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Androgens in Prostate Cancer: A Review Articles

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Abstract:

Prostate cancer represents a major health problem in men worldwide. Androgens are required for the growth and maintenance of the prostate. The androgen-signaling axis plays a pivotal role in the pathogenesis of prostate cancer. Clinical treatments that target steroidogenesis and the androgen receptor (AR) successfully postpone disease progression. The role of androgens and AR signaling has been well characterized in metastatic prostate cancer, where it has been shown that prostate cancer cells are exquisitely adept at maintaining functional AR signaling to drive cancer growth. This review summarizes the current information regarding the role of androgens in prostate cancer.

INTRODUCTION

Prostate cancer is one of the most common cancers observed in men globally and accounts for 7% of newly diagnosed cancers in men globally (15% in developed regions) (1). In addition, more than 1.2 million new cases are diagnosed and global prostate cancer-related deaths exceed 350,000 annually, making it one of the leading causes of cancer-associated death in men. Prostate cancer can often be cured with definitive local intervention (surgery or radiation), but once cancer metastasizes, it is incurable (2). Our most effective regimens for treating metastatic prostate cancer have arisen from pioneering experiments, in which suppression of testicular testosterone production was shown to cause tumor regression. Prostate cancer risk increases strongly with age and >85% of newly diagnosed individuals are >60 years of age (3).

It is a very well-known fact that prostate cancer and male sex hormones are strongly interrelated. The male sex hormones are collectively known as androgens, a word derived from the Greek Andros, man, and gennan, to produce (4). Since Huggins and Hodges first demonstrated the responsiveness of prostate cancer to androgen deprivation, it has been clear that prostate cancer is dependent on androgen receptor activation (AR) for growth and survival (5). Androgens bind to the androgen receptor (AR) to activate AR signaling and promote the development of prostate cancer. The observations that prostate development depends on androgens and AR signaling and that nearly all prostate cancer cells are critically dependent upon androgens and AR signaling for growth is the basis for the hypothesis that androgens and AR signaling play a causative role in prostate tumorigenesis; however, little is known about this process (6). It is now evident that the majority of prostate cancers express the androgen receptor (AR) throughout the disease, and, in recent years, deeper interrogation into the molecular basis of androgen signaling has offered a better understanding of how AR specifically directs cancer cell behavior (7). The initially androgen-dependent prostate cancer tumor eventually progresses regardless of the patient's hormonal status. Hence, prostate cancer, like most cancers, progresses and recurs after hormone therapy and chemotherapy to a lethally resistant phenotype despite initially encouraging therapeutic responses. However, treatment resistance is inevitable, and prostate cancer can continuously develop even without testosterone from the testes. Thus, castration-resistant prostate cancer (CRPC) was deemed to be hormone-refractory prostate cancer (HRPC) (8). Androgen deprivation therapy (ADT) was first used by Huggins and Hodges to efficiently postpone the development of prostate cancer in clinical settings. Since then, the androgen-AR-signaling axis has moved to the center stage of prostate cancer management (9).

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The purpose of this article is to review the mechanisms of androgen action and its relation to prostate cancer.

