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Review

Unveiling the latest insights into Androgen Receptors in Prostate Cancer

Suleiman Zakari[1,2,4], Christogonus Chichebe Ekenwaneze[1,2], Emmanuel Chimuebuka Amadi[1,2], Abrar AbuHamdia[3], Olubanke Olujoke Ogunlana[1,2]

[1]Department of Biochemistry, College of Science and Technology, Covenant University, Ogun State, Nigeria
[2]Covenant Applied Informatics and Communication - Africa Centre of Excellence (CApIC-ACE), Covenant University, Ogun State, Nigeria
[3]Department of Medical Laboratory Science, Faculty of Medicine and Health Sciences, An-Najah National University, Nablus, Palestine
[4]Department of Biochemistry, College of Medicine, Federal University of Health Sciences Otukpo, Benue State, Nigeria

Abstract

Prostate cancer (PCa) is a major cause of cancer-related mortality worldwide, with a rising incidence observed over the years. The androgen receptor (AR) signaling pathway plays a pivotal role in male development and maintaining masculine characteristics. Dysregulation of AR signaling in PCa can lead to disease progression and resistance to standard therapies. Understanding the intricate regulation and function of AR in both healthy and diseased states is crucial for developing effective treatment strategies. This review comprehensively explores the role of androgen receptors in PCa susceptibility, disease progression, and treatment response by analyzing recent literature. An extensive search of peer-reviewed publications in major databases, including PubMed, Scopus, and Web of Science, was conducted using specific keywords related to androgen receptor, prostate cancer, disease progression, and treatment resistance. Relevant conference abstracts and clinical trial reports were also included. The review presents an overview of the role of androgen receptors in PCa initiation, progression, and treatment resistance. It also highlights the role of SPOP as an emerging biomarker associated with AR signaling dysregulation and their potential utility for early detection and personalized treatment approaches. Additionally, recent advances in targeting the AR pathway for novel therapeutic strategies to improve patient outcomes and overcome treatment resistance in advanced PCa are discussed. The findings contribute to a comprehensive understanding of the AR signaling pathway in PCa and offer insights into its multifaceted role in disease development and treatment response. They may pave the way for innovative therapeutic interventions and precision medicine approaches based on specific AR signaling profiles, enhancing patient care and reducing the burden of this lethal disease.

Keywords: Androgen deprivation therapy, androgen receptor, AR-targeted therapies, disease progression, prostate cancer, therapeutic resistance

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Cancer, characterized by uncontrolled cell growth, remains a significant concern worldwide [1]. Prostate cancer (PCa) specifically targets the walnut-shaped prostate gland in the male reproductive system [2]. It stands as one of the most commonly diagnosed cancers among men and a leading cause of global cancer-related deaths [3]. The incidence of PCa has surged in recent years, with an estimated increase of 1 in every 52 males aged 50 to 59 [4, 5]. 1.4 million new cases were documented in 2020 [6]. Incidence rates for PCa vary among different populations and regions. Men from Europe, Latin

Address for correspondence: Olubanke Olujoke Ogunlana, PhD. Department of Biochemistry, College of Science and Technology, Covenant University, Ogun State, Nigeria; Covenant Applied Informatics and Communication - Africa Centre of Excellence (CApIC-ACE), Covenant University, Ogun State, Nigeria
Phone: +2348080454316 **E-mail:** banke.ogunlana@covenantuniversity.edu.ng **ORCID:** 0000-0001-5781-592X
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America, the Caribbean, and Northern America exhibit higher incidence rates but lower mortality compared to those from Africa and Asia, where incidence rates are lower yet PCa mortality rates are higher [6, 7]. Disparities in PCa incidence and mortality could stem from geographic and racial factors, as well as environmental influences, genetic variations, advancements in diagnostic tests, access to healthcare, and disease awareness [8]. Family history, black ethnicity, and aging are the main risk factors for PCa. To gain a more comprehensive understanding of prostate cancer's natural history and true prevalence, more extensive studies are imperative [9].

Over time, the prostate-specific antigen (PSA) test has been used to diagnose PCa. However, PSA is not specific to prostate cancer; elevated PSA levels might indicate non-cancerous conditions, like prostatitis. Yet, there is a need for precise biomarkers for early PCa detection. A digital rectal exam is conducted alongside the PSA test to strengthen the diagnosis. Technological advancements have led to innovative methods for detecting and managing PCa. Sophisticated imaging techniques, including magnetic resonance imaging (MRI), have significantly improved diagnostic precision, enabling earlier detection of the disease [9, 10]. Prostate cancer cases are predicted to rise as a result of technological advancements in diagnostic and screening tests.

The intricate process of cancer development is influenced by various genetic abnormalities, with individuals bearing tumors often exhibiting more genetic mutations [10–12]. Prostate cancer (PCa) is intensively associated with abnormalities in androgen receptor (AR) activity [11]. AR is responsible for the development and maintenance of male genitals. In PCa, the expression of AR is significantly increased, promoting the growth and survival of cancerous cells. Research indicates inhibition of AR signals hinders prostate cancer cell proliferation [12, 13]. Thus, androgen deprivation therapy (ADT) was developed. It is a common treatment for PCa patients [14]. It reduces the levels of AR-ligand interration, thus eliminating/reducing the activity of AR. However, many PCa cells eventually resist ADT and develop what is known as castration-resistant prostate cancer (CRPC). Recent research has focused on targeting AR rather than its ligand. Some approaches involve suppressing AR signaling pathways and developing AR antagonists. Moreover, studies highlight AR's interactions with other pathways, like the PI3K/Akt pathway, suggesting a potential target for PCa treatment. This review aims to outline AR's role in PCa susceptibility, diagnosis, and treatment, highlighting potential therapeutic targets for PCa [15]. Additionally, we provided an overview of androgen and androgen receptor signaling pathways to help readers comprehend the object.

Methodology and search strategy

We extensively searched various reputable databases, such as Google Scholar, PubMed, Scopus, and WOS, for relevant literature to compile this review. We employed specific search terms like "androgen receptors" or "androgen deprivation therapy" alongside "prostate cancer susceptibility," "prostate cancer progression," or "prostate cancer treatment." The search included literature until February 2023. The search terms were tailored to fit each database's unique features. Articles, theses, and dissertations that report quantitative insights into androgen receptor functions in prostate cancer, as well as information about prostate cancer susceptibility, progression, or treatment, were included. Non-English publications and those not adhering to the conclusion criteria were excluded. Two reviewers (S.Z and E.C.A) independently screened the retrieved articles by assessing titles and abstracts, followed by detailed scrutiny of the full-text versions. Discrepancies between reviewers were resolved through a third reviewer (O.O.O).

