Urol Res (2000) 28:211–219

INVITED EDITORIAL

Z. Culig · A. Hobisch · G. Bartsch · H. Klocker

Androgen receptor – an update of mechanisms of action in prostate cancer

Received: 18 November 1999 / Accepted: 1 March 2000

Abstract Androgen receptor (AR), a key nuclear transcription factor in the prostate gland, is expressed in all histological types and stages of prostate cancer. The AR regulates proliferation of prostate cancer cells by stimulation of cyclin-dependent kinases. However, in some prostate tumors AR stimulates expression of cell cycle inhibitors, thus leading to down-regulation of cellular proliferation. Androgens, by activation of the AR, control differentiation of prostate cells and synthesis of neutral lipids. There are several mechanisms by which prostate cancer cells adapt to an environment with low androgen supply during endocrine therapy. The AR expression and activity increase in several cell lines that are used as an in vitro model for monitoring changes during long-term androgen ablation. Mutant ARs are of importance for monitoring the natural course of the disease and for determining the response to anti-androgens in metastatic lesions from prostatic carcinoma. In addition, AR activity is up-regulated by various stimulators of intracellular protein kinases. Current research efforts are focused on elucidation of function of AR coregulatory proteins, coactivators and corepressors. Their inappropriate expression and/or function might critically influence cellular events in advanced carcinoma of the prostate. It is hoped that information on these coregulatory proteins will serve as a basis for a more efficient pharmacological inhibition of the AR in advanced carcinoma of the prostate.

Key words Androgen receptor · Prostate cancer · Androgen-regulated genes · Cell cycle · Prostate-specific antigen · Mutation · Non-steroidal activation · Anti-androgen · Coregulatory proteins

Z. Culig (✉) · A. Hobisch · G. Bartsch · H. Klocker
Department of Urology, University of Innsbruck,
Anichstrasse 35, 6020 Innsbruck, Austria
e-mail: zoran.culig@uibk.ac.at
Tel.: +43 512 504 4818;
Fax: +43 512 504 4817 or +43 512 504 4873

Introduction

Our understanding of the biology of advanced prostate cancer has been changed since it has become clear that the androgen receptor (AR) is expressed in nearly all prostate cancers, including therapy-refractory tumors and their metastases. This recognition has important implications for basic and translational research in carcinoma of the prostate, especially for the development of new therapies. In the past, it was presumed that AR expression is down-regulated in patients with advanced prostate cancer. This hypothesis was based on results obtained in various in vitro model systems which show a reduced or absent AR expression [82, 97]. Immunohistochemical visualization of the AR in target tissues, including prostate, was made possible by use of monoclonal and polyclonal antibodies which were raised after cloning of the AR [8, 66, 96, 99, 101]. Presence of the AR in relapsed tumors was first reported in the early 1990s [85, 101]. These studies also revealed that the percentage of AR-positive cells in tumor specimens does not correlate with duration of responsiveness to endocrine therapy. In contrast to prostatic epithelial and stromal cells, the AR is not expressed in rare small cell cancer of the prostate and in neuroendocrine cells which are present to some extent in nearly all prostate cancers [58, 101]. The stromal AR is a primary target of androgen action and its functionality appears to be particularly important during prostate development for maintaining the function of the normal prostate. It is needed for stromal to epithelial interactions that include various growth factor loops. In contrast, in late stage prostate cancers in tumor-adjacent stroma AR expression decreases [78]. In vivo growth of androgen-responsive PC 82 prostate cancer cells is dependent on their own AR pathway and not on the AR-expressing stromal cells [29]. These data suggest that there is a stromal independence of prostate tumors. The reasons why some prostate cancer cells do not express the AR were

recently studied. These studies revealed that, in DU-145 cells, methylation of the promoter CpG island is associated with the loss of AR expression [47]. In prostate cancer metastases, AR expression was first studied in those of lymph node. These samples were obtained from patients who had undergone radical prostatectomy [39]. Since these patients did not present with therapy-refractory cancer, it was not surprising that nearly all metastases were AR-positive. In 1995, it was shown by using the Northern blot technique and immunohistochemistry that distant metastases from patients who do not respond to endocrine therapy are also largely AR-positive [38, 94]. These findings greatly stimulated studies on AR function in normal and pathological situations.