Mechanism of androgen action

Androgens are responsible for the differentiation and maturation of the male sexual organs as well as the male secondary sexual characteristics (10). The biosynthesis of all steroid hormones begins with 27-carbon cholesterol, which undergoes stepwise modification by a small complement of enzymes first to 21- carbon steroids (progestins) and subsequently to 19-carbon androgens (11). Testosterone is the most important circulating androgen and its production by the testis is regulated by negative feedback regulated by the luteinizing hormone (LH) and the luteinizing hormone-releasing hormone (LHRH) via the gonad-hypothalamus- pituitary axis. Their actions are mediated by the androgen receptor (AR), a ligand-dependent nuclear transcription factor (12). The activity of the AR is controlled at multiple stages due to ligand binding and induced structural changes assisted by the fold some, compartmentalization, recruitment of coregulators, posttranslational modifications, and chromatin remodeling, leading to subsequent transcription of androgen-responsive target genes (13). The androgen receptor (AR) can be weakly stimulated by high concentrations of multiple steroids including weak androgens produced by the adrenal gland such as androst-4-ene-3, 17-dione (androstenedione), and dehydroepiandrosterone. Androgen binding to AR leads to nuclear translocation of AR, and a ligand-bound AR protein forms a complex with transcriptional coregulators to regulate target gene transcription. AR is expressed in various tissues to achieve specific physiological functions. One target of androgens is skeletal muscle, and supraphysiological doses of androgens increase muscle mass and strength. The AR weighs ~ 110 kDa and is found on the X chromosome. The activated steroid-receptor complex binds to specific DNA segments called hormone-responsive elements, which are located in promoters of hormone-regulated genes. The receptor-DNA complex will associate with transcriptional components and co-activators to promote gene transcription (13, 14, and 15).

The Androgen Signaling Axis

Testosterone and DHT mediate their actions by binding to AR, a 110-kDa phosphoprotein and a member of the nuclear receptor transcription factor superfamily (16) (Fig. 1). The gene for AR is located on the X chromosome (q11- 12) and expresses a 110-kDa protein that is 919 amino acids in length, encoded by eight exons. Common in resemblance to other nuclear hormone receptors, the structure of AR is comprised of four separate functionally distinct domains: an amino-terminal domain (NTD),

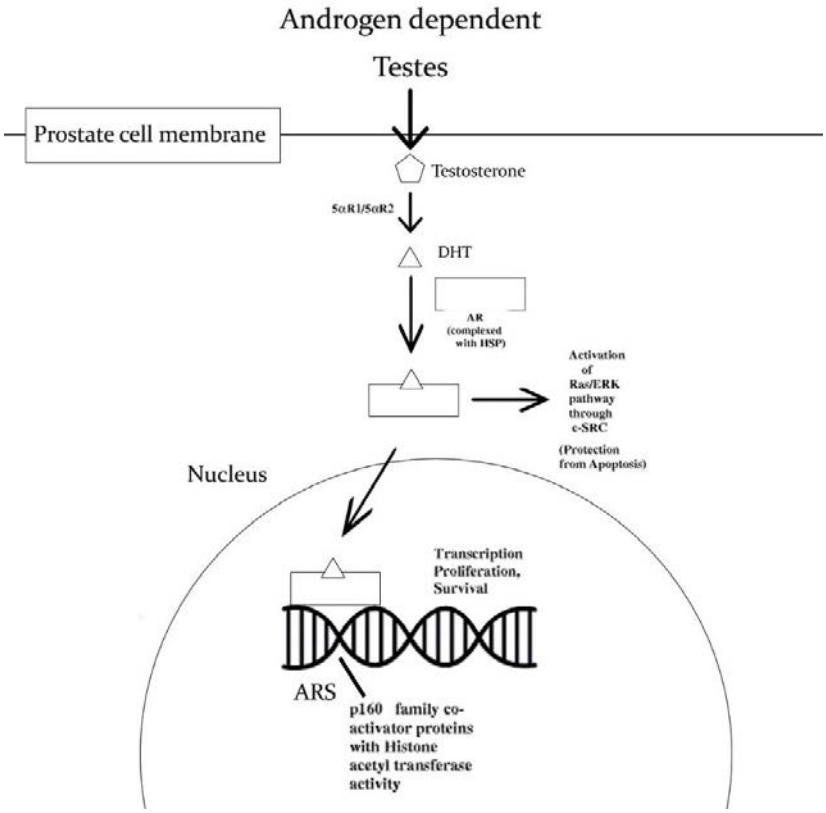

Fig. 1. Schematic representation of androgen action in prostate cancer.