For efficient comparison and interpretation of findings, we categorized samples into three groups based on information included: (1) PCa susceptibility; (2) PCa progression; and (3) PCa treatment. Moreover, to improve the grasping of various mechanisms of AR in PCa, we visually presented these mechanisms using data visualization tools such as Cloud SmartDraw and BioRender platforms.

Results and Discussion

We conducted a thorough review of the literature for studies, theses, and dissertations that reported information on the roles of AR in PCa. Our review highlights the contribution that AR plays in PCa susceptibility, progression, and treatment.

Brief history of androgen receptor (AR)

Androgen receptors are ubiquitous ligand-dependent transcription factors and are found across various target tissues. AR activity and levels change during certain cellular processes, such as malignant transformation and sexual development [16]. The earliest proof of androgen receptors came from research on the effects of androgens on the reproductive system conducted in the 1930s and 1940s. Researchers began investigating the androgens' mode of action in the 1950s and 1960s. In 1958, a group at the University of Illinois under the direction of Paul Zamboni discovered that androgens encourage the development of the prostate gland in rats, postulating that androgens exert their effects by interacting with certain cell receptors. The AR was independently identified and characterized by three researchers in the late 1960s: Ian Mainwaring, Nicholas Bruchovsky, and Shutsung Liao [17]. After eight years, a team at the University of Chicago under the direction of Elwood Jensen identified androgen receptors in rat prostate tissue. The receptors were discovered to be androgen-specific and to have a strong affinity for testosterone. This finding opened the door for understanding the role of androgens and AR in the male reproductive system [18].

AR family members

The androgen receptor (AR), glucocorticoid receptor (GR), and progesterone receptor (PR) are transcription factors that belong to the nuclear receptor superfamily. They control gene ex-

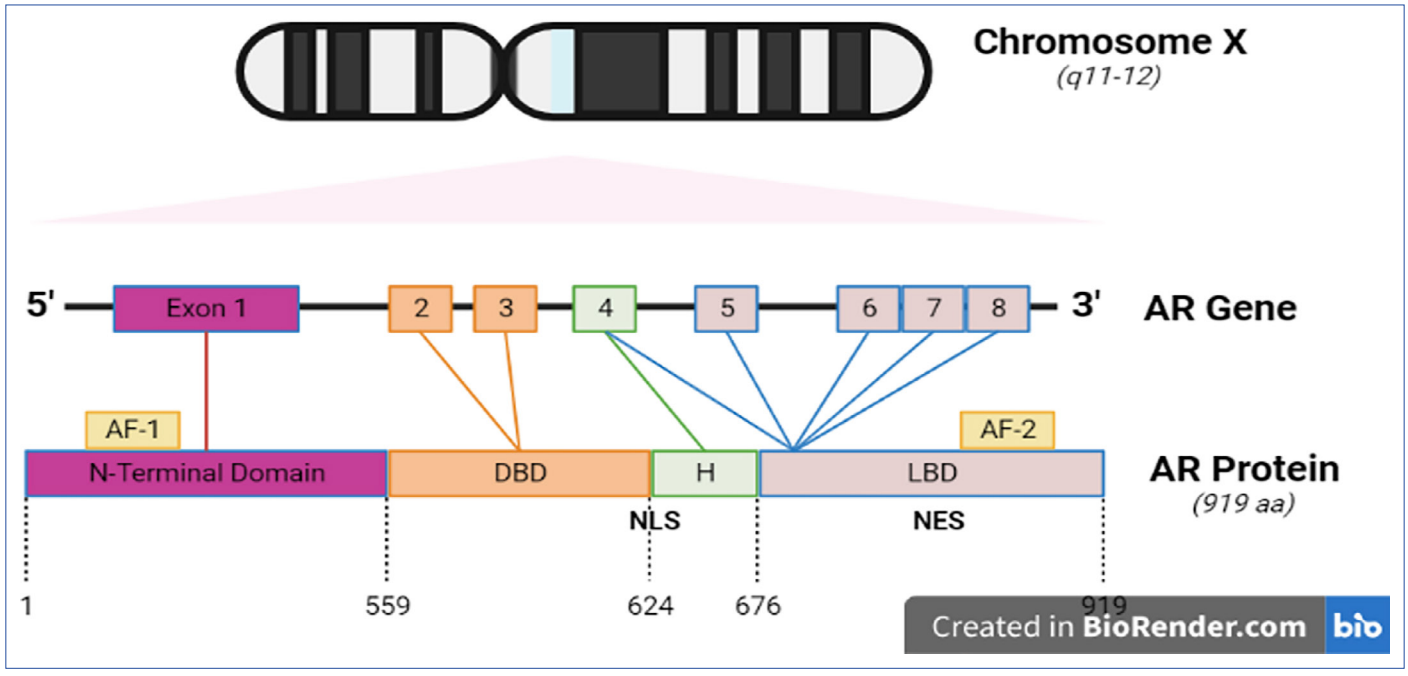

Figure 1. Androgen receptor gene and protein.

AR: Androgen receptor; AF-1: Activation function 1; DBD: DNA-binding domain; LBD: Ligand-binding domain; H: Hinge region; NLS: Nuclear localization signal; NES: Nuclear export signal.

pression in response to a hormone binding to its receptor. Each of these receptors has distinct functions and is activated by different hormones. AR is a protein that functions as an intracellular transcriptional factor. It is activated mainly by testosterone and dihydrotestosterone (DHT). Activated AR initiates sequential conformational changes in its structure, affecting receptor-protein and receptor-DNA interactions [19–21]. GR is activated by the hormone cortisol and mediates the effects of glucocorticoids in cells [22]. PR is activated by the hormone progesterone and functions in the reproductive system of females and mammary glands. PR is necessary for ovulation, implantation of the fertilized egg, and the maintenance of pregnancy [23]. These receptors play a role in many other physiological processes, including bone density, and immunological function. Deregulation of these receptors has been linked to several diseases, including cancer and autoimmune disorders [22].

AR structure

Androgens exert their effects through the binding to Androgen receptor (AR) [24, 25]. AR belongs to the superfamily of nuclear hormone and steroid receptors, including glucocorticoids, mineralocorticoids, progesterone, estrogens, and vitamin D. Steroid receptors, including the AR, have three functional domains: an NH2-terminal domain (NTD) that contains the transcriptional activation function 1 (AF-1), a central DNA-binding domain (DBD) linked to a hinge region, and a COOH-terminal ligand-binding domain (LBD), which is linked to the DBD by a hinge region and contains the transcriptional activation function 2 (AF-2) [26, 27]. The AR gene is situated on Xq11-12 and creates a protein that weighs 110 kDa and has 920 amino acids [28]. The AR gene consists of eight exons, with exon 1 encoding the NTD, exons 2–3 encoding the DBD, exon 4 encoding the HR, and exons 5–8 encoding the LBD as shown in (Fig. 1). This ligand-dependent transcription factor controls the expression of genes that are involved in the growth and differentiation of the prostate gland [29]. Family members differ in the amino-terminal domain and the hinge region that joins the core DBD to the C-terminal ligand-binding domain [30].

