTD, N-terminal domain; PEDF, pigment epithelium-derived factor; PSMA, prostate-specific membrane antigen.

bicalutamide.[76] Recently, new drugs targeting AR-LBD and ARVs mainly focus on the following types.

Niclosamide, an antiparasitic drug approved by the US Food and Drug Administration was demonstrated to suppress the expression level of AR-V7, but not androgen receptor full length (AR-FL).[77] It was also reported that niclosamide combined with current antiandrogen agents might possess a satisfactory effect in CRPC patients. Besides, drugs such as ASC-J9 (dimethylcurcumin) and inhibitors of calpain (CUDC-101 and TAS3681) might be useful for CRPC therapy by inhibiting ARVs, according to some studies.[78–81]

## Targeting the AR-DBD

Some researchers believed that the alteration of AR-DBD might be correlated with the production of ARVs, and targeting AR-DBD could be a potential therapeutic strategy for CRPC.[82]

## Targeting the AR-NTD

According to a study, the NTD of AR is responsible for AR transcriptional activity.[83] As NTD is very important for the activity of all kinds of AR, targeting AR-NTD is expected to be used in CRPC. Several AR-NTD inhibitors (EPI-506, sintokamides) have been under preclinical experiments.[82,84] As for EPI-506, it is the first agent that could suppress both canonical and variant-related AR signaling, and the ongoing Phase I/II study of EPI-506 (NCT02606123) will evaluate the benefit of EPI-506 in mCRPC patients. According to a study,[82] EPI-001, the novel depressant of AR-NTD, showed a favorable effect on eliminating the castration resistance which was caused by ARVs.

## Antagonist of AR

In clinic, bicalutamide, flutamide, nilutamide and other antiandrogen drugs are still considered as the first-line treatment for CRPC. However, the curative effects of these drugs are

not everlasting, and the prostate cancer treated with ADT might advance to CRPC after 6 months.[85]

The core ligand of cyclobutane, which was used as the fourth-generation antiandrogen drug, might be of great importance in CRPC therapy through inhibition of nuclear translocation of AR.[86]

### Targeting the coactivators of AR

According to a clinical trial, depressors of SRC kinase, such as dasatinib and saracatinib, showed a satisfactory effect in CRPC therapy by acting upon AR coactivators.[87]

### Inhibiting AR expression

It might be possible to decrease the AR level by interfering with the expression of AR at the mRNA level. ENZ-4716 is a drug that confirms this hypothesis and is currently in Phase I clinical trial.[88]

## Targeting the PI3K-AKT and WNT pathways

According to previous researches, both PI3K-AKT and WNT pathways play a vital role in the development of CRPC. BEZ235, one of the inhibitors of PI3K-mTOR, and GDC0068, one of the inhibitors of AKT, are both in Phase I clinical trials at present.[89] Inhibition of WNT signal could potentiate the antitumor activity of the Plk1 inhibitor for CRPC.[90] Besides, targeting PORCN (porcupine), which is essential for WNT pathway, might be a potential treatment method for CRPC.[91]

## Targeting DNA repair

As mentioned earlier, mutations in DNA repair genes, such as BRCA2, homologous recombination, and nucleotide excision repair and mismatch repair, are common therapy targets in oncotherapy. For instance, inhibitors of poly (ADP-ribose) polymerase, especially olaparib (AZD-2281), showed satisfactory efficacy in CRPC patients according to the clinical trials.[82]

## Targeting the rearrangement of ETS gene

ERG, ETV1, ETV6 and FLI1, which belong to the E twenty-six transcriptional factor family, are considered as the important oncogenes in different cancers.[92] As one of the most important gene rearrangements in E twenty-six family, the gene rearrangement in TMPRSS2-ERG was deemed to be a potential target in CRPC therapy. Compounds targeting the rearrangement of TMPRSS2-ERG, such as DB1255 and PLA2G7, could regulate the biological function of prostate cells.[93,94] Besides targeting the classical ERG pathway, YK-4-279 might be useful in inhibiting the proliferation and survival of CRPC cells by suppressing the FLI1 gene.[95]

## Chemotherapy for CRPC

Although the side effects of chemotherapy are inevitable, chemotherapy in CRPC is nonnegligible because it is perfectly capable of killing prostate cancer cells.

