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Targeting Androgen Receptor Variants in Castration-Resistant Prostate Cancer (CRPC)

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ABSTRACT

Castration-resistant prostate cancer (CRPC) remains a lethal stage of prostate cancer, characterized by resistance to androgen deprivation therapy (ADT) and poor clinical prognosis. One of the key drivers in CRPC progression is the androgen receptor (AR), specifically the emergence of androgen receptor variants (AR-Vs) that sustain AR signaling even in the absence of androgens. AR-Vs, such as AR-V7, promote androgen-independent activation of oncogenic pathways, leading to uncontrolled cell proliferation and therapeutic resistance. Targeting AR-Vs offers a promising therapeutic strategy to manage CRPC effectively. This review explores the molecular mechanisms underpinning AR-V expression, examines the roles of major AR variants in CRPC progression, and evaluates current and emerging therapies targeting AR-Vs. By summarizing recent advancements and the limitations of current approaches, we highlight potential future directions to improve therapeutic outcomes for CRPC patients.

Keywords: Androgen receptor variants, Castration-resistant prostate cancer, AR-V7, Androgen deprivation therapy, Targeted therapy, Oncogenic pathways

INTRODUCTION

Prostate cancer ranks as one of the most common and deadly cancers among men globally. When the disease advances to castration-resistant prostate cancer (CRPC), it enters a highly aggressive phase that poses a significant clinical challenge[1–3]. Initially, androgen deprivation therapy (ADT) is the standard of care for advanced prostate cancer, aiming to suppress androgen receptor (AR) signaling, which is central to cancer cell growth and survival[4]. However, nearly all patients eventually experience disease progression despite ADT, as prostate cancer cells adapt to survive in low-androgen conditions. A key driver of this resistance is the resurgence of AR signaling through alternative mechanisms. In CRPC, truncated androgen receptor variants (AR-Vs), particularly AR-V7, play a pivotal role. Unlike the full-length AR, which requires androgens to activate, AR-Vs lack the ligand-binding domain [5]. This structural alteration enables AR-Vs to maintain continuous, ligand-independent signaling, even in the absence of androgens. AR-V7 is the most well-studied among these variants and has been shown to drive cancer cell proliferation and survival by activating AR-dependent transcriptional programs independently, thus evading the suppressive effects of ADT [6, 7].

The clinical implications of AR-V-driven CRPC are profound. Patients with elevated levels of AR-V7, especially those detectable in circulating tumor cells, often show resistance to commonly used treatments such as enzalutamide and abiraterone, which target the androgen receptor signaling axis. As a result, alternative therapeutic approaches are urgently needed to address this treatment-resistant population. This review delves into the role of AR-Vs in CRPC, examining how these variants contribute to treatment resistance, disease progression, and poor clinical outcomes[8]. It also discusses recent advancements in therapeutic strategies targeting AR-Vs. These include the development of novel AR degraders, antisense oligonucleotides, and small molecules designed to disrupt the transcriptional activity of AR-Vs. By targeting AR-Vs directly or modifying downstream pathways, emerging therapies hold promise for improving outcomes in CRPC patients. Despite these advances, significant challenges remain, such as the need for precise detection methods for AR-Vs and a deeper understanding of their biology to tailor effective treatments for CRPC patients [9, 10].

Androgen Receptor Signaling in Prostate Cancer

The androgen receptor (AR) is a nuclear transcription factor essential for normal prostate cell growth. In prostate cancer, androgens like testosterone and dihydrotestosterone bind to the AR, activating signaling pathways that promote cell proliferation and survival. In early stages, prostate cancer responds well to ADT, which reduces androgen levels and suppresses AR signaling. However, CRPC develops when cancer cells bypass

androgen dependency through mechanisms like AR amplification, AR mutations, and expression of AR-Vs [1, 9].

AR Variants in CRPC Progression: AR variants are splice isoforms of the full-length AR that lack the ligand-binding domain, allowing them to activate AR-target genes without androgens. AR-V7 is the most extensively studied variant due to its high prevalence in CRPC. AR-V7 expression has been correlated with resistance to therapies such as enzalutamide and abiraterone, underscoring its role in promoting treatment resistance[11, 12].

