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Castration-resistant prostate cancer: Adaptive responses in the androgen axis

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ABSTRACT

The androgen signaling axis in prostate cancer is associated with multiple adaptive mechanisms in response to castration. Herein we review these adaptations with an emphasis on recent molecular insights into the growth and development of castration resistant prostate cancer (CRPC). Alterations include both conventional and novel intracrine androgen synthesis pathways and androgen transport as well as androgen receptor (AR) overexpression, mutation, and splice variation. Each of these underlying mechanisms are potentially linked to post-castration growth, especially after treatment with newer hormonal agents such as abiraterone and enzalutamide. Post-translational AR modifications are well documented and these can affect receptor activity, stability, localization, and interaction with other proteins. Changes in recruitment of androgen receptor associated co-activators/repressors and a distinct AR-induced transcriptional program can dramatically alter proliferation, invasion, and metastasis in a ligand and context-dependent manner. Numerous previously uncharacterized non-coding RNAs, some of which are androgen regulated, may also have important biological function in this disease. Taken together, the view of CRPC has changed dramatically in the last several years. This has occurred not only within the setting of multiple treatment paradigm changes, but also as a multiplicity of potential molecular mechanisms underlying this disease state have been explored and discovered.

Introduction

Prostate cancer is by far the most common non-skin cancer and currently the second leading cause of cancer death in men in the United States. Both normal and malignant prostate epithelial cells depend on androgen dependent activation of the androgen receptor (AR) for prostate-specific antigen (PSA) production and survival. Androgen deprivation therapy (ADT) via surgical or medical castration remains the standard form of treatment, and has been so for the last 70 years for clinically advanced prostate cancer [1]. Disease progression after initial ADT, despite castration levels of testosterone, is termed castrate resistant prostate cancer (CRPC). This may either be metastatic or non-metastatic and the natural history is distinct. For men with metastatic disease, castration resistance as measured by PSA rise develops approximately 16 months after initial ADT [2]. This is markedly distinct from those with no metastases. For patients who start ADT for PSA only progression, time to castration resistance is in part dependent on PSA doubling time, but has been reported to be as long as 10 years [3].

Many studies have found that AR is present in both initially diagnosed prostate cancer cells and in the vast majority of cells in prostates from CRPC patients [4]. PSA, a known AR target gene, will eventually rise in most CRPC patients, serving as a marker that the androgen axis is still functional despite low circulating levels of serum androgens. Multiple mechanisms have been proposed for the continued activation of AR and the development of CRPC. Molecular studies dissecting the androgen signaling pathways in CRPC are ongoing with multiple new insights in the last several years. This review covers a broad review of these potential mechanisms (see Table 1).

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Table 1
Proposed mechanisms for continued AR signaling in CRPC.

Intracrine synthesis of androgens
Amplification and/or overexpression of AR
Overexpression and/or polymorphism of steroid transporters
Mutation of the AR gene
Constitutively-active AR splice variants
Alteration in AR co-regulators
Crosstalk between AR and other signaling pathways
Post-translational modifications of AR
Distinct AR mediated transcriptional programs

Androgen receptor: overview

AR is a member of the steroid receptor superfamily that acts predominately as a ligand-dependent transcription factor after binding to various DNA binding sites. The AR gene is located on the X-chromosome (Xq12), made up of 8 exons [5]. AR consists of an N-terminal domain (NTD) which contains a transactivation domain (AF1) that serves as a primary transcription regulatory region (see Fig. 1). The central DNA binding domain (DBD) contains two zinc fingers that connect to the hinge region allowing DNA recognition, dimerization, and stabilization. The DBD is highly homologous with the DBD of the human glucocorticoid receptor and the human progesterone receptor. The hinge region contains a canonical nuclear localization signal that regulates the nuclear import of the receptor. The hinge region is also a target site for acetylation, ubiquitination, and methylation [6]. The C-terminal domain (CTD) contains the ligand binding domain (LBD) and the AF2 domain, a second transcriptional regulation domain. The NTD and CTD both contain transactivation domains (AF1/AF2), but AF1 is considered dominant in most AR signaling studies conducted under normal physiological conditions. This is particularly relevant in the study of AR splice variants (vide infra).

