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REVIEW ARTICLE

Intratumoral Androgens and Genetic Variants Driving Therapy Resistance in Prostate Cancer

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The persistence of castration-resistant prostate cancer (CRPC) despite androgen deprivation therapy and androgen receptor (AR) signaling inhibition underscores the need to elucidate resistance mechanisms. The AR signaling pathway plays a central role in the development of prostate cancer. Metabolic reprogramming of androgen synthesis and aberrant activation of AR signaling collectively drive CRPC development. Under therapeutic pressure, AR signaling adapts through AR amplification, ligand-binding domain mutations, splice variants, and alternative activation by cytokines/growth factors, maintaining AR transcriptional activity in low-androgen environments. Concurrently, somatic alterations (like PTEN loss) and crosstalk with key pathways such as PI3K/AKT, coupled with the evolving multifocal spatial heterogeneity, further complicate the role of AR signaling in CRPC treatment resistance. Innovations in single-cell and spatial technologies reveal tumor heterogeneity and lineage plasticity governed by genetic and epigenetic alterations. Current therapeutic innovations, including approaches such as CYP11A1 inhibition, targeting of the AR N-terminal domain, and bipolar androgen therapy, are showing promise in clinical trials. Overcoming CRPC effectively requires cotargeting androgen/AR-associated pathways and suppressing lineage plasticity through dynamic monitoring and precision interventions.

Introduction

With population aging intensifying, the age-standardized disability-adjusted life year rate for prostate cancer (PCa) was 217.83 per 100,000 population in 2021, and new cases are projected to reach 2.58 million worldwide by 2046 [1]. While localized PCa can be effectively managed through active surveillance or radical treatments (surgery or radiotherapy), the prognosis deteriorates substantially upon progression to advanced stages [2,3]. Androgen deprivation therapy (ADT), combined with androgen receptor (AR) signaling inhibitors (ARSIs), constitutes the standard systemic treatment for advanced PCa, suppressing tumor growth by reducing circulating testosterone to castration levels and attenuating intracellular AR signaling, and demonstrating significantly delayed disease progression [4]. However, therapeutic resistance is inevitable, with the majority of patients eventually developing castration-resistant prostate cancer (CRPC), a highly aggressive subtype characterized by poor prognosis and limited treatment efficacy [5].

Mechanistically, AR signaling pathway plays a profound role in PCa initiation, progression, and therapeutic resistance [6]. The vast majority of primary PCa tumors express AR and exhibit marked dependence on AR signaling for cellular proliferation and survival [7]. The mechanisms underlying CRPC resistance are multifaceted, with sustained intratumoral androgen levels and persistent AR pathway activation identified as pivotal factors [5]. Under endocrine therapy pressure, heterogeneous

alterations in the AR gene—including amplification, mutations, and splice variant generation—can perpetuate AR pathway activation [8]. Additionally, the enrichment of AR-negative or AR-low (AR^{-}/lo) cell populations contributes significantly to therapeutic resistance [8,9]. Enhanced functionality of genes directly involved in androgen synthesis (like AKR1C3) further elevates intratumoral androgen levels, sustaining AR signaling activity [10]. Concurrently, genetic aberrations in key tumor suppressors (like *PTEN* and *RB1*) and dysregulation of signaling pathways [like phosphatidylinositol 3-kinase (PI3K)] interact with AR signaling to form a complex resistance network, directly or indirectly influencing AR pathway stability and cellular genealogies [11,12]. The evolving tumor heterogeneity of these alterations, driven by multifocal PCa stem cells (PCSCs), further exacerbates the complexity of drug resistance [13].

Thus, comprehensive elucidation of the AR-centric resistance mechanisms—spanning intratumoral androgen metabolism, AR genetic alterations, multidimensional pathway crosstalk, and spatiotemporal heterogeneity—is imperative for developing precision therapies for CRPC. This review systematically synthesizes current knowledge on these interconnected drivers of therapeutic resistance, thereby providing a theoretical foundation for future individualized treatment approaches against CRPC (the core references cited in this review are provided in Table S1).

The Regulation of Intratumoral Androgen Levels and Metabolic Mechanisms

More than 90% of testosterone is secreted by the testes, with the remainder primarily derived from adrenal secretion [14]. Under ADT for PCa, detectable levels of active androgens persist within tumor tissues [15]. This phenomenon highlights the critical roles of (a) local de novo synthesis in the prostate, (b) uptake and conversion of adrenal-derived androgen precursors, and (c) intratumoral regulation of androgen metabolism, in maintaining active androgen levels within tumors under low circulating androgen conditions [15,16].

Mechanisms of androgen synthesis

The persistence of intratumoral androgens in CRPC is largely sustained through 4 major metabolic pathways: the classical, backdoor, 5α-androstanedione (5α-dione), and hydroxyandrostenedione (11OHA4) pathways (Fig. 1).

Endogenous de novo androgen synthesis utilizes cholesterol as precursor. In the classical pathway, cholesterol is converted to pregnenolone by CYP11A1, followed by sequential catalysis involving CYP17A1, HSD3B1/2, AKR1C3, and SRD5A to produce testosterone and ultimately dihydrotestosterone (DHT) [17,18]. Although some studies identified the lack of StAR, CYP11A1, and CYP17A1 in PCa tumor tissues, the up-regulation of downstream steroidogenic enzymes like SRD5A1 and

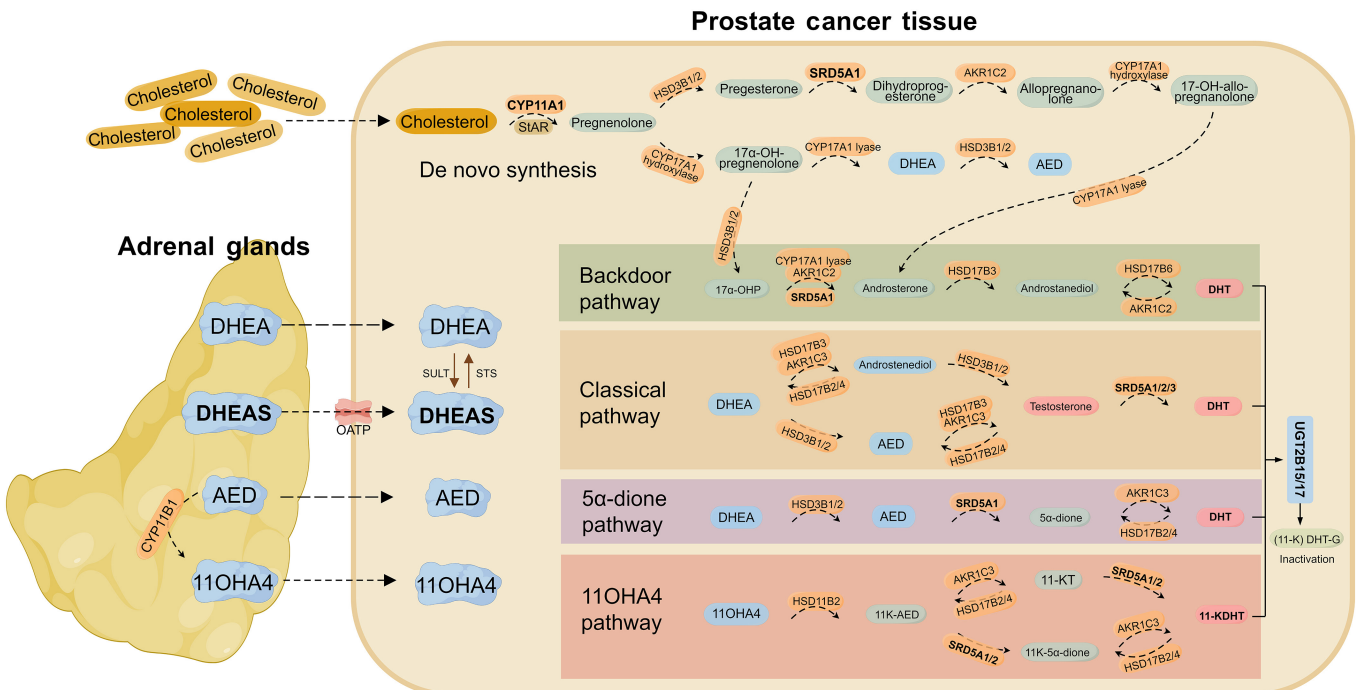


Fig. 1. Intratumoral androgen synthesis pathways in CRPC from de novo and adrenal precursors. De novo synthesis: In CRPC tumors, steroidogenic enzymes enable androgen production from cholesterol. The steroidogenic acute regulatory protein (StAR) initiates de novo androgen synthesis by mediating cholesterol transport into mitochondria. Expression of the steroidogenesis enzymes or protein can be up-regulated via paracrine signaling (e.g., by IL-6 and IGF-2) [51,52]. Adrenal precursor-based synthesis: PCa cells utilize adrenal androgen precursors—DHEAS, dehydroepiandrosterone (DHEA), androstenedione (AED), androstenediol, and 11OHA4, to synthesis androgens. DHEA-S requires active transport via organic anion-transporting polypeptides, while others diffuse passively [23]. Within PCa tissues, these precursors are converted to active androgens through multiple pathways. Classical pathway: Androgen precursor DHEA is first converted to AED/androstenediol, which is subsequently metabolized to testosterone and DHT [17,23]. Backdoor pathway: 17α-OHP is first catalyzed by SRD5A1 and then undergoes sequential enzymatic reactions to directly yield DHT, bypassing testosterone formation. 5α-dione pathway: AED is initially converted to 5α-dione by SRD5A1 and then transformed into DHT. 11OHA4 pathway: 11OHA4 can be converted to 11-ketotestosterone (11-KT) or 11-ketodihydrotestosterone (11-KDHT) through enzymes including HSD11B2 and AKR1C3 [23]. Finally, active androgens can be inactivated through glucuronidation mediated by uridine diphosphate-glucuronosyltransferase 2B15/17 (UGT2B15/17) [47,48]. The figure was created by Figdraw.

AKR1C3 enhances utilization of CYP17A1 downstream androgen precursors [19–21]. Such adaptation allows tumors to efficiently convert adrenal-derived precursors into potent androgens under castrate conditions. Notably, SRD5A1 exhibits a substrate preference for 17-hydroxyprogesterone (17α-OHP) over androstenedione (AED), and prefers AED over testosterone [21,22], which facilitates the backdoor pathway—a bypass route that directly generates DHT without testosterone as an intermediate [23,24]. Furthermore, in CRPC, due to the potential deficiency of HSD17B3 and the low catalytic efficiency of AKR1C3 toward AED [21,25], dehydroepiandrosterone (DHEA) preferentially converts to AED, which is then metabolized to DHT via 5α-androstanedione (5α-dione), forming the 5α-dione pathway [26]. Notably, DHEA can be metabolized by HSD17B into 5-androsten-3β,17β-diol, an isomer of androstenediol and a potent agonist of estrogen receptor β, which may mediate tumor-suppressive effects [27].

Following ADT, circulating testicular-derived androgens are markedly reduced, and adrenal-secreted androgen precursors—including dehydroepiandrosterone sulfate (DHEAS), DHEA, AED, androstenediol, and 11β-hydroxyandrostenedione (11OHA4)—become the primary exogenous sources of intratumoral androgens [23,28] (Fig. 1). PCa cells up-regulate organic anion-transporting polypeptides to uptake DHEAS, the major adrenal-derived precursor, which is subsequently hydrolyzed by steroid sulfatase to generate DHEA, thereby entering the androgen synthesis pathway [29]. These precursors can be metabolized through the aforementioned pathways, with the 5α-dione pathway may dominate due to its metabolic efficiency and simplicity [21,25,26,30]. Additionally, the 11OHA4 pathway is activated in CRPC, yielding 11-oxygenated androgens such as 11-ketotestosterone and 11-ketodihydrotestosterone [25,31]. These androgens exhibit AR-activating potency comparable to canonical androgens, are resistant to inactivation, and reach physiologically relevant concentrations in CRPC tissues [32].

Although CYP17A1-targeted agents like abiraterone effectively suppress androgen precursor conversion, tumor cells frequently develop resistance by compensatory up-regulation of the nonclassical pathways, coupled with mechanisms such as progesterone accumulation, leading to metabolic reprogramming of androgen axis in CRPC [20,25,33,34]. These findings highlight the necessity of tailoring therapeutic strategies for CRPC by precisely inhibiting key enzymes involved in intratumoral androgen synthesis and metabolism to block androgen regeneration.

Regulatory mechanisms of androgen metabolism

The regulation of androgen metabolism is pivotal in sustaining intracellular androgen levels and AR signaling, thereby driving resistance to endocrine therapies in CRPC. This regulation operates through multiple interconnected mechanisms, including cholesterol and lipid metabolism, epigenetic modifications, and influences from the tumor microenvironment (TME), all of which adapt under therapeutic pressure to maintain androgen availability.

Aberrant cholesterol accumulation provides abundant substrates for androgen synthesis, with levels significantly elevated in CRPC (with nuclear concentrations reaching twice the normal level) [35,36]. Sterol regulatory element-binding proteins 1/2 (SREBP1/2) are crucial transcription factors governing cholesterol metabolism, regulating the transcription of key cholesterol synthesis genes such as 3-hydroxy-3-methyl-glutaryl-CoA reductase (*HMGCR*) and fatty acid synthase [37]. Under androgen deprivation, SREBP1 dissociates from AR and translocates to the nucleus, promoting steroidogenic gene expression [38]. AR and PI3K/AKT/mammalian target of rapamycin (mTOR) signalings further up-regulate SREBP2 to amplify cholesterol production and further androgen synthesis [39]. Statins, which inhibit HMGCR to reduce cholesterol synthesis, have been shown to suppress androgen metabolism and overcome drug resistance in preclinical models. *SPOP* missense is frequently accompanied by *CHD1* deletion [40]. In PCa cells harboring *SPOP* mutations (about 12% prevalence), CHD1 deficiency leads to increased SREBP2 expression, promoting intratumoral cholesterol and androgen synthesis [40,41]. As *SPOP* mutations are associated with AR protein accumulation, *CHD1* deletion results in robust AR signaling activation [42]. Atorvastatin was demonstrated to block this compensatory pathway, revealing potential antitumor effects with abiraterone [40]. A meta-analysis further supports the potential clinical value of statins, showing they are related to improved survival in patients with advanced PCa [43].

