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Review article

Androgen receptor splicing variant 7: Beyond being a constitutively active variant☆

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ABSTRACT

In prostate cancer development, the androgen receptor (AR) signaling plays a crucial role during both formation of early prostate lesions and progression to the lethal, incurable castration resistant stage. Accordingly, numerous approaches have been developed to inhibit AR activity including androgen deprivation therapy, application of the AR antagonists as well as the use of taxanes. However, these treatments, although effective initially, resistance inevitably occur for most of the patients within several years and limiting the therapeutic efficacy. Of note, alterations and reactivation of the AR signaling pathway have been demonstrated as the major reasons for the observed resistance. Accumulating evidences have suggested that synthesis of AR splicing variants, in particular, the constitutively active AR-V7, is one of the most important mechanisms that contribute to the abnormal AR signaling. In addition, clinical data also highlight the potential of using AR-V7 as a predictive biomarker and a therapeutic target in metastatic castration resistant prostate cancer (mCRPC). In this review, we summarize the recent findings concerning the specific role of AR-V7 in CRPC progression, drug resistance and its potential value in clinical assessment.

1. Introduction

Despite considerable effort being made in recent years, prostate cancer (PCa) remains to be one of the top leading causes of cancer-related death in men worldwide [1]. It is clear that the growth of PCa cells are dependent on androgen and can be suppressed by androgen ablation before progressing to the castration-resistant prostate cancer (CRPC)state [2,3]. However, androgen receptor (AR), the major molecular target of the first-line PCa treatment, continues to function as the driver for CRPC growth, drug resistance and metastasis [4,5]. The next-generation of FDA approved AR antagonist, enzalutamide and abiraterone, although effective initially, are limited by the resistance in CRPC patients driven by the abnormal activation of the AR pathway, resulting in treatment failure [6–8]. Thus, several hypotheses have been proposed to explain the mechanism of sustained AR activation, including overexpression of the AR gene, AR mutation, stimulation by other oncogentic pathways and presence of the AR splicing variants [9–13]. Even we still lack detailed understanding of these mechanisms, targeting the abnormal AR signaling remains to be the mainstay for current PCa therapy.

Androgen receptor splicing variants (ARVs) emerge as one crucial mechanism for explaining the abnormal activation of AR and acquired resistance to therapies for metastatic CRPC (mCRPC) patients. Up to now, over 20 ARVs have been identified in PCa cell lines, human xenograft models and clinical specimens [14]. Among those variants, AR-V7 (also termed AR3) is the best characterized ARV and also determined to be the most abundant form in clinics [15]. Numerous studies have indicated that AR-V7 constitutively localizes to the nucleus and plays crucial role in mediating androgen-independent growth and resistance to PCa treatment. In this review, we will briefly summarize the major findings of AR-V7 regarding prostate cancer treatment, focusing on the transcriptional differences between AR-V7 and AR as well as recent advances about the prognostic value of AR-V7.

2. Origin of AR-V7

The full-length AR gene is comprised of 8 exons which encode 4 core domains: the N-terminal domain (NTD), the DNA binding domain (DBD), the hinge region and the C-terminal ligand binding domain (LBD) (Fig. 1). Upon binding of androgen to the LBD, AR will translocate to the nucleus, following by specific interaction between androgen response elements (AREs) in the promoters/enhancers of AR