a carboxy-terminal ligand-binding domain (LBD), a DNA-binding domain (DBD), and a flexible hinge region, which joins the LBD and the DBD (17). DHT is stronger than testosterone because it breaks down more slowly than AR and forms a compound in AR that is more resistant to degradation. In the basal, unliganded state, the AR exists in the cytoplasm in a complex with heat shock proteins (Hsp) and immunophilin chaperones such as Hsp90, 70, 56, and 23 (18). This complex is critical for the generation of a high-affinity, ligand-binding conformation of the AR. By binding to androgens, changes in the composition of this complex occur and lead to the transfer of AR to the nucleus. AR is dimerized in the nucleus and binds to androgen response elements (AREs) that are targeted in the promoter and enhancer regions of the gene. In order to activate the transcription of target genes, ARE-bound AR relies on the activity of coactivator proteins, which include the p160 family (SRC-1, GRIP1/ TIF2, RAC3/pCIP/ACTR/AIB1/TRAM1), P/CAF, CBP, Tip60, and p300 (19). These coactivators have the inherent activity of histone acetyltransferase (HAT), through which they can be directed to histone and other proteins. Also, AR can specifically recruit the AR-associated (ARA) coactivators, ARA70, ARA55, and ARA54. These large multi-protein complexes interact with the basal transcriptional machinery to regulate the level of transcription in target genes (20).

A separate ligand-dependent, nongenotropic function of AR also exists. Androgen binding can result in AR mediated activation of the Ras/extracellular signal-related kinase (ERK) pathway through nongenotropic activation of the c-Src nonreceptor tyrosine kinase. In some types of cells, androgen stimulation induces complex formation between AR and c-Src, as well as the estrogen receptor (ER) β-subunit. Importantly, AR-mediated cSrc activation can lead to increased cellular proliferation and protection from apoptosis (21, 22).

Role of androgens in prostate cancer

Because androgens are required for the growth and survival of malignant prostate cells, androgen ablation therapy either in the form of medical or surgical castration is initially effective in inhibiting the growth of these cancer cells in most patients as indicated by reduced expression of its target gene, prostate-specific antigen (PSA), and concomitant tumor regression (23). However, this prostate cancer relapse with a more aggressive and metastatic phenotype that is resistant to hormonal therapy and ultimately causes the death of the patient (24).

The direct correlation between serum androgens, especially testosterone, and the risk of prostate cancer stems from the landmark studies by Huggins and Hodges, who reported regression of metastatic prostate cancer after reduction of serum testosterone levels and progression of metastatic disease and symptoms in a patient who was treated with exogenous testosterone (25). Testosterone from the testes is the major androgen used by prostate cancer cells before ADT and is synthesized in Leydig cells in the testis. There are at least two theories to explain the relationship between prostate cancer and serum testosterone levels: the “suppression theory”, which proposes that prostate cancer cells secrete an androgen inhibitor, and the “saturation theory”, which suggests that serum levels of androgens above a sufficiently low baseline are sufficient to stimulate the growth of prostate cancer. ADT deprives the body of testosterone from the testis and reduces the circulating testosterone to less than 50 ng/dL (~1.7 nM) (25, 26, and 27).

Luminal epithelial AR plays a suppressive role during adult prostate homeostasis, but it plays a very different role in cancerous prostate tissue, which is composed primarily of luminal epithelial cells. AR gene amplification has been observed in approximately 30% of castration-resistant patients with recurrent prostate cancer (28). However, AR gene amplification does not always lead to an increase in AR protein levels. Higher levels of AR protein can result from gene amplification and also from increased transcription rates, or stabilization of the mRNA or protein. Increased AR expression sensitizes prostate cancer cells to low levels of androgen and promotes progression from hormone-dependent to CRPC. AR mutations have been identified in its ligand-binding domain, as well as the amino terminus and DNA-binding domain. These mutations are usually related to AR gain-of-function and are linked to CRPC (29).