The NH2-terminal domain: About half of the receptor's 919 amino acid core sequence is taken up by the NTD, which ranges from amino acids 1 to 559 [31]. The AR-NTD differs most from other members of the steroid receptor family in terms of amino acid variability, sharing less than 15% of its amino acid sequence with those of other steroid receptor-NTDs. It produces the AF-1, which has the Tau1 and Tau5 transcriptional activation units (Tau). When the AR-LBD is removed, the Tau5 area (amino acids 360–528) exhibits constitutive transcription of the AR-NTD without the need for ligands, whereas the Tau1 region (amino acids 141–338) is necessary for ligand-dependent transactivation of the AR [28]. Tau-5 is a signal-dependent transactivation site, in contrast to Tau-1, and is activated by signaling events from the protein kinase C related kinase (PRK-1). Other steroid receptor-NTDs do not have the three distinct homo-polymeric amino acid repeats found in the AR-NTD. There are three types of repeats: poly-glutamine (poly-Q), poly-proline (poly-P), and poly-glycine (poly-G). The poly-P tract is 9 residues long and begins at amino acid 327. The poly-glycine tract is 24 residues long and begins at amino acid 449. The poly-Q tract is found at amino acid 59 and has a usual range of 17–29 residues. Although the particular relevance of these three repetitions is unknown, the poly-Q tract has been the subject of intense study to under-

stand its involvement in AR activity. It has been demonstrated that the length of the poly-Q tract and AR transcriptional activity are inversely correlated. The AR-poly-Q tract's length may also affect how directly AR interacts with its co-regulatory proteins, which control AR-mediated transcription. Shortening the poly-Q tract of AR to 17 amino acids or less, as was described earlier, has been linked to an increased risk of prostate cancer. The AR-NTD is appealing for AR-specific protein interactions due to its distinctive sequences and characteristics, which may be crucial for guiding AR-specific responses. Finding novel protein partners that interact with the AR-NTD may help to clarify the process by which cells are able to respond to androgenic ligands in an AR-specific manner. In the reverse yeast two-hybrid system (RTA), our group has discovered a number of novel AR-NTD interacting proteins by using the N-terminus of AR as bait. An example of these proteins is the TATA binding protein Associated Factor 1 (TAF1).

The central DNA-binding domain and hinge region: The DBD and hinge region of the AR are respectively comprised of amino acids 560–623 and 624–676. These areas perform a variety of tasks, such as dimerization of active AR molecules, nuclear localization of activated receptors, and binding to DNA at consensus sequences in the promoter/enhancer region of AR-regulated genes [32]. Moreover, the DBD of AR interacts with potential transcriptional co-regulators as well as proteins that make up the basic transcriptional apparatus. It is important for the dimerization of AR and the binding of dimerized AR to certain DNA patterns. The cysteine residues in this domain, which promote the development of two zinc finger motifs, contribute to these DBD activities [28]. Two conserved zinc finger motifs in the DBD of the AR and other steroid receptors interact with DNA regulatory regions. These DNA sequences in the promoters of androgen-regulated genes are referred to as androgen response elements (ARE) for AR. Inverted palindromic sequences with two half-sites and a 3-nucleotide spacer (5'-GGA/TACAnnnTGTTCT-3') make up the ARE. Whereas the second zinc finger of the DBD stabilizes receptor-DNA connections, the first NH2-terminal zinc finger of the DBD is in charge of detecting ARE sequences and selectively binding to AREs in the main groove of DNA. The AR-second DBD's zinc finger may have an impact on how well the receptor binds to AR-specific ARE. Nuclear localization sequence (NLS) (amino acids 613–633) found in the hinge region of the AR directs the activated receptor to the nucleus. The bipartite NLS is made up of two basic amino acid clusters spaced apart by ten amino acids. Because of the disruption caused by Lys-to-Ala mutations of these residues, the hinge region's lysine residues (K630, 632, and 633) that are acetylated during receptor activation are thought to be crucial for nuclear translocation [33].

The Ligand Binding Domain: The ligand binding domain (LBD) of AR is a region within the AR protein that is responsible for binding to androgens, which are hormones that play a key role in the development and maintenance of male characteristics [34]. The LBD is located at the C-terminus of the AR protein and

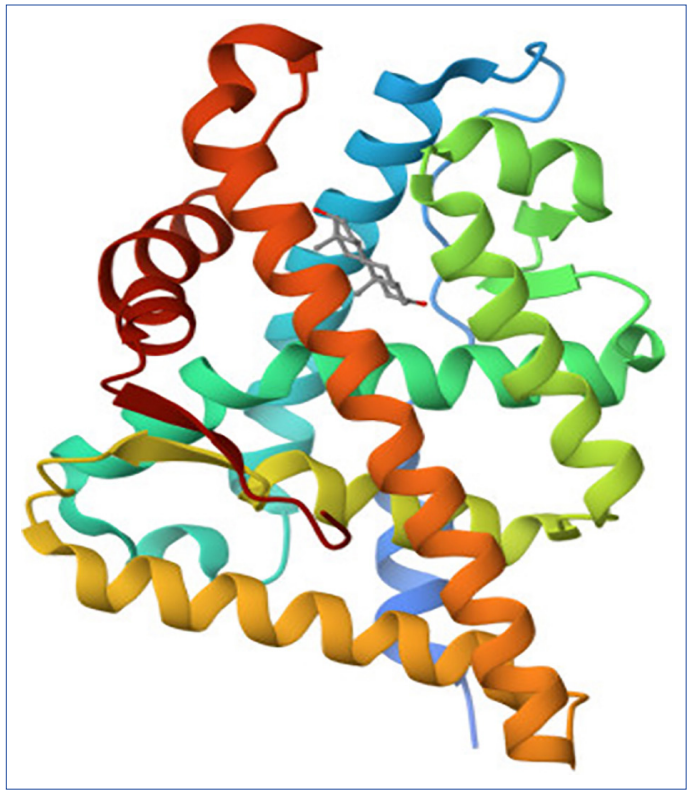

Figure 2. Structure of AR bound to DHT.
AR: Androgen receptor; DHT: Dihydrotestosterone.

is composed of several structural elements, including 12 alpha-helices and several beta-strands. The LBD of AR, which consists of amino acids 616–919, includes a hydrophobic pocket that accepts androgenic ligands such as DHT and testosterone. The LBD is well conserved among different species such as human, rat, and mouse, with degrees of homology ranging from 20–55% with LBDs of other members of the steroid receptor family. When an androgen hormone binds to the LBD of the AR, it causes a conformational change in the receptor, which allows it to translocate to the nucleus of the cell and bind to androgen response elements (AREs) on DNA (Fig. 2).