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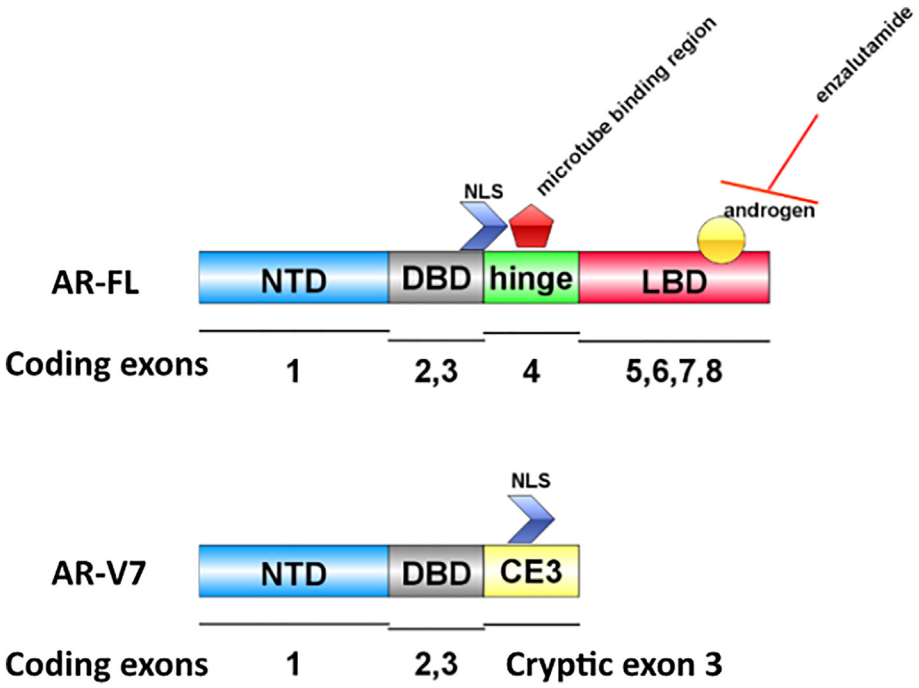

Fig. 1. Schematic structures of AR-FL and AR-V7. AR-FL and AR-V7 protein structure with coding exons, respectively. NLS of AR-FL localizes within the junction of the DBD and the hinge region while NLS of AR-V7 localizes in the CE3 region. The hinge region is responsible for the interaction between microtubule and AR-FL. Enzalutamide targets the binding between the LBD and androgen.

transcriptional targets and the DBD to initialize transcriptional activity [16]. Basically, prostate specific antigen (PSA) and transmembrane protease serine 2(TMPRSS2) represents the well-established AR-downstream targets, leading to cellular responses such as growth and survival of prostate cells [17].

In general, the best characterized feature of ARV is the absence of the LBD, which strongly correlates with their role in PCa progression and resistance to androgen deprivation therapies (ADT). Several mechanisms have been proposed for the generation of these ARVs, including the mutation-derived premature stop codon, proteolytic cleaved mediated by calcium-dependent proteinases, genomic rearrangement and alternative splicing, as reviewed in details by Ware et al. [18]. The LBD-truncated ARVs usually localize primarily in the nucleus no matter whether the androgen is present, thus leading to sustained activation of the AR pathway [19]. The first evidence of endogenous ARVs was shown in the early 2000s by observing lower bands between 90 kDa in western blot against PCa cell lines and these bands were further increased in their CRPC derivates [20]. Among all the identified ARVs, AR-V7 draws the most attention owing to its high detection frequency and the potential to be a diagnostic marker in clinics. Specifically, the presence of AR-V7 was first verified in 2009 by two groups, linking its expression to CRPC progression [21,22]. As a typical ARV, AR-V7 retains the DBD and the AR transcriptional activation domain, capable of transcriptional regulation in the absence of the LBD. Sequential studies have revealed that AR-V7 is encoded by contiguously spliced AR exons 1, 2, 3, and one additional cryptic exon 3 which is identical to a sequence identified in AR intron 3 [22]. Notably, the nuclear localization signal (NLS) of AR is located in the junction of the DBD and the hinge region [23–25]. However, AR-V7 lacks the hinge region, instead, its NLS is encoded by the cryptic exon [13] (Fig. 1). While the protein level of AR-V7 is barely detectable in benign tissues and hormone-naïve PCa cell lines like LNCaP, its expression dramatically increases as disease progression [26].

