

The Mechanism of Androgen Deprivation and the Androgen Receptor

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Abstract: Prostate cancer is a major cause of cancer-related deaths in American men. The development and growth of prostate cancer depends on the androgen receptor (AR) and its high-affinity binding of dehydrotestosterone (DHT), which derives from testosterone (T). Most prostate tumors regress after therapy to prevent testosterone production by the testes, but the tumors eventually recur and cause death. The AR, a member of the steroid receptor family that is activated by testicular androgens, is the major regulatory transcription factor in normal prostate growth and development and in the growth of androgen-dependent prostate cancer. Recent evidence suggests that the AR may also contribute to prostate cancer growth during its recurrence in the androgen-deprived patient. A role for AR-mediated gene activation in recurrent prostate cancer is supported by its expression together with the expression of androgen-regulated genes.

This review highlights the different mechanisms of the available androgen deprivation therapies and also focuses on the novel targeted therapies in advanced or metastatic prostate cancer. Furthermore, we provide a molecular basis for the AR and its role in activation and progression in recurrent or castration resistant prostate cancer.

Keywords: Prostate cancer, dihydrotestosterone, androgen receptor, gene expression, androgen-regulated genes.

SCIENTIFIC RATIONALE FOR ANDROGEN DEPRIVATION IN PROSTATE CANCER

Luteinizing hormone-releasing hormone (LHRH) is a linear decapeptide synthesized from a precursor polypeptide in the neurovascular terminals of the hypothalamus and secreted in a pulsatile pattern (every 30 - 120 min) directly into the hypophyseal portal circulation, binding and activating the cell surface LHRH receptor (LHRH-R) on the gonadotrope cells located in the anterior pituitary. The frequency and amplitude of these LHRH secretions control the synthesis and excretion of the two pituitary gonadotropins (LH and FSH), which then enter the systemic circulation and bind to receptors in the gonads where they stimulate sex steroidogenesis (regulated mainly by LH) and gametogenesis (regulated mainly by FSH) in the testes and ovaries. More specifically in males LH acts on testicular Leydig cells and stimulates *de novo* synthesis and subsequent release of androgens, mainly testosterone (T), into the blood circulation [1]. Free T enters prostate cells and 90% is converted by the enzymatic action of 5 α -reductase to dehydrotestosterone (DHT), which has a four- to five-fold higher affinity for the androgen receptor (AR) than T [2, 3]. The adrenal glands also produce androgens, including T, androstenedione and dehydroepiandrosterone (DHEA), which contribute to intraprostatic DHT production by increasing the substrate concentration. In addition, inactive metabolites of steroid hormone synthesis in the testes such as DHEA and dehydroepiandrosterone sulfate, can act as precursors in the formation of active androgens in prostate tissue [4, 5]. Inside the prostate cancer cell DHT

binds to androgen receptor (AR) and the DHT - AR complex then binds to its respective androgen response elements (ARE) in nuclear DNA, stimulating many target genes repressed by androgen. Activated transcription and translation of specific genes thereby results in *de novo* protein synthesis and tumor growth in the case of prostate cancer (Fig. 1).

About 70% of prostate cancers are testosterone-dependent [6]; the survival and growth of prostate cancer cells is regulated by androgens. Also, contrary to previous beliefs, androgen blockade therapy is not only cytostatic, but also cytotoxic [7]. That is why the treatment of patients with advanced prostate cancer is based on the suppression of endogenous androgens. Now, the guidelines by the American Society of Clinical Oncology recommend bilateral orchiectomy or LHRH agonists as initial treatment for metastatic, recurrent or progressive prostate cancer [8]. Both treatment modalities display similar efficacy and safety profiles, with response rates ranging from 17% to 70% and a median overall survival (OS) of 1.1 to 2.6 years [9].

MECHANISM OF ACTION OF LHRH AGONISTS

After Schally and his colleagues first isolated LHRH from porcine hypothalamus in 1971, they developed synthetic LHRH analogs [10, 11]. Small, potent peptide agonists such as leuprolide, goserelin, buserelin and nafarelin were subsequently developed for clinical use. These agents initially stimulate the release of LH from the pituitary, which temporarily increases serum T/DHT levels for a period of 1 week [7]. This initial T/DHT "surge" may be associated with a 10-fold rise in LH, a 5-fold rise in FSH and a 4-fold increase in estradiol levels [12]. However, continuous and high LHRH agonist concentrations result in LHRH receptor (LHRH-R) downregulation, desensitization and subsequent

