RECENT TRENDS IN THE MANAGEMENT OF HORMONE- REFRACTORY PROSTATE CANCER

Essay

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By

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Mai El-Arini
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List of Abbreviations

- ADT :Androgen Deprivation Therapy
- AIPC :Androgen-Independent Prostate Cancer
- AR :Androgen Receptor
- ARE :Androgen-response element
- ASA :Acetylsalicylic acid
- ATP :Adenosine Triphosphate
- CAB :Complete Androgen Blockade
- CALGB :Cancer and Leukemia Group B
- CaP :Cancer Prostate
- CRPC :Castration-Resistant Prostate Cancer
- CTD :Carboxyl Terminal Domain
- CTE :Carboxy Terminal Extension
- DAHRT :Docetaxel Atrasentan Hormone Refractory Prostate Cancer Trial
- DBD :DNA Binding Domain
- DES :Di-ethyl Stilbesterol
- DHEA :Dehydro-epiandrosterone
- DHT :Dihydro-Testosterone
- DNA :Deoxyribonucleic acid
- DP :Docetaxel plus Prednisone
- EAU :European Association of Urology
- ECOG :Eastern Cooperative Oncology Group
- EGFR :Epidermal growth factor receptor
- EMP :Estramustine Phosphate
- EORTC :European Organization for Research and Treatment of Cancer
- ET :Endothelin
- FSH :Follicle Stimulating Hormone
- GnRH :Gonadotrophin Releasing Hormone
- HRPC :Hormone-Refractory Prostate Cancer.
- HRQL :Health-related Quality of Life
- HSP :Heat- shock protein
- IL :Interleukin
- IL-6 :interleukin -6
- kDa :Kilodaltons
- LBD :Ligand Binding Domain
- LDH :Lactate Dehydrogenase
- LH :Leutinizing Hormone
- LHRH :Leutinizing Hormone Releasing Hormone
- MAGE :Melanoma antigen gene product
- MP :Mitoxantrone Prednisone
- mRNA :Messenger Ribonucleic Acid
- NCIC :National Cancer Institute of Canada
- NCoR :Nuclear Receptor Co-repressor
- NR :Nuclear Receptor
- NTD :Amino Terminal Domain
- OS :Overall survival
- PCa :Prostate Cancer
- PCWG :Prostate-Specific Antigen Working Group
- PDGR ;Platelet-derived growth factor
- PFS :Progression-free survival
- PlGF :Placental growth factor
- PS :Performance Status
- PSA :Prostatic Specific Antigen
- PSA-DT :Prostatic Specific Antigen doubling time

- PSAV :Prostatic Specific Antigen Velocity
- QoL :Quality of life
- RCT :Randomized Controlled Trial
- RECIST :Response Evaluation Criteria In Solid Tumours
- RNA :Ribonucleic Acid
- mRNA :Messanger Ribonucleic Acid
- RT-PCR :Reverse Transcriptase Polymerase Chain Reaction
- SAHA :Suberoylanilide hydroxamic acid
- SBG :Sex hormone-binding globulin
- SPARC :Satraplatin and Prednisone Against Refractory Cancer
- SRE :Skeletal-related event
- SWOG :Southwest Oncology Group
- T :Testosterone
- TAU :Transactivation Unit
- TBD :To be determined
- TNM :Tumor-Nodes-Metastasis
- TTP :Time to progression
- VEGF :Vascular Endothelial Growth Factor
- VEGFR :Vascular Endothelial Growth Factor receptor
- WW :Watchful waiting

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ABSTRACT

Prostate cancer is a significant health concern for men world wide. Adenocarcinoma of the prostate is currently the most frequent malignancy in men and is responsible for the second greatest number of cancer-related deaths after lung cancer Approximately 1 man in 5 will be diagnosed with prostate cancer during his lifetime, and 1 man in 33 will die of this disease. As the population ages, these numbers are expected to increase. The increase in absolute incidence can be ascribed to the combination of an aging male population, and the use of early testing, based on more sophisticated measurement of serum levels for PSA