Epigenetic mechanisms dynamically regulate androgen metabolism to maintain intratumoral androgen levels. Under high androgen conditions, the demethylase LSD1 suppresses AR expression by mediating demethylation of H3K4me1/2, and involved in suppressing androgen-synthesizing enzymes (AKR1C3 and HSD17B6) [44]. Conversely, in low-androgen environments, phosphorylated SREBP1 promotes histone H2AK130ac enrichment to enhance its own transcription and up-regulate cholesterol synthesis genes, such as *HMGCS1* [38]. Exogenous melatonin supplementation shows potential against CRPC in preclinical studies [45]. Melatonin has been reported to promote DNA methyltransferase 1 deacetylation, relieving repression of carboxylesterase 1, which reduces lipid accumulation and indirectly down-regulates steroidogenic enzymes (CYP11A1 and STARD4) [46]. Further in vitro tests demonstrated that melatonin reversed enzalutamide resistance by reducing lipid accumulation and inhibiting intratumoral androgen synthesis [46]. Additionally, the glucuronidation enzymes UGT2B15 and UGT2B17 irreversibly inactivate androgens, yet their expression is suppressed by androgens themselves, epidermal growth factor (EGF), and miR-376c [47–49]. This regulation of UGT2B15/17 creates a self-reinforcing cycle of androgen accumulation.

The PCa microenvironment further regulates local androgen synthesis through stromal–epithelial paracrine interactions and signaling pathways of diverse secretory factors. PCa-derived stromal cells could exhibit high expression of SRD5A [50] and secrete factors such as interleukin-6 (IL-6) and insulin-like growth factor-2 (IGF-2), which up-regulate enzymes like StAR, CYP11A1, CYP17A1, and AKR1C3 in tumor cells, enhancing de novo androgen synthesis [51,52]. IL-6 treatment has been shown to increase testosterone synthesis in LNCaP cells by 2-fold [52]. Additionally, insulin, luteinizing hormone, and paracrine factors like fibroblast growth factor-2 and hepatocyte growth factor were also implicated in the potential regulation of intratumoral androgen metabolism in PCa tissues [53–55]. Cancer-associated fibroblasts (CAFs), as the most abundant stromal cells, closely interact with PCa through paracrine metabolites, regulating androgen accumulation. PCa cells recruit CAFs by secreting factors such as testosterone and nerve growth factor, while CAFs promote tumor progression through androgen-dependent extracellular matrix remodeling mediated by the AR/filamin A complex [56]. Recent studies have revealed that CAFs could secrete glucosamine and ADAM9, which up-regulate

HSD3B1 and AKR1C3 expression in PCa cells, respectively [57,58]. Furthermore, microenvironmental chronic hypoxia in prostate tumors induces hypoxia-inducible factor-2α accumulation to transactivate *HSD3B1*, further fueling androgen synthesis [59]. These regulatory mechanisms ultimately promote androgen synthesis, driving the sustained progression of CRPC.

AR Signaling Pathway and AR Variants

The maintenance of sufficient intratumoral androgen levels (as discussed in the previous section) provides the ligand foundation for the sustained activation of the AR. However, as the disease progresses and therapeutic pressure increases, alterations in the AR pathway itself constitute another central pillar driving drug resistance.

Canonical AR signaling pathway

The canonical AR pathway plays a pivotal role in the development of PCa [8] (Fig. 2). AR is an intracellular steroid hormone-activated transcription factor. In its inactive state, AR predominantly binds to chaperones such as heat shock proteins [60]. Upon binding of androgens to the ligand-binding domain (LBD) of AR, a conformational change is induced, leading to nuclear translocation of AR and its subsequent binding to androgen response elements. This process regulates genes associated with cell proliferation (including *c-MYC*), senescence (including *H2AJ*), and prostate function (including *KLK2/3*) [61,62].

In certain cellular contexts, such as PC3 cells, AR may also exhibit tumor-suppressive effects by inhibiting proliferation via transactivating *P21*, and Retinoblastoma-1 (RB1) can assist in the tumor-suppressive function of AR [8]. Interestingly, in clinical practice, supraphysiological androgen therapy, such as bipolar androgen therapy (BAT), has emerged as a novel therapeutic strategy for advanced PCa in clinical trials. In the RESTORE study, enzalutamide-resistant patients were subjected to BAT with high-dose testosterone cypionate and then were rechallenged with enzalutamide following progression on BAT. The BAT achieved a PSA_{50} (50% decrease in prostate-specific antigen level) response rate of 30% [63]. Notably, in the enzalutamide–BAT–enzalutamide sequence, 68% regained PSA response to enzalutamide [63]. The recent phase II ExBAT trial (NCT04558866) further confirmed the substantial clinical efficacy of BAT [64].

Activation of noncanonical AR signaling pathways

In treatment-naïve PCa, the vast majority of tumor cells are AR^+ and rely on the canonical AR signaling pathway for growth. While androgens levels decline sharply under ADT pressure, PCa cells adapt and sustain AR signaling by activating noncanonical pathways, and AR bypass signaling, which enable persistent AR activation in low- or no-androgen environments and drive CRPC development (Fig. 2).

Hypoandrogenic conditions alleviates negative feedback inhibition on AR expression [44]. Tumor cells enhance AR

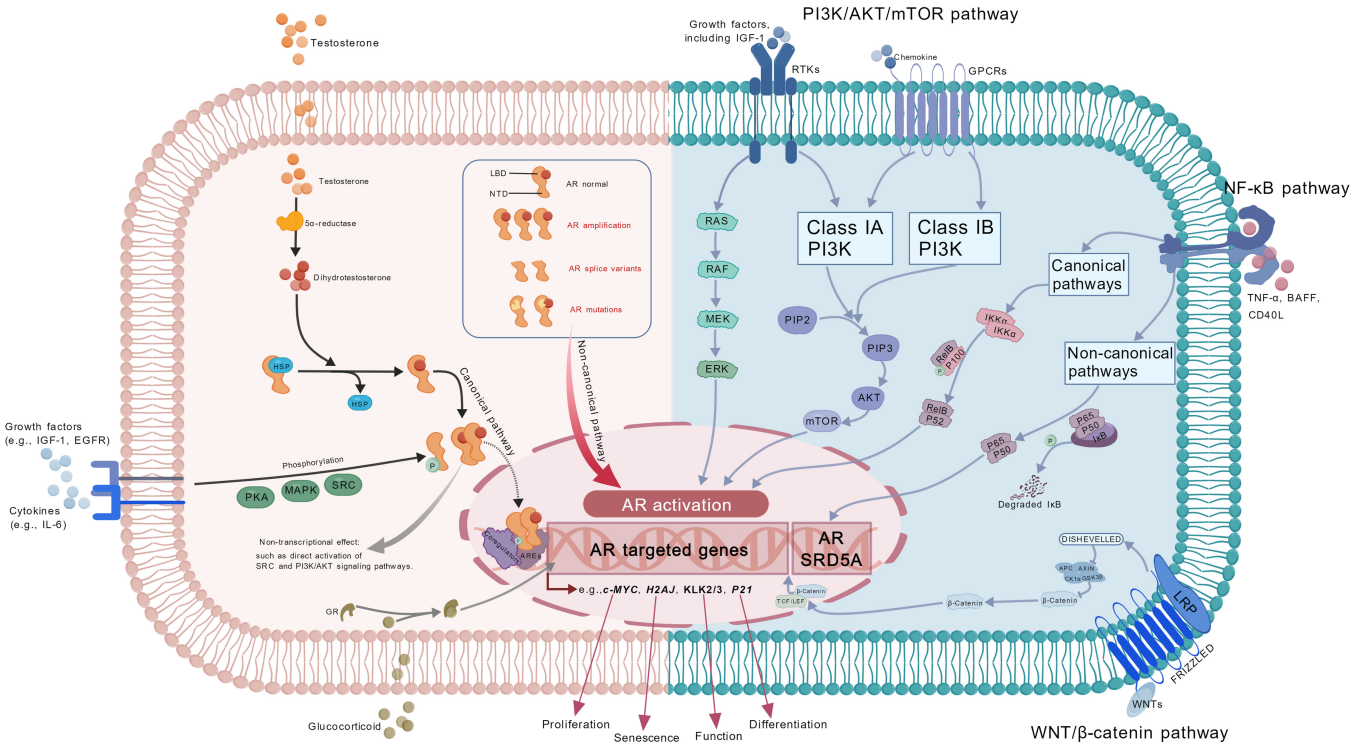


Fig. 2. Androgen signaling pathway-centric crosstalk network in CRPC. Androgen binding to AR induces dissociation of heat shock proteins (HSPs) and AR nuclear translocation, regulating functionally diverse genes. AR alterations, including AR amplification, point mutations, and splice variants, enable sustained AR signaling under endocrine therapy pressure. Growth factors and cytokines could activate AR transcription via phosphorylation pathways including PKA, MAPK, and SRC. Additionally, AR can rapidly promote cell proliferation through nongenomic activation of SRC and PI3K/AKT signaling pathways [106]. Cross-pathway interactions: The PI3K/AKT pathway is activated through class IA PI3Ks (p110α/β/δ) and class IB PI3Ks (p110γ) with the involvement of receptor tyrosine kinases (RTKs) and G protein-coupled receptors (GPCRs), promoting AR signaling [106]. The NF-κB pathway modulates AR signaling through both canonical and noncanonical pathways: canonically, via p50/p65 dimers that enhance *AR* expression; noncanonically, through p52 binding to the AR N-terminal domain to potentiate transcriptional activity [112]. Additionally, AR can increase NF-κB pathway activity by promoting IκBα degradation [115]. The WNT/β-catenin pathway regulates AR signaling via β-catenin, which functions as a transcriptional coactivator [106]. The figure was created with BioGDP [163].

expression through *AR* gene and upstream enhancer region copy number gain, and mRNA up-regulation, thereby amplifying signal output from residual low-concentration ligands [65–67]. *AR* amplification (observed in 50% to 85% of CRPC) heightens PCa sensitivity to androgens, representing both an early resistance hallmark and a core adaptive mechanism for CRPC survival in low-androgen milieus [65,68,69]. Furthermore, high AR expression enables AR antagonists (like bicalutamide) to recruit activating coregulators (like steroid receptor coactivator-1) while reducing nuclear receptor corepressor binding, thereby paradoxically activating part of androgen-sensitive genes (such as *PSA* and *KLK2*) and conferring partial agonist properties to antagonists [70,71].

AR splice variants (AR-Vs), particularly AR-V7 (constituting over 80% of CRPC cases in some studies), frequently lack LBD integrity and play pivotal roles in androgen-independent signaling and drug resistance [68,69,72]. Aberrant AR splicing is driven by multiple factors, including full-length AR (AR-FL) up-regulation, dysfunction of splicing factors, and epigenetic reprogramming [9,73,74]. Latrophilins (LPHNs) serve as critical downstream effectors of AR-V7 signaling [75]. LPHN activation induces Janus kinase 2 (JAK2)/signal transducer and activator of transcription (STAT3) phosphorylation and BCL-2 overexpression, thereby bypassing canonical AR signaling to drive tumor progression [75]. Overcoming AR-Vs resistance effectively requires targeting of AR-FL, AR-Vs, and AR-Vs downstream effectors like LPHNs. Multiple drugs, including therapeutic vaccines targeting AR splice variants, are currently under development [76–79].

AR mutations frequently occur in the LBDs (e.g., T877A, H874Y, and F877L), with a about 15% to 20% incidence in CRPC patients [9,80]. Mutant LBDs alter AR conformation and affinity, rendering antagonists ineffective and enabling AR activation even by non-androgenic ligands, including antagonists [80]. This underlies AR antagonist withdrawal syndrome [81,82]. For instance, under enzalutamide pressure, clonal expansion of AR-F877L mutants could induce an agonist-like active conformation, attenuating antagonist response and potentially converting enzalutamide into a partial agonist [83]. Enhancing the efficacy of AR antagonists against AR point mutations is a key research focus, with novel AR antagonists such as chrysin currently under investigation [84].

Additionally, growth factors (including IGF-1 and EGF) and cytokines (including IL-6) can activate AR transcription by promoting its phosphorylation via downstream kinases like protein kinase A (PKA), mitogen-activated protein kinase (MAPK), and SRC [85–87] (Fig. 2). Progesterone can even directly activate AR in a ligand-binding way [33]. Additionally, AR and glucocorticoid receptor (GR) share nearly 50% of direct target genes at the transcriptome level [88]. Therefore, GR agonists (like dexamethasone) can activate AR-sensitive target genes (such as *KLK2* and *FKBP5*) independently of AR pathway [88]. Although AR suppresses GR transcription by binding to GR introns, antiandrogen therapy induces about more than 2-fold GR expression up-regulation [88]. AR alternative signaling represents a critical mechanism for PCa progression under AR inhibition, illuminating CRPC development and therapeutic resistance.

