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AR-V7-Driven Mitochondrial Metabolic Reprogramming in Enzalutamide-Resistant Prostate Cancer: Mechanisms and Therapeutic Implications

Rongxin Chang and Zhaungzhuang Zhang*

School of Life Sciences, Anhui Medical University, Hefei 230032, Anhui, China
* Corresponding author: Zhaungzhuang Zhang, PhD, zhangzz2026@ahmu.edu.cn

ABSTRACT

Enzalutamide resistance in castration-resistant prostate cancer (CRPC) is frequently driven by androgen receptor splice variant 7 (AR-V7), a prognostic biomarker that lacks the ligand-binding domain and evades enzalutamide inhibition; however, the downstream metabolic networks sustaining resistant-cell survival remain incompletely understood. This review summarizes AR-V7 structural features, non-canonical transcriptional programs, and resulting mitochondrial dysfunction. AR-V7 occupies distinct chromatin-binding sites, preferentially activating genes involved in oxidative phosphorylation (OXPHOS), glutamine metabolism, and redox homeostasis while repressing tumor-suppressive metabolic genes. This dual transcriptional mode yields a bidirectional mitochondrial phenotype: hyperactive OXPHOS and enhanced antioxidant defense coexist with mitochondrial structural damage and ferroptosis evasion. Consequently, AR-V7-positive tumors exhibit high mitochondrial dependency, representing a targetable vulnerability. Preclinical strategies—including electron transport chain complex I inhibition, glutaminase blockade, copper ionophore-induced cuproptosis, and AR-V7-targeted degraders show promise in enzalutamide-resistant models, but normal tissue toxicity, metabolic plasticity, dynamic AR-V7 expression, and lack of validated biomarkers remain translational obstacles. In conclusion, AR-V7-driven mitochondrial metabolic remodeling is central to enzalutamide resistance; future studies should dissect AR-V7-mitochondria regulatory nodes and optimize mitochondria-targeted combination strategies.

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Introduction

Prostate cancer (PCa) is the second most prevalent malignancy and the sixth leading cause of cancer-related mortality among men worldwide [1]. Once the disease progresses to castration-resistant prostate cancer (CRPC), the therapeutic landscape has evolved from a reliance on hormonal therapy and chemotherapy alone to a precision-based system encompassing multiple mechanisms of action [2]. Current treatment selection is guided by prior treatment history and biomarker profiles, and includes androgen receptor signaling inhibitors (ARSIs) such as abiraterone and enzalutamide, taxane-based chemotherapy (e.g., docetaxel, cabazitaxel), PARP inhibitors for tumors harboring homologous recombination repair deficiencies, PSMA-targeted radioligand therapy (e.g., 177Lu-PSMA-617), and immunotherapy (e.g., sipuleucel-T) [2, 3] (Table 1). Despite this expansion, the clinical limitations of these agents remain substantial. Taxane-based chemotherapy is associated with dose-limiting myelosuppression and neurotoxicity, and multidrug resistance frequently emerges after repeated treatment. PARP inhibitors benefit only the small subset of patients with homologous recombination repair defects. 177Lu-PSMA radioligand therapy is constrained by loss of PSMA expression and renal accumulation-mediated toxicity. Immunotherapy monotherapy continues to yield low response rates in unselected patients. Consequently, treatment failure and disease progression remain nearly universal, underscoring the urgent need to dissect resistance mechanisms and identify more effective therapeutic strategies.

Among the available options, ARSIs have significantly improved clinical outcomes and now form a cornerstone of systemic therapy across multiple disease stages [4, 5]. The androgen receptor (AR) is essential for the normal function, survival,

Table 1. Treatment strategies for CRPC.

Drug category	Drug	Target and molecular mechanism	Key clinical characteristics	References
Taxane-based chemotherapy	Docetaxel (DOC)	Binds to β-tubulin to stabilize microtubule structure, blocks tumor cell mitosis at M-phase and induces apoptosis	First-line chemotherapy for mCRPC; objective response rate (ORR)≈12%; limited therapeutic efficacy with frequent drug resistance; significant toxicities including myelosuppression	[20]
	Cabazitaxel (CAB)	Second-generation taxane with a mechanism similar to docetaxel; retains activity against partial docetaxel-resistant tumors	Second-line chemotherapy after docetaxel failure; ORR14%; considerable toxicities	[21]
	Mitoxantrone (MIT)	Intercalates into DNA and inhibits topoisomerase- to trigger DNA damage	Early-stage chemotherapeutic agent with ORR ≈7%; rarely used currently and mainly for palliative therapy	[11]
Androgen receptor-signaling inhibitors (ARSIs, novel endocrine agents)	Abiraterone (ABI)	Inhibits CYP17A1 and blocks androgen biosynthesis in adrenal glands and tumor tissues	Administered before or after docetaxel; ORR ranges 6.6%-14.8%; common resistance mechanisms: AR-V7, AR amplification, intratumoral androgen resynthesis	[22, 23]
	Enzalutamide (ENZ)	Androgen receptor (AR) antagonist; binds to the AR ligand binding domain (LBD) and inhibits AR nuclear translocation and transcriptional activity	First-/later-line therapy for mCRPC; ORR ≈29%; predominant resistance drivers: AR-V7, LBD mutations, lineage plasticity-mediated transdifferentiation	[24, 25]
	Apalutamide (APA)	High-affinity AR antagonist; suppresses AR nuclear translocation and transcription of target genes	For non-metastatic and metastatic CRPC; ORR ≈50%	[11, 26]
	Darolutamide (DAR)	High-selectivity AR antagonist with low blood-brain-barrier penetration	nmCRPC/mCRPC ORR≈50%	[27]
PARP inhibitors (DNA-damage-repair-targeted agents)	Olaparib (OLA)	Inhibits PARP1/2, abrogates single-strand DNA-damage repair and induces synthetic lethality in HRR-deficient tumors	For HRR-mutated mCRPC progressing after ARSIs- or chemotherapy-based treatment; ORR ≈33%	[28]
	Rucaparib (RUC)	PARP1/2 inhibition to achieve synthetic lethality	For BRCA-altered mCRPC; ORR ≈43.5%	[29]
	Niraparib (NIR)	PARP1/2 inhibition	Superior efficacy in HRR-mutated patients whereas limited benefit in HRR-wild-type population; ORR 41% / 9% in respective subgroups	[30]
	Talazoparib (TAL)	Potent PARP trapping agent	For HRR-deficient mCRPC; therapeutic efficacy varies substantially according to genetic status	[11, 31]
PSMA-targeted radiopharmaceuticals	177-Lu-PSMA-617	Targets PSMA; β-emission induces double-strand DNA breaks in tumor cells	For PSMA-positive mCRPC after multiple-line treatments; ORR ≈51%	[32]
Bone-targeted therapies (for bone metastasis)	Zoledronic acid (ZA)	Bisphosphonate that suppresses osteoclast activity	Reduces skeletal-related events (SREs); tumor shrinkage is not its primary therapeutic goal	[33]
	Denosumab (DEN)	RANKL-targeted monoclonal antibody that inhibits osteoclast activation	Prevents bone-metastasis-related fractures and improves bone-marker responses	[11, 34]
	Radium-223 (R-223)	α-emitting radiopharmaceutical that induces DNA damage in bone-metastatic lesions	For symptomatic bone metastasis without visceral metastasis; prolongs overall survival with modest anti-tumor shrinkage effect	[35]
Immunotherapies	Sipuleucel-T S-T	Autologous cellular immunotherapy that activates prostate-antigen-specific T-cell responses	For asymptomatic/minimally symptomatic mCRPC; immune-related response rate (IRR) ≈73%; limited radiographic tumor regression	[36]
	Pembrolizumab (PEMB)	PD-1 immune-checkpoint inhibitor	Modest clinical benefit as monotherapy with ORR ≈13%; effective in MSI-H/dMMR subgroups	[37]