Despite the frequency of prostate cancer, we know little about the target cells for oncogenic change and, in particular, the tumor-initiating cell, both within the prostat and at the preferential sites of metastatic disease in bone The precise molecular events that lead from androgen-sensitive prostate cancer to androgen-refractory prostate cancer are of great interest and subject to ongoing research

Key Word

Recent Trends in The management hormone refactory prostat cancer

INTRODUCTION AND AIM OF THE WORK

Prostate cancer is a significant health concern for men world wide. Adenocarcinoma of the prostate is currently the most frequent malignancy in men and is responsible for the second greatest number of cancer-related deaths after lung cancer ***[Jemal et al, 2007].*** Approximately 1 man in 5 will be diagnosed with prostate cancer during his lifetime, and 1 man in 33 will die of this disease. As the population ages, these numbers are expected to increase ***[Pienta et al, 2006]***. The increase in absolute incidence can be ascribed to the combination of an aging male population, and the use of early testing, based on more sophisticated measurement of serum levels for PSA ***[Maitland et al, 2008]***.

Despite the frequency of prostate cancer, we know little about the target cells for oncogenic change and, in particular, the tumor-initiating cell, both within the prostate and at the preferential sites of metastatic disease in bone ***[Maitland et al, 2008].*** The precise molecular events that lead from androgen-sensitive prostate cancer to androgen-refractory prostate cancer are of great interest and subject to ongoing research.

Hormone-refractory prostate cancer (HRPC) is a very heterogeneous disease and the precise definition of recurrent or relapsed prostatic adenocarcinoma remains controversial ***[Heidenreich et al, 2008]***. Initially, almost all metastatic prostate cancers require testosterone for growth, and the role of androgen deprivation as a first-line therapy for metastatic prostate cancer has been recognized for more than 60 years. Hormone deprivation is accomplished by surgical (orchiectomy) or medical (luteinizing hormone-releasing hormone agonists, antiandrogens) castration. Hormonal therapy leads to remissions lasting 2 to 3 years; however, virtually all patients progress to a clinically androgen-independent state and can no longer be cured by conventional therapy of any type, resulting in death in ~16 to 18 months ***[Pienta et al, 2006]***.

The approach to HRPC requires information on the extent of the disease; mode and site of progression, rising prostate-specific antigen (PSA) level, new bone metastasis, visceral and nodal metastasis, presence or absence of symptoms; and response to prior endocrine treatment. The sequencing of therapeutic options for patients with CRPC typically involves using secondary hormonal manipulations for as long they are found to be effective in halting disease progression. Based on prospective randomized clinical phase III trials, several proven chemotherapeutic options are available for the management of HRPC with metastatic disease. In 2004, for the first time, a docetaxel-based chemotherapy program was shown to prolong survival in prostate cancer patients who had progressed on hormonal therapy. Growing understanding of the molecular defects responsible for prostate cancer development and progression is fueling the development of rationally designed combinations of biologic agents with cytotoxic chemotherapy for the treatment of HRPC.This has lead to a plethora of new agents being

investigated in first, and second-line settings, which makes further improvements in survival a realistic goal ***[Sternberg et al, 2008]***.

Aim of this work:

The aim of our review is to identify the biology of HRPC, the definition of HRPC and to review the novel agents on the horizon for the management of HRPC.

PATHOPHYSIOLOGY OF THE NORMAL PROSTATE

❖ Androgens And The Androgen Receptor In Normal Prostate

Androgens, the male sex steroids, are responsible for male sexual differentiation and development, as well as the maintenance and support of sexual tissues in the adult. Moreover, androgens are important for the development and progression of age-associated pathologies in men, including benign prostatic hyperplasia and prostate cancer (PCa) ***[Dehm et al, 2007]***.