AR structure

In this paper, only a brief overview of AR structure will be presented. More detailed information, can be found in comprehensive endocrinological reviews [81]. The AR is a ligand-activated transcription factor of the nuclear receptor superfamily which is composed of 919 amino acids [8]. The AR gene is located at the short arm of the chromosome X and consists of eight exons. The AR protein is composed of the three domains: (1) the well-conserved ligand-binding, (2) the DNA-binding and (3) the variable *N*-terminal domain. Present in the *N*-terminal domain are polymorphic glutamine and glycine repeats, the length of which influences receptor functional activity. The N-terminal domain is encoded by exon 1 of the AR gene. Exons 2 and 3 contain sequences for the DNA-binding domain. The DNA-binding domain amino acids are structurally organized into two zinc fingers, with each "finger" being composed of four cysteine residues bound to a zinc ion. The DNA-binding domain is involved in receptor dimerization. A part of exon 4 contains information for the hinge region that is located between the DNA- and the ligand-binding domains. The ligand-binding domain is encoded by a part of exon 4 and entire exons 5–8. Experiments in which AR deletion mutants generated by polymerase chain reaction (PCR) mutagenesis were expressed in heterologous cells revealed that the ligand-binding domain-truncated AR is active in the absence of a hormone [49]. Constitutively active receptors, however, were not detected in specimens obtained from prostate cancer patients. The hinge region is important for nuclear translocation. Transcription activation function (TAF-1, amino acids between residues 141 and 338) is located mainly in the N-terminal region but the regulatory sequences are also located in the ligand-binding domain (TAF-2) [49, 70]. The unliganded AR is distributed through the cytoplasm and nucleus and is complexed with heat-shock proteins 90, 70 and 56 that prevent constitutive activation of the receptor. Ligand binding leads to the dissociation of heat-shock proteins and causes a typical conformational change in the ligand-binding domain [52].

AR expression and function in prostate cells

Expression of AR mRNA and protein are regulated differentially in the prostate. Androgen administration leads to a rapid decrease of AR mRNA but it also stabilizes the protein and the net effect is an increased expression of the AR protein [59]. Such regulation is not observed in each target tissue. For example, in bone, AR mRNA is up-regulated by androgens [106]. Besides androgens, different peptides are involved in the regulation of the AR in prostate cells. Substances that increase intracellular cAMP up-regulate activity of the human AR promoter [69]. The AR expression is also up-regulated by 1-α, 25-dihydroxyvitamin D_3 and this up-regulation correlates with the inhibition of tumor cell proliferation [44]. The relationship between AR expression and prostate cancer cell proliferation is very complex and will be discussed later in detail. The AR mRNA and protein expression are inhibited in LNCaP cells by epidermal growth factor (EGF) [37]. Down-regulation of AR protein, but not mRNA was observed after treatment with basic fibroblast growth factor [11]. It is not clear, however, which signaling pathways are utilized by these growth factors to inhibit AR expression. The AR down-regulation in connection with inhibition of tumor proliferation was observed after treatment of prostate cancer cells with conditioned media from activated T lymphocytes and peripheral blood monocytes [16, 43]. While the mediator of effects of T lymphocytes on AR expression has not been identified, we have shown that monocyte-derived interleukin-1β (IL-1β) exhibits negative effects on AR and prostate-specific antigen (PSA) expression as well as on LNCaP cell proliferation [16]. Modulatory effects of monocyte-conditioned media on LNCaP cells were abolished after pretreatment of these supernatants with the anti-IL-1β antibody. An important intracellular event that leads to induction of apoptosis and down-regulation of AR mRNA and protein is an elevation of intracellular calcium levels [11, 32].

By activation of the AR, androgen regulates proliferative and secretory responses in prostate cancer cells as well as the synthesis of prostatic lipids and fatty acid synthase, an enzyme that is overexpressed in several human malignancies [62, 91, 92] (Table 1). Proliferation of LNCaP cells is stimulated at concentrations of dihydrotestosterone (DHT) of 10^{-9} M and lower. The mechanisms responsible for this biphasic regulation are not understood. It has been proposed that transforming growth factor-β (TGF-β) induction by higher androgen doses causes a decrease in growth rate [54].

Recent studies have provided new insights into regulation of prostate cell proliferation by androgens [64,

Table 1 Androgen-regulated genes in the prostate

Gene	Androgens cause	Significance	Reference
EGFR	Stimulation	Proliferation	87
TGF-ß	Repression	Negative growth factor	60
KGF	Stimulation	Stromal-epithelial intractions	23, 108
NEP	Stimulation	Cleavage of neuropeptides	79
ARA 70	Stimulation	Enhancement of AR function	33
CDK 2 and 4	Stimulation	Cell cycle regulation	64
p16	Repression	Cell cycle regulation	64
p21	Stimulation	Anti-apoptotic effect	5, 65
p27	Stimulation	Cell cycle arrest (LNCaP)	57
	Repression	Proliferative effect (MDA PCa)	109
bcl-2	Repression	Pro-apoptotic effect	61
PSA	Stimulation	Differentiation function	62
hGK 2	Stimulation	Differentiation function	72
Fatty acid synthase	Stimulation	Malignant phenotype	92
VEGF	Stimulation	Angiogenesis	25, 50, 63
IGF-BP-5	Stimulation	Potentiation of IGF action	34
IGF-BP-5	Inhibition		75

