Research Output Journal of Public Health and Medicine 4(2):33-37, 2024

ROJPHM

ISSN ONLINE: 1115-9715
ISSN PRINT: 1115-6147

https://rojournals.org/roj-public-health-and-medicine/

https://doi.org/10.59298/ROJPHM/2024/423337

Targeting Androgen Receptor Variants in Castration-Resistant Prostate Cancer (CRPC): A Comprehensive Review

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ABSTRACT

Castration-resistant prostate cancer (CRPC) represents a significant clinical challenge due to its aggressive progression despite androgen deprivation therapy (ADT). One of the key mechanisms driving CRPC is the emergence of androgen receptor (AR) variants (AR-Vs), particularly AR-V7, which remain active in low-androgen environments and promote tumor survival and proliferation. These AR-Vs lack the ligand-binding domain but retain the transcriptionally active N-terminal domain, making them resistant to conventional AR-targeted therapies. This review comprehensively explores the biology of AR-Vs, their role in CRPC progression, and recent advancements in targeting these variants. Emerging therapeutic strategies include AR N-terminal domain inhibitors, spliceosome-targeting therapies, and novel degraders that specifically address AR-Vs. The review also discusses potential biomarkers for AR-V-driven CRPC and highlights the challenges in translating preclinical findings into effective clinical interventions. Targeting AR-Vs offers a promising avenue for overcoming resistance in CRPC, providing new hope for patients with advanced disease.

Keywords: Castration-resistant prostate cancer, androgen receptor variants, AR-V7, androgen deprivation therapy, N-terminal domain inhibitors, spliceosome-targeting therapies,

INTRODUCTION

Prostate cancer is the most commonly diagnosed malignancy among men worldwide and is a leading cause of cancer-related mortality[1–3]. Androgen deprivation therapy (ADT) has been the mainstay treatment for advanced prostate cancer, as the androgen receptor (AR) pathway is a critical driver of prostate tumorigenesis[4, 5]. However, many patients eventually develop castration-resistant prostate cancer (CRPC), an advanced form of the disease that continues to progress despite castrate levels of androgens [4].

The persistence of AR signaling, primarily through AR variants (AR-Vs), is a well-established mechanism underlying the development of CRPC. AR-Vs, especially AR-V7, play a pivotal role in sustaining AR activity even in the absence of androgens, contributing to therapeutic resistance[6, 7]. This review provides an in-depth analysis of AR-Vs, their involvement in CRPC, and potential therapeutic strategies aimed at targeting these variants to overcome drug resistance.

The Androgen Receptor Pathway in Prostate Cancer

Structure and Function of the Androgen Receptor

The AR is a nuclear hormone receptor composed of several functional domains: the N-terminal domain (NTD), DNA-binding domain (DBD), hinge region, and ligand-binding domain (LBD). Upon binding to androgens (testosterone or dihydrotestosterone), the AR undergoes a conformational change, translocates to the nucleus, and regulates the transcription of genes involved in cell growth and survival[8, 9]. ADT aims to reduce androgen levels or block AR activity, initially leading to tumor regression. However, most patients eventually relapse, developing CRPC, where AR signaling persists despite low androgen levels. Mechanisms of resistance include AR gene amplification, AR point mutations, and, crucially, the expression of AR variants[10, 11].

Androgen Receptor Variants (AR-Vs): Structure and Mechanism

AR-V7 and Other Variants

Androgen receptor variants (AR-Vs) are truncated forms of the full-length androgen receptor (AR-FL), which lack the ligand-binding domain (LBD). This absence of the LBD makes AR-Vs constitutively active, meaning they can function without the need for androgen binding, a key mechanism that normally regulates the activity of full-length AR. Among the various AR-Vs identified, AR-V7 has gained significant attention due to its extensive study and clinical relevance, particularly in prostate cancer[12]. AR-V7 retains the amino-terminal domain (NTD) and DNA-binding domain (DBD), both of which are crucial for transcriptional regulation. These domains allow AR-V7 to drive gene expression and promote the transcription of androgen-responsive genes even in the absence of androgens. This capability is particularly significant in the context of castration-resistant prostate cancer (CRPC), where AR-V7 sustains tumor growth by bypassing the androgen dependency that typically limits cancer progression. As a result, AR-V7 plays a critical role in treatment resistance, making it a focus for targeted therapeutic strategies in advanced prostate cancer[13].