After synthesis of AR protein, a variety of conformational changes are required to generate a receptor with high-ligand-binding affinity. This requires a complex cascade of events initiated by a "foldosome" that includes complex interactions of a variety of chaperone proteins including HSP40, HSP90, and HSP23 [7]. Upon ligand binding, further conformational changes of AR occur, leading to intra-receptor NTD/CTD interaction followed by translocation of the ligand-bound receptor to the nucleus and homodimerization. Various studies now distinguish nuclear and cytoplasmic AR in both clinical specimens and pharmacological responses, with the nuclear AR contributing to androgen-axis signaling via transcriptional regulation [8].

In the nucleus, the ligand-bound AR homodimers recruit various co-activators and co-repressors, bind to androgen-response elements (ARE), and lead to a broad program of transcriptional activation in AR target genes such as PSA and TMPRSS2. AR-regulated target genes can be both up- or down-regulated and can vary according to ligand concentration. AR target genes vary in cells derived from hormone sensitive cancer as compared to cells derived from CRPC.

Intracrine synthesis of androgens

CRPC tissue exhibits persistent levels of androgens, despite ADT, albeit some androgen levels are lower compared to hormone-naïve tissue [9,10]. Studies have shown the upregulation of steroidogenic enzymes in both model CRPC systems and in tissue from CRPC patients suggesting increased intratumoral synthesis of androgens [11]. In metastases of CRPC patients, relative to primary tumors, there is increased expression of a number of genes involved in androgen metabolism including HSD3B2 (3 beta-hydroxysteroid dehydrogenase), AKR1C3 (also known as 17 hydroxysteroid dehydrogenase type 5 or hydroxysteroid 17-beta-dehydrogenase 5), AKR1C2 (3α-hydroxysteroid dehydrogenase), AKR1C1 (20 alpha-hydroxysteroid dehydrogenase), SRD5A1 (5-alpha reductase type 1), and UGT2B15 (UDP-glucuronosyltransferase 2B15). Of note, AKR1C3 is involved in the conversion of androstenedione to testosterone; SRD5A1/2 converts testosterone to DHT (see Fig. 2). Other investigators have reported variations on this theme [12–14] but taken together, from a functional perspective, these changes are compatible with the over-arching hypothesis that CRPC cells can synthesize potent androgens from various steroidal precursors.

The conventional mechanisms of androgen synthesis are emphasized by many but alternative mechanisms of testosterone and DHT synthesis are also demonstrated in CRPC (see Fig. 2). Androstenedione may be 17-keto reduced to testosterone, and/or

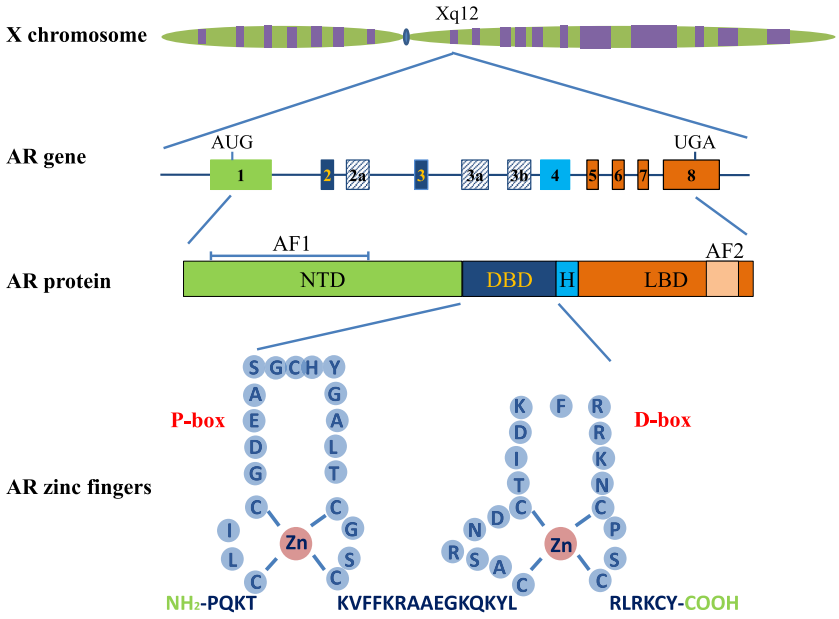

Fig. 1. Schematic representation of the structure of the AR gene, protein, and the two zinc fingers in AR DBD. H, hinge region; P-box mediates DNA recognition; D-box mediates AR DBD-dependent dimerization.