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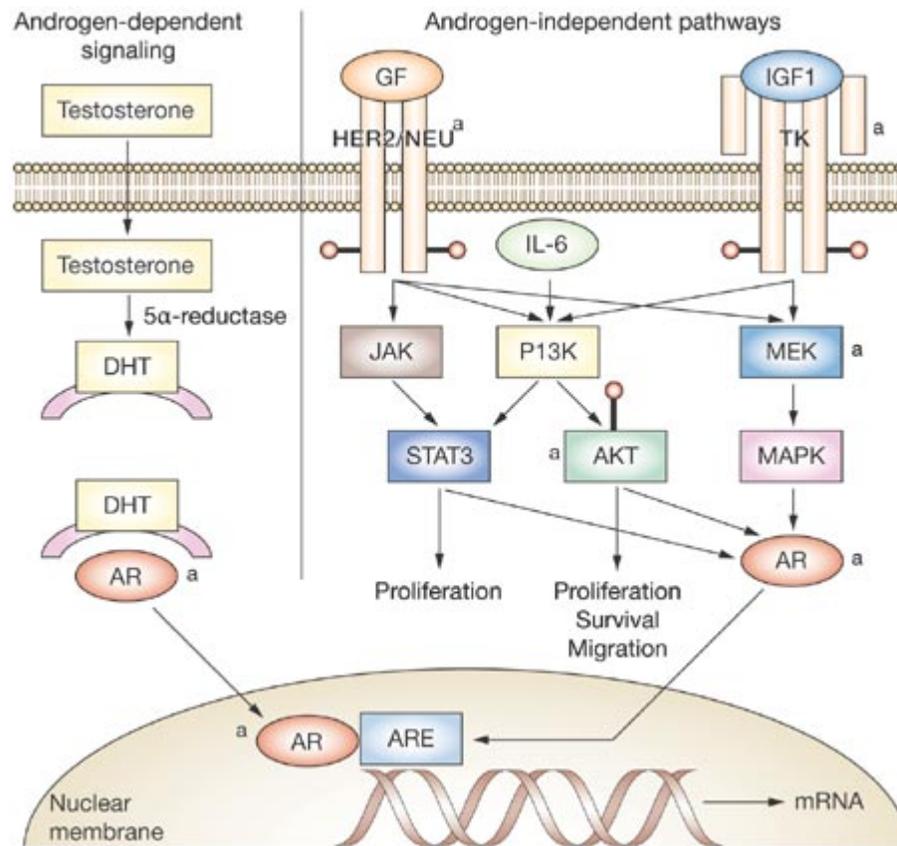


Fig. (1). Androgen-receptor signaling in prostate cancer. Hormone-dependent androgen signaling takes place through DHT stimulation of the AR (left panel). Hormone-refractory prostate cancer cells survive through stimulation of multiple signaling pathways, including the PI3K and the MAPK pathways. These culminate in androgen-receptor signaling, or alternate pathways that lead to cell proliferation, migration and survival (right panel). aHSP90-inhibitor-sensitive protein or pathway. Abbreviations: AKT, protein kinase B; GF, growth factor; IGF1, insulin-like growth factor 1; IL-6, interleukin 6; JAK, Janus kinase; MAPK, mitogen-activated protein kinase; MEK, upstream kinases of mitogen-activated protein kinases, also known as MAP2Ks; P13K, phosphatidylinositol 3 kinase; mRNA, messenger RNA; STAT3, signal transducer and activator of transcription 3; TK, tyrosine kinase.

inhibition of LH release, reducing T to levels comparable to orchiectomy [13]. These analogs are available as 1-, 3-, 4- and 12-month depot injections (subcutaneous or intramuscular), offering convenient dosing and patient adherence.

MECHANISM OF ACTION OF LHRH ANTAGONISTS

Whereas LHRH agonists have been in clinical use for > 30 years, LHRH antagonists represent a recently approved drug class designed for androgen ablation [14]. Potent antagonistic analogs of LHRH, such as cetrorelix, ganirelix, degarelix and abarelix have been synthesized. Abarelix and degarelix currently are the only 2 agents approved by the US FDA for use in prostate cancer patients [15]. In contrast to the inhibitory effects of agonists, LHRH antagonists competitively block the LHRH-R by achieving receptor occupancy without receptor coupling or signal transduction that normally induces the release of gonadotropins. This results in a major and rapid (within hours) reduction in serum T level similar to that caused by surgical orchiectomy. Although LHRH antagonists do not require receptor downregulation as the agonists do, chronic administration of antagonists has been demonstrated to produce marked downregulation of pituitary LHRH-R [16, 17].