and differentiation of prostate tissues [6, 7]. During prostate tumorigenesis, AR signaling undergoes a functional switch from a tumor-suppressive role to an oncogenic driver [8, 9]. In the castration-resistant state, reactivation of AR signaling *via* AR amplification, mutation, splice variants, or alternative pathways ultimately drives disease progression [10]. Enzalutamide, a second-generation AR antagonist, improves survival in patients with CRPC; however, acquired resistance develops in most patients within 6-12 months, and the emergence of androgen receptor splice variant 7 (AR-V7) has been identified as a central mediator of this resistance (Figure 1). Although AR-V7 lacks the ligand-binding domain and therefore escapes direct inhibition by enzalutamide, accumulating evidence indicates that its oncogenic functions extend beyond drug evasion to include reprogramming of cellular metabolism, particularly mitochondrial function. This review synthesizes current knowledge on the structural and transcriptional features of AR-V7, delineates the bidirectional mitochondrial dysfunction observed in enzalutamide-resistant CRPC, and critically evaluates mitochondrial-targeted therapeutic strategies. By linking AR-V7-driven transcriptional remodeling to mitochondrial metabolic adaptation, we aim to provide a mechanistic framework for understanding enzalutamide resistance and to highlight actionable vulnerabilities for future therapeutic exploitation.

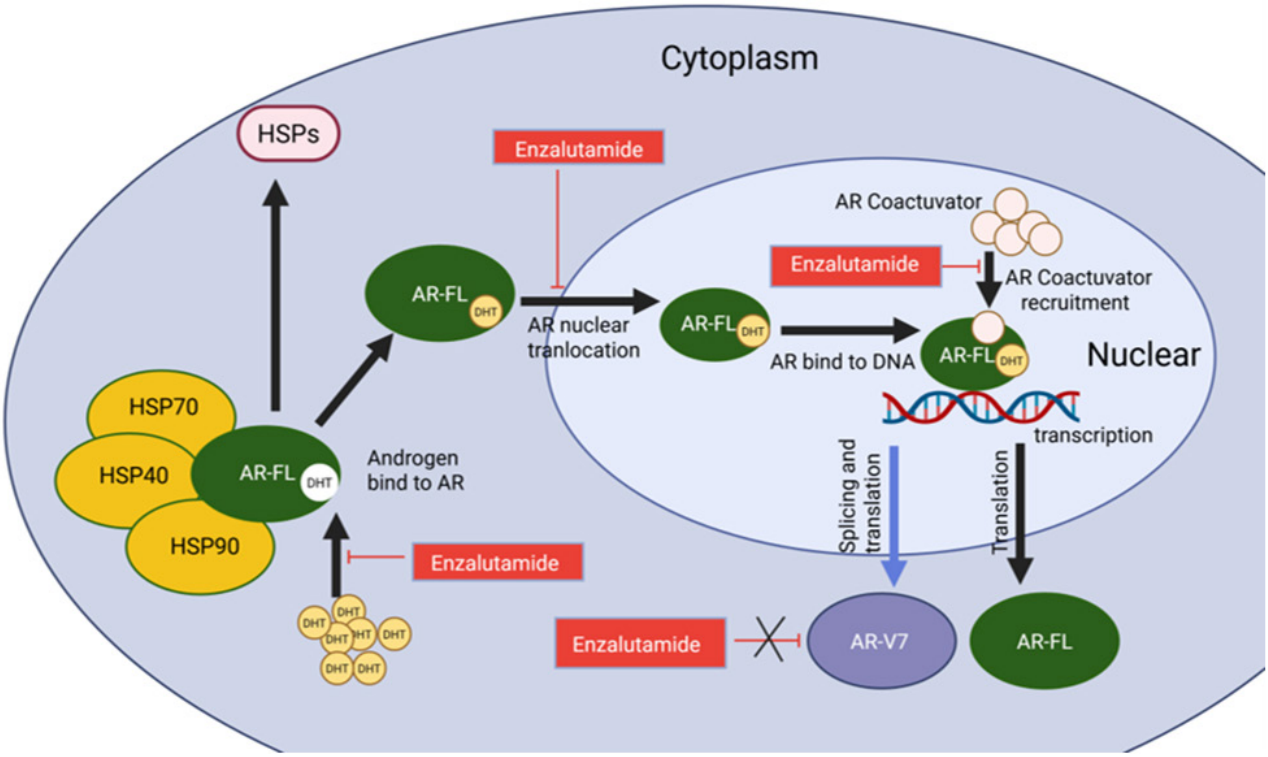
Beyond AR-centric mechanisms, metabolic reprogramming has emerged as a critical determinant of drug resistance in CRPC [11, 12]. Tumor cells exposed to ARSI treatment frequently rewire their energy metabolism to sustain survival and proliferation under therapeutic pressure. Key metabolic alterations associated with CRPC drug resistance include: (i) a shift from aerobic glycolysis toward mitochondrial oxidative phosphorylation (OXPHOS), which provides enhanced ATP production and biosynthetic intermediates [13, 14]; (ii) upregulation of glutaminolysis and reductive carboxylation to replenish tricarboxylic acid (TCA) cycle intermediates [14]; (iii) augmented antioxidant defense systems that neutralize reactive oxygen species (ROS) generated by heightened mitochondrial activity [15, 16]; and (iv) altered lipid metabolism, including enhanced de novo lipogenesis and intratumoral androgen synthesis [12, 17]. These metabolic adaptations are not merely passive byproducts of oncogenic transformation but are actively regulated by transcription factors such as AR-V7, MYC, and HIF-1α, which converge on mitochondrial function to shape the drug-resistant phenotype [18]. Notably, AR-V7, as a constitutively active AR splice variant, preferentially occupies regulatory regions of nuclear-encoded mitochondrial genes and orchestrates a transcriptional program that directly links AR signaling to cellular energy metabolism [15, 16, 19]. Delineating this AR-V7–mitochondria axis provides a mechanistic bridge between androgen receptor signaling and metabolic drug resistance and constitutes the central focus of this review.