3. Factors implicated in AR-V7 splicing

Accumulating evidences have indicated that aberrant expression of various splicing factors contributes to cancer progression and those factors could serve as potential therapeutic targets [27,28]. Specifically, there are several studies investigated the factors that function in AR-V7 generation and PCa progression: Firstly, Liu et al. demonstrated that increased AR transcription by ADT induces stronger interactions between AR pre-mRNA and splicing factors U2AF65 and ASF/SF2, which are crucial for splicing AR pre-mRNA into AR-V7 [29]. In addition, RNA binding protein Sam68 was also indicated in the upregulation of AR-V7 mRNA level by mediating the expression of the AR-V7 unique cryptic exon 3 [30]. More recently, RNA-binding splicing factor, proline and glutamine-rich (PSF/SFPQ) was shown to correlate with worse prognosis of PCa patients by promoting expression of various spliceosome genes and subsequently, generation of the constitutively active AR-V7 [31]. Similarly, using genomic approaches and clinical data assessment, scientists have identified heterogeneous nuclear ribonucleoprotein L (HNRNPL) and HNRNPH1 as another two crucial splicing factors in AR-V7 production and PCa therapy [32,33]. In 2018, Fan et al. reported that histone demethylase JMJD1A promoted alternative splicing of AR-V7 through recruiting heterogeneous nuclear ribonucleoprotein F (HNRNPF) to cryptic exon 3b, highlighting that some epigenetic regulators might be considered as novel targets for future PCa therapy [34]. Notably, inhibition of the crucial molecular chaperone of AR protein, HSP90, was also shown to induce the disruption of AR-V7 splicing and reduction of AR-V7 level [35]. In sum, considering the importance of AR-V7 splicing in PCa development, those specific factors list above could draw significant interest in future PCa research in order to figure out more specific up-stream targets.

4. Distinct transcriptional program between AR and AR-V7

Recent studies have shown that the activation of AR targeted genes requires combined function of AR, co-regulatory proteins and other collaborating transcription factors. Thus, the activity of AR is not only mediated by androgen binding but also affected by AR homodimerization and interactions with its cofactors [36]. Homodimerization is a pre-requisite step for AR nuclear localization and subsequently, trans-activating its targets [37]. Following studies have revealed that dimerization is also required for AR-V7 to exert its transcriptional activities. Interestingly, AR-V7 cannot only homodimerize but also heterodimerize with AR-FL, leading to androgen-independent AR-FL nuclear localization and transcriptional activity [38,39]. Several studies

have demonstrated that AR-V7 is cable of activating canonical AR-FL downstream targets like PSA and TMPRSS2 in the absence of AR-FL. However, AR-V7 is not as potent as AR-FL in activating these well-established AR-FL genes [40]. These observations raise the critical question that whether AR-V7 simply compensates the repressed AR-FL signaling, or is also involved in other transcriptional program in addition to canonical AR-FL downstream events.

In 2009, Wang et al. reported that under androgen independent situations, AR itself can regulate a different transcriptional program from normal androgen-regulated state. They claimed that AR selectively upregulates the expression of mitotic genes like *UBE2C* in androgen-independent PCa cells [41]. Ambiguously, following microarray analysis performed by Hu et al. suggested that AR-FL mainly associates with genes responsible for macromolecule synthesis while AR-V7 is the major driver for mitotic genes, specifically, *UBE2C* [42]. Consistent with this finding, promoter of canonical AR signaling target *PSA* was found to be co-occupied by AR-V7 and AR-FL whereas the promoter of the *UBE2C* is bound by AR-V7 only, indicating that the AR-V7/AR-FL dimers and the AR-V7/AR-V7 dimers perform different transcriptional functions [39]. In addition, cistrome and gene expression analysis of 22Rv1-ARFL^{-}/ARV^{+} cells revealed that AR-Vs can regulate a unique set of genes that is not regulated by AR-FL [43]. By using ChIP-seq and RNA-seq, another group defined numbers of ARV-preferentially bound genes, activation of which not only promote CRPC progression, but also contribute to AR antagonist resistance [44]. Notably, metabolic flux assays performed in doxycycline inducible LNCaP-AR-V7 cells also showed differential regulation of metabolic pathways by AR and AR-V7, further supporting that AR-V7 regulates unique downstream events to AR-FL [45]. In sum, these data above indicate that AR-V7 is able to mediate distinct transcriptional events to its parental AR-FL and its functions are much more complicated than simply being a constitutively active form of the well-established AR signaling pathway. Thus, figuring out the detailed regulatory network of these unique down-stream events is crucial for understanding how AR-V7 contributes to CRPC progression.