This binding leads to the activation of target genes involved in the regulation of a wide range of physiological processes, including male sexual development, muscle growth, and bone density. The AR-LBD is particularly critical for prostate cancer because it is the main target of current androgen deprivation therapies. Despite the availability of potent androgen antagonists in clinics, mutations in the AR-LBD can result in the improper activation of AR by non-androgenic substances, leading to ligand-binding promiscuity. Over 30% of prostate cancers possess AR mutations, and several AR variants have been discovered that lack receptor specificity in the absence of traditional ligands. The majority of mutations in the AR affect the ligand binding pocket and are found in three primary regions of the LBD, specifically amino acids 670–678, 710–730, and 874–910 [30]. The most frequently observed variants in tumors are T877A, T877S, and H874Y. The T877A mutation is

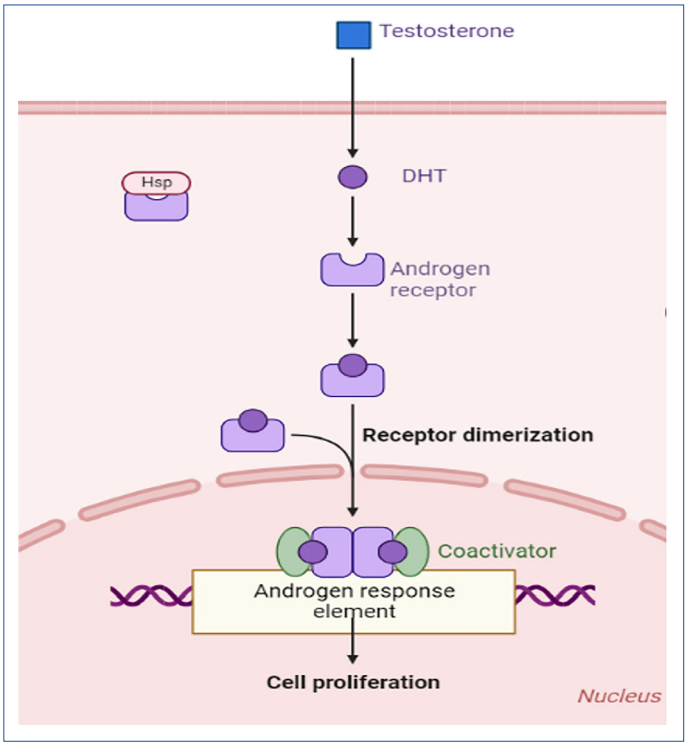

Figure 3. Androgen signaling pathway.
DHT: Dihydrotestosterone.

particularly well-known as it is found in the LNCaP human PCa cell line, as well as cases of advanced prostate cancer. Overall, these mutations make the receptor more sensitive to adrenal androgens or other steroid hormones compared to the wild type AR. This may be due to the recruitment of various co-activators, which enable the AR to bind other steroid ligands, and allow antagonists to act as agonists to activate the AR in an androgen-depleted environment [29].

AR signaling

The androgen receptor (AR) plays a vital role in the development and maintenance of male characteristics, including the development of male reproductive organs, the growth of muscle and bone mass, and the deepening of the voice during puberty. In addition, AR has been shown to play a role in the growth and function of other tissues, such as the skin, hair follicles, immune system, and brain. AR has been implicated in the development of certain diseases, including prostate cancer [22, 35].

The AR signaling pathway (Fig. 3) is a complex process that involves multiple steps and regulatory factors. AR is found in the cytoplasm, bound by several cochaperones, such as HSP90 and HSP70/HSC70, which maintain receptor conformation and prevent its degradation. When androgens bind to the AR, the receptor undergoes a conformational change, dissociates from HSP90, and translocates to the nucleus [36]. The AR subsequently attaches to motor and transport proteins, such as dynein and importin-α/-β, which recognize the nuclear localization signal of the AR and facilitate the AR complex's translocation to the nucleus. Once in the nucleus, the AR dimerizes with another AR molecule and binds to specific regions of DNA known as androgen response elements (AREs), which are located in the promoters of androgen-responsive genes. The binding of the AR to AREs initiates a cascade of events that result in the transcription of androgen-responsive genes. This process is regulated by several co-regulators, including co-activators and co-repressors, which can modulate the activity of the AR by either enhancing or inhibiting its transcriptional activity [24, 37, 38].

AR signaling is also subject to crosstalk with other signaling pathways such as the PI3K/AKT pathway, Wnt/β-catenin pathway, MAPK/ERK pathway, Hedgehog pathway, and Notch pathway [39].

Biosynthesis of androgens

Androgens are a group of steroid hormones crucial for the development, differentiation, and maintenance of the male reproductive system [35]. The androgens include testosterone, androstenedione, dehydroepiandrosterone (DHEA), DHEA sulfate (DHEA-S), and dihydrotestosterone (DHT). Androstenedione serves as a precursor for both testosterone, the male hormone, and estrogen, the female hormone. Testosterone and DHT affect male genital organs via the androgen receptor (AR) [40]. The testis and adrenal glands synthesize all androgens from cholesterol [35].

Concentrating on Leydig cells, they synthesize testosterone under the control of the pituitary gonadotropin LH. Once LH binds to its receptor on Leydig cells, it activates the cAMP/PKA pathway. This pathway leads to the activation of several enzymes involved in testosterone synthesis. Moreover, LH regulates the expression of several genes involved in cholesterol biosynthesis and uptake, such as HMG-CoA reductase, HSL, and ACAT [41].

Leydig cells could either de novo synthesize cholesterol or use stored cholesterol ester to produce testosterone. Cholesterol is first converted to pregnenolone by the enzyme CYP11A1. Pregnenolone is then converted to progesterone by the enzyme 3β-HSD. Progesterone is then converted to androstenedione by the enzyme CYP17A1. Finally, androstenedione is converted to testosterone by the enzyme 17β-HSD (Fig. 4) [41].

Androgen-binding proteins, such as sex hormone-binding globulin (SHBG), are carrier proteins that transport androgens like testosterone and dihydrotestosterone into the bloodstream. They attach to these androgens to move them through the bloodstream, and most circulating androgens (98%) are bound to these transport proteins [31]. This bound fraction of androgens is reversible and can be released from the protein binding sites as needed to exert their biological effects in target tissues. The binding of androgens to transport proteins is an important mechanism for regulating their distribution and availability in the body, and alterations in the levels of these transport proteins can have significant effects on androgen bioactivity.