Preclinical evidence suggests that FSH may play a role in the proliferation and growth of androgen independent (AI) prostate cancer [18]. FSH is only partially suppressed by LHRH agonists [19] and orchiectomy elevates FSH levels above the physiological range, in contrast to the immediate and substantial FSH suppression achieved by LHRH antagonists [20]. It is, thus, theorized that LHRH antagonist treatment may be useful in AI prostate cancer; although, so far, studies have not reported such benefit. It is possible that FSH secretion may not be entirely LHRH dependent and that LHRH antagonist therapy in combination with agents that directly antagonize the FSH receptor may prove more effective. In addition, further research is needed regarding the ability of LHRH antagonists to maintain long-term hypogonadal T/DHT levels.

LHRH antagonists do not cause T surge thereby eliminating its associated complications, however they induce histamine release from mast cells, which in turn increases the risk of severe allergic reactions. These life-threatening complications may occur after the initial, as well as in all subsequent, LHRH antagonist injections. Other adverse effects such as asthenia, nausea, hot flashes, headache and fatigue have been reported [12, 15].

NOVEL SECONDARY HORMONAL THERAPY IN ADVANCED PROSTATE CANCER

Despite the castrate levels of testosterone, many patients demonstrate progression of the disease (mainly in metastatic setting) and develop castration-resistant prostate cancer (CRPC); however patients still remain sensitive to secondary hormonal manipulations aimed at further lowering androgen levels. Moreover, approximately 25% of T in the prostate cancer tissue remains after castration [21]. These results suggest that ADT for prostate cancer requires not only surgical or medical castration using LHRH agonists but also an antiandrogen agent [22].

1. Antiandrogens

Antiandrogens work by directly blocking the actions of DHT on prostate cancer cells. There are two types of antiandrogens: steroidal antiandrogens, such as cyproterone acetate and megestrol acetate; and non-steroidal types, which include flutamide, bicalutamide and nilutamide. Non-steroidal antiandrogens have purely antiandrogenic effects and work by competitively inhibiting androgen binding in prostate tissue. Also they have various potencies for blocking the activities of AR [23, 24]. In hormone refractory prostate cancer xenograft models, development of resistance to antiandrogen therapy was associated with an increase in AR mRNA. In addition, all these compounds demonstrated agonistic properties in cells with increased AR levels [25]. MDV3100 (Medivation, Inc., San Francisco, CA) is a novel AR antagonist. Importantly, MDV3100 maintains antagonistic properties in the setting in which standard antiandrogens function as agonists [25].

Randomized trials have shown that non-steroidal antiandrogens as a monotherapy have inferior OS rates compared to when they are combined with LHRH agonists [26]. On the other hand, concomitant administration of LHRH agonists with a non steroidal antiandrogen is an acceptable alternative especially in patients at high risk of spinal compression, bladder neck obstruction or paravertebral masses [8]. In clinical practice, an antiandrogen is typically added upon development of castration resistance, if it was not included in initial treatment.

2. Inhibitors of Adrenal Androgen Synthesis

T and DHT are also converted from DHEA and androstenedione secreted by the adrenal gland. It is reported that approximately 40% of androgens in the prostatic tissue are derived from the adrenal gland [27]. In castrated men, up to 10% of baseline circulating T is due to peripheral conversion of adrenal steroids [27]. More recently, the theory that CRPC is driven by activation of the AR by alternative androgens, specifically adrenal androgens like DHEA, DHEA-sulfate (DHEAS), and androstenedione, has been supported by various studies. These androgens have been shown to activate both wild-type and mutant AR *in vitro* [28, 29]. Given these findings, agents that block adrenal conversion of steroid precursors into androgen have been investigated for their therapeutic potential in CRPC [30-33].

Aminoglutethimide and ketoconazole are the two drugs in widest use for this purpose. Aminoglutethimide blocks formation of pregnenolone from cholesterol and inhibits 11-

b-hydroxylase and peripheral aromatase [31]. Ketoconazole inhibits multiple cytochrome P450 enzymes involved in adrenal steroid synthesis, including cholesterol side chain cleavage to pregnenolone and 11-b-hydroxylation as well as cytochrome P450 17-a-hydroxylase/17,20-lyase (CYP 17). Concomitant reductions in cortisol synthesis typically necessitate the need for corticosteroid replacement in most patients. Aminoglutethimide is rarely used clinically for toxicity reasons and because a phase III randomized controlled trial that included aminoglutethimide as an optional agent failed to demonstrate definitive activity in unselected patients [34]. Multiple phase I and II studies with ketoconazole have demonstrated a clinical response and a prostate-specific antigen (PSA) response in CRPC [35-37], which led to eventual phase III evaluation of ketoconazole as a second-line therapy after antiandrogen withdrawal (AAWD).