AR-V7 as a Key Driver of Enzalutamide Resistance in CRPC: Clinical Evidence and Mechanistic Gaps

Enzalutamide, a second-generation androgen receptor (AR) antagonist, is widely used as a first-line ARSI for metastatic castration-resistant prostate cancer (mCRPC) and improves early survival (Figure 1); however, more than half of patients develop acquired resistance within 6-12 months, and no standardized salvage regimen exists thereafter. Persistent activation of AR signaling constitutes a central intrinsic driver of enzalutamide resistance. Multiple mechanisms have been implicated, including AR gene amplification or protein overexpression, AR ligand-binding domain mutations, generation of AR splice variants (AR-Vs), AR-driven lineage plasticity leading to neuroendocrine differentiation, and aberrant activation of bypass pathways such as Wnt, PI3K, and NF-κB [20-26]. Among these, AR-V7 has emerged as one of the most robust clinical biomarkers and a key mediator of resistance to enzalutamide and other ARSIs [27, 28].

Clinical evidence consistently demonstrates that AR-V7 positivity is associated with markedly inferior outcomes in enzalutamide-treated CRPC patients. Prospective studies show that AR-V7-positive patients exhibit lower prostate-specific antigen (PSA) response rates, shorter PSA-progression-free survival, shorter clinical/radiographic progression-free survival, and reduced overall survival compared with AR-V7-negative patients [29, 30]. Furthermore, enzalutamide treatment itself can further upregulate AR-V7 expression, establishing a feed-forward loop that reinforces the resistant phenotype [31]. Although the clinical association between AR-V7 and enzalutamide resistance is well established, the downstream effector networks through which AR-V7 sustains tumor cell survival under drug stress remain incompletely defined. In particular, whether AR-V7 functions by reprogramming central hubs of cellular energy metabolism, such as mitochondria, has not

Figure 1. Mechanisms by which enzalutamide inhibits AR signaling in CRPC. Enzalutamide impedes AR-FL signaling via three distinct mechanisms: competitive displacement of DHT from the androgen receptor, abrogation of AR nuclear translocation, and inhibition of co-activator recruitment. Nevertheless, this agent is ineffective against AR-V7, an LBD-deficient splice variant that mediates ligand-independent transcriptional activation. Expression of AR-V7 thereby confers therapeutic resistance in castration-resistant prostate cancer (CRPC).



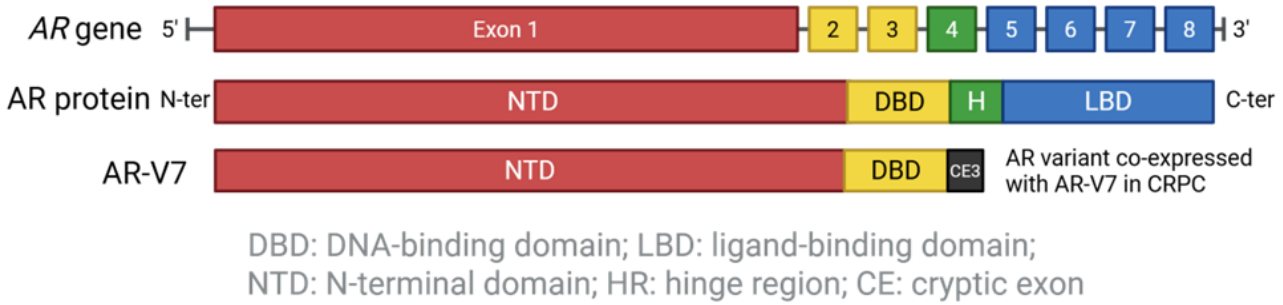
been systematically addressed. This gap constitutes the central rationale for the present review, which focuses on the crosstalk between AR-V7 and mitochondrial dysfunction.

Current mechanistic interpretations of AR-V7-mediated resistance are largely confined to the notion that AR-V7 lacks the ligand-binding domain and therefore cannot be bound and inhibited by enzalutamide. While this explains how AR-V7 evades direct drug targeting, it fails to construct a complete upstream-to-downstream regulatory chain linking AR-V7-driven transcriptional reprogramming, mitochondrial metabolic remodeling, and tumor cell survival under therapeutic stress. Emerging multi-omics evidence indicates that AR-V7 possesses a chromatin-binding profile distinct from that of full-length AR and preferentially regulates genes enriched in mitochondrial respiration, glutamine metabolism, and redox homeostasis [15, 16, 19], suggesting that mitochondria may serve as central metabolic effectors downstream of AR-V7. However, the causal relationships among AR-V7 transcriptional activity, mitochondrial dysfunction, and drug resistance have not been systematically integrated. This review therefore connects the molecular features of AR-V7, its unique transcriptional regulatory programs, the phenotypic manifestations of mitochondrial dysfunction, and mitochondria-targeted reversal strategies. By synthesizing these aspects, we aim to fill a critical gap in the literature regarding the interplay between AR-V7 and mitochondrial metabolism and to provide a comprehensive theoretical framework for understanding the metabolic basis of enzalutamide resistance and for developing novel sensitization strategies.

Structural Organization and Biogenesis of AR-V7

The gene encoding full-length androgen receptor (AR-FL) is located at Xq11-Xq12 on the X chromosome [32] and was first cloned by Chang et al. in 1988 [33]. AR-FL comprises approximately 919 amino acids organized into four functional domains: the N-terminal domain (NTD), DNA-binding domain (DBD), hinge domain (HD), and ligand-binding domain (LBD) [34-36] (Figure 2). Under the selective pressure of androgen receptor signaling inhibitor (ARSI) therapy, particularly in castration-resistant prostate cancer (CRPC), alternative splicing of the AR pre-mRNA generates multiple androgen recep-

Figure 2. Structures of androgen receptor and splice variant 7.



tor splice variants (AR-Vs). Several mechanisms have been implicated in AR-V biogenesis, including AR gene rearrangement, the predominant mechanism underlying AR-V7 and AR-V567es generation, AR gene point mutations, post-translational modifications, and dysregulation of splicing factors such as hnRNPA1, U2AF2, and Sam68 [37-44].

AR-Vs were first identified by Tepper et al. more than two decades ago [45], and over 20 variants have since been characterized [46]. Most AR-Vs retain the NTD and DBD but lack the HD and LBD; exceptions include AR8, which has a transcriptionally inactive DBD; AR-V3, which lacks the DBD zinc-finger motif; and AR45, which is devoid of the NTD [46]. Among these variants, AR-V7 has attracted particular attention because of its clinical association with enzalutamide resistance.