65, 109]. Androgenic hormones induce the expression of cyclin-dependent kinase (CDK) 2 and 4 and down-regulate the cell cycle inhibitor p16 [64]. A CDK inhibitor that is up-regulated by activation of the AR is p21 (waf1/cip1) [65]. However, it was recently suggested that p21 may have anti-apoptotic properties in prostate cancers in vivo. High expression of p21 was significantly associated with high Gleason score, DNA aneuploidy, high S-phase fraction, expression of Ki-67, bcl-2 and cyclin A and D proteins [1]. The p21 overexpression was found in a subgroup of patients with advanced prostate cancer with a high proliferation rate [5]. Androgenic hormones also down-regulate the expression of the cell survival protein bcl-2 [61]. The AR is implicated in the repression of expression of the TGF-β gene, which is the major negative growth factor in the prostate [60]. It should be mentioned that the stromal AR is activated by androgen to induce expression of the keratinocyte growth factor (KGF) gene, which is essential for signal transduction from stromal to epithelial cells in the prostate [23, 108]. The AR is also important for regulation of expression of the insulin-like growth factor (IGF)-binding protein 5. However, these studies that were carried out in two different tumor models yielded divergent results [33, 34, 75]. The AR is indirectly involved in the regulation of neuropeptide-induced prostate tumor proliferation. The enzyme neutral endopeptidase (NEP) 24.11 which cleaves and inactivates neuropeptides is down-regulated in prostate cancer cells which do not express the AR [79].

Recent studies convincingly demonstrated involvement of androgens in the induction of angiogenesis. Proliferation of endothelial cells rapidly declines after castration in adult rats [25]. Up-regulation of the vascular endothelial growth factor (VEGF) by androgen was shown by several research groups [46, 50, 63].

In contrast to the biphasic regulation of cellular proliferation, prostatic specific-proteins, such as PSA and human glandular kallikrein 2 (hGK 2), are up-regulated by androgenic hormones in a concentration-dependent manner [71, 113]. Prostatic lipids and enzymes involved in their synthesis are also regulated by androgen in a concentration-dependent manner [91, 92].

Alterations of AR function after long-term androgen withdrawal

Cell lines derived from independent laboratories after long-term androgen ablation share some common properties. These cell lines are valuable tools for studying molecular changes during endocrine therapy and prostate cancer progression. During long-term androgen ablation, AR mRNA and protein increase gradually. In transactivation assays, androgen induces reporter gene activity more efficiently in these ablated cells [17, 30, 56]. The AR amplification, which occurs in about one third of the patients with therapy-resistant carcinoma of the prostate, was not observed in any of the sublines developed after androgen ablation in vivo [17, 57]. There are also specific alterations in AR function in individual cell lines generated after long-term withdrawal of androgenic hormones. One of the most important changes is acquisition of agonistic properties of the non-steroidal anti-androgen bicalutamide in LNCaP-abl cells generated in our laboratory [17]. Although reporter gene activity measured in response to bicalutamide alone was lower than that induced by androgens, consistent stimulatory effects on proliferation in vitro and tumor growth in vitro were observed in these androgen-depleted cells. Induction of apoptosis by retinoic acid was delayed in the long-term steroid-deprived cell line compared to parental LNCaP cells [30]. Up-regulation of the AR in ablated cells is, most probably, associated with a selective up-regulation of androgen-responsive genes. One would expect that, in cells that express a hyperactive AR, the PSA gene is up-regulated. However, long-term androgen ablation is obviously associated with progressive dedifferentiation in vitro and thus there is no evidence that PSA expression is enhanced in androgen-ablated sublines [17, 30].

AR structural alterations: implications for endocrine therapy

When grown in steroid-depleted medium, LNCaP cells are stimulated not only by androgens but also by estrogenic and progestagenic steroids and non-steroidal anti-androgens hydroxyflutamide and nilutamide [105]. The AR in LNCaP cells was sequenced and the mutation in the exon H of the AR gene was detected [36, 102]. This mutation leads to an exchange of the wild-type threonine at position 877 to alanine and to an increased binding affinity for estradiol, progesterone, synthetic progestin R5020, progestagenic anti-androgen cyproterone acetate, hydroxyflutamide and nilutamide [103]. The LNCaP AR, in contrast to many mutant ARs found in patients with androgen insensitivity syndromes, binds androgens and its transcriptional activity could be induced by ligands [102]. As with androgen, it was shown that hydroxyflutamide enhances nuclear translocation of the AR and promotes the dissociation of a heat shock protein-receptor complex [104]. Transcriptional activity of the LNCaP AR is upregulated by estrogenic and progestagenic steroids, hydroxyflutamide and nilutamide [102]. Although in the majority of clinical studies a low frequency of AR mutations was reported, there is still an uncertainty as to the percentage of tumor cells bearing mutations. The AR was sequenced in both early prostate cancers and in the therapy-resistant disease [7, 12, 13, 21, 22, 74]. However, in the study by Tilley and associates AR point mutations were detected in 11 out of 25 primary prostate cancers sampled prior to initiation of hormonal therapy [98]. In that patient collective, altogether 15 missense, one nonsense and seven silent mutations were detected. Patients with AR point mutations showed a poor response to subsequent hormonal therapy. Tilley et al. used single-strand conformational polymorphism analysis to detect AR mutations [98]; however, this approach was also used by other investigators [7, 21, 22, 89]. In primary tumors there may be a contamination of samples with benign tissue and mutations may thus remain undetected. In metastatic lesions from human prostate cancer, AR point mutations may occur more frequently than in primary tumors. Point mutations in the AR gene were detected in bone lesions from five out of ten patients examined [94]. Unfortunately, studies on AR structure in metastatic lesions are hampered because of a limited availability of these samples. In prostate cancer, both somatic [12, 74] and germ-line mutations [22] were detected.