Despite the central role of androgens in established prostate cancer, whether androgens are responsible for the initiation of prostate cancer has been more controversial. The fact that aging, one of the strongest risk factors for prostate cancer is associated with a gradual decline in testosterone levels does not preclude a pathogenic role for androgens, given the long preclinical phase of prostate cancer (30, 31).

Androgen deprivation therapy (ADT)

Androgen deprivation therapy (ADT) remains the most effective therapy for metastatic prostate cancer. ADT reduces the levels of androgen hormones, with drugs or surgery, to prevent the prostate cancer cells from growing (32). The pharmaceutical approaches include antiandrogens and chemical castration. However, androgen depletion is usually associated with the recurrence of prostate cancer. The therapeutic efficacy of ADT is due to upregulation in the expression of proapoptotic genes that are normally repressed by androgen receptor activation (33). Medical ADT with long-acting gonadotrophin-releasing hormone (GnRH) agonists is currently the most commonly used

ADT as they are considered to be equally effective in reducing testosterone levels as orchiectomy, with less psychological effect. An interesting feature of CRPC is that, despite low levels of systemic androgen after castration, active AR signaling is maintained in these recurrent prostate cancers. AR amplification/ overexpression has been suggested by many studies as one of the mechanisms leading to ADT failure. Newer androgen-based therapies include abiraterone acetate, an inhibitor of cytochrome P-450 17A1 (CYP17A1), a key enzyme in androgen biosynthesis which is expressed at extra-gonadal sites (34).

ADT is well established to have important clinical benefits, including improvement in survival, when used in the appropriate clinical context. ADT has long been the standard treatment option for metastatic disease and is mandatory in symptomatic patients because it reduces disease-associated morbidity and improves the quality of life, and innovative androgen-based therapy improves survival (35).

CONCLUSION

Prostate cancer afflicts patients mentally and physically, even though it is not lethal in most patients. Numerous studies have defined the importance of the androgen/AR signaling axis in prostate development, homeostasis, and established prostate cancers (36). Many clinical trials and animal studies support the hypothesis that age-related decline in androgen levels is positively associated with the initiation of human prostate cancer; however, few studies have focused on deciphering the mechanism(s) that underlie this association. The hope is that these ongoing efforts will translate into greater precision in AR targeting and novel therapeutic options in the near future for men with prostate cancer (37).

REFERENCES

1.Toivanen R, Shen MM. Prostate organogenesis: tissue induction, hormonal regulation and cell type specification. Development. 2017 Apr 15;144(8):1382-98.McNeal JE. Normal and pathologic anatomy of prostate. Urology. 1981;17:11-6.

2.Pernar CH, Ebot EM, Wilson KM, Mucci LA. The epidemiology of prostate cancer. Cold Spring Harbor perspectives in medicine. 2018 Dec 1;8(12):a030361.

3.Tafuri A, Porcaro AB, Shakir A, Migliorini F, Verratti V, Brunelli M, Cerruto MA, Antonelli A. Serum testosterone and obesity in prostate cancer biology: a call for health promotion in the ageing male. Aging Clinical and Experimental Research. 2021 May;33(5):1399-401.

4.H Lajis N, Abas F, Othman I, Naidu R. Mechanism of anti-cancer activity of curcumin on androgen-dependent and androgen-independent prostate cancer. Nutrients. 2020 Mar;12(3):679.

5.Chatterjee P, Schweizer MT, Lucas JM, Coleman I, Nyquist MD, Frank SB, Tharakan R, Mostaghel E, Luo J, Pritchard CC, Lam HM. Supraphysiological androgens suppress prostate cancer growth through androgen receptor–mediated DNA damage. The Journal of clinical investigation. 2019 Oct 1;129(10):4245-60.

6.Fujita K, Nonomura N. Role of androgen receptor in prostate cancer: a review. The world journal of men's health. 2019 Sep 1;37(3):288-95.

7.Ghashghaei M, Paliouras M, Heravi M, Bekerat H, Trifiro M, Niazi TM, Muanza T. Enhanced radiosensitization of enzalutamide via schedule dependent administration to androgen-sensitive prostate cancer cells. The Prostate. 2018 Jan;78(1):64-75.