A promising result of the efforts to optimize the effects of ketoconazole without the associated side effects is the development of abiraterone acetate, an orally available prodrug of abiraterone, which was developed as a highly selective inhibitor of CYP450c17 (17-a-hydroxylase/C17,20-lyase), an enzyme in the synthetic pathway of adrenal androgens. In preclinical models, abiraterone acetate is approximately 7 times more potent in inhibiting CYP 17 than ketoconazole [38]. Data from a US study of 30 patients with CRPC were presented at the 2008 American Society of Clinical Oncology (ASCO) annual meeting [39]. After 12 weeks of therapy, 16 of 30 patients demonstrated a greater than 50% decline in PSA. Interestingly, 10 of 19 patients who had previously received ketoconazole showed a greater than 50% PSA response. Analysis of patient data showed each tested dose led to decreased plasma levels of T and DHEAS. Adverse effects associated with abiraterone use can be traced in part to its partial inhibition of the adrenal synthesis pathways and a concomitant increase in the production of nonandrogen steroids by the adrenal cortex. These included hypertension, edema, and hypokalemia, associated with an elevation of serum adrenocorticotrophic hormone (ACTH). Many of these adverse effects were managed by corticosteroids to reduce ACTH-stimulated mineralocorticoid induced by the drug.

3. 5- α -Reductase Inhibitors

DHT, the primary prostatic androgen, is transformed from T by types 1 and 2 5 α -reductase. The predominant isoenzyme in normal prostate is type 2 5 α -reductase. Immunostaining studies have shown that type 1 5 α -reductase expression increases and type 2 5 α -reductase expression decreases in prostate cancer, compared with nonmalignant prostate tissue. Both isoenzymes appear increased in high-grade compared with low-grade localized prostate cancer. Therefore inhibition of both isoenzymes may be effective in preventing or delaying the growth of prostate cancer.

The two 5 α -reductase inhibitors currently available for clinical use are finasteride and dutasteride. Unlike finasteride, which only inhibits the type II isoenzyme, dutasteride blocks both type I and type II isoenzymes and has an inhibitory effect in prostate cancer [40]. Dutasteride is 45-fold more effective in inhibiting type 1 5 α -reductase and 2-fold more effective in inhibiting type 2 than finasteride [41]. This dual inhibition translates into a greater degree of DHT sup-

pression [41], thereby underlying the hypothesis that inhibition of both type 1 and type 2 would provide correspondingly greater protection than inhibition of type 2 alone.

Fundamental differences exist between androgen ablation and 5 α -reductase inhibition. Castration decreases serum T and DHT, resulting in hypogonadism. It decreases intraprostatic DHT by 50% to 80% and the remaining DHT arises from the conversion of adrenal androgen precursors. The inhibition of 5 α -reductase markedly decreases serum DHT but, because T is not decreased, sexual dysfunction is uncommon. Although 5 α -reductase inhibition causes a more marked intraprostatic DHT reduction than castration, intraprostatic T increases. Therefore, the effect of 5 α -reductase inhibition on prostate function is not as great as castration and the combination of the 2 methods has been shown to be more effective than either alone in an animal model of prostate cancer [42].

Dutasteride is being studied in combination with ketoconazole in patients with prostate cancer progression who were receiving ketoconazole as a single agent [43]. Preliminary results suggest evidence of PSA decline and a phase II trial is underway.

THE ANDROGEN RECEPTOR

Androgen receptor (AR) is a member of the super-family of nuclear hormone receptors which acts as a ligand-activated transcription factor [44]. AR has two native ligands, T and its more potent metabolite DHT, both of which binds AR and activates or represses the target gene expression at the transcriptional level (for example prostate-specific antigen, PSA). There is now compelling evidence that the AR is involved in all stages of prostate tumorigenesis including initiation, progression and treatment resistance [45].