In the case of the LNCaP AR, increased activation occurs as a consequence of an increased receptor binding affinity for other steroids and anti-androgens. However, changes in functional activity are not always associated with alterations in binding affinity. The mutant ARs 715val $\rightarrow$ met, 726arg $\rightarrow$ leu and 730val $\rightarrow$ met do not show discernible changes in relative binding affinity but are more efficiently activated by steroid hormones other than androgen [12, 21, 80]. We also demonstrated that the increased transactivation by the mutant receptors did not result from measurable changes in conformation of the liganded receptors [80]. Thus, the mechanism responsible for AR functional alterations in prostate cancer remains elusive.

The results from several laboratories imply that AR point mutations may be relevant to the natural course of the disease and to responsiveness to pharmacological agents. Adrenal androgens and DHT metabolites induce a weak transactivational activity of the wild-type AR but are more potent in the presence of mutated ARs 715val $\rightarrow$ met, 730val $\rightarrow$ met, 874his $\rightarrow$ tyr and 877thr $\rightarrow$ ala [12, 80, 93]. Although the effects of adrenal androgens on proliferation of prostate cells that express mutant ARs have not been assessed, it is likely that the mechanism described contributes to a progressive tumor growth. In addition to adrenal steroids, the effects of estradiol on mutant ARs might also contribute to proliferation of these tumor cells. Estradiol is generated by aromatization of testosterone and has an important role in the pathogenesis of prostate diseases.

Major differences between hydroxyflutamide and bicalutamide have been observed in several functional studies on mutant ARs. Hydroxyflutamide acts as a partial agonist at higher concentrations even with the wild-type AR; it promotes DNA binding of the hormone-receptor complex and enhances reporter gene activity [80, 107]. It should be kept in mind that plasma levels of hydroxyflutamide in prostate cancer patients are in the micromolar range [6]. Enhanced AR activation by hydroxyflutamide is described in the presence of the mutated ARs 715val $\rightarrow$ met, 730 val $\rightarrow$ met, 874 his $\rightarrow$ tyr, 877 thr $\rightarrow$ ser and 877 thr $\rightarrow$ ala [24, 80, 93, 102]. Up until now, there is no evidence of an agonistic effect from bicalutamide with any of the mutated receptors being detected in patient tissue. However, a paradoxical improvement of the clinical status after cessation of bicalutamide from therapeutic protocols has been reported [76, 87, 88]. At present, data on the AR sequence in patients who have experienced a paradoxical response to anti-androgens are lacking; a direct association between the anti-androgen withdrawal syndrome and an AR mutation was reported in Japanese patients who were treated with the progestagenic anti-androgen chlormadinone acetate [90]. Interestingly, in a subgroup of patients who received bicalutamide after flutamide treatment failed, a clinical improvement was observed [51]. The AR mutations were found in five out of 16 patients who received complete androgen blockade with flutamide. Those patients responded to the second-line treatment with bicalutamide [95]. Collectively, these clinical and basic science findings suggest that any of the anti-androgens currently available might contribute to tumor progression. Agonist/antagonist balance of a particular compound might be influenced by structure of AR and by duration of treatment.