It is reasonable that AR-V7 can recruit distinct cofactors in order to mediate a different transcriptome. Although AR cofactors are widely-accepted to play critical roles in modulating AR activity, the AR-V7 specific transcriptional machinery has been barely addressed. FOXA1 is a well-known pioneer factor for AR signaling, which plays a vital role in AR transcription initiation by acting upstream of GATA2 and AR-FL [46]. However, Krause et al. showed that selective regulation of target genes by AR-FL, but not AR-V7, depends on FOXA1, indicating the existence of AR-V7 specific transcriptional complex in certain cellular context [40]. In supporting of this observation, homeobox protein HoxB13 was recently found to be a novel pioneer factor for AR-V7 binding to its specific oncogenetic targets [47]. Intriguingly, previous studies claimed that HoxB13 can interact with the NTD of AR-FL to suppress the expression of AR target genes like *PSA* [48,49]. Nevertheless, MED1 (TRAP220), another well-established collaborating factor for AR recruitment to its targets, seems contributing to both AR-FL and ARV signaling [50–52]. These observations indicate that although AR-FL and AR-V7 transcriptional network share some of the cofactors, they may have distinct role or regulatory mechanisms. It is also worth noting that both corepressors and coactivators interact with AR to mediate its transcriptional activity. For example, FOXO1 is found to be an important corepressor of AR-FL as well as several ARVs [53–55]. Strikingly, Cato el al. recently reported that AR-V7 preferentially interacts with the NCOR transcriptional co-repressors while AR-FL can associate with both co-activators and co-repressors. In other words, AR-V7, unlike its parental AR-FL, mainly functions as a transcriptional repressor in certain cellular context. More importantly, this study highlighted a novel regulatory mechanism of AR-V7 in repressing growth inhibitory genes, paving another potential way for explaining the oncogenetic role of AR-V7 in CRPC [56]. In summary, even we still know very few about the AR-V7 protein interactome for activating its specific targets, future research about them will be of significant importance for targeting the AR-V7-driven CRPC progression.

5. Post-translational regulation of AR-V7

As the expression of AR-V7 strongly correlates to the malignant behaviors of PCa cells, post-translational regulation of AR-V7 was also studied by several groups. Firstly, increasing protein degradation of AR-V7 was purposed to be one potential approach to inhibit AR-V7 in PCa [57]. The FDA approved oral small molecule, galeterone, was demonstrated to induce protein degradation of both AR-FL and AR-V7, suppressing the progression of CRPC xenografts in-vivo [58]. Moreover, resveratrol, another well-documented drug for PCa, was recently shown to exert its anti-neoplastic function by promoting the degradation of AR-V7 [59]. Also, niclosamide, a FDA approved anti-helminthic drug, was shown to significantly downregulate AR-V7 protein level through the proteasome pathway and overcome enzalutamide resistance in PCa [60]. Currently, several clinical trials with niclosamide in CRPC are ongoing either by combining with enzalutamide or abiraterone [61]. In addition, AR-V7 expression was also shown to be correlated with phosphorylation events. For example, Aurora A kinase activity was indicated in the regulation of AR-V7 expression [62]. Interestingly, one mechanistic study has revealed that the E3 ligase Mdm2 is able to induce AR-V7 poly-ubiquitination and protein degradation by recognizing p-S213 residue of AR-V7 [63].Previous data indicated that both AR-FL and AR-V7 signaling are positively correlate with the activity of mitotic kinase, Plk1 [64,65]. Thus, considering that AR-V7 preferentially activates mitotic genes in CPRC cells, it will be interesting to figure out how these mitotic kinases cooperate with AR-V7 in promoting androgen-independent growth and drug resistance. Overall, the knowledge of AR-V7 specific post-translational modifications is rather limited and requires further investigation.