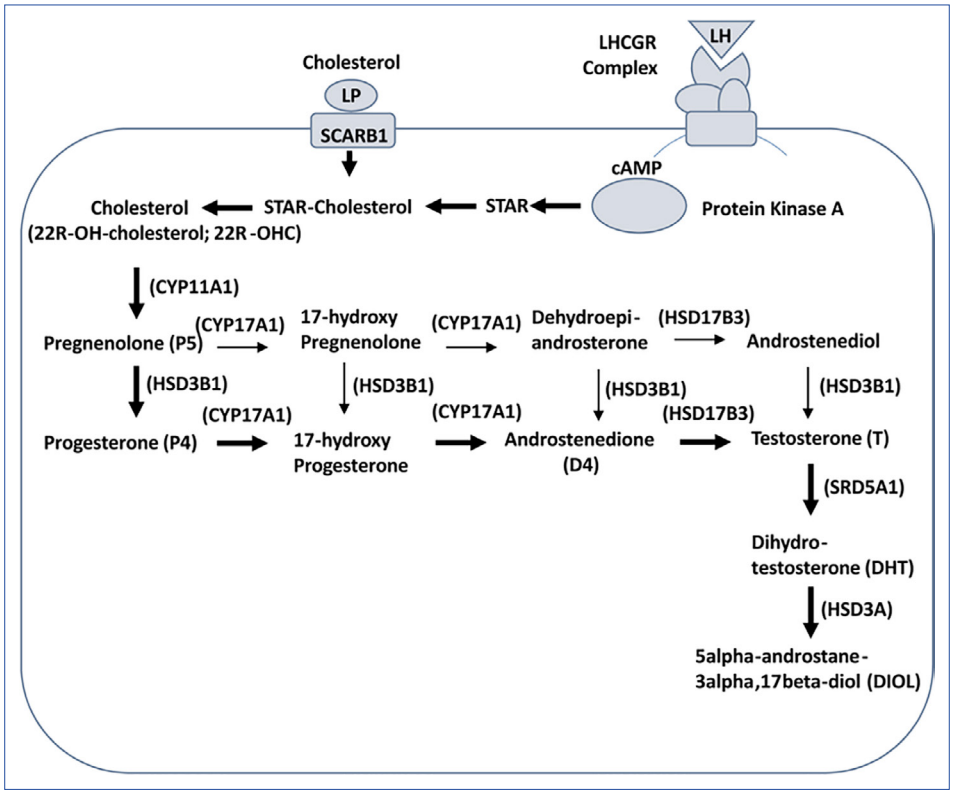

Figure 4. Androgen biosynthesis.

In males, androgen-binding proteins transport androgens in the testis and epididymis, vasa deferentia, seminal vesicles, and ejaculatory ducts. These structures are androgen-sensitive tissues that respond to testosterone during fetal development and at puberty [42, 43]. However, the effect of testosterone and DHT differs in various tissues. For instance, DHT binds to the AR with higher affinity than testosterone in certain tissues, such as the prostate gland, scrotum, urethra, and penis [31].

Association of genetic variation with PCa susceptibility

Genetics, alongside lifestyle and environmental factors, significantly influence prostate cancer susceptibility [44]. Factors such as family history and specific ethnic backgrounds increase the likelihood of developing prostate cancer. It is estimated that hereditary factors contribute to about 5–15% of prostate cancer cases. Alterations in the androgen receptor (AR) play a pivotal role in prostate cancer development. Studies indicate that genetic variations in the AR gene heighten the risk of prostate cancer. These variations can modify AR function, intensify its activity, and subsequently elevate the risk of prostate cancer development. Investigations into polymorphisms in androgen-related genes have revealed that variations in the androgen receptor impact prostate cancer risk [45]. A specific polymorphism sequence involves CAG repeats encoding polyglutamine found in the first exon of AR, responsible for the N-terminal domain crucial for transactivational regulation. The length of CAG repeats varies across racial/ethnic groups, with white individuals typically exhibiting longer repeats compared to African-Americans [46]. Longer CAG repeats are associated with androgen insensitivity syndrome, while shorter repeats correlate with heightened AR transcriptional activity and an increased risk of prostate cancer.

Notably, certain other genetic mutations, including those in mismatch repair genes (MMR, MLH1, MSH2, MSH6, and PMS2) and homologous recombination genes (BRCA1/2, ATM, PALB2, and CHEK2), are frequently associated with prostate cancer susceptibility [47, 48]. Additionally, mutations in BRCA1 and BRCA2 genes are established risk factors not only for prostate cancer but also for breast and ovarian cancer. Although mutations in HOXB13, BRP1, NSB1, RNASEL, and MSR1 genes are linked to prostate cancer development, further research is imperative [49]. Understanding the genetic underpinnings of prostate cancer has facilitated the development of genetic testing to identify high-risk individuals [50]. This testing empowers at-risk individuals to take proactive measures such as routine screening and lifestyle adjustments to mitigate their risk.

Crosstalk between AR and other pathways

The androgen receptor (AR) orchestrates gene expression linked to cell proliferation, differentiation, and survival. Yet, its signaling pathway doesn't operate in isolation; it frequently intersects with other pathways, shaping AR activity and influencing prostate cancer development. Multiple pathways engage in cross-talk with AR signaling, namely

the PI3K/AKT, Wnt/β-catenin, MAPK/ERK, SRC, IL-6/STAT3, Hedgehog, and Notch pathways. Activation of these pathways follows genomic changes in PCa, bolstering tumor growth, genotype-phenotype connections, and responses to the tumor microenvironment. These active signals trigger epithelial-mesenchymal transition (EMT), cancer stem cell (CSC)-like characteristics, and neuroendocrine differentiation (NED), impacting PCa behavior [51].

Phosphatidylinositol 3-kinase (PI3K) is an essential enzyme for cellular processes like cell division,growth, and proliferation. The intricate interplay between AR and hosphatidylinositol 3-kinase (PI3K)signaling revealed synergistic suppression when both pathways were inhibited, leading to reduced prostaticcell proliferation and enhanced apoptosis [52]. Of note, the AR-driven metabolic program hinges on mTORpathway activation [39].The PI3K/AKT/mTOR pathway governs cell-cycle regulation. Impairment of this pathway has contributedto 20–40% of PCa and 50% of metastatic castration-resistant PCa [53]. The PI3K enzyme converts PIP2 (phosphatidylinositol-(4,5)-bisphosphate) into PIP3 (phosphatidylinositol(3,4,5)-triphosphate). PIP3 attractsproteins with pleckstrin homology domains to the cell membrane, including AKT kinase, and activates it.Then, the activated AKT moves to the cell nucleus and triggers downstream pathways, such as mTOR. mTORsignaling is involved in angiogenesis, growth, migration, cell division, and survival. After that, PTEN acts asnegative feedback, removes phosphate from PIP3, and converts it back to PIP2. Dysregulation of PTEN--either by bi-allelic loss or hotspot mutations--or PIK3CA/B mutations, amplifications, and activating fusionsor AKT activating mutations, often triggers hyperactivity in this pathway, promoting prostate cancerdevelopment and progression. An *in vitro* study showed mutual feedback mechanisms betweenPI3K/AKT/mTOR and AR signaling: when deleting PTEN, the PI3K/AKT/mTOR pathway is eitherupregulated leading to downregulation of AR, or the opposite [53].