1. Androgen Receptor Structure

To elucidate in greater detail the role of AR in the pathogenesis of prostate cancer it is important to have a comprehensive understanding of the key determinants of AR structure and function. AR is organized into functional domains [46], consisting of an N-terminal regulatory domain (NTD), a DNA-binding domain (DBD), a small hinge region (H) and a ligand-binding domain (LBD). Two isoforms of the AR

(A, 87 kDa and B, 110 kDa) have been identified [47]. AR-A is N-terminally truncated (lacks the first 187 amino acids) compared with full length AR-B (Fig. 2). AR-NTD serves as a primary mediator for the recruitment and assembly of co-regulators and members of the cell and gene specific effects of androgens [48]. The cysteine-rich DBD contains two zinc finger motifs. The first zinc finger mediates DNA sequence recognition, facilitating the binding of the receptor in the major groove of DNA and the second zinc finger stabilizes the DNA bound receptor complex [49, 50]. The agonist binding induces a conformational change in the LBD which mediates high affinity binding of the AR to androgenic agonist. NH₂-terminal activation function (AF-1) works in a ligand-independent manner when artificially separated from the LBD, creating a constitutively active receptor. A ligand-dependent AF-2 function is located in the LBD, and mutation or deletion of the AF-2 domain dramatically reduces transcriptional activation in response to a ligand [51, 52].

2. Molecular Basis of Androgen Action

In the absence of androgenic hormone, the AR localizes primarily in the cytoplasm bound to heat shock proteins (HSPs). The binding of hormone to the LBD initiates a cascade of events that alters AR conformation, promotes AR phosphorylation, dimerization, dissociation of AR from HSPs, and translocation into the nucleus [53]. It is only subsequent to these events that the AR dimer binds to ARE located in the regulatory regions of target genes [54], and actively recruits essential cofactors and assembles the transcriptional machinery required to regulate the expression of androgen-regulated genes [54, 55]. A critical component of AR signaling is the ability of the receptor to undergo dimerization which is mediated through the AR-DBD; moreover there's also dimerization on the surface of LBD. By assembling on DNA targets, the AR homodimer specifically binds DNA to regulate the expression of AR target genes [45] (Fig. 3).

The transcriptional activity of AR is regulated by AR co-regulators, which influence the ligand selectivity and DNA binding capacity of AR. As of May 2007, the list of proteins that have been classified as potential AR coregulators contains 169 members. Remarkably, these coregulators display a diverse array of functions and are involved in multiple cellular pathways [54]. These proteins were arranged according to

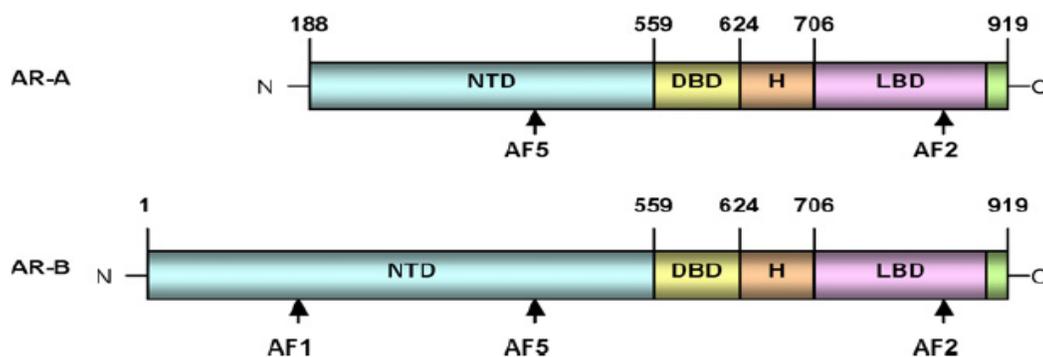


Fig. (2). Structural domains of the two isoforms (AR-A and AR-B) of the human AR. Numbers above the bars refer to the amino acid residues which separate the domains starting from the N-terminus (left) to C-terminus (right). NTD, N-terminal domain; DBD, DNA-binding domain; LBD, ligand-binding domain; AF, activation function.