8.Pierorazio PM, Ferrucci L, Kettermann A, Longo DL, Metter EJ, Carter HB. Serum testosterone is associated with aggressive prostate cancer in older men: results from the Baltimore Longitudinal Study of Aging. BJU international. 2010 Mar;105(6):824.

9.Kalra R, Bhagyaraj E, Tiwari D, Nanduri R, Chacko AP, Jain M, Mahajan S, Khatri N, Gupta P. AIRE promotes androgen-independent prostate cancer by directly regulating IL-6 and modulating tumor microenvironment. Oncogenesis. 2018 May 25;7(5):1-5.

10.Zhang C, Li P, Wen Y, Feng G, Liu Y, Zhang Y, Xu Y, Zhang Z. The promotion on cell growth of androgen-dependent prostate cancer by antimony via mimicking androgen activity. Toxicology letters. 2018 May 15;288:136-42.

11.Lombardi AP, Vicente CM, Porto CS. Estrogen receptors promote migration, invasion and colony formation of the androgen-independent prostate cancer cells PC-3 through β-catenin pathway. Frontiers in Endocrinology. 2020 Apr 9;11:184.

12.Berchuck JE, Viscuse PV, Beltran H, Aparicio A. Clinical considerations for the management of androgen indifferent prostate cancer. Prostate cancer and prostatic diseases. 2021 Sep;24(3):623-37.

13.Lamb DJ, Weigel NL, Marcell M. Androgen receptors and their biology.

14.Bakouny Z, Yekedüz E, Braun DA, Berchuck JE, Hirsch L, Utkan G, Lee Y, Trinh QD, Choueiri TK, Ürün Y. Neurotoxicities of novel non-steroidal anti-androgens for prostate cancer: A systematic review and meta-analysis. Critical reviews in oncology/hematology. 2021 Oct 1;166:103463.

15.A.H. Davies, H. Beltran, A. Zoubeidi, Cellular plasticity and the neuroendocrine phenotype in prostate cancer, Nat. Rev. Urol. 15 (2018) 271–286.

16.Hou Z, Huang S, Li Z. Androgens in prostate cancer: A tale that never ends. Cancer Letters. 2021 Sep 28;516:1-2.

17.Bakouny Z, Yekedüz E, Braun DA, Berchuck JE, Hirsch L, Utkan G, Lee Y, Trinh QD, Choueiri TK, Ürün Y. Neurotoxicities of novel non-steroidal anti-androgens for prostate cancer: A systematic review and meta-analysis. Critical reviews in oncology/hematology. 2021 Oct 1;166:103463.

18.Hao L, Dong Y, Zhang JJ, He HG, Chen JG, Zhang SQ, Zhang QJ, Wu W, Han CH, Shi ZD. Melatonin decreases androgen-sensitive prostate cancer growth by suppressing SENP1 expression. Translational Andrology and Urology. 2022 Jan;11(1):91.

19.Castoria G, Lombardi M, Barone MV, Bilancio A, Di Domenico M, Bottero D, Vitale F, Migliaccio A, Auricchio F. Androgen-stimulated DNA synthesis and cytoskeletal changes in fibroblasts by a nontranscriptional receptor action. The Journal of cell biology. 2003 May 12;161(3):547-56.

20.Rao A, Moka N, Hamstra DA, Ryan CJ. Co-Inhibition of Androgen Receptor and PARP as a Novel Treatment Paradigm in Prostate Cancer—Where Are We Now?. Cancers. 2022 Feb 4;14(3):801.

21.Anjaly K, Tiku AB. Caffeic acid phenethyl ester induces radiosensitization via inhibition of DNA damage repair in androgen-independent prostate cancer cells. Environmental Toxicology. 2022 Jan 10.