6. AR-V7 and AR antagonist

It is widely accepted that CRPC cells are not strictly androgen-independent and continue to rely on AR signaling for survival and growth [66]. Thus, synthesis of androgen and activity of AR are still the major targets of PCa therapy. However, AR-V7 was reported to promote PCa treatment resistance due to its constant activation under the pressure of ADT and commonly used LBD-targeting drugs [67,68]. As mentioned above, AR-V7 is overexpressed in CRPC compared to hormone-naïve PCa and depletion of AR-V7 can significantly reduce androgen-independent growth of PCa cells and human xenografts. More recently, many studies have declared the importance of AR-V7 in regulating resistance to novel FDA approved AR antagonists, enzalutamide and abiraterone [68,69]. Basically, enzalutamide exerts its antitumor function through interfering ligand binding of AR while abiraterone is targeting the *de-novo* androgen synthesis pathway of PCa cells. So, it is expected that the presence of the LBD-independent variant AR-V7 may contribute to resistance of both drugs. Indeed, expression of AR-V7 was validated to be negative correlate with the efficacy of enzalutamide and abiraterone in PCa cell lines, pre-clinical xenografts and clinical studies by numerous groups [70–73]. Interestingly, Cao et al. suggested that AR-V7 can also stimulate AR-FL nuclear localization in an androgen-independent manner, thus promoting enzalutamide resistance in addition to its own escaping mechanism [39].

These promising results listed above suggest that AR-V7 may serve as a predictive biomarker in future years in regards of using the next-generation anti-androgen agents. In one study, Antonarakis et al. detected AR-V7 mRNA level in circulating tumor cells (CTC) from mCRPC patients before the treatment with enzalutamide or abiraterone. As a result, none of the patients with AR-V7-positive CTC showed meaningful decrease of PSA after taking these two drugs [69]. Later, they expanded their cohort size to over 200 to confirm the importance of CTC-based AR-V7 mRNA status in predicting outcomes in mCRPC

patients receiving first- and second-line AR inhibitors [74]. Moreover, the prognostic value of AR-V7 in enzalutamide and abiraterone was further validated in another clinical study using CTC cluster detection - based AR-V7 mRNA assay of 98 mCRPC patients. In general, PSA responses, PSA progression-free survival (PSA-PFS) and overall survival (OS) data all indicate that patients with AR-V7 negative CTC cluster had better response [75]. Importantly, testing of AR-V7 mRNA levels in whole blood was also shown by one study to serve as a predicting approach for treatment outcome in mCRPC patients receiving enzalutamide or abiraterone [76]. In summary, these clinical studies consistently indicate the fundamental role of AR-V7 in the treatment of second-generation AR antagonists.

Because the expression of AR splicing variants such as AR-V7 induces resistance against the traditional AR-targeting therapies, novel agents which can block the activity of AR-Vs have been proposed. In particular, molecules targeting the AR NTD can inhibit the protein-protein interaction between AR/ARV and their co-activators like histone acetlytransferase p300/CBP, thus disabling transcription and decreasing the AR-dependent cell growth [77–80]. In addition, ARN-509, a compound which inhibit AR nuclear localization and the DBD binding to ARE, was reported to show certain potency in mCRPC patients who were not treated with enzalutamide or abiraterone before [81,82]. Currently, these promising compounds, either using alone or in combination with first-line drugs, are still under clinical trials. Nevertheless, with limited clinical data and detailed information about the effect of ARVs in these experiments, the role of AR-V7 in these novel AR antagonists remain to be determined.