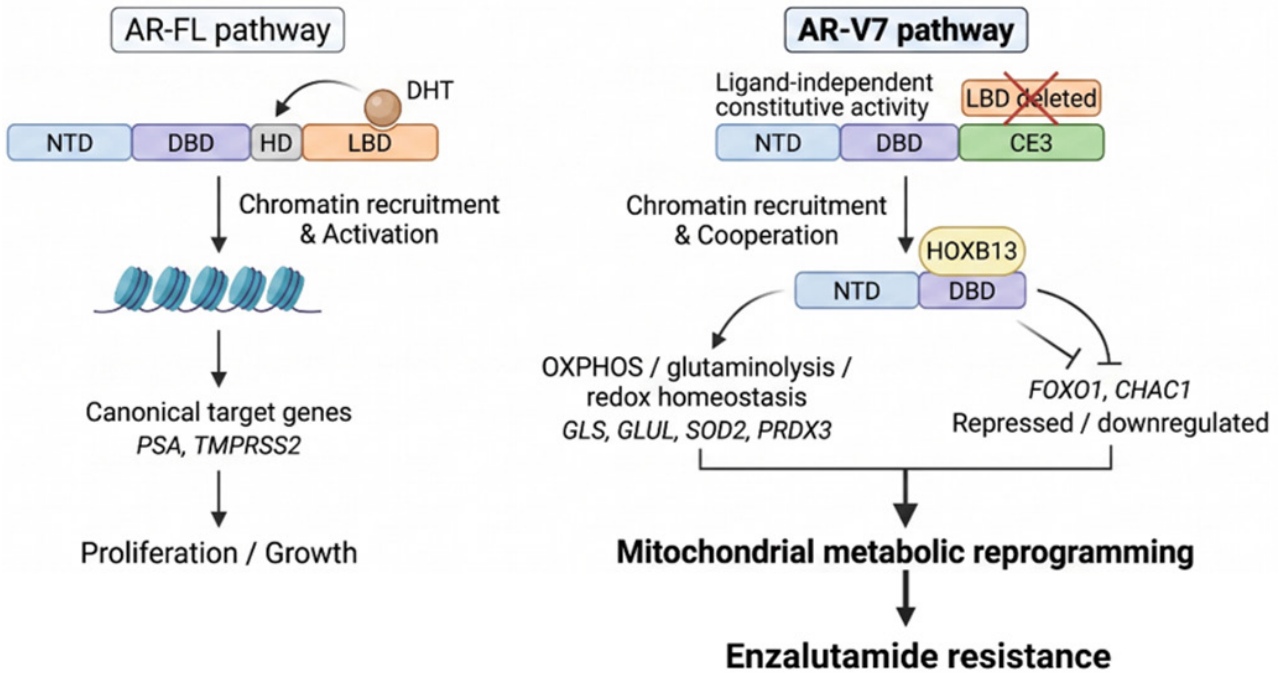
AR-V7 retains the intact NTD and DBD but lacks the HD and LBD; the deleted C-terminal region is replaced by a unique short peptide encoded by cryptic exon 3 (CE3) [47]. This structural alteration preserves the AF-1 transactivation domain within the NTD while removing the ligand-binding region, thereby rendering AR-V7 constitutively active and capable of driving target gene transcription in an androgen-independent manner [48] (Figure 2). This constitutive activity provides the structural basis for AR-V7 to reprogram downstream transcriptional networks, including those governing mitochondrial metabolism, as discussed in the following sections.

AR-V7 Exhibits a Distinct Transcriptional Regulatory Program Enriched for Mitochondrial and Metabolic Genes

Although AR-V7 has historically been regarded as a truncated AR-FL isoform lacking the ligand-binding domain, recent chromatin immunoprecipitation sequencing (ChIP-seq) and RNA sequencing (RNA-seq) studies demonstrate that its transcriptional functions are not merely a subset of AR-FL activity. Basil et al. showed that AR-V7 occupies distinct genomic binding sites and regulates a broader repertoire of target genes than AR-FL, with a significant enrichment for genes involved in metabolic pathways, mitochondrial function, and redox homeostasis [15]. Consistently, Sugiura et al. identified a set of genes specifically activated by AR-V7 but not bound by AR-FL, including those encoding glutamine metabolism enzymes, electron transport chain (ETC) subunits, and reactive oxygen species (ROS)-responsive factors [16].

A landmark study by Cato et al. further delineated the unique transcriptional landscape of AR-V7 in CRPC cells. Using integrated ChIP-seq and RNA-seq, they demonstrated that the chromatin-binding profile of AR-V7 differs substantially from that of AR-FL and exerts bidirectional transcriptional regulation. AR-V7 not only activates a distinct panel of metabolism-related genes, such as ETC subunits, the glutamine transporter SLC1A5, and redox-regulatory enzymes, but also directly represses multiple tumor-suppressive metabolic genes, including those involved in ROS scavenging and iron homeostasis [19]. This dual regulatory mode provides a mechanistic framework for the seemingly paradoxical coexistence of heightened OXPHOS dependence and enhanced antioxidant defense in drug-resistant cells. By simultaneously driving mitochondrial ATP production and suppressing oxidative-damage pathways, AR-V7 enables tumor cells to meet energy demands while evading metabolic stress-induced cell death. Notably, AR-V7 directly binds and represses genes associated with glutathione metabolism and ferroptosis, including FOXO1 and CHAC1, thereby establishing a comprehensive metabolic adaptation program at the transcriptional level [19].

Figure 3. Distinct transcriptional programs of AR-full and AR-V7 in CRPC.



The selective targeting of metabolic genes by AR-V7 is further modulated by lineage-specific transcription factors. A 2018 study demonstrated that HOXB13 extensively co-localizes with AR-V7 at chromatin-binding sites in prostate cancer cells. Knockout of HOXB13 selectively attenuates AR-V7-mediated activation of metabolic target genes without affecting canonical AR target genes, indicating that HOXB13 acts as a critical co-regulator bridging AR-V7 to the transcriptional control of mitochondrial and metabolic genes [49]. This interaction may explain the preferential association of AR-V7 with mitochondrial functional pathways.

Functionally, AR-V7 can drive transcriptional programs independently of AR-FL. Liang et al. showed that knockout of AR-FL does not impair the chromatin-binding capacity of AR-V7, and the two receptors can regulate AR-associated transcriptional networks in parallel [50]. Given that AR-V7 retains an intact NTD with the AF-1 transactivation domain and a functional DBD, its constitutive activity sustains the activation of downstream metabolic regulatory axes under androgen-deprived conditions. Among AR-V7 target genes, multiple mitochondrial ETC subunits (e.g., NDUFA, SDHB) and ROS-scavenging enzymes (e.g., SOD2, PRDX3) are markedly upregulated, suggesting that AR-V7 reprograms the mitochondrial transcriptome to reshape cellular redox balance [15, 16]. This capacity likely represents an important mechanism underlying AR-V7-mediated drug resistance, although the precise regulatory nodes remain to be systematically identified.

Whether AR-V7 requires heterodimerization with AR-FL to exert its biological functions remains an area of ongoing debate [19, 51]. Nevertheless, the transcriptomic evidence strongly indicates that AR-V7 possesses intrinsic potential to regulate mitochondrial metabolism, independent of any obligatory partnership with AR-FL. Collectively, these multi-omics findings establish that AR-V7 has a chromatin-binding profile distinct from AR-FL, with its specific target genes markedly enriched in mitochondrial pathways including the ETC, glutamine metabolism, and ROS homeostasis. This positions mitochondria as central metabolic effectors downstream of AR-V7 and provides the rationale for examining the dual roles of mitochondrial dysfunction in enzalutamide resistance in the following section (Figure 3).

