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Androgen Receptor Splice Variants in Prostate Cancer

Abstract

Prostate cancer is one of the leading causes of male mortality in Western countries. The importance of reactivation of androgen signaling via generation of alternative spliced variants of the androgen receptor is discussed. The role of androgen receptor splice variants in progression of castration-resistant prostate cancer and development of resistance to currently used androgen receptor-targeted therapeutics is also discussed.

Keywords: Androgen Receptor; Prostate Cancer; AR-Vs; Target genes

Mini Review

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Abbreviations: Pca: Prostate Cancer; AR: Androgen Receptor; CRPC: Castration-Resistant Prostate Cancer; FL AR: Full-Length AR; LBD: Ligand-Binding-Domain; PIN: Prostatic Intraepithelial Neoplasia; CTCs: Circulating Tumor Cells; NTD: N-Terminal Domain; DBD: DNA-Binding Domain; EMT: Epithelial-To-Mesenchymal Transition

Introduction

Prostate cancer (PCa) remains one of the cancers with high incidence and mortality rates among men in the US. Androgen signaling driven by the androgen receptor (AR) plays a central role in PCa tumorigenesis and hence the standard-of-care treatment for PCa is androgen deprivation by a variety of strategies such as luteinizing hormone-releasing hormone agonists, anti-androgens, estrogens, orchiectomy and drugs preventing both intra tumoral and adrenal androgen production [1]. While responsive to androgen deprivation therapy (ADT) initially, most patients with PCa exhibit progression to castration resistance, which poses the principal challenge to PCa researchers. Castration-resistant prostate cancer (CRPC) evades androgen ablation by activating AR-dependent signaling through alternative mechanisms. Reactivation of AR signaling is a hallmark of PCa progression and has also been associated with patient response to therapy. Reactivation of AR signaling may be mediated by multiple mechanisms including AR over expression, mutations in the AR, interactions with other signaling pathways and increased generation of alternative splice variants lacking the ligand-binding domain [2].

Androgen Receptor Variants in PCa

A major form of ADT-resistance in PCa is the generation of truncated AR splicing variants (AR-Vs) that lack the ligand-binding-domain (LBD), thus evading the binding of anti-androgens. AR-Vs are constitutively nuclear and active even in the absence of androgens, thus indicating their potential role in the acquisition of the CRPC phenotype [3,4]. Expression of AR-Vs arises from the inclusion of cryptic exons located in introns 2 and 3 of the AR gene, which inserts premature stop codons and termination sites, yielding shorter AR proteins of 75–80 kDa lacking the androgen-binding domain [5,6]. Known AR-Vs and their characteristics are detailed in Table 1. Experimental evidence from many studies shows that splice variants such as AR-V7 are expressed in both PCa cells and normal prostate epithelial cells [7-9]. AR-V7 (AR3) and ARv567es can function independently of the full-length AR (FL AR), and their selective knockdown can suppress the androgen-independent growth of CRPC cells. Alternatively, AR-Vs may play important roles in activating the FL AR in a ligand-independent manner [10]. In PCa xenografts, AR-Vs are rapidly induced after androgen deprivation and are suppressed after restoration of androgen supply [11]. Prostate-specific expression of ARv567es can induce carcinogenesis in a transgenic mouse model [12], while AR-V7 overexpression in the prostate leads to Prostatic Intraepithelial Neoplasia (PIN) [13].

The mechanisms mediating increased expression of aberrant AR-Vs in PCa are still largely unknown. One possible cause of defective splicing is the genomic rearrangement and/or intragenic deletions of the AR locus in CRPC [14]. Alternatively, aberrant expression/recruitment of specific splicing factors such as ASF/SF2 and U2AF65 [15] or hnRNPA1 [16] in PCa cells may contribute to unbalanced splicing and aberrant recognition of cryptic exons in the AR gene. Understanding the molecular mechanisms of production of AR-Vs will facilitate the design of mechanism-based inhibitors to extend the efficacy of ADT, and possibly treating progression of CRPC and prolonging patient survival.

AR-Vs in PCa Treatment Resistance

Due to rapid development of resistance to first generation anti-androgens such as flutamide and Casodex, efforts were redoubled in the last decade to identify and characterize more potent and longer-lasting anti-androgens for continuation of ADT. As a result of such concerted efforts, the second generation anti-androgen enzalutamide [17] and androgen-synthesis inhibitor abiraterone [18] have recently been approved for treatment of CRPC with or without prior chemotherapy. But like earlier ADT, these new therapies have a short duration of efficacy due to primary or acquired resistance. The failure of AR-targeted therapeutics to

inhibit activation of AR-Vs is due to lack of the C-terminal LBD, which diminishes their ability to act as competitive inhibitors of androgen binding. AR-Vs can also facilitate nuclear localization of FL AR in the absence of androgen, thus mitigating the ability of enzalutamide to inhibit AR signaling. Hence, induction of AR-Vs is a potent mechanism for CRPC to acquire resistance to enzalutamide or abiraterone. Two recent studies using circulating tumor cells (CTCs) from patients either being treated with enzalutamide or abiraterone or awaiting therapy switch, showed that expression of AR-V7 can predict primary or secondary resistance to enzalutamide or abiraterone [19,20]. These studies indicate that AR-V7 status may be a predictive biomarker for choice of therapy, even though the numbers of patients used in the studies were small and the results would need to be validated in larger cohorts [21]. AR-Vs can also mediate resistance to other prostate cancer therapies such as Heat Shock Protein 90 (Hsp90) inhibitors. Both AR-V7 and ARv567es do not bind to Hsp90 and hence are resistant to inhibitors of Hsp90 such as Geldanamycin [22,23]. Enhanced expression of AR-V7 confers resistance to conventional chemotherapeutics such as taxanes [24-26]. In vitro, AR-V7 does not associate with microtubules and hence AR-V7-expressing tumor xenografts are not susceptible to treatment with taxanes (which disrupt microtubule architecture). On the other hand, ARv567es (which interacts with microtubules) expressing xenografts are sensitive to taxane treatment [24]. A recent prospective study suggested that expression of AR-V7 is not associated with primary resistance to taxane therapy, while reversal of AR-V7 positive to AR-V7 negative status occurred in patients treated with docetaxel or cabazitaxel [27], indicating that taxanes remain a viable option for patients exhibiting either primary or secondary resistance to enzalutamide or abiraterone.