Interactions between AR and CDK/pRb drive cell cycle progression, presenting a promising therapeutic strategy in prostate cancer (PCa), particularly with combined AR and CDK4/6 inhibition, AR regulates the cell cycle and G1-S phase transition, enhancing CDK activity and inactivating pRb [52]. Additionally, in yeast and mammalian two-hybrid tests, β-catenin directly interacts with AR. The interaction sites were found in the AR's LBD and β-catenin's armadillo repeats. This interaction modifies transcriptional signaling of the p160 coactivator transcriptional mediators/intermediary factor 2 (TIF2) and NTD. In the absence of androgen, β-catenin primarily resides in the cytoplasm, while in the presence of DHT, it co-localizes with AR in the nucleus. This translocation seems unique to AR, as other liganded receptors fail to move β-catenin into the nucleus. Moreover, the presence of agonist-bound AR is necessary for β-catenin translocation, indicated by the inability of AR antagonists like bicalutamide and hydroxyflutamide to facilitate this translocation. Notably, co-translocation of β-catenin and AR occurs independently of several pathways, including GSK3, p42/44 ERK/MAPK, and PI3K. E-cadherin expression in E-cadherin null PCa cells redistributes cytoplasmic β-catenin to the cell membrane and reduces AR signaling. Thus, the absence of E-cadherin increases β-catenin and AR signaling, contributing to PCa development and progression [54].

Studies using gene editing mouse models demonstrate Wnt/β-catenin signaling's oncogenic roles in CRPC proliferation maintenance, EMT and NED encouragement, and transition of stem cell-like properties to PCa cells. β-catenin enhances AR to advance CRPC, acting as a coactivator with mutant AR (W741C and T877A) and recruiting AR to specific promoter regions (Myc, cyclin D1, and PSA). Conversely, increased AR expression amplifies Wnt/β-catenin signaling's transcriptional activity. Activation of SOX9 transcriptional factor facilitates Wnt/β-catenin-AR feedback signaling. Notably, AR possesses the capability to induce β-catenin translocation into the nucleus, whether in AR-expressing LNCaP cells or AR-lacking PC3 cells [51].

SPOP dysregulation as emerging biomarkers associated with AR signaling

Recent findings suggest that mutations in the speckle-type POZ protein (SPOP) gene significantly contribute to the development and progression of prostate cancer [55]. SPOP operates as an E3-ubiquitin ligase. It mediates the proteasomal breakdown of various substrate proteins, including the androgen receptor (AR). It has emerged as a key regulator of AR signaling, directly influencing AR protein stability and transcriptional activity by targeting it for ubiquitination and subsequent degradation. Notably, SPOP mutations occur predominantly in the substrate-binding MATH domain of SPOP [56]. Their impact on AR signaling varies based on context. In certain instances, SPOP mutations heighten AR protein stability, increasing transcriptional activity and causing persistent androgen-dependent growth of PCa even in castration-resistant prostate cancer (CRPC). Conversely, specific SPOP mutations hinder AR binding, reducing AR protein stability and diminishing AR signaling. This intricate interplay between androgen receptor (AR) signaling and SPOP dysregulation is a critical aspect of prostate cancer pathogenesis [57].

Here are several ways in which AR signaling and SPOP dysregulation interact in prostate cancer:

1. **AR protein stability and degradation:** Mutations in SPOP's substrate-binding MATH domain disrupt its interaction with AR by impairing AR ubiquitination and increasing AR protein stability [57, 58]. This results in increased AR resistance to degradation and higher transcriptional activity, fostering abnormal cell growth and survival in prostate cancer.

2. **AR-ARV interaction:** SPOP dysregulation can influence the stability of AR variants (ARVs). ARVs are truncated forms of AR that lack the ligand-binding domain and are risk factors for castration-resistant prostate cancer (CRPC). Specific SPOP mutations target ARVs, enhancing ARV sta-

bility and transcriptional activity [59]. This contributes to resistance to androgen deprivation therapy and the development of CRPC.

3. **Impact on other signaling pathways:** Dysregulated SPOP can affect pathways intersecting with AR signaling, such as the phosphoinositide 3-kinase (PI3K) pathway. The interaction between SPOP and these signaling pathways could modulate AR signaling, impacting disease progression and treatment resistance.

4. **SPOP-AR signaling feedback loop:** Dysregulated AR activity due to SPOP mutations can drive the expression of genes linked to tumorigenesis and treatment resistance [60].

Understanding this intricate crosstalk between AR signaling and SPOP dysregulation is crucial for developing targeted therapies for prostate cancer. Targeting the AR signaling axis or restoring SPOP function holds therapeutic promise for treating SPOP-mutated prostate cancers or those with dysregulated AR signaling.

Targeting AR in prostate cancer

Androgen deprivation therapy (ADT): Androgen Deprivation Therapy (ADT) has been a standard treatment option for PCa for many years [36]. ADT slows the growth of PCa by reducing the levels of androgens, thus reducing AR activity, the main player in PCa development and progression [61]. Often, ADT is used alone or combined with radiation therapy or chemotherapy, depending on the stage and severity of the cancer. Despite its benefits in symptom alleviation and impeding PCa spread, many patients start to develop resistance to the drug, leading to the development of castration-resistant prostate cancer (CRPC) [4, 33, 61, 62].

Over the past two decades, discoveries have revealed that AR signaling is responsible for tumor growth, even post-castration. This insight spawned novel hormonal drugs like Abiraterone, Enzalutamide, Darolutamide, and Apalutamide, designed to enhance anticancer activity [63]. Additionally, LHRH analogs, mostly administered via injection, are part of this therapeutic landscape. However, these treatments often have adverse effects like metabolic syndrome, cardiovascular risk, and cognitive and sexual symptoms, necessitating the quest for alternatives. One such development is Relugolix, an orally available nonpeptide LHRH antagonist. It competitively binds to and blocks the LHRH receptor in the pituitary gland, decreasing LH secretion and subsequently testosterone production in the testes.

The limitations of ADT therapies have moved recent research focuses to targeting AR rather than androgens in PCa, exploring AR antagonists, interference with AR signal transduction, and second-generation anti-androgens and androgen receptor signaling inhibitors (ARSIs). These therapies, showing promise in clinical trials, especially in CRPC, aim to enhance outcomes for advanced PCa patients [36, 64].