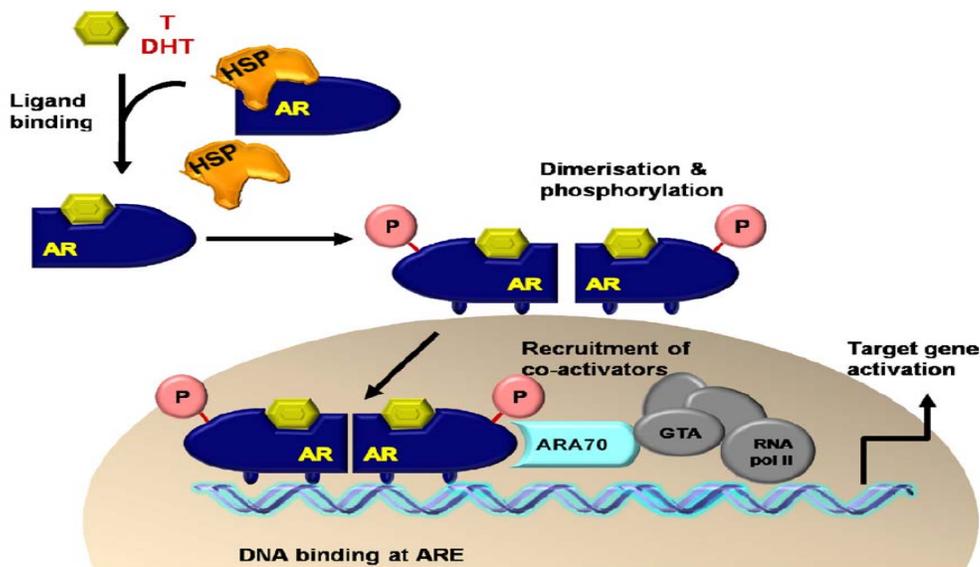


Fig. (3). Ligand-binding positively or negatively controls gene expressions of target genes by AR through switching of co-regulators; most of them form histone-modifying enzyme complexes, together with histone remodeling by ATP-dependent chromatin remodelling complexes.

their apparent primary function and includes components of the chromatin remodeling complex and ubiquitination/proteasome pathway; histone modifiers: acetyltransferases, deacetylases, methyltransferases and demethylases; and proteins involved in splicing and RNA metabolism [54].

3. Pathways to Androgen-Independence in Prostate Cancer

Even at an advanced stage, prostate cancer is the best-known example of an androgen-dependent meaning prostate cancer cells being hormone sensitive. However, tumors become androgen independent as the disease progresses. The androgen independent (AI) cell clones are either selected in response to ADT or exist *de novo* (a hypothesis supported by the cancer stem cell theory) [56]. The AI phenotype of prostate cancer is mainly developed at the metastatic sites [57]. Below, we will review the potent mechanisms in the development and progression of castration-resistant prostate cancer (CRPC).

A. Change in AR Expression

Immunohistochemical studies in the early 1990s showed that AR protein was highly expressed in CRPC, and a correlation between CRPC and increasing levels of serum prostate-specific antigen (PSA, encoded by the AR-regulated KLK3 gene), a marker for AR activity, indicated that AR transcriptional activity was reactivated in CRPC [58].

Studies have found that approximately 25-30% of AI tumors that arise after hormonal therapy have AR gene amplification with resultant AR expression [59]. The increase in receptor abundance results in sufficient ligand concentrations for sustained AR signaling in castrate levels of androgens. This is consistent with the reports that patients with AR gene amplification have disease recurrence while on therapy and have a greater likelihood to respond to second line hormonal therapy than patients without AR gene amplification. Furthermore, an analysis of seven different prostate cancer xenograft models showed that AR gene expression increased

during progression from androgen dependence to androgen independence in each case [25].

Numerous studies show that most primary and advanced stage prostate cancers express the AR regardless of stage and grade, or hormone sensitivity [60-63]. However, the majority of reports have noted significant heterogeneous staining of the AR in many prostate tumor specimens in contrast to the homogeneous AR staining in normal prostate epithelium. These findings suggest that not only the increased AR expression but the variability in AR content increases with the progression of the disease and might in part account for hormone resistance [60-63].

Moreover, absence of AR expression has been shown in the AI human prostate tumor cell lines DU145 and PC3 [64, 65]. The loss of AR expression in these AI cells appears to occur through CpG methylation and histone deacetylation of the AR gene promoter but not through deletion or mutation of the AR gene [66-69]. This epigenetic alteration of the AR gene promoter may play a role in the development of hormone independence in a subset of prostate cancers that do not express AR. Hypermethylation of the AR promoter is more frequently found in hormone-refractory prostate cancer tissues (29%) compared with untreated primary tissues (10%) [70-72].

B. Development of Mutant ARs

The overall frequency of somatic AR gene mutations in patients treated initially with surgical castration or LHRH AGONISTS is quite low, and this is unlikely to be a major mechanism for progression to CRPC [73]. Nonetheless, mutant ARs that are stimulated by the AR antagonist flutamide are much more frequent in patients treated long term with this drug in combination with castration as their initial hormonal therapy (combined androgen blockade). Moreover, these patients also have increased responses to another AR antagonist (bicalutamide) that can still block the mutant ARs [23, 74]. Finally, the AR mutation in codon 741 that allows bicalutamide to function as an agonist has been found in pa-

tients treated with bicalutamide, and in LNCaP cells after long term culture with bicalutamide [73, 75, 76]. Taken together, these findings demonstrate that AR antagonists can generate strong selective pressure for mutations that enhance AR activity [77].