Multidimensional Drug Resistance Network of AR

PCa exhibits extensive genetic alterations that interact with core signaling pathways, forming an AR-centric multidimensional drug resistance network (Fig. 2). These alterations drive tumor progression and drug resistance by modulating AR signaling, activating AR compensatory survival pathways, or inducing epigenetic reprogramming to drive lineage plasticity, collectively escalating therapeutic complexity (Table 1).

AR signaling-related genetic alterations

PCa progression is driven by a spectrum of somatic genetic alterations that interact with AR signaling and influence therapeutic responses. Early events include *TMPRSS2-ERG* fusions, *PTEN* loss, and *SPOP* mutations, while *KMT2C*, *TP53*, *RB1*, and *AR* alterations are more enriched in advanced disease [69,89].

Approximately 50% of PCa exhibit *TMPRSS2-ERG* gene fusion, resulting in *ERG* overexpression that synergizes with *PTEN* deletion (8% to 17% of PCa) to activate the, AKT-pS21-EZH2 pathway, promoting tumor growth and invasion in CRPC [69,90,91]. Zhou et al. [92] reported that *TMPRSS2-ERG* may enhance tumor proliferation via soluble guanylyl cyclase (sGC)–cyclic guanosine monophosphate (cGMP) pathway activation. However, recent studies revealed suppression of sGC activity in CRPC, whereas the sGC agonist riociguat restores cGMP signaling to induce apoptosis, suggesting therapeutic potential in targeting this pathway [93]. *SPOP* mutation could antagonize the *ERG* overexpression pathway by stabilizing ZMYND11, and impair AR ubiquitination-mediated degradation, increasing AR protein stability [41]. *SPOP*-mutant tumors exhibit higher AR signaling dependence than do *ERG*-fusion tumors, correlating with greater endocrine therapy sensitivity and improved clinical outcomes [41,42,94]. *FOXA1* alterations, presented in >34% of metastatic CRPC (mCRPC), promote CRPC by regulating AR bidirectionally: I176M/R261G mutations enhance AR transcriptional activity, whereas D226G mutation impairs AR enhancer recruitment to suppress AR signaling [95], and C-terminal truncations such as P358fs activate the WNT/β-catenin pathway to drive invasion and metastasis [96].

Furthermore, deficiencies of KMT2C, TP53, and RB1 drive tumor lineage plasticity via epigenetic mechanisms. Research has successfully induced adenocarcinoma-to-NEPC (neuroendocrine prostate cancer) conversion in a *PTEN*/*Rb1*/*Trp53* triple-knockout mouse model and adenocarcinoma-to-DNPC (double-negative prostate cancer) transition in *KMT2C*-deficient human patient-derived organoids (PDOs), establishing that genetic mutations promote this transformation through lineage plasticity [89,97]. *KMT2C* loss attenuates ADT-induced *ASPP2* enhancer binding, down-regulating ASPP2 to activate key squamous factor ΔNp63-dependent transdifferentiation, enabling adenocarcinoma-to-AR-negative squamous tumor transition [89]. *TP53*/*RB1* deficiency suppresses AR and luminal gene (like *Krt8*) expression via EZH2-mediated epigenetic silencing [97]. These dual pathways jointly promote lineage plasticity, AR loss, and neuroendocrine (NE) differentiation [98]. AR-negative PCa variants confer intrinsic resistance to endocrine therapies.

DDR defects and synergy with AR signaling

Genomic defects in DNA damage repair (DDR) pathways occur in >20% mCRPC, primarily affecting homologous recombination repair (HRR)-related genes, such as *BRCA1/2* and *ATM* [99]. The proteins encoded by these genes are involved in repairing DNA double-strand breaks, and HRR deficiency leads to genomic instability and apoptosis [99].

Table 1. Current progress in promising clinical trials of novel AR pathway-related and AR-independent PCa-targeting drugs.

Therapeutic strategies	Pathway mechanisms	Therapeutic interventions	Treatment mechanisms	Clinical trials, ID (treatment plans)	Therapeutic efficacy
AR-targeting strategies	CYP11A1 inhibition blocks initial steroid synthesis [164]	ODM-208	Targeted inhibition of CYP11A	Phase I/II CYPIDES, NCT03436485 (ODM-208 monotherapy)	In mCRPC patients with a median follow-up of 5.8 months, the PSA_{50} rate was 53.3% in patients with AR mutation in phase 2 [164]
	High androgens induce AR hyperactivation, causing DNA damage and cell cycle arrest, and suppress AR and its variants [63]	BAT	Cell cycle interference, DNA damage, down-regulation of AR alterations, restoration of AR pathway therapeutic sensitivity [63]	Phase II ExBAT, NCT04558866 (alternating sequential administration of BAT and darolutamide)	Among mCRPC patients post-abiraterone treatment, the median rPFS was 9.0 months, with a PSA_{50} rate of 16.7% and median OS of 23 months [64]
	AR variants (amplification, LBD mutations, splice variants) sustain AR signaling in low-androgen environments [80]	BMS-986365	PROTAC BMS-986365 binds to the AR's LBD, inducing AR degradation via ubiquitin–proteasome pathway, and locking AR in inactive conformation [165]	Phase I, NCT04428788 (BMS-986365 monotherapy)	In mCRPC patients with a median follow-up of 17.7 months, the overall PSA_{50} rate was 32%, with rPFS of 6.3 months; the AR LBD mutation subgroup exhibited a PSA_{50} rate of 55%, with rPFS of 6.3 months [165]
		ARV-766	PROTAC ARV-766 targets the LBD of AR (including the LBD mutations L702H, H875Y, and T878A) for AR degradation [166]	Phase I/II, NCT05067140 (ARV-766 monotherapy)	For mCRPC patients with AR LBD mutations, the PSA_{50} rate reached 50.0% [166]
	AR NTD mediates DNA binding and transcription; tumors with NTD but no LBD resist antiandrogen therapies [6]	EPI-7386	Third-generation ARSI EPI-7386, targets AR NTD to block transcription, independent of LBD status [167]	Phase I/II, NCT05075577 (EPI-7386 plus enzalutamide versus enzalutamide)	In mCRPC patients, the PSA_{90} rate of 13/16 patients was 81%. 5/16 evaluable patients showed measurable disease, with 3/5 (60%) partial response and 2/5 (40%) stable disease [167]
AR-related strategies	PI3K/AKT pathway promotes progression via AKT-mediated apoptosis suppression, mTOR-involved metabolic reprogramming, and reciprocal crosstalk with AR signaling [107]	Ipatasertib	Selective inhibition of AKT1/2/3	Phase III IPATential150, NCT03072238 (ipatasertib plus abiraterone versus placebo plus abiraterone)	In mCRPC patients with a median follow-up of 33.9 months, patients with NGS-detected PTEN deletions were associated with prolonged OS (36.8 months, HR = 0.76), as were PIK3CA/AKT1/PTEN alterations (37.1 months, HR = 0.70) [168]
	PARP-1/2 participates in single-strand break repair; BRCA1/2 participates in double-strand break repair; defects increase genomic instability [99,103]	Olaparib	Inhibition of PARPs in BRCA mutation patients, inducing lethal DNA double-strand breaks	Phase III PROpel, NCT03732820 (olaparib plus abiraterone versus placebo plus abiraterone)	mCRPC patients in the experimental arm achieved rPFS of 25 months (HR = 0.66), significantly superior to controls. The BRCA-mutated subgroup demonstrated further improved rPFS (HR = 0.24) and OS (HR = 0.30) [169]

(Continued)

Table 1. (Continued)

Therapeutic strategies	Pathway mechanisms	Therapeutic interventions	Treatment mechanisms	Clinical trials, ID (treatment plans)	Therapeutic efficacy
AR-independent strategies	EZH2 catalyzes H3K27me3 to repress tumor suppressors, and promotes *AR* transcription directly, driving cell proliferation and NE transition [133]	Mevrometostat	Inhibition of EZH2, the core subunit of the histone methyltransferase PRC2 complex	Phase I, NCT03460977 (mevrometostat plus enzalutamide)	In mCRPC patients with a median follow-up of 9.7 months, the PSA_{50} rate was 14.9%, with rPFS of 17.0 months and ORR of 27.3% [170]
	AURKA drives NEPC progression by stabilizing N-MYC protein [171]	Alisertib	Inhibition of AURKA	Phase II, NCT01799278 (alisertib monotherapy)	In mCRPC patients with a median follow-up of 9.7 months, results showed median PFS of 2.2 months and OS of 9.5 months [171]
	BET proteins up-regulate oncogenic genes such as *MYC*, promoting tumorigenesis and progression [172]	ZEN-3694	Inhibition of BET proteins, the epigenetic readers of histone acetylation	Phase Ib/IIa, NCT02711956 (ZEN-3694 plus enzalutamide)	In mCRPC patients, the PSA_{50} rate was 8% and rPFS was 9.0 months, while the AR-low subgroup achieved rPFS of 10.4 months [172]

AR, androgen receptor; mCRPC, metastatic castrate resistant prostate cancer; PI3K, phosphatidylinositol 3-kinase; BAT, bipolar androgen therapy; ARSI, androgen receptor signaling inhibitor; PROTAC, proteolysis-targeting chimeras; HRR, homologous recombination repair; PARP, poly(ADP-ribose) polymerase; LBD, ligand-binding domain; NTD, N-terminal domain; NE, neuroendocrine; EZH2, enhancer of zeste homolog 2; AURKA, Aurora kinase A; H3K27me3, H3K27 trimethylation; BET, bromodomain and extra-terminal domain; GR, glucocorticoid receptor; PSA_{50}, 50% decrease in PSA level; PSA_{90}, 90% decrease in PSA level; rPFS, radiographic progression-free survival; OS, overall survival; ORR, overall response rate

AR can directly promote the expression of DDR-related genes to maintain genomic integrity during cell proliferation [100,101]. Inhibition of AR signaling down-regulates HRR gene expression, increasing DNA damage accumulation [100]. Notably, exposure to ARSIs can induce a "BRCAness" state in HRR-wild-type tumors, conferring HRR-deficient characteristics [102]. Poly(adenosine diphosphate-ribose) polymerases (PARPs) exhibit dual functions that critically bridge DDR and AR pathways. PARPs not only serve as a core component of the DDR pathway but also function as a transcriptional co-regulator [103,104]. For example, PARP-1 enhances the transcriptional activity of the AR through its enzymatic activity-dependent chromatin remodeling capabilities—including modulation of GATA2 recruitment, histone modifications, and chromatin accessibility [103]. For patients with HRR defects, particularly those carrying *BRCA1/2* mutations, dual targeting of AR and DDR (PARP inhibitors) pathways significantly enhances the efficacy of endocrine therapy [105].

Mutation/activation of AR-related pathways

The AR pathway crosstalk with multiple signaling pathways (including PI3K/AKT, WNT/β-catenin, and NF-κB) can drive treatment resistance [106]. Genetic mutations like *PTEN* deletion/*PIK3CA* mutation [107], and *CTNNB1*/*APC* mutation [106,108], and aberrant up-regulation of inflammatory signals [109], can activate the AR alternative pathways, which disrupts the dynamical balance with AR signaling, driving tumor growth and treatment resistance (Fig. 2).

The PI3K/AKT/mTOR pathway is pivotal in PCa progression. AR can rapidly activate PI3K/AKT nontranscriptionally to provide rapid survival signals and promote tumor glycolysis and lipid metabolism [106,107]. mTOR can directly interact with AR in the nucleus to promote metabolic reprogramming [106,107,110]. However, long-term AR–PI3K signaling exhibits bidirectional crosstalk. On one hand, the PI3K pathway suppresses AR signaling at both protein and translational levels by inhibiting the FOXO1–HER2/3 axis[106,111]. Conversely, AR could reduce AKT activity through the PHLPP/FKBP51/IKKα complex [107]. This equilibrium leads to compensatory activation of the alternate pathway upon single-pathway targeted therapy, resulting in resistance.

AR and NF-κB pathway exhibit positive synergy. NF-κB can promote *AR* and *SRD5A1/2/3* expression through its p50/p65 heterodimer, while NF-κB activates AR transcription via its p52 subunit binding to the N-terminal domain under androgen-deprived conditions, multi-dimensionally activating AR signaling [112–114]. Moreover, AR and AR-V7 can up-regulate MALT1 expression, thereby inducing IκBα phosphorylation and degradation, which subsequently promotes nuclear translocation of the p50/p65 heterodimer and ultimately forms a positive feedback loop to activate the AR–NF-κB pathway [115].

WNT/β-catenin signaling up-regulates AR mRNA expression via recruiting lymphoid enhancer-binding factor 1/T cell factor complex [116]. WNT signaling also enables β-catenin to form transcriptional complexes with AR, enhancing proliferative gene expression (such as *MYC*) [106]. Notably, *CTNNB1* mutation could cause nuclear β-catenin accumulation [117].

Excess β-catenin inhibits AR through 2 distinct mechanisms: direct physical binding and the induction of noncanonical WNT5a/NF-κB signaling, which suppresses AR expression [117]. Conversely, AR reciprocally represses WNT5a expression and noncanonical WNT signaling, establishing a bidirectional inhibitory loop between AR and WNT pathways [117].

The IGF-1–AR positive feedback loop exacerbates AR signaling. TME-derived excessive IGF-1 induces ligand-independent AR activation and nuclear translocation via IGF-1 receptor (IGF-1R), and activation of IGF-1R also increased cytoplasmic and nuclear levels of β-catenin, further enhancing AR-mediated transcription [108,118]. In PCa cells, *IGF1R* is also a direct AR target gene, and AR could elevate IGF-1 activity by suppressing IGF-binding protein 3, creating a self-reinforcing cycle [108,119].