Taxanes and epothilones are the typical drugs targeting the microtubules, while docetaxel and cabazitaxel are classical taxane drugs used in CRPC,[96] and pemetrexed could be used for CRPC under docetaxel-resistant condition.[97] As a newer trend of CRPC chemotherapy, the effect of applying taxanes in an earlier hormone-naive clinical setting of prostate cancer has been proved by studies.[98,99] Cabazitaxel, the next generation of taxane drugs, has been shown to be an effective antitumor agent in docetaxel resistance cell lines.[100,101] In recent years, some reports indicate that the taxanes may have cross-resistance with enzalutamide and abiraterone. As a result, the application of enzalutamide in prostate cancer patients has only a modest effect following docetaxel treatment.[102–104]

Besides the drugs mentioned earlier, several novel chemotherapy drugs have appeared recently. Saikosaponin-d possesses therapeutic potential for CRPC by reversing EMT and inhibiting the expression of MMP2/9 and WNT/β-actin.[105] Moreover, the expression of pigment epithelium-derived factor also could enhance the efficacy of low-dose chemotherapy and improve the prognosis in CRPC.[106]

## Immunotherapy in CRPC

Although immunotherapy in CRPC is still in its initial stage, the prospect of immunotherapy has received more attention in recent decades. Immunotherapy might be of significant importance in both therapy and prevention of CRPC.[107]

### Vaccines for prostate cancer

After the idea of tumor vaccine came up, much effort was put into this field. Up to now, the application of vaccines in prostate cancer has mainly focused on the following:

1. Peptide vaccine: PROSTVAC-VF is a kind of peptide vaccine using PSA as the target antigen and is integrated with avipoxvirus, vaccinia and TRICOM. PROSTVAC-VF could prolong the survival time of the CRPC patients with a satisfactory tolerance according to the clinical trials.[108]

2. Nucleic acid vaccine: Nucleic acid vaccine is a kind of vaccine that could express the related target antigen and induce the related immunoreaction. PTVG-HP is a typical nucleic acid vaccine, and its target antigen is prostatic acid phosphatase. According to reports, PTVG-HP could induce the related immunoreaction and has shown a potential usage for CRPC.[109]
3. Whole-cell vaccine (WCV): The WCV could induce multiple kinds of antibodies, but the application of WCV is limited because the immunogenicity of WCV is poor in general. For prostate cancer and CRPC, GVAX, which is modified with costimulators, was effective in Phase I and II clinical trials, but was unsatisfactory in Phase III clinical trial.[110] Under this condition, the application of WCV in prostate cancer still needs more research.
4. Dendritic cell (DC) vaccine: As the most effective antigen-presenting cell, DC is the first choice for preparation of autogenous cell vaccine. For CRPC, Sipulencel-T is the representative of DC vaccine and is able to induce CD4 and CD8 contraposing prostate cancer cells.[111] According to studies, Sipulencel-T could improve the prognosis of the CRPC patients as well.

### Immune checkpoints in prostate cancer

In the immune system, the immune checkpoint is a kind of inhibitory signal pathway, which is important for maintaining self-tolerance and regulating the duration. For prostate cancer, targeting cytotoxic T-lymphocyte-associated antigen-4 and programmed death protein-1 is the most effective strategy for immune checkpoint-related therapies.[112] Ipilimumab, which could block or inhibit the cytotoxic T-lymphocyte-associated antigen-4, might prolong the progression-free survival time of CRPC patients, according to clinical trials.[113] Nivolumab and pembrotizumab represent the immune drugs targeting the programmed death protein-1, but the therapeutic effect of them is not obvious.[114]

Recently, tasquinimod and lenalidomide that target the myeloid-derived suppressor cell showed the antitumor ability by the regulation of immune system and inhibition of angiogenesis in CRPC.[115]