Clinical and Preclinical Evidence Establishing AR-V7 as a Driver of Enzalutamide Resistance

Sharp et al. examined AR-V7 protein expression in 358 primary prostate tumor specimens and 293 metastatic biopsies, revealing that AR-V7 positivity is extremely rare (< 1%) in treatment-naïve primary prostate cancer, but detectable in 75% of patients following androgen deprivation therapy (ADT) [52].

In patients receiving enzalutamide, AR-V7 protein expression is further elevated, suggesting that enzalutamide treatment promotes AR-V7 biogenesis. However, enzalutamide is not the sole determinant of AR-V7 generation. Consistent with this notion, Sciarra et al. stratified 56 treatment-naïve prostate cancer patients by clinical risk and found that AR-V7 was positive in 24 of 32 high-risk patients, 4 of 13 intermediate-risk patients, and only 2 of 11 low-risk patients [53]. These findings indicate that AR-V7 can be detected by immunohistochemistry in more than 50% of treatment-naïve patients with non-metastatic prostate cancer and that AR-V7 positivity correlates significantly with clinical risk stratification ($p < 0.001$). Collectively, these observations demonstrate that AR-V7 expression is not exclusively a consequence of enzalutamide exposure; rather, it can arise under disease progression and selective pressure from AR-targeted therapies.

Among patients receiving enzalutamide for CRPC, AR-V7 positivity is strongly associated with adverse clinical outcomes. In a prospective study by Antonarakis et al., 31 patients treated with enzalutamide or abiraterone were analyzed; within the enzalutamide-treated cohort, PSA response rates were markedly lower in AR-V7-positive patients than in AR-V7-negative patients (0% versus 53%, $p = 0.004$) [29]. Furthermore, AR-V7-positive patients exhibited significantly shorter PSA-progression-free survival (median 1.4 versus 6.0 months, $p < 0.001$), shorter clinical/radiographic progression-free survival (median 2.1 versus 6.1 months, $p < 0.001$), and shorter overall survival (median 5.5 months versus not reached, $p = 0.002$). These data demonstrate that AR-V7 positivity is associated with reduced sensitivity to enzalutamide and poor therapeutic responses in CRPC patients. Additional studies detecting AR-V7 in circulating tumor cells (CTCs) from peripheral blood of high-risk CRPC patients receiving enzalutamide have reached consistent conclusions: AR-V7 expression represents an independent risk factor for shortened clinical progression-free survival and overall survival [30]. Moreover, continued enzalutamide therapy in AR-V7-positive patients generally fails to achieve meaningful clinical benefit, underscoring the need for alternative therapeutic strategies in this subgroup.

Preclinical studies have further established a causal role for AR-V7 in enzalutamide resistance. In CRPC cell models, enzalutamide treatment elevates AR-V7 expression and promotes the transcription of its downstream target genes, while AR-V7 knockdown restores enzalutamide sensitivity, indicating that AR-V7 is a pivotal mediator of drug resistance [54]. Consistently, using patient-derived xenograft (PDX) models, Zhu et al. demonstrated that tumors with high expression of full-length AR (AR-FL) alone develop resistance to first-generation AR signaling inhibitors but not to the second-generation inhibitor enzalutamide [55]. Their subsequent cellular experiments revealed that the establishment of enzalutamide resistance requires concurrent high-level AR-FL expression and AR-V7 levels reaching a critical threshold. Together, these findings provide direct experimental evidence linking AR-V7 to the acquisition of enzalutamide resistance, rather than merely serving as a passive biomarker.

Collectively, abundant clinical and preclinical data consistently demonstrate that high AR-V7 expression serves as an independent risk factor for poor enzalutamide efficacy and unfavorable prognosis in CRPC. However, as a biomarker alone, AR-V7 does not fully explain the metabolic mechanisms that sustain drug-resistant cell survival under therapeutic pressure. A comprehensive mechanistic interpretation requires integration with mitochondrial metabolic reprogramming, which is the focus of the following section.

The Dual Role of Mitochondrial Dysfunction in Enzalutamide Resistance: OXPHOS Hyperactivation and Mitochondrial Impairment

Metabolic reprogramming, energy deregulation, and mitochondrial dysfunction operate as an interconnected tripartite regulatory axis that governs the acquisition and persistence of enzalutamide resistance in CRPC. Metabolic reprogramming rewires core catabolic–anabolic pathways, including enhanced oxidative phosphorylation, glutaminolysis, and fatty acid oxidation, to generate sufficient ATP and biosynthetic precursors for sustained proliferation under AR-targeted therapeutic pressure [13, 14, 56]. Energy deregulation, exemplified by altered adenine nucleotide ratios and compensatory activation of stress-responsive kinases, triggers mitochondrial biogenesis and adaptive autophagy [57], enabling resistant cells to cope with nutrient deprivation and drug-induced stress [18, 58]. Mitochondria serve as the central integrator of this regulatory network: beyond ATP production via the electron transport chain, they coordinate ROS homeostasis, calcium signaling, and apoptotic threshold determination

[15, 16, 59]. In AR-V7-positive resistant tumors, emerging evidence indicates that AR-V7-driven transcriptional remodeling converges upon all three components of this axis: it upregulates metabolic genes to boost bioenergetic output [15, 16], induces antioxidant enzymes to neutralize excessive mitochondrial ROS [19], and may reshape mitochondrial respiratory capacity through modulation of ETC subunit expression [15, 16, 19]. The synergistic interplay among altered metabolism, perturbed energy sensing, and mitochondrial adaptation builds a self-reinforcing pro-survival circuit that confers enzalutamide refractoriness. Importantly, preclinical studies demonstrate that targeting only one component frequently provokes compensatory activation of alternative arms [13, 60], highlighting the necessity of combinatorial therapeutic strategies to disrupt this entire axis [61].

As described above, AR-V7 activates a broad set of mitochondrial-associated target genes, positioning it as a central molecular link between AR signaling and cellular energy metabolism. In enzalutamide-resistant cells, two seemingly opposing mitochondrial phenotypes coexist: hyperactivated oxidative phosphorylation (OXPHOS) and concurrent mitochondrial structural damage with functional decline. The unique bidirectional transcriptional regulatory mode of AR-V7 offers a unifying mechanistic explanation for this apparent paradox. This section reviews these two mitochondrial dysregulation phenotypes, their associated metabolic vulnerabilities, and the therapeutic potential of targeted intervention.