Spatiotemporal Heterogeneity and Dynamic Evolution of AR Signaling

The androgen metabolic regulation, AR variants, and multidimensional drug resistance networks described above constitute the core molecular basis of PCa treatment resistance. However, these molecular alterations are neither uniformly distributed throughout the tumor nor static during disease progression. The spatial structural heterogeneity of tumors and their dynamic evolution under therapeutic pressure result in highly complex and individualized resistance mechanisms, posing challenges to clinical management (Fig. 3).

Spatial heterogeneity

Approximately 80% of PCa exhibit multifocal independent clones, with tumors of identical Gleason scores demonstrating marked differences in histology, molecular characteristics, and prognosis [69,120,121]. This heterogeneity originates from genome instability during the clonal evolution of PCSCs [13]. Large heterogeneity emerges between primary lesions (including intralesional regions) and metastatic sites, which includes regional variations in *AR* expression and function, ultimately leading to heterogeneous treatment responses [8].

Primary lesions are predominantly composed of AR^{+} cells but contain a minority of AR^{-}/lo cells (Fig. 3). Liu et al. [122] performed AR immunofluorescence analysis on 11 untreated

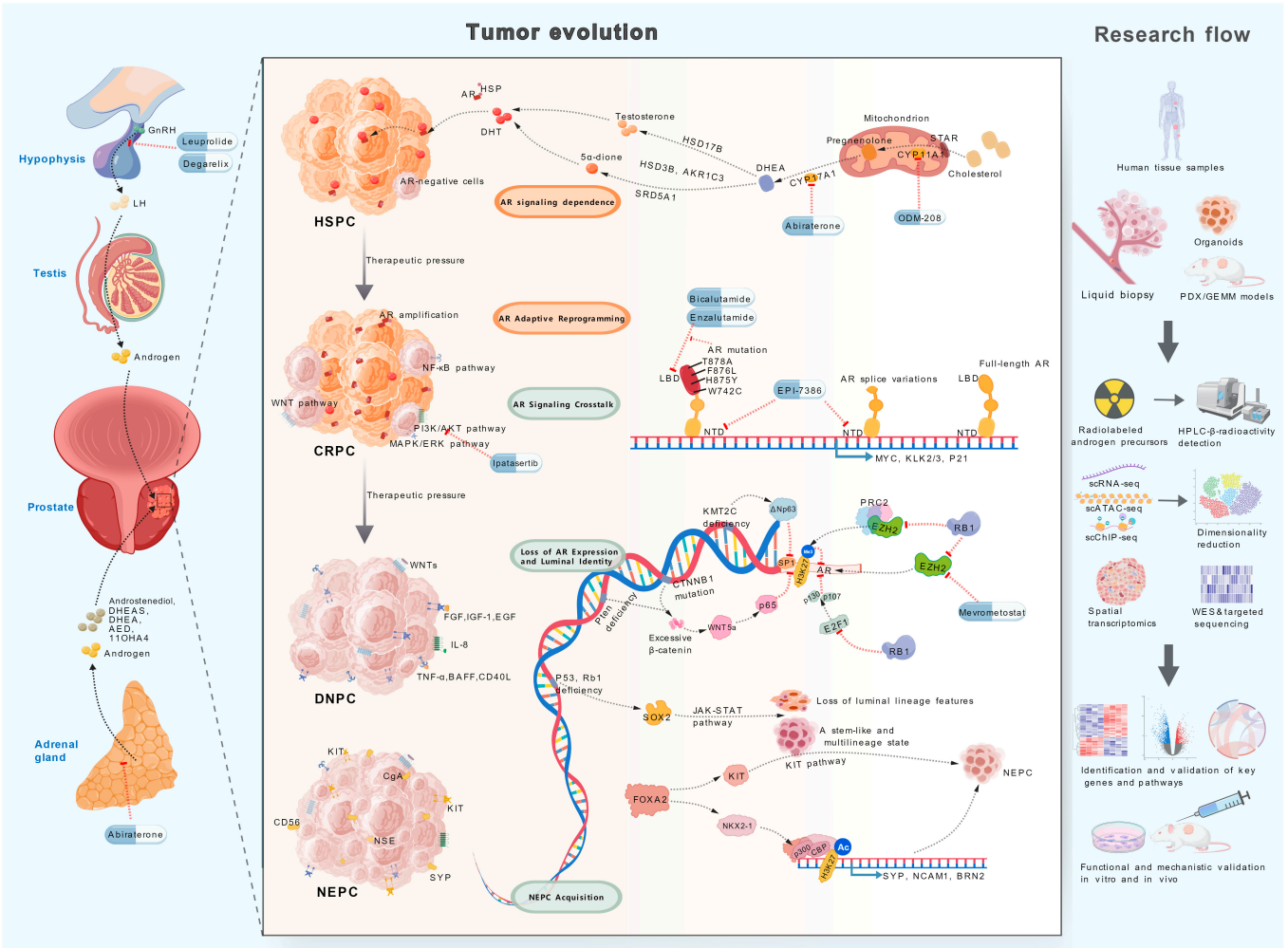


Fig. 3. Dynamic progression of PCa to therapy-resistant states and corresponding interventions. Under therapeutic pressure and through accumulating genetic alterations, PCa progresses from hormone-sensitive disease (HSPC) to CRPC, and further to aggressive, AR-independent subtypes like DNPC and NEPC. Key resistance mechanisms—including intratumoral androgen metabolism, AR genetic alterations, and activation of alternative signaling pathways—are highlighted alongside stage-specific therapeutic strategies. To further investigate drug resistance mechanisms, integrated approaches utilizing serial patient samples, liquid biopsies, multi-omics profiling, patient-derived organoids, and preclinical models (like patient-derived tumor xenograft, genetically engineered mouse models) are recommended. The figure was created with BioGDP [163].

primary PCa clinical samples and detected an AR^- cell subpopulation in all of the samples, with AR^+ cancer cells representing the majority. The AR^-/lo cell population lacks AR-mediated differentiation signaling, exhibits enriched stem cell features, demonstrates poor differentiation and high invasiveness, and displays intrinsic resistance to endocrine therapy [8,120]. AR^-/lo tumor cells drive androgen-independent growth through activation of alternative pathways including PI3K/AKT, NF-κB, and WNT/β-catenin, as well as overexpression of *MYC* and *BCL-2* [120]. AR variants are rare in primary lesions, where *ERG*, *SPOP*, and *PTEN* alterations are more common [69]. AR function also shows tissue-specific heterogeneity: While it primarily promotes proliferation in stromal and luminal epithelial cells, it suppresses invasion and metastasis in basal epithelial cells, contributing to differential endocrine therapy responses [123].

Metastatic lesions often exhibit monoclonal origins, with higher molecular similarity between lesions than between regions within primary tumors [69]. However, metastatic lesions demonstrate higher frequencies of both AR pathway hyperactivation and AR^-/lo phenotypes compared to primary lesions [124–126]. Labrecque et al. [127] reported that AR^+ metastases are most prevalent, while about 14.7% of patients with multiple metastases exhibit interlesional molecular phenotypic disparities. *AR* amplifications/mutations frequently occur synchronously across multiple metastatic sites, whereas AR^-/lo phenotypes display pronounced heterogeneity [126]. Concurrently, metastatic lesions also show reduced expression of androgen synthases like CYP11A1 and CYP17A1 [25]. Metastatic lesions (particularly mCRPC) are enriched for *PTEN*, *TP53*, and *RB1* deletions compared to primary tumors, forming the basis of highly aggressive subtypes [97,126,128]. During endocrine therapy resistance, metastatic lesions develop AR alterations and undergo phenotypic transitions from AR^+NE^- cells to AR^- (DNPC) or NE phenotypes (NEPC) [120]. In deceased mPCa patients, studies suggest that 65% harbor coexisting AR^+/NE^- and AR^+/NE^+ cells across different metastases [129].

Temporal heterogeneity

Temporal heterogeneity refers to the clonal evolution of molecular features in tumor cells during disease progression and under therapeutic pressure. At the early stage of PCa, AR alternations are not common [69]. Certain mutations, like *SPOP*, can lead to aberrant AR signaling activation [94]. A small part of PCSCs originating from mutations in normal basal/luminal cells exhibit an AR^-/lo phenotype [13], and studies suggest that primary lesions harbor adaptive CRPC-like cell subpopulations early on, which persistently expand during progression [7,130]. Taavitsainen et al. [131] utilized single-cell RNA sequencing and single-cell assay for transposase-accessible chromatin with sequencing to identify preexisting and persistently surviving drug-resistant cell subpopulations in pretreatment enzalutamide models. These subpopulations exhibited open chromatin sites enriched with transcription factor motifs including MYC and E2F1, and their accessibility patterns remained unperturbed by drug treatment, indicating that intrinsic epigenetic features may mediate resistance [131].

Endocrine therapy reshapes the AR pathway and drives resistance through dual mechanisms of induction and selection. On one hand, ADT and ARSIs are more effective against *SPOP*-mutated and AR^+ subpopulations [41,69], allowing AR^-/lo cells to gradually dominate in CRPC and accelerate resistance development [132]. Additionally, AR elimination abrogates the tumor-suppressive role of AR in certain cell types (like epithelial basal intermediate cells), enhancing tumor aggressiveness [123]. On the other hand, the therapeutic pressure prompts AR^+ tumor subpopulation adaptation via enhanced androgen synthesis, activation of noncanonical AR or alternative pathways, or down-regulation of *AR* expression through intricate genetic and epigenetic mechanisms [9,35,67,88]. In *CTNNB1* mutation tumors, the excessive accumulation of β-catenin could repress AR expression through WNT5a/NF-κB signaling [117]. PTEN deficiency could synergistically enhance the oncogenic activity of β-catenin and collectively drive AR-independent CRPC [117]. In RB1-deficient tumors, the loss of RB1 function leads to aberrant activation of both E2F and EZH2 [97]. EZH2 mediates PRC2-dependent H3K27me3 deposition at the AR promoter, and E2F1 directly binds the AR promoter alongside pocket proteins p107 and p130, together repressing AR expression [124,133]. Additionally, the deficiency of epigenetic checkpoint KMT2C could up-regulate ΔNp63, which in turn represses SP1, a crucial transcriptional regulator of the AR gene [89]. Under sustained ADT and ARSI pressure, AR^-/lo cells become enriched in CRPC (with AR detectable in only about 40% of mCRPC cells in some studies) [124]. When AR expression is lost in the absence of NE marker expression, PCa progresses to the DNPC. There is a theory proposing that DNPC is an intermediate stage between AR-positive adenocarcinoma and NEPC, while some studies regard both DNPC and NEPC as distinct terminal subtypes of CRPC [134].

Concurrently, accumulation of DDR-related mutations along with increased clonal loss of tumor suppressor genes such as *TP53*/*RB1* drives genome instability and enhances lineage plasticity [67,135–137]. In the early stage of NEPC, following TP53/RB1 loss, SOX2-driven ectopic JAK–STAT activation promotes the loss of luminal identity and the acquisition of a stem-like, multilineage state in tumor cells [138]. Under ADT pressure, FOXA2 and ASCL1 are up-regulated. ASCL1 promotes NE lineage transition from $KRT8^+$ luminal epithelial cells, while FOXA2 directly promotes the KIT signaling pathway within tumor cells to sustain NEPC proliferation and tumor growth [139,140]. In addition, a recent study found that FOXA2 could induce NKX2-1 expression, and they cooperatively recruit p300/CBP to NE enhancers to catalyze H3K27ac, thereby activating the expression of NE marker genes such as *SYP*, *NCAM1*, and *BRN2*, driving NEPC transdifferentiation [98].

Challenges and Future Directions

The development of therapeutic resistance in PCa is driven by the complex interplay of intratumoral androgen anabolic reprogramming, AR alterations, multidimensional crosstalk networks, and genetic lineage reprogramming, all of which exhibit pronounced spatiotemporal heterogeneity. A primary challenge lies in moving beyond static research paradigms. Current research predominantly relies on static samples (including radical prostatectomy specimens or metastatic biopsies at limited time points), which fails to capture the real-time coevolution of the intratumoral androgen microenvironment and genomic alterations under therapeutic pressure [69,120]. Overcoming these barriers requires a multidimensional understanding of AR signaling adaptation, stem cell plasticity, and NE transformation [141]. Future studies should emphasize the use of serial patient samples, liquid biopsies, genetically engineered mouse

models, and PDOs, integrated with high-resolution single-cell and spatial multi-omics technologies [142].

Current research extensively focuses on the transcriptional/epigenetic regulatory functions of AR signaling and targeting alternative pathways (like PI3K-AKT). Future investigations should actively explore the therapeutic potential of cotargeting the AR signaling with other alternative pathways, such as NF-κB, and focus on interactive nodes beyond AR itself [143]. The impact of epigenetics on androgen metabolism is largely underexplored. Future work should investigate whether and how androgens serve as substrates to influence epigenetics, thereby silencing tumor suppressor genes [8]. Deeper exploration into how posttranslational modifications reshape the expression profile of androgen metabolic enzymes is needed to elucidate the cross-talk between metabolism and epigenetics [38]. The metabolic regulation of the immune microenvironment is another crucial direction. PCa is considered an "immunologically cold" tumor, and immunotherapy has yet to achieve breakthrough success in this area [144]. Evidence suggests that endocrine therapy and the intratumoral immune microenvironment can influence each other [4,145]. Single-cell sequencing is a powerful tool for dissecting interactions between tumor cells and immune/stromal cells, and for identifying tumor subtypes most likely to benefit from immunotherapy [145]. Future research needs to elucidate whether intratumoral androgen metabolism/pathways can regulate the function of specific immune cells (like regulatory T cells and myeloid-derived suppressor cells) and whether immune cell-derived cytokines (like IL-10) can feedback to affect tumor cell androgen synthesis/signaling, forming a "metabolism–immune" axis of resistance. Furthermore, there exist potential interactions between immune responses, circadian rhythms, and cellular senescence, and future studies should also explore their potential cross-talk with androgen metabolic pathways in PCa [146]. Proteomic studies often overlook proteins encoded/regulated by traditionally defined "noncoding" genomic regions, which may play important roles in tumor biology [147]. Future research should explore the interactions and links between these noncanonical proteins and the androgen pathway in PCa.