Castration-resistant state

Castration-resistant state (CRPC) is developed when cancer cells gain the ability to grow in the absence of androgens. Several mechanisms underlie this resistance, including AR gene mutations, increased levels of co-activators, or enhanced synthesis of potent androgens like dihydrotestosterone [13]. These mechanisms ultimately result in androgen-independent AR activation, conferring resistance to anti-androgen therapy such as flutamide, bicalutamide, and enzalutamide. The hyperactive AR in CRPC increases cell proliferation and survival, stemness, resistance to apoptosis (programmed cell death), and cell migration and invasion, leading to metastasis. Research shows that the AR gene consistently up-regulates with over 80% of CRPCs having high nuclear AR and metastasis of cancer to the bone [65].

The shift from androgen dependence to a castration-resistant state involves molecular mechanisms divided into pathways that either bypass or operate through the AR receptor (Fig. 5). These pathways are not mutually exclusive and often coexist in castration-resistant prostate cancer. These pathways are intricate and still not fully understood. Studies reported that, in the AR-bypass pathway, castration resistance can be reached by impacting apoptotic genes like PTEN and Bcl-2, which are downregulated, boosting cell survival. While in the AR-operating pathway, prostate cancer cells manage to survive via dysregulated cytokines, anomalies in receptor genetics or amplitude, autocrine synthesis of active androgens, altered co-activator expression, and the presence of alternatively spliced AR variants.

Early-stage disease can be managed with radical prostatectomy or radiation ablation of the prostate gland [66]. However, once cancer cells spread beyond the prostate capsule, treatment becomes considerably more challenging. For patients where surgery is no longer an option—representing one-third of PCa patients—androgen withdrawal is used. Androgen ablation therapy eliminates hormones, preventing the growth-promoting effects of androgens, leading to cancer cell apoptosis and tumor regression. However, the average overall survival time is less than 2–3 years. While these therapies have significantly improved outcomes, their limitations necessitate exploring alternative strategies.

Androgen receptor signaling inhibitors (ARSIs): Androgen receptor signaling inhibitors (ARSIs) are a diverse class of medications used to treat prostate cancer (PCa). These drugs interfere with androgen receptor (AR) signaling, impacting tumor growth [27]. ARSIs operate through various mechanisms, not solely by blocking androgen receptors. They include:

1. **Anti-androgens:** These drugs impede androgen binding to receptors, hindering cancer cell growth. Examples include bicalutamide, flutamide, and nilutamide.

2. **GnRH agonists:** These drugs suppress gonadotropin-releasing hormone (GnRH), lowering testicular androgen

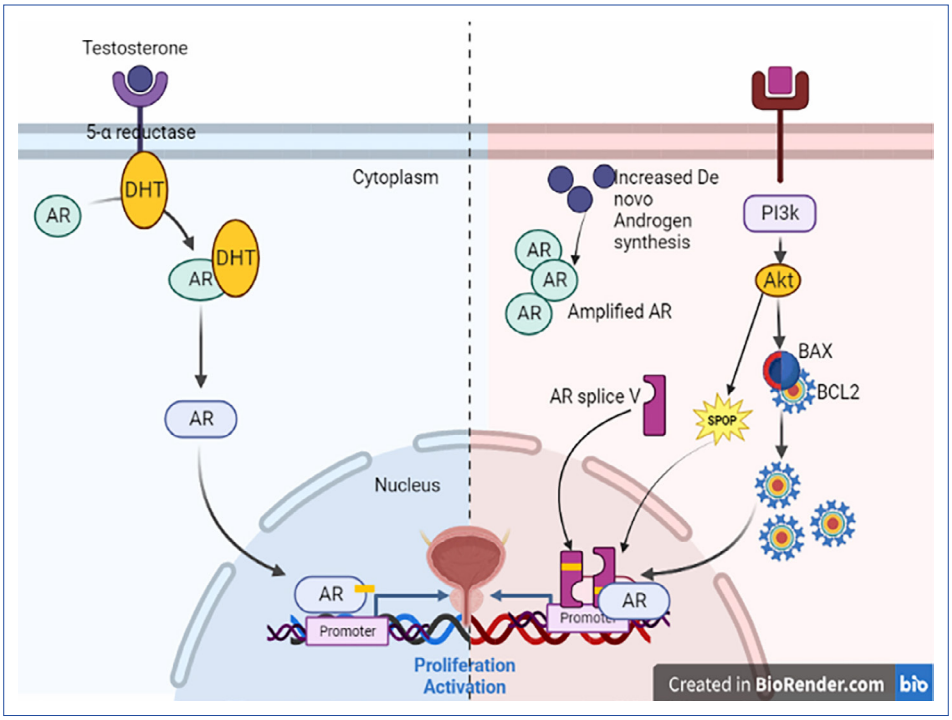

Figure 5. Androgen-dependent vs. castration-resistant PCa progression.
PCa: Prostate cancer.

production and slowing prostate cancer growth. Notable examples are leuprolide and goserelin.

3. **CYP17 inhibitors:** These drugs target the enzyme CYP17, disrupting androgen synthesis in both adrenal glands and prostate cancer cells. An example is abiraterone acetate.

4. **Androgen receptor antagonists:** These drugs directly impede androgen receptor activity, curbing prostate cancer cell growth. Examples include enzalutamide and apalutamide.

These drugs could be used alone or in combination with other treatments, such as chemotherapy or radiation therapy, to treat prostate cancer and manage its symptoms. Abiraterone, enzalutamide, apalutamide, and darolutamide are recommended by the NCCN, aiming to restore balance and impede AR signaling [67].

Abiraterone is an FDA-approved CYP17A1 inhibitor. Although it effectively suppresses androgen synthesis in the testis and adrenal glands, improving prostate cancer outcomes, it is associated with significant adverse reactions. Prednisone is added to abiraterone to mitigate its adverse effects. Studies have reported that the co-administration of these drugs has increased the survival rate of CRPC patients. However, some patients eventually develop resistance to abiraterone. Increased CYP17A1 expression and mutations activate de novo androgen synthesis, promoting pathways like "backdoor" and "alternative" androgen formation. Concurrently, aberrant expression of 3-HSDs and AKR1C3 elevates these pathways while reducing the metabolism of active androgens, contributing to abiraterone resistance. Additionally, exogenous glucocorticoids, used to mitigate adverse effects, might inadvertently activate mutated AR, fostering drug resistance. Various factors like truncated androgen receptor variants (e.g., AR-V7) and the activation of pathways like PI3K/AKT/mTOR and ErbB2 also play roles in abiraterone resistance.

New-generation AR inhibitors like apalutamide and darolutamide demonstrate improved central nervous system (CNS) safety compared to enzalutamide. However, resistance could develop due to AR mutations, splicing variants, and PI3K pathway activation. Darolutamide is an oral non-steroidal AR inhibitor that inhibits AR function and cell growth in PCa without crossing the blood-brain barrier (BBB), resulting in fewer CNS side effects. Studies on darolutamide resistance are limited, but there is evidence of cross-resistance with other AR inhibitors and significant inhibition of AR-mutated variants.