Role of AR-Vs in CRPC Progression

AR-V7 (androgen receptor variant 7) is a truncated form of the androgen receptor (AR) that lacks the ligand-binding domain but retains the ability to activate gene transcription. This variant has been strongly implicated in the progression of castration-resistant prostate cancer (CRPC), a stage of prostate cancer that continues to grow despite androgen deprivation therapy (ADT), which reduces androgen levels or blocks AR signaling. AR-V7 is of particular clinical interest because its expression has been associated with resistance to AR-targeted therapies, including enzalutamide and abiraterone, both of which are widely used in CRPC treatment. Enzalutamide and abiraterone work by inhibiting AR signaling—enzalutamide by directly blocking AR from binding to DNA and abiraterone by reducing androgen synthesis[14]. However, AR-V7 lacks the ligand-binding domain targeted by these drugs, rendering them ineffective. Consequently, the presence of AR-V7 allows prostate cancer cells to continue driving tumor progression even in the absence of androgens or under AR-targeted therapy, leading to treatment resistance[14].

Studies have shown that the expression of AR-Vs, particularly AR-V7, correlates with a poor prognosis in CRPC patients. Elevated AR-V7 levels are linked to more aggressive disease, shorter overall survival, and diminished responses to conventional therapies. As a result, AR-V7 has emerged as a critical biomarker and therapeutic target in CRPC management. Given its role in therapeutic resistance, current research is focused on developing novel treatment strategies that specifically target AR-V7 or its downstream signaling pathways[13]. These include drugs that degrade AR-Vs, block AR-V7-mediated transcription, or inhibit key pathways that remain active in AR-V7-positive CRPC. Additionally, detecting AR-V7 in circulating tumor cells (CTCs) has become an important diagnostic tool to predict resistance to AR-targeted therapies and guide more personalized treatment decisions. In summary, AR-V7 plays a pivotal role in driving CRPC progression and resistance to current AR-targeted therapies, highlighting the need for innovative treatment approaches that address this variant's activity in prostate cancer management[15].

Therapeutic Strategies Targeting AR Variants

N-terminal Domain Inhibitors

Given that AR-Vs lack the LBD, targeting the NTD has emerged as a viable strategy. The NTD is essential for the transcriptional activity of both AR-FL and AR-Vs. EPI-7386, an NTD inhibitor, has shown promise in preclinical models by disrupting AR-V-driven transcription, and early-phase clinical trials are underway to evaluate its efficacy in CRPC[16].

Spliceosome-targeting Therapies

AR-Vs are generated through alternative splicing, making the spliceosome machinery a potential therapeutic target. Spliceosome inhibitors, such as those targeting SF3B1, have been explored to reduce the expression of AR-Vs. This approach aims to prevent the formation of AR-Vs by modulating the splicing process[17].

AR Degraders

Proteolysis-targeting chimeras (PROTACs) are bifunctional molecules designed to degrade AR proteins, including AR-Vs. AR degraders offer a novel approach by promoting the ubiquitination and subsequent degradation of AR, thus inhibiting its transcriptional activity. ARV-110, a PROTAC targeting AR, is currently being tested in clinical trials for CRPC treatment.[18, 19]

Biomarkers and Clinical Implications

AR-V7 as a Biomarker

Androgen receptor splice variant 7 (AR-V7) detection in circulating tumor cells (CTCs) has garnered significant attention as a biomarker for resistance to androgen receptor (AR)-targeted therapies in prostate cancer, particularly in patients with castration-resistant prostate cancer (CRPC)[14]. The AR-V7 variant lacks the ligand-binding domain, which is the target of AR inhibitors like enzalutamide and abiraterone, two commonly used therapies for advanced prostate cancer. Because AR-V7 lacks this domain, the drugs cannot effectively inhibit the receptor's activity, leading to persistent AR signaling and tumor progression, even in the