22.Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, De Wit R, Mulders P, Chi KN, Shore ND, Armstrong AJ. Increased survival with enzalutamide in prostate cancer after chemotherapy. New England Journal of Medicine. 2012 Sep 27;367(13):1187-97.

23.Lu Y, Zhang Z, Yu H, Zheng SL, Isaacs WB, Xu J, Sun J. Functional annotation of risk loci identified through genome-wide association studies for prostate cancer. The Prostate. 2011 Jun 15;71(9):955-63.

24.Ewing CM, Ray AM, Lange EM, Zuhlke KA, Robbins CM, Tembe WD, Wiley KE, Isaacs SD, Johng D, Wang Y, Bizon C.

Germline mutations in HOXB13 and prostate-cancer risk. New England Journal of Medicine. 2012 Jan 12;366(2):141-9.
25. Sharifi N, Auchus RJ. Steroid biosynthesis and prostate cancer. Steroids. 2012 Jun 1;77(7):719-26.
26. Fontana F, Anselmi M, Limonta P. Molecular mechanisms and genetic alterations in prostate cancer: From diagnosis to targeted therapy. Cancer Letters. 2022 Mar 8:215619.
27. Mirzakhani K, Kallenbach J, Rasa SM, Ribaudo F, Ungelenk M, Ehsani M, Gong W, Gassler N, Leeder M, Grimm MO, Neri F. The androgen receptor—lncRNASAT1-AKT-p15 axis mediates androgen-induced cellular senescence in prostate cancer cells. Oncogene. 2022 Feb;41(7):943-59.
28. Suarez-Almazor ME, Pundole X, Cabanillas G, Lei X, Zhao H, Elting LS, Lopez-Olivo MA, Giordano SH. Association of Bone Mineral Density Testing With Risk of Major Osteoporotic Fractures Among Older Men Receiving Androgen Deprivation Therapy to Treat Localized or Regional Prostate Cancer. JAMA network open. 2022 Apr 1;5(4):e225432-.
29. Knudsen KE, Scher HI. Starving the addiction: new opportunities for durable suppression of AR signaling in prostate cancer. Clinical Cancer Research. 2009 Aug 1;15(15):4792-8.
30. Grossmann M, Zajac JD. Management of side effects of androgen deprivation therapy. Endocrinology and Metabolism Clinics. 2011 Sep 1;40(3):655-71.
31. Ryan CJ, Smith MR, De Bono JS, Molina A, Logothetis CJ, De Souza P, Fizazi K, Mainwaring P, Piulats JM, Ng S, Carles J. Abiraterone in metastatic prostate cancer without previous chemotherapy. New England Journal of Medicine. 2013 Jan 10;368(2):138-48.
32. Westaby D, Maza MD, Paschalis A, Jimenez-Vacas JM, Welti J, de Bono J, Sharp A. A new old target: Androgen receptor signaling and advanced prostate cancer. Annual review of pharmacology and toxicology. 2021 Aug 24;62.
33. Spitzer M, Huang G, Basaria S, Travison TG, Bhasin S. Risks and benefits of testosterone therapy in older men. Nature reviews Endocrinology. 2013 Jul;9(7):414-24.
34. Formaggio N, Rubin MA, Theurillat JP. Loss and revival of androgen receptor signaling in advanced prostate cancer. Oncogene. 2021 Feb;40(7):1205-16.
35. Evans AJ. Treatment effects in prostate cancer. Modern Pathology. 2018 Jan;31(1):110-21.
36. Dai C, Heemers H, Sharifi N. Androgen signaling in prostate cancer. Cold Spring Harbor perspectives in medicine. 2017 Sep 1;7(9):a030452.
37. Crawford ED, Heidenreich A, Lawrentschuk N, Tombal B, Pompeo AC, Mendoza-Valdes A, Miller K, Debruyne FM, Klotz L. Androgen-targeted therapy in men with prostate cancer: evolving practice and future considerations. Prostate cancer and prostatic diseases. 2019 Mar;22(1):24-38.