Androgens are produced primarily in the form of testosterone by Leydig cells in the testes and are generally found circulating throughout the body ***[Lindzey et al, 1994]***. In addition, adrenal androgens, such as androstenedione, dehydro-epiandrosterone (DHEA), and its sulfate, are secreted by the adrenal cortex; although not as potent as testosterone, adrenal androgens do contribute to androgenic effects in the body. Production of androgens in the Leydig cells is regulated through the hypothylamic–pituitary–gonadal axis. The hypothalamus secretes pulses of gonadotropin-releasing hormone (GnRH) every 90-120 minutes. GnRH binds to gonadotropes in the anterior pituitary and stimulates the release of luteinizing hormone (LH) and follicle-stimulating hormone. When LH reaches the Leydig cells, it stimulates production of androgens, which, in turn, feed back on the pituitary to inhibit the secretion of GnRH and LH. In prostate tissue, DHT is the primary ligand for the androgen receptors and is synthesized from testosterone by 5-α reductase enzymes ***[Grossman et al, 2001]***.

❖ Androgen Action At The Cellular Level In The Prostate

Testosterone in the serum arrives at the prostate bound to albumin and to the steroid-binding globulins. Free testosterone enters the prostate cell by diffusion, where it is then subjected to a variety of steroid metabolic steps that appear to regulate the activity of the steroid hormone and its downstream effectors ***[Veltri et al, 2007]***. A simplified schematic of the temporal sequence of intracellular events is depicted in Figure 1.

In the plasma, testosterone (T) is bound to serum-binding globulins (SBG), such as testosterone-binding globulin and albumin. Unbound testosterone is transported by passive diffusion into the prostate, where it is enzymatically converted to dihydrotestosterone (DHT) by 5α-reductase (type II) and further metabolized to diols (3α or 3β) and irreversibly metabolized into the more water-soluble triols (6α or 7α). DHT binds to a cytoplasmic receptor (androgen receptor) that is activated and translocated to the nucleus. There the androgen receptor localizes in matrix acceptor sites and subsequently activates or represses certain target genes by regulating production of their mRNA. The RNA is then transported to the cytoplasm, where it is translated into a variety of proteins (e.g., secretory proteins such as PSA) ***[Veltri et al, 2007]***.