To advance from common treatment toward precision intervention, there is an urgent need to develop novel biomarkers and combination strategies. The predictive value of existing biomarkers like PSA is limited, necessitating more comprehensive subtyping tools and dynamic monitoring systems. Future research should leverage longitudinal liquid biopsy techniques, such as the combined analysis of circulating tumor DNA epigenetic profiles and androgen metabolite profiles, to noninvasively monitor the dynamic reprogramming of intratumoral androgen synthesis pathways and the evolutionary trajectory of emerging resistant clones [148]. Direct dynamic monitoring of androgen metabolism via tritium-labeled androgen precursors and high-performance liquid chromatography (HPLC)–β-radioactivity detection can further uncover genetic regulators of intratumoral androgen dynamics [149]. Simultaneously, the application of spatial multi-omics technologies enables in situ analysis of the TME, helping to reveal the spatial colocalization of androgen metabolism "hotspots" with cells harboring specific genetic variants, thereby identifying "cellular neighborhood effects" that drive resistance [58,150]. In therapeutic testing, bioprinting technology and PDOs can serve as functional biomarker platforms to directly test tumor sensitivity to novel targeted drugs in vitro, combined with their genetic variant profiles, enabling the simultaneous development of "drug–biomarker" pairs [151]. Furthermore, artificial intelligence models integrating patient multi-omics data can predict compensatory resistance pathways most likely to be activated, providing a rationale for future therapeutic testing of relevant combination strategies [152].

The seeds of therapeutic resistance may be sown early, even at diagnosis. Future research needs to focus on earlier stage. Challenges such as the lack of standardized biomarkers for the early detection of lineage plasticity transitions hinder timely clinical intervention. Multi-omics analysis (like digital pathology combined with single-cell sequencing) of tumor biopsies could be used to develop a "therapy resistance risk score" to identify high-risk patients, prompting consideration of adjuvant targeted interventions following radical treatment to prevent the expansion of resistant clones in micrometastases [153]. Additionally, novel AR regulatory mechanisms should be explored, focusing on the activation mechanisms of noncanonical androgen signaling (like membrane-associated AR) in low-androgen environments, laying the groundwork for developing novel AR functional inhibitors [154]. For advanced tumors, particularly aggressive subtypes like NEPC driven by epigenetic dysregulation and metabolic reprogramming, active investigation should focus on lineage-specific targets and potential combination strategies [89,139]. Butler et al. [155] discovered that the glycosylated protein glypican-3 is specifically highly expressed on the surface of NE cells, while it is scarcely expressed in hormone-sensitive prostate cancer. Knockdown of glypican-3 inhibits the proliferation and survival of NE cells, making it a potential target for the precise diagnosis and treatment of NEPC [155]. The accumulation of DNA replication mutations and genomic instability under therapeutic pressure in advanced disease may render cellular senescence a potential therapeutic target [156]. PARP inhibitors can exacerbate replication stress in HRR-deficient cancer cells and may potentially induce senescence in PCa [157]. Aging is associated with decreased melatonin secretion and circadian rhythm disruption, which collectively exacerbate oxidative stress and inflammation, promoting tumor progression [158]. Advanced PCa exhibits marked glycolipid metabolic abnormalities. DNPC exhibits aberrant activation of SREBP1c-driven fatty acid metabolic pathways and promotes growth via the MAPK/ERK (extracellular signal-regulated kinase) pathway [89], whereas NEPC demonstrates enhanced glycolysis to sustain AR-independent survival [159]. Tumor metabolic reprogramming may offer therapeutic targets for advanced aggressive PCa [160]. Additionally, lysosomal function is closely linked to cellular metabolism [161]. Future research needs to explore the link between lysosomal function and glycolipid metabolism regulation in late-stage disease and its potential as a therapeutic target.

Integrating diverse data streams—from genomic, transcriptomic, epigenomic, and metabolic analyses—could improve the selection and adaptation of personalized combination therapies throughout the disease course, moving beyond static biopsies to a continuous management model [162].

Conclusion

This review systematically synthesizes the multidimensional drug resistance network in PCa, encompassing intratumoral androgen metabolism, AR genetic alterations, pathway cross-talk, and spatiotemporal heterogeneity. It underscores the necessity of cotargeting androgen metabolic reprogramming

and AR-interacting pathways via precision interventions, coupled with dynamic monitoring technologies to track and counteract the evolution of resistant clones. Future efforts should focus on identifying key targets within the androgen signaling axis and developing synergistic therapeutic and translational strategies to suppress lineage plasticity, thereby overcoming resistance barriers in PCa.

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Supplementary Materials

Table S1

References

1. Feng DC, Li DX, Wu RC, Wang J, Xiao YH, Yoo KH, Ye X, Wei WR, Kong DP, Tuo ZT. Global burden and cross-country inequalities in urinary tumors from 1990 to 2021 and predicted incidence changes to 2046. *Mil Med Res*. 2025;12(1):12.
2. Wilt TJ, Brawer MK, Jones KM, Barry MJ, Aronson WJ, Fox S, Gingrich JR, Wei JT, Gilhooly P, Grob BM, et al. Radical prostatectomy versus observation for localized prostate cancer. *N Engl J Med*. 2012;367(3):203–213.
3. Williams IS, McVey A, Perera S, O'Brien JS, Kostos L, Chen K, Siva S, Azad AA, Murphy DG, Kasivisvanathan V, et al. Modern paradigms for prostate cancer detection and management. *Med J Aust*. 2022;217(8):424–433.
4. Wang Z, Wang J, Li D, Wu R, Huang J, Ye L, Tuo Z, Yu Q, Shao F, Wusiman D, et al. Novel hormone therapies for advanced prostate cancer: Understanding and countering drug resistance. *J Pharm Anal*. 2025;15(9):Article 101232.
5. Montgomery RB, Mostaghel EA, Vessella R, Hess DL, Kalhorn TF, Higano CS, True LD, Nelson PS. Maintenance of intratumoral androgens in metastatic prostate cancer: A mechanism for castration-resistant tumor growth. *Cancer Res*. 2008;68(11):4447–4454.
6. Rhee J, Adzavon YM, Sun Z. Stromal androgen signaling governs essential niches in supporting prostate development and tumorigenesis. *Oncogene*. 2024;43(47):3419–3425.
7. Cheng Q, Butler W, Zhou Y, Zhang H, Tang L, Perkinson K, Chen X, Jiang XS, McCall S, Inman BA, et al. Pre-existing castration-resistant prostate cancer-like cells in primary prostate cancer promote resistance to hormonal therapy. *Eur Urol*. 2022;81(5):446–455.
8. Jamroze A, Chatta G, Tang DG. Androgen receptor (AR) heterogeneity in prostate cancer and therapy resistance. *Cancer Lett*. 2021;518:1–9.
9. Watson PA, Arora VK, Sawyers CL. Emerging mechanisms of resistance to androgen receptor inhibitors in prostate cancer. *Nat Rev Cancer*. 2015;15(12):701–711.
10. Zhou J, Wang Y, Wu D, Wang S, Chen Z, Xiang S, Chan FL. Orphan nuclear receptors as regulators of intratumoral androgen biosynthesis in castration-resistant prostate cancer. *Oncogene*. 2021;40(15):2625–2634.
11. Visvader JE. Cells of origin in cancer. *Nature*. 2011;469(7330):314–322.
12. Kim WK, Buckley AJ, Lee DH, Hiroto A, Nenninger CH, Olson AW, Wang J, Li Z, Vikram R, Adzavon YM, et al. Androgen deprivation induces double-null prostate cancer via aberrant nuclear export and ribosomal biogenesis through HGF and Wnt activation. *Nat Commun*. 2024;15:1231.
13. Banerjee P, Kapse P, Siddique S, Kundu M, Choudhari J, Mohanty V, Malhotra D, Gosavi SW, Gacche RN, Kundu GC. Therapeutic implications of cancer stem cells in prostate cancer. *Cancer Biol Med*. 2023;20(6):401–420.
14. Smith MR. Androgen deprivation therapy for prostate cancer: New concepts and concerns. *Curr Opin Endocrinol Diabetes Obes*. 2007;14(3):247–254.
15. Geller J, Albert J, Loza D, Geller S, Stoeltzing W, de la Vega D. DHT concentrations in human prostate cancer tissue. *J Clin Endocrinol Metab*. 1978;46(3):440–444.
16. Page ST, Lin DW, Mostaghel EA, Hess DL, True LD, Amory JK, Nelson PS, Matsumoto AM, Bremner WJ. Persistent intraprostatic androgen concentrations after medical castration in healthy men. *J Clin Endocrinol Metab*. 2006;91(10):3850–3856.
17. Dillard PR, Lin MF, Khan SA. Androgen-independent prostate cancer cells acquire the complete steroidogenic potential of synthesizing testosterone from cholesterol. *Mol Cell Endocrinol*. 2008;295(1–2):115–120.
18. Miller WL, Auchus RJ. The molecular biology, biochemistry, and physiology of human steroidogenesis and its disorders. *Endocr Rev*. 2011;32(1):81–151.
19. Snaterse G, Taylor AE, Moll JM, O'Neil DM, Teubel WJ, van Weerden WM, Arlt W, Hofland J. Prostate cancer androgen biosynthesis relies solely on CYP17A1 downstream metabolites. *J Steroid Biochem Mol Biol*. 2024;236:Article 106446.
20. Hofland J, van Weerden WM, Dits NFJ, Steenbergen J, van Leenders GJLH, Jenster G, Schröder FH, de Jong FH. Evidence of limited contributions for Intratumoral steroidogenesis in prostate cancer. *Cancer Res*. 2010;70(3):1256–1264.
21. Zhang H, Zhou Y, Xing Z, Sah RK, Hu J, Hu H. Androgen metabolism and response in prostate cancer anti-androgen therapy resistance. *Int J Mol Sci*. 2022;23(21):13521.