Mitochondrial dysfunction in drug-resistant tumors is bidirectional. A subset of enzalutamide-resistant cells displays high dependence on mitochondrial oxidative phosphorylation (OXPHOS). Overexpression of steroid sulfatase (STS) in enzalutamide-resistant cells leads to transcriptomic enrichment of oxidative phosphorylation and electron transport chain (ETC) pathways. Seahorse metabolic assays show that STS overexpression markedly increases cellular oxygen consumption rate (OCR) and mitochondrial complex I enzymatic activity, and blockade of STS with the specific inhibitor SI-2 rapidly reverses these mitochondrial respiration parameters and abrogates the drug-resistant phenotype [12]. Multi-omics metabolic flux analyses further demonstrate that enzalutamide-resistant cells (e.g., C4-2B, CWR22RV1) undergo a global metabolic switch from aerobic glycolysis toward OXPHOS, accompanied by substantially enhanced electron transport system (ETS) activity compared with drug-sensitive cells [13]. Functionally, the ETS complex I-selective inhibitor IACS-010759 and the glutaminase inhibitor CB-839 exert markedly augmented growth-suppressive effects in enzalutamide-pretreated cells [13]. Clinically, among circulating tumor cells (CTCs) isolated from patients receiving androgen receptor-targeted therapy, high mitochondrial ETS activity was associated with the development of acquired enzalutamide resistance within six months, suggesting that mitochondrial ETS activity in CTCs may serve as a dynamic predictive biomarker for therapeutic resistance [13].

In contrast to the OXPHOS-enhancing phenotype, a genome-wide CRISPR-screen-based study uncovered an independent role for impaired mitochondrial function in drug resistance. Knockout of PRKCD or key components of the NF-κB pathway (IKBKG) in tumor cells conferred resistance to androgen deprivation, including enzalutamide treatment. Mechanistically, proteomic analyses and electron microscopy observations demonstrated that these resistant cells display markedly reduced OXPHOS levels together with disrupted mitochondrial ultrastructure. This mitochondrial dysfunction further compromises the ferroptosis-signaling axis, thereby enabling tumor cells to evade macrophage-mediated clearance [59].

These two seemingly opposing mitochondrial adaptation phenotypes are not mutually exclusive but can be mechanistically unified within the AR-V7-driven transcriptional regulatory framework. The work by Cato et al. demonstrated that AR-V7 simultaneously upregulates OXPHOS-related genes and directly represses tumor-suppressive metabolic genes such as FOXO1 and CHAC1, thereby attenuating cellular capacity for oxidative damage clearance and ferroptosis execution [19]. This dual regulation establishes a metabolic phenotype characterized by elevated respiratory output coupled with potent antioxidant compensation, endowing drug-resistant cells with the plasticity to switch compensatory pathways upon exposure to mitochondria-targeted agents. This plasticity likely explains why single-agent OXPHOS-targeting therapies fail to fully eradicate drug-resistant tumor cells.

The bidirectional mitochondrial adaptation states described above, particularly OXPHOS hyperactivation, represent targetable metabolic vulnerabilities. Under enzalutamide treatment, tumor cells exhibit increased mitochondrial dependency, rendering them highly susceptible to cytotoxicity induced by copper ionophores such as elesclomol or disulfiram. Mechanistically, this synergistic effect is associated

with hallmark features of cuproptosis, including accumulation of lipoylated proteins and destabilization of iron-sulfur-cluster proteins, and can be completely reversed by copper-specific chelators [61]. This phenomenon has been validated in enzalutamide-resistant CRPC cells and in the 22RV1 xenograft model. Furthermore, the expression level of FDX1, a mitochondrial-matrix reductase, is selectively correlated with elesclomol sensitivity, suggesting its potential as a predictive biomarker to guide the clinical application of cuproptosis-inducing agents [61].

In summary, enzalutamide-resistant tumor cells undergo AR-V7-driven bidirectional mitochondrial remodeling. High OXPHOS dependency represents a core metabolic vulnerability, yet the direct molecular links between AR-V7 transcriptional activity and specific mitochondrial functional alterations remain incompletely defined.

AR-V7-Mediated Mitochondrial Dysfunction: Emerging Molecular Nodes and Regulatory Mechanisms

Although AR-V7 has been established as a core driver of enzalutamide resistance, and enzalutamide-resistant cells exhibit AR-V7-dependent bidirectional mitochondrial dysfunction, the key molecular nodes through which AR-V7 directly modulates mitochondrial function remain incompletely characterized. Existing evidence has nonetheless begun to delineate regulatory clues across multiple dimensions, including mitochondrial biogenesis and dynamics, reactive oxygen species (ROS) homeostasis, and membrane structural organization. This section synthesizes these emerging clues, highlights unresolved questions, and outlines their therapeutic implications.

*Mitochondrial biogenesis and dynamics***.**

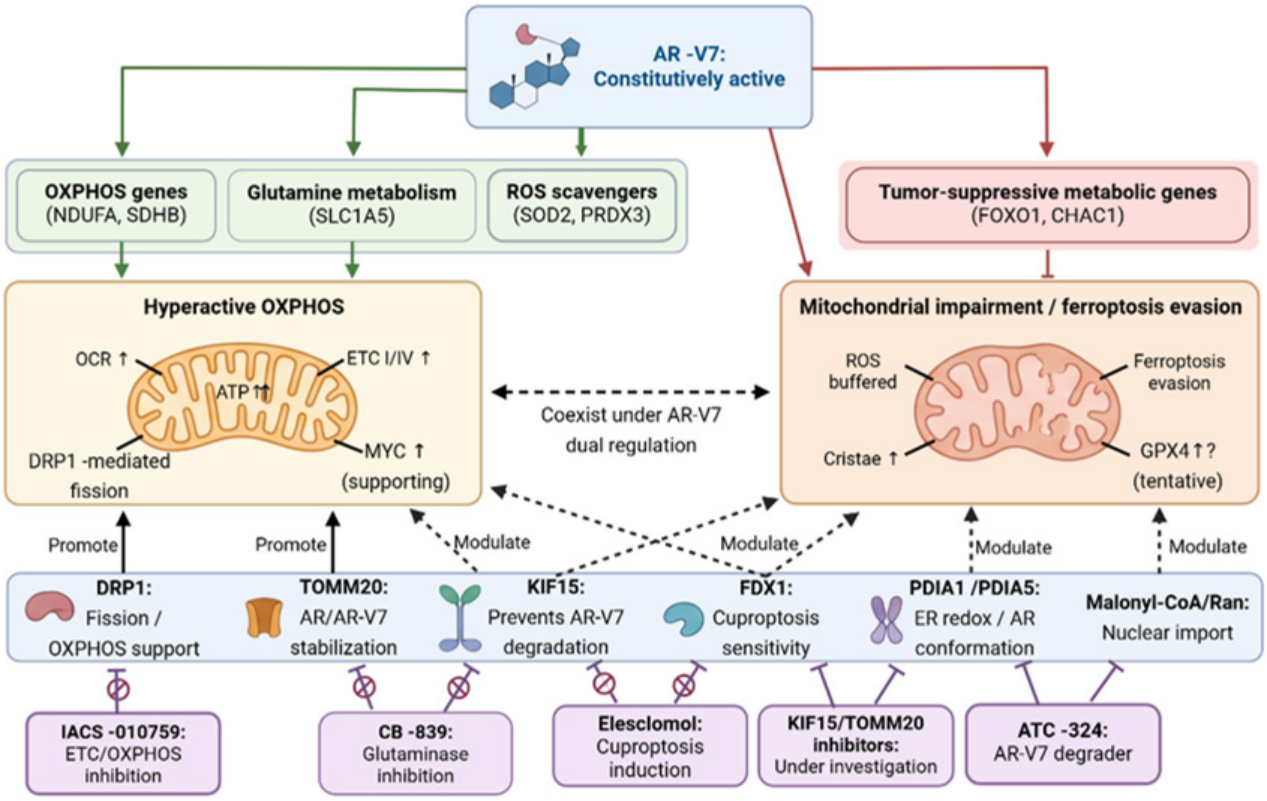
Studies using an inducible LNCaP cell model revealed that although both AR-V7 and AR-FL stimulate glycolysis, AR-V7 uniquely enhances glutaminolysis and reductive carboxylation to replenish tricarboxylic acid (TCA) cycle intermediates and sustain substrate supply for mitochondrial respiration [14]. In parallel, AR signaling promotes mitochondrial fission by upregulating dynamin-related protein 1 (DRP1), thereby accelerating mitochondrial pyruvate import to support oxidative phosphorylation (OXPHOS) [60]. Although AR-V7 was not directly examined in that study, its retention of the N-terminal and DNA-binding domains suggests that AR-V7 may similarly maintain DRP1 expression. Integrated multi-omics analyses further revealed that pharmacological AR blockade triggers a sequential shift characterized by glycolysis suppression, mitochondrial elongation, and compensatory OXPHOS elevation. Constitutively active AR-V7 may sustain high-level expression of MYC and DRP1, thereby anchoring drug-resistant cells in a hyperactive steady state of "fission-driven OXPHOS" [18]. Additionally, the discovery of AR-V7 phase-separated condensates provides new insight into its potent transcriptional regulation of mitochondrial-related genes. In CRPC cells, AR-V7 forms transcription-competent molecular condensates that drive target gene expression in an androgen-independent manner; cysteine residues C327 and C406 within the AF-1 domain are critical for condensate formation and AR-V7-driven functions [62]. AR-V7 can also promote osteoblastic bone metastasis by activating transcriptional programs distinct from those governed by AR-FL [63], suggesting that its modulatory effects on the tumor metabolic microenvironment may extend beyond mitochondrial regulation. Nevertheless, whether AR-V7 directly binds mitochondrial DNA or enhancer regions of nuclear-encoded mitochondrial genes remains an open question.