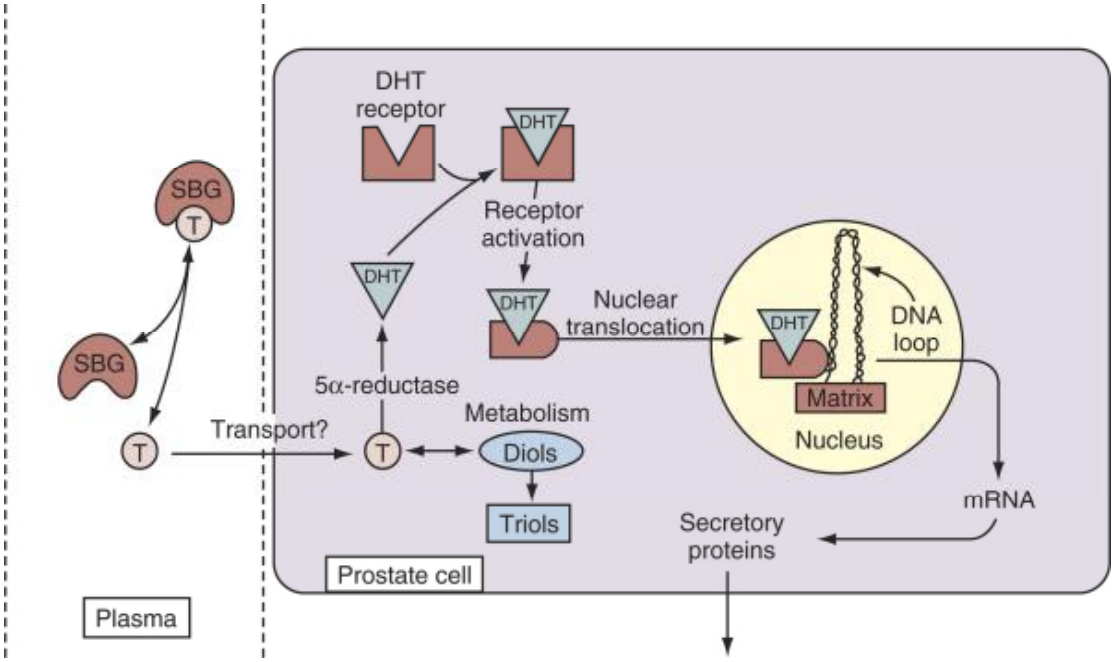

Figure 1: Simplified schematic of the effects of testosterone in inducing growth in an epithelial cell. **[Veltri et al, 2007]**

❖ ANDROGEN RECEPTOR STRUCTURE AND FUNCTION

Androgen action is exerted through the androgen receptor (AR), a 110-kDa phosphoprotein that mediates the actions of testosterone and dihydrotestosterone (DHT) by acting as a transcription factor ***[Lindzey et al, 1994]***. The AR is found in many tissues of both sexes but is most abundant in male sex tissues. The best characterized functions of the AR are to promote the growth and differentiation of the male urogenital structures. It is also essential for the initiation and maintenance of spermatogenesis ***[Grossman et al, 2001]***.

The AR gene is located on the long arm of the X chromosome at position Xq11.2-q12. Since there is only one X chromosome in a male, it is a single copy on only one allele. The coding sequence on this gene is divided into 8 exons that are transcribed and processed into mRNA and then subsequently translated into protein ***[Veltri et al, 2007]***. The androgen receptor is a member of the steroid hormone receptor superfamily, which is a group of ligand-activated nuclear transcription factors. The steroid hormone receptors share a common gene structure with other receptors such as the estrogen, progesterone, glucocorticoid, retinoid, mineralocorticoid and thyroid hormone receptor. Despite the similarity in structural organization of all the nuclear receptors, activation of different receptors results in markedly different cellular responses ***[Culig et al, 2003]***.

The AR is capable of binding to both testosterone and DHT, although DHT has a higher affinity for the AR (approximately twofold to 10-fold) and is

consequently the primary androgen bound by the AR. The AR is also capable of being phosphorylated, and reversible phosphorylation appears to play a role in both ligand-dependent and ligand-independent AR activation ***[Lindzey et al 1994]***. In addition to its action as a classic nuclear transcription factor, AR also mediates rapid effects of androgens, such as the activation of intracellular kinases and up-regulation of calcium levels. The impact of these cellular events on prostate cancer has yet to be determined ***[Culig et al, 2003]***.

The AR contains four functional regions: an amino terminal regulatory domain (AF-1 site), a DNA-binding domain composed of two zinc fingers, a hinge region containing a nuclear localization signal, and a carboxy-terminal ligand-binding domain (AF-2 coactivator binding surface). Understanding the structural basis of AR could be important for the design of more potent AR-targeted compounds that could serve as better long-term agents for PCa therapy ***[Taplin et al, 2007]***.

❖ ANDROGEN RECEPTOR REGULATION

Activation of the androgen receptor appears to be a function of multiple steps including initial complex formation with certain chaparonins, binding of ligand, post-translational modifications, dimerization, nuclear localization, and binding of the receptor to certain transcriptional co-activator complexes that remodel chromatin, target the initiation site, and stabilize the RNA polymerase II machinery for repeated rounds of transcription (Figure 2) ***[Veltri et al, 2007]***.