Enzalutamide, a second-generation androgen receptor antagonist, impedes AR translocation and induces apoptosis in CRPC cells. However, resistance may arise due to changes in AR structure or quantity, over-activation of GR, and other signaling pathways like Wnt, and genetic alterations, leading to neuroendocrine trans-differentiation of CRPC cells.

The majority of these AR-targeted therapies target the LBD. The limitations of these LBD-specific therapies are due to genetic variations and the presence of AR variants in many cases. Thus, targeting the DNA-binding domain (DBD) and N-terminal domain (NTD) has emerged as a potential strategy to combat this

Table 1. Combination therapies targeting AR and PI3K/AKT/mTOR pathways

Target	Agent	Phase	Administration	Condition	I.D on Clinicaltrial.gov
AKT	AZD5363	III	Docetaxel	mCRPC	NCT05348577
	MK2206	II	Bicalutamide	High-Risk of Progression	NCT01251861
	Capiversertib	II	Abiraterone acetate	High Risk Localized PCa	NCT05593497
PI3K	AZD8186	I	Docetaxel	mPCa with PTEN Mut	NCT03218826
	GSK2636771	I	Enzalutamide	PTEN(-) mCRPC Mut	NCT02215096
mTOR	Sepanisertib	II	Monotherapy	CRPC	NCT02091531
	Everolimus	I	+ standard radiation therapy	PCa with rising PSA	NCT01548807

AR: Androgen receptor; PI3K: Phosphatidylinositol 3-kinase; AKT: Protein kinase B also known as PKB; mTOR: Mammalian traget of rapamycin.

resistance and enhance the efficacy of existing therapies [68]. The amino-terminal domain (NTD) of the androgen receptor contains AF-1, a crucial element for AR transcriptional activity. EPI-001, pioneered by Marianne Sadar and Raymond Andersen, represents the first inhibitor targeting this domain [29]. EPI-001 operates as an antagonist, disrupting vital protein-protein interactions necessary for AR transcriptional activity by covalently binding to the AR's NTD [69]. It showed potential in managing advanced prostate cancer cases resistant to traditional anti-androgens like enzalutamide, holding immense promise in the clinical development of treatments for castration-resistant prostate cancer (CRPC). By inhibiting NTD, it may be possible to enhance men's longevity and living conditions, and acquired resistance to current therapies will all be improved.

Emerging therapies targeting AR: Precision medicine is emerging as a critical avenue, aiming to tailor treatments to individual needs across various prostate cancer types. Emerging therapies for PCa encompass diverse approaches, such as immunotherapy, targeted therapies, radiopharmaceuticals, gene therapy, and nanoparticle-based therapies [70].

- **Immunotherapy:** A form of therapy that aids the immune system's recognition and destruction of cancerous cells [70]. Several immunotherapy drugs, such as checkpoint inhibitors, CAR-T cells, and cancer vaccines, are being developed and tested in clinical trials for prostate cancer.
- **Targeted therapies:** Drugs that specifically target cancer cells based on their genetic mutations or other specific characteristics. For prostate cancer, several targeted therapies are being developed, including drugs that target the androgen receptor pathway and drugs that target specific enzymes and proteins involved in prostate cancer growth.
- **Radiopharmaceuticals:** Drugs that include radioactive materials and can be used to target and eliminate cancer cells. Several radiopharmaceuticals, such as radium-223 and lutetium-177, are being developed and tested for prostate cancer.
- **Gene therapy:** A type of treatment that involves inserting or altering genes in a person's cells to treat or prevent disease. For prostate cancer, several gene therapies are being developed, including therapies that target the androgen receptor pathway and therapies that use viruses to deliver therapeutic genes to cancer cells.
- **Nanoparticle-based therapies:** Nanoparticles are tiny particles that can be used to deliver drugs directly to cancer cells. Several nanoparticle-based therapies, such as liposomes and polymer nanoparticles, are being developed and tested for prostate cancer.

It is crucial to mention that many of these treatments are still in the developmental or research phase and might take time before becoming widely accessible [70].

Combinational therapies: There's a well-established correlation between PI3K/AKT/mTOR and AR signaling in PCa [61]. This understanding has fueled interest in combination therapies targeting these pathways, showing promise in both preclinical and clinical studies. One potential strategy involves combining AR inhibitors like enzalutamide or abiraterone acetate with PI3K inhibitors such as buparlisib or idelalisib. These combinations have demonstrated a synergistic impact, reducing cancer cell proliferation and boosting apoptosis. Table 1 outlines several of these dual-targeting combination therapies.

In a preclinical study, it was observed that merging a PI3K/AKT inhibitor with an anti-androgen prolonged disease stabilization in a CRPC model [71]. An example of such an inhibitor is AZD5363. It exhibited anti-cancer activity in both androgen-sensitive and castration-resistant phases of the LNCaP mouse xenograft, reducing cell propagation and inducing apoptosis in AR-expressing PCa cell lines [72]. However, resistance to AZD5363 emerged after around 30 days of treatment, marked by rising PSA levels. Investigations revealed that AZD5363 boosted AR transcriptional activity, AR binding to androgen response elements, and AR-dependent gene expression, including PSA and NKX3.1 [71]. Combining AZD5363 with the antiandrogen bicalutamide effectively countered these effects, prolonging tumor growth inhibition and stabilizing PSA levels in CRPC *in vivo*.

It's worth noting that combination therapy targeting both AR and PI3K/AKT pathways might entail increased toxicity compared to using a single agent. Hence, careful selection and monitoring are crucial to ensuring the safety and efficacy of these treatments. Overall, combinational therapies in prostate cancer present a hopeful avenue for enhancing patient outcomes. Nonetheless, further research is necessary to understand the action of these combinations and their long-term side effects better.

Conclusion

Androgen receptors (AR) play a pivotal role in prostate cancer (PCa) susceptibility, progression, and treatment. This pivotal role warrants continued exploration and strategic intervention. Integrating advanced diagnostic strategies and technologies represents a promising avenue for improving PCa detection. Further investigation into the intricate mechanisms underlying AR's influence on PCa initiation and progression is imperative. Overcoming resistance to androgen deprivation therapy necessitates novel strategies targeting AR, informed by identifying genetic variations impacting AR activity and innovating AR-targeted therapies. Future research should intensify efforts to elucidate AR's molecular mechanisms, circumvent resistance, and develop predictive biomarkers, thereby optimizing treatment strategies tailored to individual patient profiles. Such initiatives hold profound potential to revolutionize PCa diagnosis and treatment paradigms by deepening our comprehension of AR's multifaceted involvement.

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