The molecular nodes linking AR signaling to mitochondrial function remain incompletely defined in CRPC. Parallel evidence from AI-resistant breast cancer demonstrates that AR directly transactivates CRAT, the rate-limiting enzyme for mitochondrial fatty acid import via the carnitine shuttle, thereby coupling AR signaling to OXPHOS capacity[64]. Whether AR-V7 retains this CRAT-regulatory capacity, or whether it preferentially targets distinct mitochondrial entry points such as glutamine transporters (e.g., SLC1A5), remains to be experimentally resolved.

Mitochondrial ROS homeostasis.

Multiple ROS-scavenging enzymes among AR-V7 target genes, including SOD2 and PRDX3, exhibit markedly elevated transcriptional levels [15, 16], suggesting that AR-V7 actively remodels cellular redox balance to evade oxidative stress-induced apoptosis. Consistent with this, endoplasmic reticulum protein disulfide isomerases PDIA1 and PDIA5 preserve full-length AR conformation by catalyzing disulfide bond formation within the AR ligand-binding domain. Although inhibition of these enzymes cannot directly degrade LBD-deficient AR-V7, it elicits global redox

Figure 4. Schematic overview of AR-V7-mediated mitochondrial regulatory nodes in CRPC.



stress and exerts cytotoxic effects through endoplasmic reticulum stress and mitochondrial dysfunction [65]. This indicates that manipulating cellular redox status may bypass the AR-V7-mediated barrier. However, direct experimental evidence is still lacking as to whether AR-V7, by modulating the mitochondrial ROS production rate, stabilizes its own protein and thereby establishes a positive "metabolism-transcription" feedback loop (Figure 4).

Mitochondrial membrane architecture and protein translocation.

The outer mitochondrial membrane translocase TOMM20 has been identified as a chaperone-like protein capable of stabilizing AR conformation independently of canonical heat shock proteins; TOMM20 knockdown promotes AR degradation *via* the ubiquitin-proteasome pathway [66]. Given that AR-V7 lacks the LBD, whether TOMM20 similarly sustains AR-V7 protein stability by interacting with its NTD or DBD remains to be experimentally validated. In parallel, KIF15 directly binds the N-terminal domain of AR/AR-V7 and prevents their degradation by reinforcing the association between USP14 and AR/AR-V7, thus establishing a positive feedback loop [67]. Furthermore, abnormally accumulated malonyl-CoA in CRPC enhances Ran activity through lysine malonylation at the K141 residue of Ran, markedly boosting nuclear import efficiency of AR and sustaining robust AR transcriptional output even under androgen-deprivation conditions [17]. This regulatory cascade - metabolite accumulation, lysine malonylation, enhanced nuclear import - reveals a ligand-binding-independent layer of AR regulation; however, its impact on AR-V7 nuclear localization remains to be directly validated (Figure 4).

Therapeutic implications.

Collectively, these multidimensional clues suggest that AR-V7-positive tumors exhibit high dependency on mitochondrial OXPHOS, creating a targetable synthetic-lethal therapeutic window. Enzalutamide treatment further amplifies mitochondrial dependency in CRPC cells, rendering tumor cells highly susceptible to cuproptosis triggered by copper ionophores such as elesclomol, and this synergistic effect persists in drug-resistant cells[61]. Mechanistically, ligand-bound AR directly binds to cis-regulatory elements of FDX1 and drives FDX1 upregulation upon exposure to AR antagonists. Elevated FDX1 promotes Cu^{+} accumulation, destabilizes iron-sulfur-cluster proteins, and disrupts mitochondrial metabolism,

thereby establishing a pro-cuproptosis state [68]. Whether this mechanism operates in AR-V7-positive cells represents a critical issue governing the clinical applicability of cuproptosis-inducing therapies. Directly resolving the causal relationship between AR-V7 and mitochondrial function therefore remains a priority for future investigation (Figure 4).

Preclinical Mitochondrial-Targeted Strategies and Translational Challenges in Enzalutamide-Resistant Prostate Cancer

Given the metabolic hallmark of high mitochondrial OXPHOS dependency driven by AR-V7 signaling, targeting mitochondrial metabolic pathways represents a promising direction for overcoming enzalutamide resistance. This section reviews key preclinical combination strategies, including electron transport chain inhibition, cuproptosis induction, AR-V7 degradation, and modulation of AR-V7 stability networks, compares their synergistic antitumor effects, and systematically examines translational barriers such as systemic toxicity, metabolic plasticity, and limitations of predictive biomarkers.