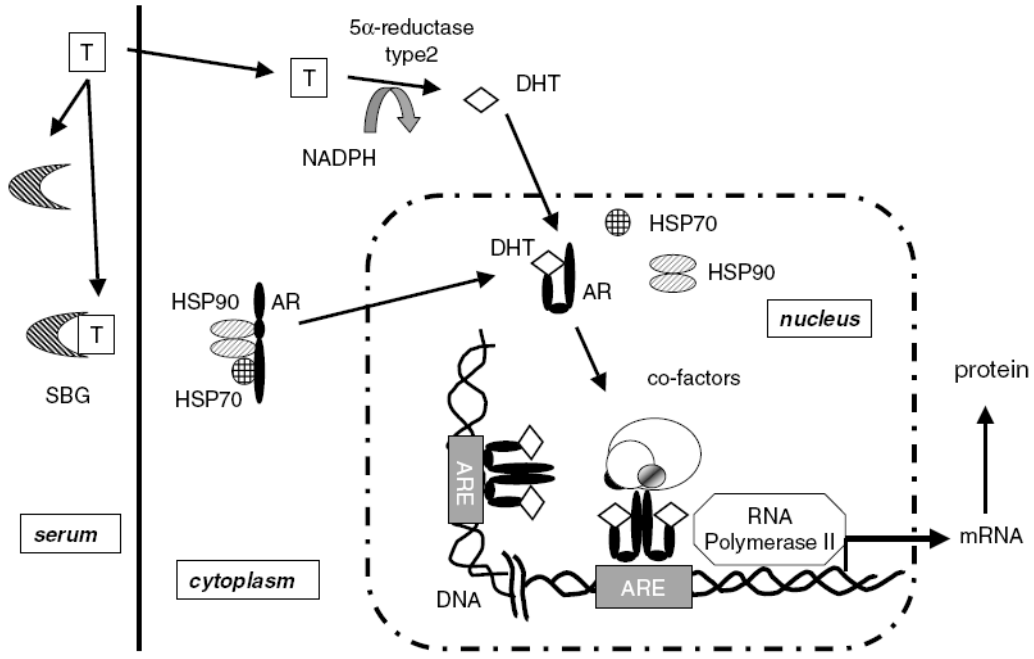

Figure 2. Mechanism of ligand-dependence of AR ***[H Suzuki et al, 2003].***

- **Chaparonin Binding:**

Unliganded ARs are located primarily in the cytoplasm. Before ligand binding, the AR is thought to be in an inactive state, in which it aggregates with chaperone proteins (including heat-shock protein 90[Hsp90], heat-shock protein 70[Hsp70], FK501 Binding Protein [FKBP51], Hsc70 interacting protein [Hip], Hsp70/Hsp90 organizing protein [Hop], and so forth). The chaperone complex serves to stabilize the ARs' tertiary structure in a high affinity conformation that permits androgen binding ***[Febbo et al, 2002]***.

Of the known AR chaperones, Hsp90 has perhaps the most significant impact on AR activity. Inhibition of Hsp90 function results in proteosomal degradation of proteins that require this chaperone for stability, including AR ***[Solit et al, 2002]***. In prostate cancer models, inhibition of Hsp90 has been shown to modify the effect of dihydrotestosterone (DHT) and to inhibit the growth of hormone-sensitive and resistant tumors ***[Harashima et al, 2005]***.

Another chaperone, FKBP51, is androgen regulated, directly binds to the AR, and may also affect AR transcription ***[Febbo et al, 2005]***. Although these proteins dissociate from AR on ligand binding, these studies suggest that they have a role in AR signaling and are potential therapeutic targets. While the androgen receptor is uncomplexed, it is susceptible to various different post-translational processing steps, including phosphorylation or glycosylation. Such interactions may then inhibit reaggregation with the chaparonins, leading to ligand-dependent activation, ligand-independent activation, or receptor inactivation with proteasome-mediated degradation ***[Balakumaran et al, 2006]***.