Mechanisms of AR Variant Generation and Function

AR-Vs arise through alternative splicing or exon rearrangements of the AR gene. These truncated forms retain the N-terminal domain (NTD) and DNA-binding domain (DBD) but lack the C-terminal ligand-binding domain (LBD), making them constitutively active. Key mechanisms of AR-V function include[13–15]:

Constitutive nuclear localization: Unlike full-length AR, AR-Vs are permanently localized in the nucleus, leading to continuous gene transcription.

Activation of oncogenic pathways: AR-Vs can activate a subset of AR-regulated genes associated with cell proliferation and survival, independent of androgen binding.

Resistance to AR-targeted therapies: AR-Vs evade inhibition by current AR antagonists, which target the LBD, making them difficult to suppress with conventional treatments.

Therapeutic Approaches Targeting AR Variants in CRPC

Efforts to target AR-Vs directly or disrupt their activity have focused on several strategies, including novel AR antagonists, AR degradation enhancers, and combination therapies.

Direct Inhibition of AR-V Transcriptional Activity

N-terminal domain (NTD) inhibitors: Since AR-Vs rely on their intact NTD for transcriptional activity, NTD inhibitors such as EPI-506 and EPI-7386 show promise in preclinical and clinical studies. These agents bind to the NTD and prevent AR-Vs from activating gene transcription, potentially circumventing resistance to LBD-targeted therapies[16].

AR Degradation Enhancers

Proteolysis-targeting chimeras (PROTACs): These molecules facilitate the degradation of AR and AR-Vs through the ubiquitin-proteasome pathway. ARV-110, a novel PROTAC, has shown efficacy in degrading AR-Vs in CRPC models and is being tested in clinical trials[17].

Selective AR degraders (SARDs): SARDs promote degradation of both full-length AR and AR-Vs, potentially improving outcomes in CRPC by reducing the overall AR signaling load.[18]

RNA Interference and Gene Editing

Antisense oligonucleotides (ASOs): ASOs target AR pre-mRNA, blocking the production of AR-Vs by interfering with the splicing process. The ASO drug AZD5312 has demonstrated AR-V suppression in preclinical models and offers a gene-specific approach to limiting AR-V-driven CRPC[19].

CRISPR/Cas9 gene editing: CRISPR technology offers a potential avenue to delete or modify AR variants directly, though the delivery and specificity challenges remain[20]. Further research into CRISPR approaches may open new therapeutic possibilities for directly targeting AR-Vs.

Combination Therapies: Combining AR-V-targeting therapies with conventional treatments like enzalutamide may enhance treatment efficacy and delay resistance. Additionally, co-targeting pathways upregulated by AR-Vs, such as the PI3K/AKT and MAPK pathways, could reduce compensatory survival signaling in CRPC cells, making them more susceptible to AR inhibition.

Limitations and Challenges in Targeting AR Variants

Despite progress, targeting AR variants in CRPC presents several challenges:

Heterogeneity of AR variants: The presence of multiple AR splice variants in individual patients complicates the efficacy of single-agent therapies.

Drug resistance: Resistance to NTD inhibitors and AR degraders can develop, necessitating combination approaches to sustain therapeutic effects.

Toxicity and specificity: Some approaches, such as PROTACs, pose off-target toxicity risks, highlighting the need for more selective targeting mechanisms.

Future Directions and Emerging Strategies

Future research should focus on understanding the regulation of AR splicing to prevent AR-V formation, developing novel AR-V-specific inhibitors, and identifying biomarkers predictive of AR-V expression. Personalized approaches leveraging biomarker-guided therapies and patient-derived models can help optimize treatment regimens for CRPC patients based on their unique AR-V profiles.

CONCLUSION

AR variants represent a key driver of castration resistance in prostate cancer, significantly contributing to disease progression and therapeutic resistance. Targeting these variants requires innovative strategies beyond conventional ADT. Although NTD inhibitors, PROTACs, and ASOs offer promising avenues, the complexity of AR-V biology demands continued exploration. Addressing the underlying molecular mechanisms of AR-V

generation and identifying effective combination regimens hold the potential to enhance CRPC management and improve patient outcomes.

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