22. Auchus RJ. Non-traditional metabolic pathways of adrenal steroids. *Rev Endocr Metab Disord*. 2009;10(1):27–32.
23. Shiota M, Endo S, Blas L, Fujimoto N, Eto M. Steroidogenesis in castration-resistant prostate cancer. *Urol Oncol*. 2023;41(5):240–251.
24. Deb S, Pham S, Ming DS, Chin MY, Adomat H, Hurtado-Coll A, Gleave ME, Guns EST. Characterization of precursor-dependent steroidogenesis in human prostate cancer models. *Cancers (Basel)*. 2018;10(10):343.
25. Barnard M, Mostaghel EA, Auchus RJ, Storbeck KH. The role of adrenal derived androgens in castration resistant prostate cancer. *J Steroid Biochem Mol Biol*. 2020;197: Article 105506.
26. Dai C, Chung YM, Kovac E, Zhu Z, Li J, Magi-Galluzzi C, Stephenson AJ, Klein EA, Sharifi N. Direct metabolic interrogation of dihydrotestosterone biosynthesis from adrenal precursors in primary prostatectomy tissues. *Clin Cancer Res*. 2017;23(20):6351–6362.
27. Schwartz AG. Dehydroepiandrosterone, cancer, and aging. *Aging Dis*. 2022;13(2):423–432.
28. He D, Falany CN. Inhibition of SULT2B1b expression alters effects of 3beta-hydroxysteroids on cell proliferation and steroid hormone receptor expression in human LNCaP prostate cancer cells. *Prostate*. 2007;67(12):1318–1329.
29. Arakawa H, Nakanishi T, Yanagihara C, Nishimoto T, Wakayama T, Mizokami A, Namiki M, Kawai K, Tamai I. Enhanced expression of organic anion transporting polypeptides (OATPs) in androgen receptor-positive prostate cancer cells: Possible role of OATP1A2 in adaptive cell growth under androgen-depleted conditions. *Biochem Pharmacol*. 2012;84(8):1070–1077.
30. Cai C, Balk SP. Intratumoral androgen biosynthesis in prostate cancer pathogenesis and response to therapy. *Endocr Relat Cancer*. 2011;18(5):R175–R182.
31. du Toit T, Bloem LM, Quanson JL, Ehlers R, Serafin AM, Swart AC. Profiling adrenal 11β-hydroxyandrostenedione metabolites in prostate cancer cells, tissue and plasma: UPC2-MS/MS quantification of 11β-hydroxytestosterone, 11keto-testosterone and 11keto-dihydrotestosterone. *J Steroid Biochem Mol Biol*. 2017;166:54–67.
32. Barnard M, Quanson JL, Mostaghel E, Pretorius E, Snoep JL, Storbeck KH. 11-oxygenated androgen precursors are the preferred substrates for aldo-keto reductase 1C3 (AKR1C3): Implications for castration resistant prostate cancer. *J Steroid Biochem Mol Biol*. 2018;183:192–201.
33. Hou Z, Huang S, Mei Z, Chen L, Guo J, Gao Y, Zhuang Q, Zhang X, Tan Q, Yang T, et al. Inhibiting 3βHSD1 to eliminate the oncogenic effects of progesterone in prostate cancer. *Cell Rep Med*. 2022;3(3):Article 100561.
34. Koh E, Noda T, Kanaya J, Namiki M. Differential expression of 17beta-hydroxysteroid dehydrogenase isozyme genes in prostate cancer and noncancer tissues. *Prostate*. 2002;53(2):154–159.
35. Kong Y, Cheng L, Mao F, Zhang Z, Zhang Y, Farah E, Bosler J, Bai Y, Ahmad N, Kuang S, et al. Inhibition of cholesterol biosynthesis overcomes enzalutamide resistance in castration-resistant prostate cancer (CRPC). *J Biol Chem*. 2018;293(37):14328–14341.
36. Škara L, Turković AH, Pezelj I, Vrtarić A, Sinčić N, Krušlin B, Ulamec M. Prostate cancer-focus on cholesterol. *Cancer*. 2021;13(18):4696.
37. Xue L, Qi H, Zhang H, Ding L, Huang Q, Zhao D, Wu BJ, Li X. Targeting SREBP-2-regulated mevalonate metabolism for cancer therapy. *Front Oncol*. 2020;10:1510.
38. Nguyen T, Sridaran D, Chouhan S, Weimholt C, Wilson A, Luo J, Li T, Koomen J, Fang B, Putluri N, et al. Histone H2A Lys130 acetylation epigenetically regulates androgen production in prostate cancer. *Nat Commun*. 2023;14(1):3357.
39. Zhang Z, Hou X, Shao C, Li J, Cheng J-X, Kuang S, Ahmad N, Ratliff T, Liu X. Plk1 inhibition enhances the efficacy of androgen signaling blockade in castration-resistant prostate cancer. *Cancer Res*. 2014;74(22):6635–6647.
40. Chen F, Li H, Wang Y, Tang X, Lin K, Li Q, Meng C, Shi W, Leo J, Liang X, et al. CHD1 loss reprograms SREBP2-driven cholesterol synthesis to fuel androgen-responsive growth and castration resistance in SPOP-mutated prostate tumors. *Nat Cancer*. 2025;6(5):854–873.
41. Bernasocchi T, Tekle GE, Bolis M, Mutti A, Vallerga A, Brandt LP, Spriano F, Svinkina T, Zoma M, Ceserani V, et al. Dual functions of SPOP and ERG dictate androgen therapy responses in prostate cancer. *Nat Commun*. 2021;12(1):734.
42. Nakazawa M, Fang M, Marshall CH, Lotan TL, Velho PI, Antonarakis ES. Clinical and genomic features of SPOP-mutant prostate cancer. *Prostate*. 2022;82(2):260–268.
43. Jayalath VH, Clark R, Lajkosz K, Fazelzad R, Fleshner NE, Klotz LH, Hamilton RJ. Statin use and survival among men receiving androgen-ablative therapies for advanced prostate cancer: A systematic review and meta-analysis. *JAMA Netw Open*. 2022;5(11):Article e2242676.
44. Cai C, He HH, Chen S, Coleman I, Wang H, Fang Z, Chen S, Nelson PS, Liu XS, Brown M, et al. Androgen receptor gene expression in prostate cancer is directly suppressed by the androgen receptor through recruitment of lysine-specific demethylase 1. *Cancer Cell*. 2011;20(4): 457–471.
45. Megerian MF, Kim JS, Badreddine J, Hong SH, Ponsky LE, Shin JI, Ghayda RA. Melatonin and prostate cancer: Anti-tumor roles and therapeutic application. *Aging Dis*. 2023;14(3):840–857.
46. Zhou L, Zhang C, Yang X, Liu L, Hu J, Hou Y, Tao H, Sugimura H, Chen Z, Wang L, et al. Melatonin inhibits lipid accumulation to repress prostate cancer progression by mediating the epigenetic modification of CES1. *Clin Transl Med*. 2021;11(6):Article e449.
47. Shafiee-Kermani F, Carney ST, Jima D, Utin UC, Farrar LB, Oputa MO, Hines MR, Kinyamu HK, Trotter KW, Archer TK, et al. Expression of UDP glucuronosyltransferases 2B15 and 2B17 is associated with methylation status in prostate cancer cells. *Epigenetics*. 2021;16(3):289–299.
48. Liu W, Li J, Zhao R, Lu Y, Huang P. The uridine diphosphate (UDP)-glycosyltransferases (UGTs) superfamily: The role in tumor cell metabolism. *Front Oncol*. 2023;12:1088458.
49. Chouinard S, Barbier O, Bélanger A. UDP-glucuronosyltransferase 2B15 (UGT2B15) and UGT2B17 enzymes are major determinants of the androgen response in prostate cancer LNCaP cells. *J Biol Chem*. 2007;282(46):33466–33474.
50. Mizokami A, Koh E, Izumi K, Narimoto K, Takeda M, Honma S, Dai J, Keller ET, Namiki M. Prostate cancer stromal cells and LNCaP cells coordinately activate the androgen receptor through synthesis of testosterone and dihydrotestosterone from dehydroepiandrosterone. *Endocr Relat Cancer*. 2009;16(4):1139–1155.

51. Lubik AA, Gunter JH, Hollier BG, Ettinger S, Fazli L, Stylianou N, Hendy SC, Adomat HH, Gleave ME, Pollak M, et al. IGF2 increases de novo steroidogenesis in prostate cancer cells. *Endocr Relat Cancer*. 2013;20(2):173–186.
52. Chun JY, Nadiminty N, Dutt S, Lou W, Yang JC, Kung HJ, Evans CP, Gao AC. Interleukin-6 regulates androgen synthesis in prostate cancer cells. *Clin Cancer Res*. 2009;15(15):4815–4822.
53. Vasileiou C, Befani C, Dimas K, Liakos P, Papandreou C. FGF-2 and HGF reverse abiraterone's effect on intracellular levels of DHT in androgen-dependent and androgen independent prostate cancer cell lines. *J BUON*. 2020;25(2):1141–1147.
54. Lubik AA, Gunter JH, Hendy SC, Locke JA, Adomat HH, Thompson V, Herington A, Gleave ME, Pollak M, Nelson CC. Insulin increases de novo steroidogenesis in prostate cancer cells. *Cancer Res*. 2011;71(17):5754–5764.
55. Pinski J, Xiong S, Wang Q, Stanczyk F, Hawes D, Liu SV. Effect of luteinizing hormone on the steroidogenic pathway in prostate cancer. *Prostate*. 2011;71(8):892–898.
56. Donato MD, Zamagni A, Galasso G, Zazzo ED, Giovannelli P, Barone MV, Zanoni M, Gunelli R, Costantini M, Auricchio F, et al. The androgen receptor/filamin a complex as a target in prostate cancer microenvironment. *Cell Death Dis*. 2021;12(1):127.
57. Le TT-H, Hsieh C-L, Lin I-H, Chu C-Y, Do AD, Chen S-H, Shigemura K, Kitagawa K, Fujisawa M, Liu M-C, et al. The ADAM9/UBN2/AKR1C3 axis promotes resistance to androgen-deprivation in prostate cancer. *Am J Cancer Res*. 2022;12(1):176–197.
58. Cui D, Li J, Zhu Z, Berk M, Hardaway A, McManus J, Chung YM, Alyamani M, Valle S, Tiwari R, et al. Cancer-associated fibroblast-secreted glucosamine alters the androgen biosynthesis program in prostate cancer via HSD3B1 upregulation. *J Clin Invest*. 2023;133(7): Article e161913.
59. Qin L, Berk M, Chung YM, Cui D, Zhu Z, Chakraborty AA, Sharifi N. Chronic hypoxia stabilizes 3βHSD1 via autophagy suppression. *Cell Rep*. 2024;43(1):Article 113575.
60. Tyagi A, Chandrasekaran B, Shukla V, Tyagi N, Sharma AK, Damodaran C. Nutraceuticals target androgen receptor-splice variants (AR-SV) to manage castration resistant prostate cancer (CRPC). *Pharmacol Ther*. 2024;264:Article 108743.
61. Özturan D, Morova T, Lack NA. Androgen receptor-mediated transcription in prostate cancer. *Cells*. 2022;11(5):898.
62. Heidari Horestani M, Atri Roozbahani G, Baniahmad A. H2AJ is a direct androgen receptor target Gene that regulates androgen-induced cellular senescence and inhibits mesenchymal markers in prostate cancer cells. *Cancer*. 2025;17(5):791.
63. Markowski MC, Wang H, Sullivan R, Rifkind I, Sinibaldi V, Schweizer MT, Teply BA, Ngomba N, Fu W, Carducci MA, et al. A multicohort open-label phase II trial of bipolar androgen therapy in men with metastatic castration-resistant prostate cancer (RESTORE): A comparison of post-abiraterone versus post-enzalutamide cohorts. *Eur Urol*. 2021;79(5):692–699.
64. Isaacsson P, Soares A, Fontes Jardim DL, Maluf FC, Morbeck IAP, Girardi DM, Dias MF, Souza VC, Silva AGE, de Jesus RG, et al. Extreme bipolar androgen therapy: Alternating darolutamide and testosterone cypionate in patients with metastatic castration-resistant prostate cancer (mCRPC; ExBAT trial/LACOG 0620). *J Clin Oncol*. 2025;43(5_suppl):178.
65. Scher HI, Sawyers CL. Biology of progressive, castration-resistant prostate cancer: Directed therapies targeting the androgen-receptor signaling axis. *J Clin Oncol*. 2005;23(32):8253–8261.
66. Visakorpi T, Hyytinen E, Koivisto P, Tanner M, Keinänen R, Palmberg C, Palotie A, Tammela T, Isola J, Kallioniemi OP. In vivo amplification of the androgen receptor gene and progression of human prostate cancer. *Nat Genet*. 1995;9(4):401–406.
67. Weiss S, Lamy P, Rusan M, Nørgaard M, Ulhøi BP, Knudsen M, Kassentoft CG, Farajzadeh L, Jensen JB, Pedersen JS, et al. Exploring the tumor genomic landscape of aggressive prostate cancer by whole-genome sequencing of tissue or liquid biopsies. *Int J Cancer*. 2024;155(2):298–313.
68. Schalken J, Fitzpatrick JM. Enzalutamide: Targeting the androgen signalling pathway in metastatic castration-resistant prostate cancer. *BJU Int*. 2016;117(2):215–225.
69. Cotter K, Rubin MA. The evolving landscape of prostate cancer somatic mutations. *Prostate*. 2022;82(Supp. l):S13–S24.
70. Chen CD, Welsbie DS, Tran C, Baek SH, Chen R, Vessella R, Rosenfeld MG, Sawyers CL. Molecular determinants of resistance to antiandrogen therapy. *Nat Med*. 2004;10(1):33–39.
71. Waltering KK, Helenius MA, Sahu B, Manni V, Linja MJ, Jänne OA, Visakorpi T. Increased expression of androgen receptor sensitizes prostate cancer cells to low levels of androgens. *Cancer Res*. 2009;69(20):8141–8149.
72. Cato L, de Tribolet-Hardy J, Lee I, Rottenberg JT, Coleman I, Melchers D, Houtman R, Xiao T, Li W, Uo T, et al. ARv7 represses tumor-suppressor genes in castration-resistant prostate cancer. *Cancer Cell*. 2019;35(3):401–413.e6.
73. He MX, Cuoco MS, Crowdis J, Bosma-Moody A, Zhang Z, Bi K, Kanodia A, Su MJ, Ku SY, Garcia MM, et al. Transcriptional mediators of treatment resistance in lethal prostate cancer. *Nat Med*. 2021;27(3):426–433.
74. Fan L, Zhang F, Xu S, Cui X, Hussain A, Fazli L, Gleave M, Dong X, Qi J. Histone demethylase JMJD1A promotes alternative splicing of AR variant 7 (AR-V7) in prostate cancer cells. *Proc Natl Acad Sci USA*. 2018;115(20): E4584–E4593.
75. Teramoto Y, Najafi MAE, Matsukawa T, Sharma A, Goto T, Miyamoto H. Latrophilins as downstream effectors of androgen receptors including a splice variant, AR-V7, induce prostate cancer progression. *Int J Mol Sci*. 2024;25(13):7289.
76. Marek RD, Halabi S, Wang M-E, Bane JM, Wei J, Wang T, Yang X, Liu C, Lei G, Lyerly HK, et al. Vaccination against androgen receptor splice variants to immunologically target prostate cancer. *Vaccine*. 2024;12(11):1273.
77. Zammit CM, Nadel CM, Lin Y, Koirala S, Ahani E, Potts PR, Nomura DK. Covalent destabilizing degrader of AR and AR-V7 in androgen-independent prostate cancer cells. *J Am Chem Soc*. 2025;147(24):20512–20524.
78. Xue L, Yu X, Zhao L, Garrett A, Wu D, Liu HY. Targeted delivery of AR-V7 siRNA with bivalent PSMA aptamers effectively suppresses the growth of enzalutamide-resistant prostate cancer. *Mol Pharm*. 2024;21(11):5749–5760.
79. Ha S, Ji C, Yang J, Xiao M, Xu Z, Pan WW, Xiang H, Luo G. Discovery of a highly potent, N-terminal domain-targeting degrader of AR-FL/AR-V7 for the treatment of prostate cancer. *Eur J Med Chem*. 2025;282:Article 117079.