C. Increased Intratumoral Androgen Synthesis

More recent studies indicated that increased intratumoral androgen synthesis is a mechanism for AR reactivation in CRPC [78-80]. Page *et al.* demonstrated in healthy subjects treated with a LHRH AGONISTS, despite a 94% decrease in serum T concentrations, intraprostatic T and DHT levels remained at 20-30% of control values [81]. Similarly, Nishiyama and colleagues measured levels of DHT in patients treated with ADT [82]. They found that the levels of prostatic DHT remained at approximately 25% following ADT, compared to levels measured prior to therapy. By contrast, measurements examining serum levels of DHT in these same individuals demonstrated that DHT levels fell by over 90%. Also, Mostaghel *et al.* examined intraprostatic androgen levels and patterns of androgen regulated gene expression in normal men and in archival prostate cancer specimens following varying lengths of ADT [83]. The results demonstrated several major features. First, intraprostatic levels of T and DHT showed marked variations between individuals following short-term ADT. Second, androgen-regulated gene expression, as indicated by the levels of PSA expression, persisted and were substantially reduced only in those subjects with the most profound suppression of intraprostatic androgen levels.

D. Cross-talk with Growth Factors

Numerous studies indicate that the AR can be activated by interaction with non steroid molecules or in a ligand-independent manner. Growth factors that are ligands for receptor tyrosine kinases including epidermal growth factor (EGF), insulin-like growth factor (IGF), vascular endothelial growth factor (VEGF) and transforming growth factor- β (TGFB), can initiate a signaling cascade that culminates in AR activation [84]. While the initiating signaling event differs, all of these mechanisms employ a phosphorylation cascade, including the well known AKT and MAPK pathways [85].

E. Increased Expression of AR Co-activators

An important new mechanism whereby co-regulators can change androgen sensitivity was identified in men with recurrent prostate cancer after castration, in whom up-regulation of two AR co-activators potently increases cellular androgen sensitivity [58].

Some of the best studied AR co-activators are members of the family of SRC-1 and transcriptional intermediary factor 2 (TIF2) [86, 87]. These proteins possess histone acetylase activities, but are also able to recruit other histone acetylases such as the CREB-binding protein p300 and PCAF [88]. An analysis of prostate cancer samples from patients, who failed endocrine therapy, showed that expression of SRC-1 and TIF2 was more intense than in those from patients with benign prostatic hyperplasia or androgen dependent tumors [58].

NOVEL CONCEPTS IN ANDROGEN RECEPTOR BLOCKADE

Indeed, it is now well established that such "AI" prostate cancer remains exquisitely dependent on AR function [25, 89]. Therefore, as has been reviewed by Litvinov *et al.* [90], ADT is not curative because of the accumulation of molecular changes inducing gain of function in the AR signaling pathway that results in activation of novel AR-dependent signaling pathway but without requiring androgen ligand binding. It is noteworthy that a number of the signaling pathways that are involved in bypassing the requirement for androgens interact with each other. Therefore, modulations of several signaling pathways may synergize to confer androgen independence. If multiple alterations are required for the development of androgen independence, targeting one pathway may be insufficient to inhibit tumor growth. The challenge is to identify the altered pathways in individual tumors to design the most effective therapeutics. In this section, we will review the most recent treatment strategies involving modulation of those signaling pathways.

1. AR Dimerization Antagonists

Developing antagonists of AR dimerization may be effective in inhibiting AR function and therefore provides an alternative strategy to conventional receptor antagonists that typically target ligand binding. Evidence to support this strategy has already been provided through studies that target the AR in prostate cancer cells using dominant-negative AR, which have been shown to act through the dimerization domains in the AR-DBD and -LBD [91, 92]. Ligand-independent activation of the AR also occurs by the NTD, making it a potential target for the treatment of hormone refractory prostate cancer [93]. Quayle *et al.* [93] demonstrated that overexpression of AR NTD peptide could create decoy molecules which competitively bind the interacting proteins required for activation of AR. The *in vivo* study also showed evidence that expression of AR NTD decoys decreased tumor incidence and inhibited the growth of prostate cancer tumors.