(1) Inhibition of the electron transport chain and glutamine metabolism

Enzalutamide-resistant cells (e.g., C4-2B, 22RV1) exhibit substantially higher electron transport system (ETS) activity than drug-sensitive counterparts. Treatment with the ETS complex I-selective inhibitor IACS-010759 or the glutaminase inhibitor CB-839 produces markedly augmented growth-suppressive effects in resistant cells [13]. However, single-agent OXPHOS inhibition frequently triggers compensatory upregulation of glycolysis, and combination with glycolysis inhibitors such as 2-deoxyglucose may be required to achieve durable therapeutic efficacy.

(2) Induction of cuproptosis

Gao et al. demonstrated that the combination of enzalutamide and the copper ionophore elesclomol synergistically induces cuproptosis in drug-resistant cells, as evidenced by accumulation of lipoylated proteins and destabilization of iron-sulfur-cluster proteins. This phenotype has been validated in the 22RV1 xenograft model, and FDX1 expression correlates with elesclomol sensitivity, suggesting its utility as a predictive biomarker [61]. Subsequent mechanistic studies revealed that the AR signaling axis itself transcriptionally regulates FDX1; AR antagonists drive FDX1 upregulation, thereby establishing a pro-cuproptotic state [68]. This strategy exploits the high OXPHOS dependency of drug-resistant cells and holds considerable translational potential.

(3) Degradation of AR-V7 protein

ATC-324, developed using the AUTOTAC platform, is an autophagy-targeting chimera that efficiently degrades prevalent AR mutants in prostate cancer. It achieves co-degradation of AR-V7 via heterodimer formation with full-length AR, thereby reducing nuclear AR abundance, downregulating AR/AR-V7 target genes, and exerting cytotoxicity in AR-positive prostate cancer cells [69]. This approach provides a direct means of eliminating AR-V7 and may synergize with mitochondria-targeted agents.

(4) Targeting the regulatory network governing AR-V7 protein stability

KIF15 prevents AR/AR-V7 degradation by reinforcing the interaction between USP14 and AR/AR-V7; inhibition of KIF15, alone or in combination with enzalutamide, markedly suppresses proliferation of drug-resistant cells and xenograft tumor progression [67]. TOMM20 acts as a non-canonical chaperone stabilizing AR [66], and inhibitors targeting PDIA1/5 can bypass AR-V7-mediated resistance by activating the endoplasmic reticulum–mitochondria stress axis [65]. These strategies remain in early-stage exploration, and their target specificity and in vivo safety require further optimization.

(5) Dietary intervention combined with targeted therapy

As a non-pharmacological approach, alternate-day fasting suppresses AR translation, reduces AR abundance and downstream signaling, and potentiates enzalutamide antitumor activity. This effect is mechanistically linked to reduced intratumoral amino acid levels and global protein synthesis repression [70]. Although primarily studied in the context of full-length AR, these findings suggest that nutritional status can modulate the AR/AR-V7 axis and open a new dimension for combinatorial strategies.

Nevertheless, mitochondrial-targeted therapeutics face multiple translational challenges. First, normal tissues, particularly cardiac and skeletal muscle, exhibit high OXPHOS dependency, and systemic metabolic inhibitors are associated with dose-limiting toxicities. Second, tumor cells possess robust metabolic plasticity; upon OXPHOS inhibition, they rapidly shift toward glycolysis or fatty acid oxidation, leading

to rebound drug resistance. Third, AR-V7-positive tumors display heterogeneous degrees of mitochondrial dependency, and biomarkers such as FDX1 require validation in large clinical cohorts. Fourth, current strategies remain largely confined to preclinical cellular and animal models, and the translational gap from in vitro sensitivity to in vivo therapeutic efficacy must be urgently addressed. Fifth, AR-V7 expression fluctuates dynamically during ARSI treatment, posing temporal challenges for precisely capturing the therapeutic "metabolic window." Overcoming these obstacles will require integrated efforts to identify robust predictive biomarkers, optimize combination regimens, and design clinical trials that account for the dynamic nature of AR-V7 expression and mitochondrial adaptation.

Conclusion and Future Perspectives

This review has systematically examined the role of AR-V7 in enzalutamide resistance, spanning its structural features, non-canonical transcriptional regulatory programs, clinical and preclinical evidence, bidirectional mitochondrial dysfunction, and mitochondria-targeted therapeutic strategies. A central theme emerging from the available evidence is that AR-V7 functions not merely as a truncated AR-FL variant that evades ligand-binding domain- targeted inhibition, but as a distinct transcriptional regulator that reshapes the mitochondrial and metabolic landscape of CRPC cells. Through its unique chromatin-binding profile, AR-V7 simultaneously activates oxidative phosphorylation (OXPHOS)-related genes and represses tumor-suppressive metabolic and ferroptosis-regulatory genes, thereby establishing a phenotype of high mitochondrial dependency coupled with enhanced antioxidant defense. This bidirectional mitochondrial remodeling provides a mechanistic explanation for the paradoxical coexistence of respiratory hyperactivity and mitochondrial impairment in enzalutamide-resistant cells and identifies OXPHOS addiction as a potential synthetic-lethal vulnerability.

Despite these advances, several critical gaps remain. Direct experimental evidence linking AR-V7 to specific mitochondrial regulatory nodes, such as DRP1-mediated fission, TOMM20-dependent protein stabilization, or FDX1-driven cuproptosis sensitivity, is still lacking or largely correlative. The dynamic regulation of AR-V7 expression during ARSI treatment further complicates the timing and patient selection for mitochondria-targeted interventions. Moreover, the metabolic plasticity of resistant cells enables rapid compensatory shifts between OXPHOS, glycolysis, and fatty acid oxidation, limiting the durability of single-agent metabolic inhibitors.

Future research should prioritize three interrelated directions. First, at the mechanistic level, studies are needed to directly dissect how AR-V7 interacts with the mitochondrial transcriptome, proteome, and metabolome, and to determine whether the AR-V7–mitochondria axis operates independently of AR-FL in physiologically relevant models. Second, at the translational level, combination strategies that pair mitochondrial-targeted agents (e.g., OXPHOS inhibitors, cuproptosis inducers, AR-V7 degraders) with existing ARSIs should be optimized in preclinical models that recapitulate the dynamic evolution of resistance. Third, at the clinical level, robust predictive biomarkers, such as FDX1 expression, ETS activity in circulating tumor cells, or AR-V7 condensate status, must be validated in prospective cohorts to enable the precise selection of patients most likely to benefit from mitochondrial-targeted therapies. Addressing these gaps will be essential to translate the emerging concept of AR-V7-driven mitochondrial vulnerability into meaningful clinical advances for patients with enzalutamide-resistant prostate cancer.

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Author contributions

Rongxin Chang: Conceptualization, Literature search, Writing-original draft, Visualization (figure preparation). Zhuangzhuang Zhang: Supervision, Writing-review & editing. All authors read and approved the final version of the manuscript.

Competing interests

The authors declare no competing interests.

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