80. Li C, Cheng D, Li P. Androgen receptor dynamics in prostate cancer: From disease progression to treatment resistance. *Front Oncol*. 2025;15:1542811.
81. Bohl CE, Gao W, Miller DD, Bell CE, Dalton JT. Structural basis for antagonism and resistance of bicalutamide in prostate cancer. *Proc Natl Acad Sci USA*. 2005;102(17):6201–6206.
82. Borgmann H, Lallous N, Ozistanbullu D, Beraldi E, Paul N, Dalal K, Fazli L, Haferkamp A, Lejeune P, Cherkasov A, et al. Moving towards precision urologic oncology: Targeting enzalutamide-resistant prostate cancer and mutated forms of the androgen receptor using the novel inhibitor Darolutamide (ODM-201). *Eur Urol*. 2018;73(1):4–8.
83. Korpal M, Korn JM, Gao X, Rakiec DP, Ruddy DA, Doshi S, Yuan J, Kovats SG, Kim S, Cooke VG, et al. An F876L mutation in androgen receptor confers genetic and phenotypic resistance to MDV3100 (enzalutamide). *Cancer Discov*. 2013;3(9):1030–1043.
84. Carranza-Aranda AS, Santerre A, Segura-Cabrera A, Cárdenas-Vargas A, Martínez-Velázquez M, Hernández-Gutiérrez R, Herrera-Rodríguez SE. Chrysin: A potential antiandrogen ligand to mutated androgen receptors in prostate cancer. *Curr Mol Pharmacol*. 2024;17:Article e18761429350210.
85. Lin SR, Yeh HL, Liu YN. Interplay of epidermal growth factor receptor and signal transducer and activator of transcription 3 in prostate cancer: Beyond androgen receptor transactivation. *Cancer*. 2021;13(14):3452.
86. Danielli L, Tassinari E, Marchetti A, Rosellini M, Mollica V, Cheng L, Massari F. Current androgen receptor antagonists under investigation for resistant prostate cancer: Progress and challenges. *Expert Rev Anticancer Ther*. 2025;25(5):457–470.
87. Davey RA, Grossmann M. Androgen receptor structure, function and biology: From bench to bedside. *Clin Biochem Rev*. 2016;37(1):3–15.
88. Arora VK, Schenkein E, Murali R, Subudhi SK, Wongvipat J, Balbas MD, Shah N, Cai L, Efstathiou E, Logothetis C, et al. Glucocorticoid receptor confers resistance to antiandrogens by bypassing androgen receptor blockade. *Cell*. 2013;155(6):1309–1322.
89. Guo J, Li N, Liu Q, Hao Z, Zhu G, Wang X, Wang H, Pan Q, Xu B, Han Y, et al. KMT2C deficiency drives transdifferentiation of double-negative prostate cancer and confer resistance to AR-targeted therapy. *Cancer Cell*. 2025;43(7):1261–1278.e10.
90. Zoma M, Curti L, Shinde D, Albino D, Mitra A, Sgrignani J, Mapelli SN, Sandrini G, Civenni G, Merulla J, et al. EZH2-induced lysine K362 methylation enhances TMPRSS2-ERG oncogenic activity in prostate cancer. *Nat Commun*. 2021;12(1):4147.
91. Aurilio G, Cimadamore A, Mazzucchelli R, Lopez-Beltran A, Verri E, Scarpelli M, Massari F, Cheng L, Santoni M, Montironi R. Androgen receptor signaling pathway in prostate cancer: From genetics to clinical applications. *Cells*. 2020;9(12):2653.
92. Zhou F, Gao S, Han D, Han W, Chen S, Patalano S, Macoska JA, He HH, Cai C. TMPRSS2-ERG activates NO-cGMP signaling in prostate cancer cells. *Oncogene*. 2019;38(22):4397–4411.
93. Zhang L, Troccoli CI, Mateo-Victoriano B, Misiara Lincheta L, Jackson E, Shu P, Plastini T, Tao W, Kwon D, Chen XS, et al. Stimulating soluble Guanylyl cyclase with the clinical agonist Riociguat restrains the development and progression of castration-resistant prostate cancer. *Cancer Res*. 2025;85(1):134–153.
94. Cancer Genome Atlas Research Network. The molecular taxonomy of primary prostate cancer. *Cell*. 2015;163(4):1011–1025.
95. Teng M, Zhou S, Cai C, Lupien M, He HH. Pioneer of prostate cancer: Past, present and the future of FOXA1. *Protein Cell*. 2021;12(1):29–38.
96. Parolia A, Cieslik M, Chu SC, Xiao L, Ouchi T, Zhang Y, Wang X, Vats P, Cao X, Pitchiaya S, et al. Distinct structural classes of activating FOXA1 alterations in advanced prostate cancer. *Nature*. 2019;571(7765):413–418.
97. Ku SY, Rosario S, Wang Y, Mu P, Seshadri M, Goodrich ZW, Goodrich MM, Labbé DP, Gomez EC, Wang J, et al. Rb1 and Trp53 cooperate to suppress prostate cancer lineage plasticity, metastasis, and antiandrogen resistance. *Science*. 2017;355(6320):78–83.
98. Lu X, Keo V, Cheng I, Xie W, Gritsina G, Wang J, Lu L, Shiau CK, He Y, Jin Q, et al. NKX2-1 drives neuroendocrine transdifferentiation of prostate cancer via epigenetic and 3D chromatin remodeling. *Nat Genet*. 2025;57(8):1966-1980.
99. Piombino C, Pipitone S, Tonni E, Mastrodomenico L, Oltrecolli M, Tchawa C, Matranga R, Roccabruna S, D'Agostino E, Pirola M, et al. Homologous recombination repair deficiency in metastatic prostate cancer: New therapeutic opportunities. *Int J Mol Sci*. 2024;25(9):4624.
100. Matos AC, Lima M, Miranda-Gonçalves V, Indraccolo S, Jerónimo C, Saraiva L. Overcoming radioresistance in prostate cancer by targeting DNA damage repair. *Cancer Lett*. 2025;639:Article 218183.
101. Polkinghorn WR, Parker JS, Lee MX, Kass EM, Spratt DE, Iaquinta PJ, Arora VK, Yen WF, Cai L, Zheng D, et al. Androgen receptor signaling regulates DNA repair in prostate cancers. *Cancer Discov*. 2013;3(11):1245–1253.
102. Li L, Karanika S, Yang G, Wang J, Park S, Broom BM, Manyam GC, Wu W, Luo Y, Basourakos S, et al. Androgen receptor inhibitor-induced "BRCAness" and PARP inhibition are synthetically lethal for castration-resistant prostate cancer. *Sci Signal*. 2017;10(480):eaam7479.
103. Schiewer MJ, Goodwin JF, Han S, Brenner JC, Augello MA, Dean JL, Liu F, Planck JL, Ravindranathan P, Chinnaiyan AM, et al. Dual roles of PARP-1 promote cancer growth and progression. *Cancer Discov*. 2012;2(12):1134–1149.
104. Gui B, Gui F, Takai T, Feng C, Bai X, Fazli L, Dong X, Liu S, Zhang X, Zhang W, et al. Selective targeting of PARP-2 inhibits androgen receptor signaling and prostate cancer growth through disruption of FOXA1 function. *Proc Natl Acad Sci USA*. 2019;116(29):14573–14582.
105. McKay RR, Morgans AK, Shore ND, Dunshee C, Devgan G, Agarwal N. First-line combination treatment with PARP and androgen receptor-signaling inhibitors in HRR-deficient mCRPC: Applying clinical study findings to clinical practice in the United States. *Cancer Treat Rev*. 2024;126:Article 102726.
106. Shorning BY, Dass MS, Smalley MJ, Pearson HB. The PI3K-AKT-mTOR pathway and prostate cancer: At the crossroads of AR, MAPK, and WNT signaling. *Int J Mol Sci*. 2020;21(12):4507.
107. Raith F, O'Donovan DH, Lemos C, Politz O, Haendler B. Addressing the reciprocal crosstalk between the AR and the

PI3K/AKT/mTOR signaling pathways for prostate cancer treatment. *Int J Mol Sci*. 2023;24(3):2289.
108. Adzavon YM, Culig Z, Sun Z. Interactions between androgen and IGF1 axes in prostate tumorigenesis. *Nat Rev Urol*. 2025;22(5):268–275.
109. Thapa D, Meng P, Bedolla RG, Reddick RL, Kumar AP, Ghosh R. NQO1 suppresses NF-κB-p300 interaction to regulate inflammatory mediators associated with prostate tumorigenesis. *Cancer Res*. 2014;74(19):5644–5655.
110. Martin PL, Yin JJ, Seng V, Casey O, Corey E, Morrissey C, Simpson RM, Kelly K. Androgen deprivation leads to increased carbohydrate metabolism and hexokinase 2-mediated survival in Pten/Tp53-deficient prostate cancer. *Oncogene*. 2017;36(4):525–533.
111. Carver BS, Chapinski C, Wongvipat J, Hieronymus H, Chen Y, Chandarlapaty S, Arora VK, Le C, Koutcher J, Scher H, et al. Reciprocal feedback regulation of PI3K and androgen receptor signaling in PTEN-deficient prostate cancer. *Cancer Cell*. 2011;19(5):575–586.
112. Austin DC, Strand DW, Love HL, Franco OE, Grabowska MM, Miller NL, Hameed O, Clark PE, Matusik RJ, Jin RJ, et al. NF-κB and androgen receptor variant 7 induce expression of SRD5A isoforms and confer 5ARI resistance. *Prostate*. 2016;76(11):1004–1018.
113. Mehraein-Ghomi F, Church DR, Schreiber CL, Weichmann AM, Basu HS, Wilding G. Inhibitor of p52 NF-κB subunit and androgen receptor (AR) interaction reduces growth of human prostate cancer cells by abrogating nuclear translocation of p52 and phosphorylated AR(ser81). *Genes Cancer*. 2015;6(9-10):428–444.
114. Al-Rashidi RR, Noraldeen SAM, Kareem AK, Mahmoud AK, Kadhum WR, Ramírez-Coronel AA, Iswanto AH, Obaid RF, Jalil AT, Mustafa YF, et al. Malignant function of nuclear factor-kappaB axis in prostate cancer: Molecular interactions and regulation by non-coding RNAs. *Pharmacol Res*. 2023;194:Article 106775.
115. Chang K-S, Chen S-T, Sung H-C, Hsu S-Y, Lin W-Y, Hou C-P, Lin Y-H, Feng T-H, Tsui K-H, Juang H-H. Androgen receptor upregulates mucosa-associated lymphoid tissue 1 to induce NF-κB activity via androgen-dependent and -independent pathways in prostate carcinoma cells. *Int J Mol Sci*. 2023;24(7):6245.
116. Yang X, Chen MW, Terry S, Vacherot F, Bemis DL, Capodice J, Kitajewski J, de la Taille A, Benson MC, Guo Y, et al. Complex regulation of human androgen receptor expression by Wnt signaling in prostate cancer cells. *Oncogene*. 2006;25(24):3436–3444.
117. Patel R, Brzezinska EA, Repiscak P, Ahmad I, Mui E, Gao M, Blomme A, Harle V, Tan EH, Malviya G, et al. Activation of β-catenin cooperates with loss of Pten to drive AR-independent castration-resistant prostate cancer. *Cancer Res*. 2020;80(3):576–590.
118. Liu X, Choi RY, Jawad SM, Arnold JT. Androgen-induced PSA expression requires not only activation of AR but also endogenous IGF-I or IGF-I/PI3K/Akt signaling in human prostate cancer epithelial cells. *Prostate*. 2011;71(7):766–777.
119. Hiroto A, Kim WK, Pineda A, He Y, Lee DH, Le V, Olson AW, Aldahl J, Nenninger CH, Buckley AJ, et al. Stromal androgen signaling acts as tumor niches to drive prostatic basal epithelial progenitor-initiated oncogenesis. *Nat Commun*. 2022;13(1):6552.
120. Tang DG. Understanding and targeting prostate cancer cell heterogeneity and plasticity. *Semin Cancer Biol*. 2022;82:68–93.
121. Thompson IM Jr, Goodman PJ, Tangen CM, Parnes HL, Minasian LM, Godley PA, Lucia MS, Ford LG. Long-term survival of participants in the prostate cancer prevention trial. *N Engl J Med*. 2013;369(7):603–610.
122. Liu X, Chen X, Rycaj K, Chao HP, Deng Q, Jeter C, Liu C, Honorio S, Li H, Davis T, et al. Systematic dissection of phenotypic, functional, and tumorigenic heterogeneity of human prostate cancer cells. *Oncotarget*. 2015;6(27):23959–23986.
123. Niu Y, Chang TM, Yeh S, Ma WL, Wang YZ, Chang C. Differential androgen receptor signals in different cells explain why androgen-deprivation therapy of prostate cancer fails. *Oncogene*. 2010;29(25):3593–3604.
124. Davis JN, Wojno KJ, Daignault S, Hofer MD, Kuefer R, Rubin MA, Day ML. Elevated E2F1 inhibits transcription of the androgen receptor in metastatic hormone-resistant prostate cancer. *Cancer Res*. 2006;66(24):11897–11906.
125. Cyrta J, Prandi D, Arora A, Hovelson DH, Sboner A, Rodriguez A, Fedrizzi T, Beltran H, Robinson DR, Gopalan A, et al. Comparative genomics of primary prostate cancer and paired metastases: Insights from 12 molecular case studies. *J Pathol*. 2022;257(3):274–284.
126. Wang G, Zhao D, Spring DJ, DePinho R. Genetics and biology of prostate cancer. *Genes Dev*. 2018;32(17–18):1105–1140.
127. Labrecque MP, Coleman IM, Brown LG, True LD, Kollath L, Lakely B, Nguyen HM, Yang YC, da Costa RMG, Kaipainen A, et al. Molecular profiling stratifies diverse phenotypes of treatment-refractory metastatic castration-resistant prostate cancer. *J Clin Invest*. 2019;129(10):4492–4505.
128. Zhang Z, Wu X, Bao S, Sun X, Yang F, Zhang Y, Yang Z, Zhang L, Chen R, Xing P, et al. Proteogenomic characterization of high-grade lung neuroendocrine carcinoma deciphers molecular diversity and potential biomarkers of different histological subtypes in Chinese population. *Research*. 2025;8:0671.
129. Roudier MP, Gulati R, Sayar E, Patel RA, Tratt M, Richards HM, Cejas P, Gomez MM, Qiu X, Xie Y, et al. Patterns of intra- and inter-tumor phenotypic heterogeneity in lethal prostate cancer. *J Clin Invest*. 2025;135(15):Article e186599.
130. Qin J, Liu X, Laffin B, Chen X, Choy G, Jeter CR, Calhoun-Davis T, Li H, Palapattu GS, Pang S, et al. The PSA(-/lo) prostate cancer cell population harbors self-renewing long-term tumor-propagating cells that resist castration. *Cell Stem Cell*. 2012;10(5):556–569.
131. Taavitsainen S, Engedal N, Cao S, Handle F, Erickson A, Prekovic S, Wetterskog D, Tolonen T, Vuorinen EM, Kiviaho A, et al. Single-cell ATAC and RNA sequencing reveal pre-existing and persistent cells associated with prostate cancer relapse. *Nat Commun*. 2021;12(1):5307.
132. Li Q, Deng Q, Chao HP, Liu X, Lu Y, Lin K, Liu B, Tang GW, Zhang D, Tracz A, et al. Linking prostate cancer cell AR heterogeneity to distinct castration and enzalutamide responses. *Nat Commun*. 2018;9(1):3600.
133. Park SH, Fong KW, Mong E, Martin MC, Schiltz GE, Yu J. Going beyond Polycomb: EZH2 functions in prostate cancer. *Oncogene*. 2021;40(39):5788–5798.