### Targeting the prostate-specific membrane antigen (PSMA)

PSMA, which is upregulated after ADT, has received more attention in recent decades. J591 is a monoclonal antibody of PSMA and might decrease the PSA level and prolong the survival time of CRPC patients.[116]

## The therapy of bone metastasis in CRPC

Bisphosphonates and denosumab, which are the typical drugs for bone metastasis, also show their effectiveness in CRPC by targeting the osteoclasts, while denosumab might inhibit the metastasis of CRPC through RANKL pathway.[117]

Besides chemotherapy, radiotherapy could improve the prognosis of CRPC patients with bone metastasis. Radium-223, a kind of alpha particle radiopharmaceutical, has been proved to be effective in bone metastasis patients and prognosis with low clinical risks.[118] According to the reports, ACK1/AR pathway could induce the phosphorylation of AR, as well as the upregulation of ataxia-telangiectasia mutated and the regulation of DNA damage, to accelerate the resistance to radiotherapy. AIM-100, an inhibitor of ACK1, could improve the effect of radiotherapy in CRPC.[119]

## Other drugs for CRPC

### Inhibitors of tyrosine kinase

IGF-1R, a member of tyrosine kinase, could interact with MAPK, PI3K/AKT and other signaling pathways to modulate the development of CRPC. It has been reported that figitumumab, an antibody of IGF-1R, could decrease the expression level of PSA and AR.[120] Cabozantinib, another oral tyrosine kinase inhibitor, has a significant effect on decreasing the PSA level and suppressing the development of CRPC.[121]

### Inhibitors of BET protein

As mentioned before, BER protein plays a vital role in CRPC through the AR signal pathway. GSK525762, which is the first inhibitor for BRD4 in clinical trial, shows satisfactory therapeutic effects for CRPC patients, while the clinical therapeutic effect of another inhibitor for BRD4, OTX015, still needs to be confirmed by more researches in the future.[122,123]

### Inhibitors for NOTCH pathway

According to the recent research, NOTCH pathway is correlated with the development of CRPC. A novel inhibitor for NOTCH, RO4929097, could suppress the development of CRPC and might be a potential therapeutic target for CRPC.[124]

### Apoptosis and cell cycle pathway

Escin, a natural compound that is extracted from buckeye, has been used for anti-inflammation and detumescence for a long time.[125] A latest study demonstrated that escin could suppress the proliferation and survival of CRPC cells by regulating cell cycle and inducing apoptosis.[126]

## Conclusion

Concomitant with the researches in the mechanism of CRPC and therapy for CRPC, more breakthrough progress has been made. Through comprehensive consideration, the predominant mechanism of CRPC might be the AR signal axis concomitant with other carcinogenesis signals, stress, immunity, tumor microenvironment and so on. With the latest findings in tumor microenvironment, tumor immunity and tumor metabolism, these fields might play indispensable roles in CRPC. However, the interactions between the above mechanisms and the other novel potential mechanisms are still uncertain.

Meanwhile, the clinical guidelines that were established by the European Association of Urology or the American Urological Association are the authoritative references for making therapeutic strategy for CRPC in clinic up to now. With the guidance of clinical guidelines for CRPC, the specific state of each patient, the affordability of the patients and other factors also need to be considered when formulating the therapeutic strategy. Unfortunately, the therapeutic effect is not satisfactory in some CRPC patients nowadays. Therefore, novel and effective therapeutic strategy for CRPC patients is very necessary and exigent in clinic. We hold that the detection of vital gene of CRPC and the application of targeting drugs for CRPC might play an important part in future, while targeting the individual gene expression will bring big rewards for the therapeutic effect and avoid the side effect. Furthermore, the immunotherapy and tumor vaccine of CRPC might be the focus of research in CRPC therapy in future. Although there are still numerous unsolved difficulties in the research upon the mechanism and therapy of CRPC, we believe that great progress would be made with the efforts of researchers all over the world in the future.

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## Author contributions

KC contributed to designing this study. KSW and HLR contributed to the collection and analysis of data, discussion, and writing of the manuscript. TBX, DL, HMY and XPZ contributed to the correction of grammatical errors in this article. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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