Control of AR function by protein kinase activators

Similarly to other steroid receptors, the wild-type AR is involved in cross-talk with the signaling pathways of growth factors, neurotransmitters and peptide hormones. The evidence for AR interaction with other signal transduction cascades is increasing (Table 2). In DU-145 cells transfected with an androgen-inducible reporter gene and an AR expression plasmid, the three polypeptide growth factors, IGF-I, KGF and EGF, activated the AR to different extents in the absence of androgen [14]. Ligand-independent activation of the AR was also reported for substances which directly activate the protein kinase A and C signaling pathways [18, 72, 73, 84]. All these substances were able to potentiate the effects of low concentrations of androgen thus reducing a concentration of steroid needed for a maximal activation of the AR [15]. This type of activation may be particularly important in patients with advanced prostate cancer in which serum levels of androgen are continuously suppressed. The outcome of non-steroidal activation of the AR depends on a cellular and promoter context [19, 83]. Mechanisms responsible for AR activation by protein kinase activators are only partly understood. It seems that multiple signaling pathways are required for AR non-steroidal activation, as evidenced in experiments in which inhibitors of protein kinase pathways were used [40, 73]. The protein kinase A pathway that is activated by substances which increase intracellular cyclic adenosine monophosphate is needed for both steroidal as well as for non-steroidal activation. Administration of a specific protein kinase A inhibitor, PKI, caused a partial inhibition of androgen-induced reporter gene activity whereas it completely abolished the effects of non-steroidal activators. In addition, mitogen-activated protein kinase (MAPK) and protein kinase C pathways are involved in AR activation by interleukin-6 (IL-6) [40]. IL-6 is a pleiotropic cytokine which causes a dose-dependent inhibition of proliferation of LNCaP cells but induces prostate-specific proteins by activation of the AR. These data show that AR activation is not necessarily associated with stimulation of tumor cell proliferation.

In several experimental studies on non-steroidal activation of the AR, anti-androgens showed a consistent inhibitory effect on reporter gene activity [14, 15, 35, 40, 72, 73, 83]. However, in the case of AR activation by the protein kinase C activator phorbol ester (TPA), inability of hydroxyflutamide to efficiently inhibit reporter gene activity was reported [18]. As stated above, frequently anti-androgens are capable of effectively antagonizing non-steroidal activation of the AR. Thus, they differ from several antagonists of the estrogen, progesterone and glucocorticoid receptors which switch to transcriptional agonists in the presence of substances which elevate intracellular cAMP levels [27, 77, 86].

In 1999, new data on non-steroidal modulation of AR signaling have been obtained. In the LAPC-4 prostate cancer xenograft, overexpression of the HER-2/neu receptor tyrosine kinase resulted in ligand-independent tumor growth [10]. The PSA promoter could be induced by HER-2/neu in a ligand-independent and synergistic fashion. Similar activation was observed in LNCaP cells in which it was demonstrated that the MAP kinase pathway is essential for induction of androgen target genes [112]. Hydroxyflutamide blocked the induction of the PSA promoter only incompletely. Non-steroidal stimulation of the AR by MAPK kinase kinase 1 activates apoptosis in prostate cancer [3]. Taken together, the results of these studies show that ligand-independent activation of the AR is implicated in the regulation of proliferation, apoptosis and differentiation. Interestingly, D-type cyclins which were found to induce estrogen receptor activity inhibit AR transcriptional transactivation ability [55].

AR coactivators in prostate cancer

Activity of a steroid receptor in a particular cell line depends not only on the levels of expression of a receptor protein itself, but also on those of coregulatory proteins. Steroid receptors activate transcription of target genes by binding to the hormone response element in promoter regions and formation of the stable form of the preinitiation complex. Receptor cofactors are large nuclear proteins that bridge the receptors to the preinitiation complex. Some steroid receptor coactivators acetylate histones thus leading to the loosening of the structure of nucleosomes and making the DNA more accessible to transcription factors [100]. Interaction of the AR with several steroid receptor coactivators was reported [45]. This interaction usually leads to a ligand-

Table 2 Compounds that activate the androgen receptor (AR) in a ligand-independent and/or synergistic manner. *TR* transfected AR, *EN* endogenous AR, *AA* anti-androgens, *PK* protein kinase

Activator	Activation of	Blockade by	Reference
IGF-I	TR, EN	AA	14
KGF	TR, EN	AA	14
EGF	TR, EN	AA	14, 35
TPA (PKC)	TR	AA (incomplete)	18, 19
Forskolin (PKA)	TR, EN	AA, PK inhibitors	72, 73, 84
db cAMP	TR, EN	AA	15
IL-6	TR, EN	AA, PK inhibitors	40
LHRH	TR	AA	15
Her-2/neu	EN	AA (incomplete), PK inhibitors	10

dependent enhancement of AR activity. The steroid receptor coactivator CREB (cAMP-response element binding protein)-binding protein (CBP) is a limiting factor for regulation of AR activity by the AP-1 complex, which is composed of Fos and Jun oncoproteins [2, 26]. A series of AR coactivators, ARAs, has been discovered: ARA 70, ARA 54, ARA 55, ARA 24 and ARA 160 [28, 41, 42, 53, 110] (Table 3). Initially, it was postulated that ARA 70 is an AR-specific coactivator [110]. However, latter studies revealed interactions between ARA 70 and human estrogen and glucocorticoid receptors [4]. In addition, the magnitude of enhancement of reporter gene activity by ARA 70 differs in various reports [4, 31, 110]. However, Chang's group reported that ARA 70 promotes acquisition of agonistic effects of non-steroidal anti-androgens hydroxyflutamide and bicalutamide and enhances AR activation by estradiol and δ5-androstanediol [67, 68, 111].