134. Brennen WN, Zhu Y, Coleman IM, Dalrymple SL, Antony L, Patel RA, Hanratty B, Chikarmane R, Meeker AK, Zheng SL, et al. Resistance to androgen receptor signaling inhibition does not necessitate development of neuroendocrine prostate cancer. *JCI Insight*. 2021;6(8): Article e146827.
135. Li W, Shen MM. Prostate cancer cell heterogeneity and plasticity: Insights from studies of genetically-engineered mouse models. *Semin Cancer Biol*. 2022;82:60–67.
136. Liu G, Lin W, Zhang K, Chen K, Niu G, Zhu Y, Liu Y, Li P, Li Z, An Y. Elucidating the prognostic and therapeutic significance of TOP2A in various malignancies. *Cancer Genet*. 2024;288–289:68–81.
137. Lim DV, Woo WH, Lim JX, Loh XY, Soh HT, Lim SYA, Lee ZY, Yow HY, Hamzah SB, Sellappans R, et al. Targeting mutant-p53 for cancer treatment: Are we there yet? *Curr Mol Pharmacol*. 2024;17:Article e140923221042.
138. Deng S, Wang C, Wang Y, Xu Y, Li X, Johnson NA, Mukherji A, Lo UG, Xu L, Gonzalez J, et al. Ectopic JAK-STAT activation enables the transition to a stem-like and multilineage state conferring AR-targeted therapy resistance. *Nat Cancer*. 2022;3(9):1071–1087.
139. Romero R, Chu T, González Robles TJ, Smith P, Xie Y, Kaur H, Yoder S, Zhao H, Mao C, Kang W, et al. The neuroendocrine transition in prostate cancer is dynamic and dependent on ASCL1. *Nat Cancer*. 2024;5(11):1641–1659.
140. Han M, Li F, Zhang Y, Dai P, He J, Li Y, Zhu Y, Zheng J, Huang H, Bai F, et al. FOXA2 drives lineage plasticity and KIT pathway activation in neuroendocrine prostate cancer. *Cancer Cell*. 2022;40(11):1306–1323.e8.
141. Ubaid S, Kushwaha R, Kashif M, Singh V. Comprehensive analysis of oncogenic determinants across tumor types via multi-omics integration. *Cancer Genet*. 2025;298–299:44–62.
142. Hong R, Tong Y, Tang H, Zeng T, Liu R. eMCI: An explainable multimodal correlation integration model for unveiling spatial Transcriptomics and intercellular signaling. *Research*. 2024;7:0522.
143. Rodriguez BN, Huang H, Chia JJ, Hoffmann A. The noncanonical NFκB pathway: Regulatory mechanisms in health and disease. *WIREs Mech Dis*. 2024;16(6): Article e1646.
144. Jeong SH, Kwak C. Immunotherapy for prostate cancer: Requirements for a successful regime transfer. *Investig Clin Urol*. 2022;63(1):3–13.
145. Ding T, He L, Lin G, Xu L, Zhu Y, Wang X, Liu X, Guo J, Lei F, Zuo Z, et al. Integrated analysis of single-cell and bulk transcriptomes uncovers clinically relevant molecular subtypes in human prostate cancer. *Chin J Cancer Res*. 2025;37(1):90–114.
146. Shao F, Wang Z, Ye L, Wu R, Wang J, Yu QX, Wusiman D, Tuo Z, Yoo KH, Shu Z, et al. Basic helix-loop-helix ARNT like 1 regulates the function of immune cells and participates in the development of immune-related diseases. *Burns Trauma*. 2025;13:tkae075.
147. Rajinikanth N, Chauhan R, Prabakaran S. Harnessing noncanonical proteins for next-generation drug discovery and diagnosis. *WIREs Mech Dis*. 2025;17(3):Article e70001.
148. Herberts C, Annala M, Sipola J, Ng SWS, Chen XE, Nurminen A, Korhonen OV, Munzur AD, Beja K, Schönlau E, et al. Deep whole-genome ctDNA chronology of treatment-resistant prostate cancer. *Nature*. 2022;608(7921):199–208.
149. Zhang X, Wang Z, Huang S, He D, Yan W, Zhuang Q, Wang Z, Wang C, Tan Q, Liu Z, et al. Active DHEA uptake in the prostate gland correlates with aggressive prostate cancer. *J Clin Invest*. 2023;133(24):Article e171199.
150. Patel P, Nallandhighal S, Scoville D, Cotta B, Knuth Z, Triner D, Tran L, Udager AM, Rao A, Morgan TM, et al. Spatial transcriptomic profiling to characterize the nature of peripheral- versus transition-zone prostate cancer. *Eur Urol Focus*. 2025;11(2):226–234.
151. Wang G, Mao X, Wang W, Wang X, Li S, Wang Z. Bioprinted research models of urological malignancy. *Exploration*. 2024;4(4):20230126.
152. Lin E, Hahn AW, Nussenzveig RH, Wesolowski S, Sayegh N, Maughan BL, McFarland T, Rathi N, Sirohi D, Sonpavde G, et al. Identification of somatic gene signatures in circulating cell-free DNA associated with disease progression in metastatic prostate cancer by a novel machine learning platform. *Oncologist*. 2021;26(9):751–760.
153. Xu X, Zhang Z. Prudent application of single-cell RNA sequencing in understanding cellular features and functional phenotypes in cancer studies. *Chin J Cancer Res*. 2021;33(6):719–723.
154. Kalyanaraman H, Casteel DE, China SP, Zhuang S, Boss GR, Pilz RB. A plasma membrane-associated form of the androgen receptor enhances nuclear androgen signaling in osteoblasts and prostate cancer cells. *Sci Signal*. 2024;17(821):eadi7861.
155. Butler W, Xu L, Zhou Y, Cheng Q, Hauck JS, He Y, Marek R, Hartman Z, Cheng L, Yang Q, et al. Oncofetal protein glypican-3 is a biomarker and critical regulator of function for neuroendocrine cells in prostate cancer. *J Pathol*. 2023;260(1):43–55.
156. Tufail M, Huang YQ, Hu JJ, Liang J, He CY, Wan WD, Jiang CH, Wu H, Li N. Cellular aging and senescence in cancer: A holistic review of cellular fate determinants. *Aging Dis*. 2024;16(3):1483–1512.
157. Ray SK, Mukherjee S. Exploring replication stress and cellular senescence as key targets in novel cancer therapies. *Cancer Genet*. 2025;298–299:78–87.
158. Feng D, Xiao Y, Wang J, Wu R, Tuo Z, Yoo KH, Wei W, Wusiman D, Wang Z, Li D, et al. Unraveling links between aging, circadian rhythm and cancer: Insights from evidence-based analysis. *Chin J Cancer Res*. 2024;36(3):341–350.
159. Choi SYC, Ettinger SL, Lin D, Xue H, Ci X, Nabavi N, Bell RH, Mo F, Gout PW, Fleshner NE, et al. Targeting MCT4 to reduce lactic acid secretion and glycolysis for treatment of neuroendocrine prostate cancer. *Cancer Med*. 2018;7(7):3385–3392.
160. Qiong L, Shuyao X, Shan X, Qian F, Jiaying T, Yao X, Hui L. Recent advances in the glycolytic processes linked to tumor metastasis. *Curr Mol Pharmacol*. 2024;17: Article e18761429308361.
161. Liu B, Yang C, Liu J, Peng M, Mao J, Tang S, Huang W. Targeting of lysosomes as a therapeutic target in cancer. *Curr Mol Pharmacol*. 2024;17:Article e18761429354659.
162. Wang J, Shao F, Yu QX, Ye L, Wusiman D, Wu R, Tuo Z, Wang Z, Li D, Cho WC, et al. The common hallmarks and interconnected pathways of aging, circadian rhythms, and cancer: Implications for therapeutic strategies. *Research*. 2025;8:0612.
163. Jiang S, Li H, Zhang L, Mu W, Zhang Y, Chen T, Wu J, Tang H, Zheng S, Liu Y, et al. Generic diagramming platform (GDP):

A comprehensive database of high-quality biomedical graphics. *Nucleic Acids Res*. 2025;53(D1):D1670–D1676.
164. Fizazi K, Bernard-Tessier A, Roubaud G, Utriainen T, Barthélémy P, Fléchon A, van der Voet J, Gravis G, Ratta R, Jones R, et al. Targeted inhibition of CYP11A1 in castration-resistant prostate cancer. *NEJM Evid*. 2024;3(1):EVIDoa2300171.
165. Rathkopf DE, Patel MR, Choudhury AD, Rasco D, Lakhani N, Hawley JE, Srinivas S, Aparicio A, Narayan V, Runcie KD, et al. Safety and clinical activity of BMS-986365 (CC-94676), a dual androgen receptor ligand-directed degrader and antagonist, in heavily pretreated patients with metastatic castration-resistant prostate cancer. *Ann Oncol*. 2025;36(1):76–88.
166. Petrylak DP, McKean M, Lang JM, Gao X, Dreicer R, Geynisman DM, Stewart TF, Gandhi M, Appleman LJ, Dorff TB, et al. ARV-766, a proteolysis targeting chimera (PROTAC) androgen receptor (AR) degrader, in metastatic castration-resistant prostate cancer (mCRPC): Initial results of a phase 1/2 study. *J Clin Oncol*. 2024;42(16_suppl):5011.
167. Kyriakopoulos C, Chatta G, Laccetti AL, Iannotti N, Sokolova AO, Hotte SJ, Tutrone R, Markowski MC, Nordquist LT, Pili R, et al. 1641P phase I/II trial of oral masofaniten (EPI-7386) in combination with enzalutamide (Enz) compared to enz alone in metastatic castration-resistant prostate cancer (mCRPC) subjects. *Ann Oncol*. 2024;35:S990.
168. de Bono JS, He M, Shi Z, Nowicka M, Bracarda S, Sternberg CN, Chi KN, Olmos D, Sandhu S, Massard C, et al. Final overall survival and molecular data associated with clinical outcomes in patients receiving Ipatasertib and Abiraterone in the phase 3 IPATential150 trial. *Eur Urol*. 2025;87(6):672–682.
169. Fallah J, Xu J, Weinstock C, Brave MH, Bloomquist E, Fiero MH, Schaefer T, Pathak A, Abukhdeir A, Bhatnagar V, et al. FDA approval summary: Olaparib in combination with Abiraterone for treatment of patients with BRCA-mutated metastatic castration-resistant prostate cancer. *J Clin Oncol*. 2024;42(5):605–613.
170. Schweizer MT, Penkov K, Choudhury AD, Calvo E, Frank RC, Liu L, Mittapalli RK, Tougias J, Andreu-Vieyra C, Bowler TG, et al. Phase 1 trial of mevrometostat (PF-06821497), a potent and selective inhibitor of enhancer of zeste homolog 2 (EZH2), in castration-resistant prostate cancer (CRPC). *J Clin Oncol*. 2024;42(16_suppl):5061.
171. Beltran H, Oromendia C, Danila DC, Montgomery B, Hoimes C, Szmulewitz RZ, Vaishampayan U, Armstrong AJ, Stein M, Pinski J, et al. A phase II trial of the Aurora kinase A inhibitor alisertib for patients with castration-resistant and neuroendocrine prostate cancer: Efficacy and biomarkers. *Clin Cancer Res*. 2019;25(1):43–51.
172. Aggarwal R, Schweizer MT, Nanus DM, Pantuck AJ, Heath EI, Campeau E, Attwell S, Norek K, Snyder M, Bauman L, et al. A phase 1b/2a study of the Pan-BET Bromodomain inhibitor ZEN-3694 in combination with enzalutamide in patients with metastatic castration resistant prostate cancer. *Clin Cancer Res*. 2020;26(20):5338–5347.