- **Transcriptional Coactivators and Corepressors:**

In the presence of agonists, AR binds to DNA and activates transcription. During this process, the AR also interacts with transcriptional coactivators and corepressors that modulate AR activity ***[Wang et al, 2005]***. Steroid-receptor coactivator– 1 and transcriptional intermediary factor 2 are transcriptional coactivators that are recruited by the DNA-bound ligand–AR complex to activate transcription of androgen responsive genes ***[Chen et al, 1998]***. When overexpressed, these proteins are able to increase AR-activated transcription even in the presence of low levels of androgens, and these coactivators have been found to be overexpressed in recurrent prostate cancer ***[Gregory et al, 2001]***. AR transcriptional activation may alternatively be limited by nuclear corepressors, such as nuclear receptor corepressor (NCoR) and silencing mediator of retinoid and thyroid receptors. NCoR interacts directly with AR and represses AR transcriptional activity ***[Cheng et al, 2002]***. RU486 mifepristone at nanomolar concentrations promotes the interaction of AR and NCoR and suggests a novel mechanism for AR antagonism ***[Hodgson et al, 2005]***. Thus, AR signaling can be profoundly affected by coregulators and disrupted by small molecules altering these critical interactions.

- **Other Signaling Pathways Affecting AR Signaling:**

In addition to chaperones and coregulators, other signaling pathways affect AR signaling. Enhancement of ligand-dependent AR transcription can occur when AR interacts with beta-catenin ***[Song et al, 2005]***, and ligand-independent enhancement of AR-dependent transcription has been demonstrated for the human epidermal growth factor receptor/ c-erb B-2 (HER2/neu) ***[Craft et al, 1999]***. Alternatively, mothers against decapentaplegic homolog 3(Smad3), a downstream effector of transforming growth factor–beta (TGF-b) signaling, specifically inhibits transcriptional activation mediated by AR, and loss of TGF-b will enhance AR-mediated activation ***[Hayes et al, 2001]***. Similarly, PIASy (a member of the protein inhibitor of activated signal transducer and activator of transcription (STAT) family) and Daxx can also repress transcriptional activity of AR through direct binding and recruitment of histone deacetylases ***[Lin et al, 2004]***.

It is inevitable that more interactions between signaling pathways commonly implicated in prostate cancer pathogenesis and AR signaling will be discovered. These interactions have great potential to affect therapy for hormone-refractory disease. For example, gene knock-down experiments using RNAi together with a dual Epidermal Growth Factor Receptor (EGFR)/HER2 kinase inhibitor (PKI-166) demonstrated that the HER2 pathway activity profoundly affects AR signaling through increased binding of AR to DNA target sites and protection from the ubiquitin-mediated degradation ***[Mellinghoff et al, 2004]***. Thus, the transformation of inhibitory mechanisms of pathways interacting with AR signaling into therapeutic strategies for hormone-resistant prostate cancer has strong scientific rationale and is the focus of significant preclinical and clinical investigation.

- **Androgen Receptor Protein Modification**

The AR protein is clearly subjected to phosphorylation, acetylation, sumoylation, and additional protein modifications, but the biologic importance of these posttranslational events in the development or progression of prostate cancer remains unclear. The AR has long been recognized as having sites for phosphorylation ***[Brinkmann et al, 1992]***, and recent work has found that phosphorylation at Serine 650 may accentuate AR-mediated transcription ***[Gioeli et al, 2006]***. Proteins that have been found to phosphorylate AR include G-protein coupled receptor ligands ***[Daaka et al, 2004]***, stress kinases ***[Gioeli et al, 2006]***, and glycogen synthesis kinase–3 beta ***[Salas et al, 2004]***, among others. However, the downstream effect on AR transcription has been alternately shown to be permissive ***[Gioeli et al, 2006]*** or inhibitory ***[Salas et al, 2004]***.

Good evidence indicates that acetylation of AR increases transcriptional activity ***[Huang et al, 2003]***. E1A binding protein 300 (p300), p300/CBP-associated factor (TIP60 - HIV-1 Tat Interacting Protein 60 P/CAF), and HIV-1 Tat Interacting Protein 60 (TIP60) can acetylate AR ***[Fu et al, 2004]***, and acetylation of AR can increase AR activation, most likely through increased association with coregulatory proteins ***[Kang et al, 2004]***. Similarly, SENP1