The role of ARA 70 in modulation of AR-mediated effects remains elusive. Studies on regulation of expression of ARA 70 in prostate cancers were performed in the human prostate cancer xenograft CWR 22 [33]. ARA 70 is up-regulated by androgens but its level increases when the tumor relapses. One possible explanation for this regulation is that protein kinase activators substitute for androgen in the stimulation of ARA70 gene expression. At present, data on expression of these AR-coregulatory proteins in human prostate cancer are not available. It could be speculated that overexpression of AR coactivators or reduced expression of corepressors leads to a hyperstimulation of an androgen signaling cascade and increased expression of AR-regulated genes. In breast cancer cells, there is development of estrogen receptor hypersensitivity following long-term estradiol deprivation [48]. However, it has been reported that the expression of coactivator SRC-1 does not differ between parental cells and an estrogen-hypersensitive breast cancer subline.

Inhibition of AR expression and function in carcinoma of the prostate

In contrast to breast cancer in which some pure steroid receptor antagonists down-regulate receptor levels, AR down-regulation has not been reported for any of the pharmacological agents currently used for therapy. In vitro down-regulation of the AR by a hammerhead ribozyme was recently achieved [9]. This approach is based on cleavage of the rat AR mRNA at the position 1827/1828. The ribozyme caused a decline of AR immunoreactivity and inhibition of androgen-inducible CAT activity by 70%. Morphologically detectable cellular abnormalities were not observed after application of the ribozyme. Another approach which may be useful in AR inhibition is application of AR antisense oligonucleotides [20]. However, AR has also a profound role in differentiation of prostate cells and therefore much more information from basic science is needed to assess possible effectiveness of this therapy. Therapeutic approaches may also include modulation of expression and function of AR-coregulatory proteins, coactivators and corepressors in carcinoma of the prostate.

Table 3 Regulation of cellular events by androgen receptor coregulatory proteins. *DHT* dihydrotestosterone, *OHF* hydroxyflutamide

Coactivator	Cellular event regulated	Reference
ARA 70	Promotion of agonistic effects of anti-androgens	68
	Stimulation of AR by oestradiol	111
	AR activation by androstanediol	67
ARA 54	Interaction with the LNCaP AR	53
ARA 55	Stimulation of AR by DHT, OHF and oestradiol	28
CBP	Reverses inhbition of AR activity by the AP-1 complex	2, 26

References

1. Aaltomaa S, Lipponen P, Eskelinen M, Ala-Opas M, Kosma VM (1999) Prognostic value and expression of p21 (waf1/cip1) protein in prostate cancer. Prostate 39: 8
2. Aarnisalo P, Palvimo JJ, Janne OA (1998) CREB binding protein in androgen receptor-mediated signaling. Proc Natl Acad Sci USA 95: 2122
3. Abreu-Martin MT, Chari A, Palladino AA, Craft NA, Sawyers CL (1999) Mitogen-activated protein kinase kinase kinase 1 activates androgen receptor-dependent transcription and apoptosis in prostate cancer. Mol Cell Biol 19: 514
4. Alen P, Claessens F, Schoenemakers E, Swinnen JV, Verhoeven G, Rombauts W, Peeters B (1999) Interaction of the putative androgen receptor-specific coactivator ARA70/ELE1 alpha with multiple steroid receptors and identification of an internally deleted ELE1beta isoform. Mol Endocrinol 13: 117
5. Baretton GB, Klenk U, Diebold J, Schmeller N, Lohrs U (1999) Proliferation- and apoptosis-associated factors in advanced prostatic carcinomas before and after androgen deprivation therapy: prognostic significance of p21/WAF1/CIP1 expression. Br J Cancer 80: 546
6. Belanger A, Giasson M, Couture J, Dupont A, Cusan L, Labrie F (1988) Plasma levels of hydroxy-flutamide in patients with prostatic cancer receiving the combined hormonal therapy: an LHRH agonist and flutamide. Prostate 12: 79
7. Castagnaro M, Yandell D, Dockhorn-Dworniczak B, Wolfe H, Poremba C (1993) Androgen receptor gene mutations and p53 gene analysis in advanced prostate cancer. Verh Dtsch Ges Pathol 77: 119
8. Chang CS, Kokontis J, Liao ST (1988) Structural analysis of complementary DNA and amino acid sequences of human and rat androgen receptors. Proc Natl Acad Sci USA 86: 9534
9. Chen S, Song CS, Lavrovsky Y, Bi B, Vellanoweth R, Chatterjee B, Roy AK (1998) Catalytic cleavage of the androgen receptor messenger RNA and functional inhibition of androgen receptor activity by a hammerhead ribozyme. Mol Endocrinol 12: 1558
10. Craft N, Shostak Y, Carey M, Sawyers CL (1999) A mechanism for hormone-independent prostate cancer through modulation of androgen receptor signaling by the HER-2/neu tyrosine kinase. Nat Med 5: 280
11. Cronauer MV, Nessler-Menardi C, Klocker H, Maly K, Hobisch A, Bartsch G, Culig Z (2000) Androgen receptor protein is down-regulated by basic fibroblast growth factor in prostate cancer cells. Br J Cancer 82: 39