7. AR-V7 and taxanes

Taxanes are first-line chemotherapeutic drugs for mCRPC patients, docetaxel and its novel derivate cabazitaxel are still widely used in clinics even resistant incidents are quite common [83,84]. Since 2004, docetaxel has been approved by FDA as a major chemotherapeutic drug for patients diagnosed with mCRPC [85]. This well-acknowledged mitotic poison can inhibit cell growth by blocking microtubule de-polymerization and activating the spindle check point [86]. However, the efficacy of docetaxel in PCa was recently reported to be closely related to the AR signaling. Basically, through the impairment of microtubule dynamics, docetaxel can inhibit AR nuclear shuttling, which is the prerequisite for survival and growth of PCa cells [87]. Indeed, this notion was further confirmed in other independent assays and also determined to be one crucial factor for clinical response of mCRPC patients to docetaxel treatment [88,89]. Notably, our group previous work also demonstrated that phosphorylations of two crucial regulators of microtubule dynamics, CLIP-170 and p150 (Glued), by Polo-like kinase 1(Plk1) activate AR nuclear shuttling and inhibit cellular responses to taxanes [90]. Thus, abnormal activity of AR signaling has been recently considered as another contributing factor for docetaxel resistance. In 2016, Kumora et al. reported that increased activity of AR signaling negatively correlates with the effect of docetaxel in numerous PCa cell lines [91]. Following mechanistic studies have revealed that the hinge domain of AR mediates its interaction with microtubule. And AR-V7, which is lacking the hinge domain, cannot interact with microtubules and dynein motor protein [92]. Consequently, nuclear accumulation and transcriptional activity of AR-V7 is not affected by taxane treatment. In contrast, ARV567es, another commonly detected ARV in clinics, showed certain response to taxanes in patient-derived xenografts as the hinge region is intact in this variant [92]. Consistent with these findings, AR-V7 was found to be significantly overexpressed in docetaxel-resistant PCa cells and forced expression of AR-V7 significantly impairs the efficacy of taxanes [93]. Furthermore, this group also showed that the nuclear import of AR-V7 is dependent on importin α/β machinery, supporting the notion that AR and AR-V7 have distinct mechanism for nuclear translocation [93]. Interestingly, similar to what AR-V7 did in AR-antagonist story, it can also impair the function of taxanes in retaining AR-FL in the cytoplasm, further contributing to the drug resistance [93]. However, the detailed interacting mechanism between AR and AR-V7 nuclear import is still lacking.

Although clinical evidences of AR-V7 are relatively well established in resistance to AR targeted therapies, data has just started to emerge in analyzing its role in taxane resistance. A clinical study published in 2015 investigated the responses to taxane (docetaxel and cabazitaxel) chemotherapy in 37 mCRPC patients with different AR-V7 status in their CTCs. In contrast to previous cell and xenograft-based studies, taxanes appear to show stronger effect than enzalutamide or abiraterone in AR-V7–positive men, while in AR-V7–negative men, taxanes and enzalutamide or abiraterone have comparable efficacy [94]. This finding implies that AR-V7 may not mediate the efficacy of taxanes like it does for the AR antagonists. Also, from 2012 to 2015, a clinical trial of up to 161 patients was conducted to determine if AR-V7 status in CTCs is a treatment-specific marker for response to AR inhibitors and taxanes. What they implicated was, once AR-V7–positive CTCs are detected, the preferred mCRPC therapy should be taxane rather than AR inhibitors [95]. Thus, these studies seem unable to verify the negative role of AR-V7 in taxanes treatment that observed in pre-clinical models. More recently, a novel clinical trial called TAXYNERGY applied digital droplet PCR (ddPCR) assay to measure AR splicing variant expression in CTCs from 83 mCRPC patients receiving docetaxel or cabazitaxel. As a result, absence of AR-V7 in patients CTCs associate with significant better response, indicating AR-V7 primarily mediated the prognostic impact [96]. These controversial observations might result from the detection methods of AR-V7 in CTCs, for example, the principle for determining whether a patient is AR-V7 positive or negative. Currently, there are still some false positive cases reported during the use of these liquid biopsies like checking circulating tumor DNA(ctDNA) and CTCs [97]. Another concern is that: whether the increased level of AR-V7 during CRPC progression simply results from the innative feature of advanced cancer state or being a crucial factor in mediating taxane resistance. In addition, the limited sample sizes require us to further warrant the exact role of AR-V7 in taxane therapy.