2. Non-ligand Inhibitors of AR Activity

All available antiandrogens target only ligand binding, either by reduction of available hormone or by competitive antagonism. New strategies are needed, and could have an important impact on therapy. One approach could be to target other cellular mechanisms required for receptor activation. Jones *et al.* [94] identified 2 compounds which activate AR independent of the ligand binding: pyrvinium pamoate, a Food and Drug Administration-approved drug, and harmol hydrochloride, a natural product. Each compound functions by a unique, non-competitive mechanism and synergizes with competitive antagonists to disrupt AR activity. Harmol blocks DNA occupancy by AR, whereas pyrvinium does not. Pyrvinium inhibits AR-dependent gene expression in the prostate gland *in vivo*, and induces prostate atrophy. Neither PP nor HH have chemical structures similar to known AR ligands. HH and PP do not prevent DHT binding, yet they block ligand-induced conformation change and inhibit subsequent AR activity. Neither drug affects AR protein stability or nuclear accumulation.

3. HSP90 Inhibitors

HSP90, a molecular chaperonin, is required for the refolding of denatured proteins. In addition, it is required to maintain the proper baseline folding of several important proteins in oncogenesis, including AR, Her2, AKT, and mutagenic BRAF. Geldanamycin, a natural compound produced by *Streptomyces hygroscopicus*, binds the ATP binding pocket of HSP90 and causes degradation of client proteins [95]. Tanespimycin (17-AAG), a more stable geldanamycin derivative, inhibits AR-positive prostate cancer xenografts without significant toxicity to the murine hosts. Treatment resulted in 80% loss of AR expression and 97% loss of HER2 expression [96]. In an independent unbiased validation that HSP90 inhibition targets AR activity, Hieronymus *et al.* screened a library of chemical compounds that decreased expression of AR regulated genes. Two compounds that scored in this screen, celastrol and gedunin, were subsequently discovered to be HSP90 inhibitors and cause the same gene expression perturbations as 17-AAG [97].

4. HDAC Inhibitors

Acetylation of lysine residues is regulated by the balance of histone acetyltransferases (HAT) and histone deacetylases (HDAC). More recently, numerous other proteins have been found to be acetylated, including p53, HSP90, and AR.

HDAC inhibitors have been noted to have greater anti-proliferative effects on AR-positive prostate cancer cells than their AR-negative counterparts, and inhibit xenograft growth in both castration sensitive and resistant models [98, 99]. One proposed mechanism is that HDAC inhibitors target HDAC6 which deacetylates HSP90 and decreases AR stability [100]. Furthermore, HDAC inhibitors directly suppress AR transcription [99, 101]. Several HDAC inhibitors, including depsipeptide, SAHA, and LBH589 are in Phase I/II clinical trials in CRPC.

5. Kinase Inhibitors

Agents targeting EGFR or HER2, including small molecule kinase inhibitors (gefitinib, erlotinib, and lapatinib) and monoclonal antibodies (trastuzumab and pertuzamab) have been studied clinically in CRPC, but showed disappointing results. Since these inhibitors are most active in tumors where the target is mutated or amplified (e.g. EGFR mutation in lung cancer and HER2 amplification in breast cancer), one explanation is that EGFR/HER2 is not a relevant target in CRPC despite showing activity in preclinical models. Alternatively, there is mounting evidence that the loss of PTEN mediates resistance to EGFR-targeted and HER2-targeted therapies in both breast cancer and glioblastoma [102-105]. PTEN loss is common in high grade and metastatic CRPC and mediates early development of castration resistance in mouse models [106, 107]. Therefore, combination treatment with novel PI3K inhibitors with EGFR/HER2 inhibitors may be warranted. Dasatinib, currently approved as an ABL kinase inhibitor for the treatment of chronic myelogenous leukemia [108], is also a nanomolar SRC inhibitor. Phase II clinical trials of dasatinib in CRPC are ongoing.

CONCLUSION

In summary, current data indicate that prostate cancer cells adapt to ADT by multiple mechanisms, which include

increasing AR gene expression and androgen biosynthesis, and activation of multiple pathways that can directly or indirectly enhance AR activation by low levels of androgen. Secondary hormonal therapies with available inhibitors of androgen synthesis (ketoconazole, finasteride, dutasteride) or AR antagonists (bicalutamide, flutamide, nilutamide) have modest efficacy, but responses may be improved with more potent agents that are in clinical trials. An alternative approach is to target AR folding and stability by the Hsp90 chaperone complex, which can be suppressed by direct Hsp90 inhibitors or indirectly by HDAC inhibitors that prevent HDAC6 mediated deacetylation of Hsp90. Identification of intracellular factors that mediate the effects of these compounds could vastly improve our understanding of nuclear receptor biology.

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