12. Culig Z, Hobisch A, Cronauer MV, Cato ACB, Hittmair A, Radmayr C, Eberle J, Bartsch G, Klocker H (1993a) Mutant androgen receptor detected in an advanced stage of prostatic carcinoma is activated by adrenal androgens and progesterone. Mol Endocrinol 7: 1541
13. Culig Z, Klocker H, Eberle J, Kaspar F, Hobisch A, Cronauer MV, Bartsch G (1993b) DNA sequence of the androgen receptor in prostatic tumor cell lines and tissue specimens assessed by means of the polymerase chain reaction. Prostate 22: 11
14. Culig Z, Hobisch A, Cronauer MV, Radmayr C, Trapman J, Hittmair A, Bartsch G, Klocker H (1994) Androgen receptor activation in prostatic tumor cell lines by insulin-like growth factor-I, keratinocyte growth factor, and epidermal growth factor. Cancer Res 54: 5474
15. Culig Z, Hobisch A, Hittmair A, Cronauer MV, Radmayr C, Zhang J, Bartsch G, Klocker H (1997) Synergistic activation of androgen receptor by androgen and luteinizing hormone-releasing hormone in prostatic carcinoma cells Prostate 32: 106
16. Culig Z, Hobisch A, Herold M, Hittmair A, Thurnher M, Eder I, Cronauer MV, Rieser C, Ramoner R, Bartsch G, Klocker H, Konwalinka G (1998) Interleukin-1ß mediates the modulatory effects of monocytes on LNCaP human prostate cancer cells. Br J Cancer 78: 1004
17. Culig Z, Hoffmann J, Erdel M, Eder I, Hobisch A, Hittmair A, Bartsch G, Utermann G, Schneider M, Parczyk K, Klocker H (1999) Switch from antagonist to agonist of the androgen receptor blocker bicalutamide is associated with prostate tumour progression in a new model system. Br J Cancer 81: 242
18. Darne C, Veyssiere G, Jean C (1998) Phorbol ester causes ligand-independent activation of the androgen receptor. Eur J Biochem 256: 541
19. de Ruiter PE, Teuwen R, Trapman J, Dijkema R, Brinkmann AO (1995) Synergism between androgens and protein kinase-C on androgen-regulated gene expression. Mol Cell Endocrinol 110: R1
20. Eder IE, Bartsch G, Klocker H, Culig Z (1998) Downregulation of androgen receptor expression by antisense phosphorothioate oligodeoxynucleotides. Proc Am Assoc Cancer Res 39: 13
21. Elo JP, Kvist L, Leinone K, Isomaa V, Henttu P, Lukkarinen O, Vihko P (1995) Mutated human androgen receptor gene detected in a prostate cancer patient is also activated by estradiol. J Clin Endocrinol Metab 80: 3494
22. Evans BAJ, Harper ME, Daniells CE, Watts CE, Matenhelia S, Green J, Griffiths K (1996) Low incidence of androgen receptor gene mutations in human prostatic tumors using single strand conformation polymorphism analysis. Prostate 28: 162
23. Fasciana C, van der Made AC, Faber PW, Trapman J (1996) Androgen regulation of the rat keratinocyte growth factor (KGF/FGF7) promoter. Biochem Biophys Res Commun 220: 858
24. Fenton MA, Shuster TD, Fertig AM, Taplin ME, Kolvenbag G, Bubley GJ, Balk SP (1997) Functional characterization of mutant androgen receptors from androgen-independent prostate cancer. Clin Cancer Res 3: 1383
25. Franck-Lissbrant I, Haggstrom S, Damber JE, Bergh A (1998) Testosterone stimulates angiogenesis and vascular regrowth in the ventral prostate in castrated adult rats. Endocrinology 139: 451
26. Fronsdal K, Engedal N, Hagsvold T, Saatcioglu F (1998) CREB binding protein is a coactivator for the androgen receptor and mediates cross-talk with AP-1. J Biol Chem 273: 31853
27. Fujimoto N, Katzenellenbogen BS (1994) Alteration in the agonist/antagonist balance of antiestrogens by activation of protein kinase A signaling pathways in breast cancer cells: antiestrogen selectivity and promoter dependence. Mol Endocrinol 8: 296
28. Fujimoto N, Yeh S, Kang HY, Inui S, Chang HC, Mizokami A, Chang C (1999) Cloning and characterization of androgen receptor coactivator, ARA 55 in human prostate. J Biol Chem 274: 8316