8. Conclusion and future direction

The emerging data of AR-V7 in recent years have made more scientists realizing the importance of this variant in PCa progression. As a result, AR-V7 is implicated in the regulation of AR-FL signaling, drug resistance, hormone-independent growth, metastasis and cell-cycle control, etc. [15,21,22,39,42,45,62,69,92,93,98,99] (Fig. 2). Obviously, deepening the understanding of this crucial variant will not only better explaining the abnormal AR signaling after androgen independency but also provides a potential biomarker for predicting the efficacy of CRPC treatments. For instance, the promising clinical results of AR-V7 in patients receiving AR-antagonists motivate similar studies in other commonly used chemotherapeutic drugs like taxanes. Even we are still currently lack of clinically-approved small molecule which specifically targets AR-V7, some AR NTD inhibitors as well as compounds which can induce degradation of AR-V7 are already in various clinical trials. Ideally, better outcomes from these clinical trials will largely benefit the treatment for AR-V7 positive patients.

However, considering the dramatic differences between canonical AR downstream events and AR-V7 specifically mediated pathways as discussed above, we still need more mechanism-based studies to determine the AR-V7 regulatory network. For example, defining the role of those AR-V7 regulated mitotic genes in CRPC development and drug resistance will likely help us establish novel therapeutic strategies with better efficacy and specificity. Also, the recent publication about the transcriptional repressive role of AR-V7 is another interesting direction for future investigation. Possibly, AR-V7 can not only activate novel oncogenetic pathways but also inhibit the function of some tumor suppressors and pro-apoptotic proteins.

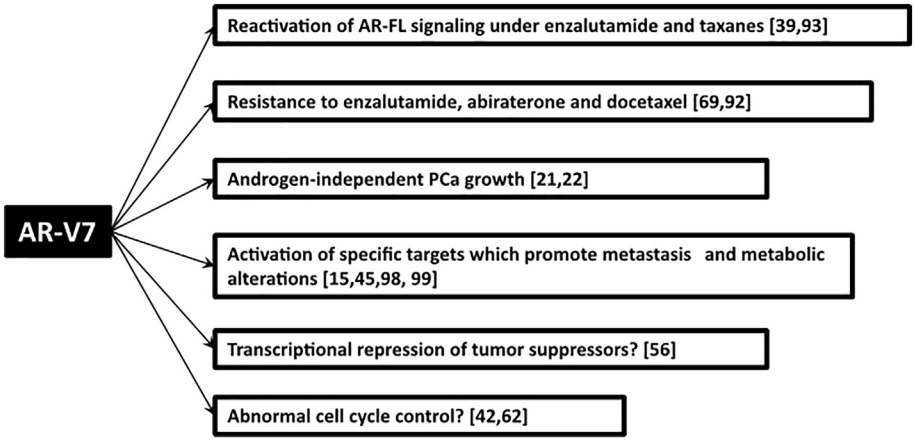

Fig. 2. Simplified model of the role of AR-V7 in PCa progression.

Abbreviation

PCa	prostate cancer
CRPC	castration-resistant prostate cancer
mCRPC	metastatic castration-resistant prostate cancer
AR	androgen receptor
AR-FL	full-length androgen receptor
AR-V7	androgen receptor splicing variant 7
FDA	Food and Drug Administration
NTD	N-terminal domain
DBD	DNA-binding domain
LBD	ligand-binding domain
ARE	androgen response element
PSA	prostate specific antigen
ADT	androgen deprivation therapy
CTC	circulating tumor cell
ctDNA	circulating tumor DNA
ChIP	chromatin immunoprecipitation
Plk1	polo-like kinase 1

Disclosure of potential conflicts of interest

No potential conflicts of interest are disclosed by the authors.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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