Table 1: Alternatively spliced AR-Vs in prostate cancer and their tissue or cell line expression characteristics are shown.

Name	Splice Junction	Transcriptional Activity	Tissue Expression	Cell line Expression	Alternative Names
AR-V1	3/CE1	Conditional	Benign, hormone-naïve, CRPC	CWR-R1, 22Rv1, VCaP	AR4
AR-V2	3/3/CE1	Unknown	NA	22Rv1	None
AR-V3	2/CE4	Constitutive	NA	22Rv1	AR-1/2/2b
AR-V4	3/CE4	Constitutive	NA	CWR-R1, 22Rv1	AR-1/2/3/2b; AR5
AR-V5	3/CE2	Unknown	CRPC	22Rv1	None
AR-V6	3/CE2	Unknown	CRPC	22Rv1	None
AR-V7	3/CE3	Constitutive	Benign, hormone-naïve, CRPC	LNCaP, C-81, C4-2, C4-2B, LNCaP95, VCaP, CWR-R1, 22Rv1	AR3
AR-V8	3/intron3	Unknown	NA	VCaP	None
AR-V9	3/CE5	Conditional	CRPV	VCaP, 22Rv1	None
AR-V10	3/intron3	Unknown	NA	VCaP	None
AR-V11	3/intron3	Unknown	NA	VCaP	None
AR-V12	4/8/2009	Constitutive	Benign, hormone-naïve, CRPC	LuCaP86.2, LuCaP136, 22Rv1, VCaP	ARv567es
AR-V13	9-Jun	Unknown	CRPC	22Rv1	None
AR-V14	9-Jul	Unknown	CRPC	22Rv1	None
AR-V15	9-Jun	Unknown	NA	VCaP	None
AR-V16	9-Aug	Unknown	NA	VCaP	None
AR-V18	9-Jun	Unknown	NA	VCaP	None
AR8	1/intron2/3/ CE3	Inactive	Benign, malignant	CWR-R1, C4-2, C4-2B, CWR22	None
AR23	2/intron2	Ligand-stimulated	CRPC	NA	None
AR45	1b/2	Conditional	Benign	NA	None
ARQ640X	Lacks 5,6,7,8	Constitutive	CRPC	NA	None

Target Genes of AR-Vs

Even though AR-Vs regulate some of the classical FL AR target genes such as PSA, NKX3.1 and FKBP5, they also have a distinct transcriptional program due to the recruitment of different co-regulators. Cell cycle genes such as UBE2C are induced by AR-V7 whereas FL AR induced genes relate to biosynthesis, metabolism and secretion [28]. Some studies found that the gene signature of AR-Vs represented a subset of the broader FL-AR-androgen transcriptional program [29]. It is likely that the repertoire of AR-V target genes is complex and cell-specific and may overlap

with that of the FL AR. AR-Vs can act as either heterodimers with AR or as homodimers and it is likely that they recruit different co-regulators and regulate different gene sets in different scenarios in different cell types [30,31].

Therapies to Target AR-Vs

As AR-Vs are resistant to therapies targeting the LBD, strategies are being devised to target the N-terminal domain (NTD), the DNA-binding domain (DBD) or the hinge region to effectively address the problem of increased expression of AR-Vs in CRPC. EPI-001, EPI-002 and EPI-506, which bind the NTD and inhibit transcriptional activity, have been shown to exhibit efficacy against cell lines which harbor high levels of AR-Vs [32,33]. Pyrvinium pamoate and small molecule derivatives of morpholine can inhibit AR signaling via the DBD [34-36]. Several neutraceuticals such as EGCG, sulforaphane, berberine etc. have been explored for inhibition of androgen signaling [37].

Conclusions and Future Perspectives

In summary, current research suggests that AR-Vs may play important roles in prostate cancer initiation, progression as well as epithelial-to-mesenchymal transition (EMT). Several studies also demonstrated that AR-Vs could facilitate resistance to ADT and other non-AR-targeted therapies. But the significance of AR-Vs in the clinical setting remains somewhat uncertain due to the lower levels of expression of AR-Vs compared to FL AR in patients undergoing treatment. More sensitive and quantitative assays are needed for precise quantification of AR-V levels in patient tumors and to establish the correlation between time to progression or development of resistance. Such assays may help identify whether prostate cancer progression is driven by AR reactivation or by AR-independent pathways, and better inform the selection of treatment choices. Similarly, agents targeting AR-Vs specifically are also needed to distinguish between the clinical significance of FL AR over expression and/or AR-Vs expression. Distinct AR-V target genes that play a key role in prostate tumor progression and/or treatment resistance also remain to be identified. These aspects of AR-V role in PCa are under intense investigation and are likely to lead to expansion of therapeutic options in PCa.

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