presence of these treatments. Several studies have validated the clinical relevance of AR-V7 detection. Patients with AR-V7-positive CTCs tend to exhibit poorer responses to AR-targeted therapies compared to those who are AR-V7-negative. In one prominent study, AR-V7-positive patients demonstrated significantly lower progression-free survival and overall survival rates when treated with enzalutamide or abiraterone, confirming that AR-V7 positivity correlates with therapeutic resistance[20]. As a result, detecting AR-V7 in CTCs could be a pivotal tool in clinical decision-making. For instance, patients who test positive for AR-V7 might be steered away from AR-targeted therapies and toward alternative treatment options such as taxane-based chemotherapy (e.g., docetaxel or cabazitaxel), or emerging therapies like PARP inhibitors or immunotherapy, which may provide better outcomes for these patients. In this way, AR-V7 detection serves as a personalized approach to treatment, ensuring that patients receive the most effective therapy based on their tumor's molecular characteristics[21]. Moreover, AR-V7 testing can prevent the unnecessary administration of ineffective therapies, reducing potential side effects and improving overall patient management by minimizing the time spent on unproductive treatments. This makes AR-V7 not only a prognostic biomarker but also a predictive one, guiding clinicians toward more targeted and individualized therapeutic strategies.

Combination Therapies

Castration-resistant prostate cancer (CRPC) presents a significant challenge in oncology due to its ability to progress despite androgen deprivation therapy (ADT), a standard treatment aimed at lowering androgen levels that fuel prostate cancer growth. Over time, CRPC develops mechanisms to bypass the effects of ADT, one of which includes the expression of androgen receptor splice variants (AR-Vs) like AR-V7, which are not reliant on androgens for activation and can continue driving cancer progression. Given this complexity, researchers are exploring combination therapies that target multiple pathways simultaneously to improve treatment efficacy and address the multifactorial nature of resistance. One such approach involves combining AR-V-targeted therapies with other therapeutic agents. AR-V-targeted therapies aim to inhibit the activity of AR-Vs like AR-V7, which are implicated in treatment resistance. By directly targeting these androgen-independent pathways, these therapies may reduce the cancer's ability to thrive without androgens.

When combined with other agents, such as PARP inhibitors or immune checkpoint inhibitors, these strategies offer a multifaceted attack on CRPC:

1. PARP inhibitors: These agents block the repair of DNA damage in cancer cells, particularly in cancers with defects in DNA repair mechanisms like BRCA1 or BRCA2 mutations. CRPC often develops vulnerabilities in its DNA repair machinery, making it susceptible to PARP inhibitors. Combining AR-V-targeted therapies with PARP inhibitors can potentially amplify the therapeutic effect by inducing DNA damage that cancer cells cannot efficiently repair, leading to cell death[22, 23].

2. Immune checkpoint inhibitors: Immune checkpoint inhibitors, such as those targeting the PD-1/PD-L1 pathway, enhance the immune system's ability to recognize and destroy cancer cells. CRPC is often characterized by an immunosuppressive tumor microenvironment that allows cancer cells to evade immune detection[24]. Combining AR-V-targeted therapies with immune checkpoint inhibitors aims to both inhibit cancer cell growth directly and reverse the immunosuppressive environment, potentially leading to a more robust immune response against the tumor[24]. These combination therapies are being investigated in clinical trials, with the goal of enhancing overall treatment efficacy, delaying resistance, and potentially improving survival outcomes for patients with advanced CRPC. By addressing both androgen-dependent and androgen-independent pathways, such strategies may offer more durable responses compared to single-agent therapies, which often lead to resistance over time.

Challenges and Future Directions

Translational Challenges

Despite promising preclinical results, translating AR-V-targeted therapies into the clinic has been challenging. The heterogeneity of AR-V expression and the adaptive mechanisms of prostate cancer cells pose significant hurdles. Furthermore, the development of drug resistance to NTD inhibitors and AR degraders remains a concern.

Future Perspectives

Ongoing research efforts are focused on improving the specificity and efficacy of AR-V-targeted therapies. The development of more potent NTD inhibitors, the refinement of spliceosome-targeting drugs, and the optimization of AR degraders hold great potential for improving outcomes in CRPC patients. Additionally, advances in biomarker development could enable more personalized treatment approaches based on AR-V expression.

CONCLUSION

AR variants, particularly AR-V7, play a central role in the development of CRPC and resistance to current therapies. Targeting these variants represents a promising strategy to overcome therapeutic resistance. Although significant progress has been made in understanding AR-V biology and developing potential therapies, challenges remain in translating these findings into effective clinical treatments. Future research

should focus on refining these therapeutic approaches and developing biomarkers to guide personalized treatment for CRPC patients.

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CITE AS: Mercy Latricia. (2024). Targeting Androgen Receptor Variants in Castration-Resistant Prostate Cancer (CRPC): A Comprehensive Review. Research Output Journal of Public Health and Medicine 4(2):33-37. https://doi.org/10.59298/ROJPHM/2024/423337