29. Gao J, Isaacs JT (1998) Development of an androgen receptor-null model for identifying the initiation site for androgen stimulation of proliferation and suppression of programmed (apoptotic) death of PC-82 human prostate cancer cells. Cancer Res 58: 3299
30. Gao M, Ossowski L, Ferrari AC (1999) Activation of Rb and decline in androgen receptor protein precede retinoic acid-induced apoptosis in androgen-dependent LNCaP cells and their androgen-independent derivative. J Cell Physiol 179: 336
31. Gao T, Brantley K, Bolu E, McPhaul MJ (1999) RFG (ARA70, ELE1) interacts with the human androgen receptor in a ligand-dependent fashion, but functions only weakly as a coactivator in cotransfection assays. Mol Endocrinol 13: 1645
32. Gong Y, Blok LJ, Perry JE, Lindzey JK, Tindall DJ (1995) Calcium regulation of androgen receptor expression in the human prostate cancer cell line LNCaP. Endocrinology 136: 2172
33. Gregory CW, Hamil KG, Kim D, Hall SH, Pretlow TG, Mohler JL, French FS (1998) Androgen receptor expression in androgen-independent prostate cancer is associated with increased expression of androgen-regulated genes. Cancer Res 58: 5718
34. Gregory CW, Kim D, Ye P, D'Ercole AJ, Pretlow TG, Mohler JL, French FS (1999) Androgen receptor up-regulates insulin-like growth factor binding protein-5 (IGFBP-5) expression in a human prostate cancer xenograft. Endocrinology 140: 2372
35. Gupta C, Chandorkar A, Nguyen AP (1996) Activation of androgen receptor in epidermal growth factor modulation of fetal mouse sexual differentiation. Mol Cell Endocrinol 123: 89
36. Harris SE, Rong Z, Harris MA, Lubahn DB (1990) Androgen receptor in human prostate carcinoma LNCaP/Adep cells contains a mutation which alters the specificity of the steroid-dependent transcriptional activation region. Program and Abstracts, 72nd Annual Meeting of the Endocrine Society, Atlanta, Ga., p 93
37. Henttu P, Vihko P (1993) Growth factor regulation of gene expression in the human prostatic carcinoma cell line LNCaP. Cancer Res 53: 1051
38. Hobisch A, Culig Z, Radmayr C, Bartsch G, Klocker H, Hittmair A (1995) Distant metastases from prostatic carcinoma express androgen receptor protein. Cancer Res 55: 3068
39. Hobisch A, Culig Z, Radmayr C, Bartsch G, Klocker H, Hittmair A (1996) Androgen receptor status of lymph node metastases from prostate cancer. Prostate 28: 129
40. Hobisch A, Eder IE, Putz T, Horninger W, Bartsch G, Klocker H, Culig Z (1998) Interleukin-6 regulates prostate-specific protein expression in prostate carcinoma cells by activation of the androgen receptor. Cancer Res 58: 4640
41. Hsiao PW, Chang C (1999) Isolation and characterization of ARA160 as the first androgen receptor N-terminal-associated coactivator in human prostate cells. J Biol Chem 274: 22373
42. Hsiao PW, Lin DL, Nakao R, Chang C (1999) The linkage of Kennedy's neuron disease to ARA24, the first identified androgen receptor polyglutamine region-associated coactivator. J Biol Chem 274: 20229
43. Hsieh TC, Xu W, Chiao JW (1995) Growth regulation and cellular changes during differentiation of human prostatic cancer LNCaP cells as induced by T lymphocyte-conditioned medium. Exp Cell Res 218: 137
44. Hsieh TY, Ng CY, Mallouh C, Tazaki H, Wu JM (1996) Regulation of growth, PSA/PAP and androgen receptor expression by 1 alpha,25-dihydroxyvitamin D3 in the androgen-dependent LNCaP cells. Biochem Biophys Res Commun 223: 141
45. Ikonen T, Palvimo JJ, Jänne OA (1997) Interaction between the amino- and carboxyl-terminal regions of the rat androgen receptor modulates transcriptional activity and is influenced by nuclear receptor coactivators. J Biol Chem 272: 29821

46. Jain RK, Safabaksh N, Sckell A, Chen Y, Jiang P, Benjamin L, Yuan F, Keshet E (1998) Endothelial cell death, angiogenesis, and microvascular function after castration in and androgen-dependent tumor: role of vascular endothelial growth factor. Proc Natl Acad Sci USA 95: 10820
47. Jarrard DF, Kinoshita H, Shi Y, Sandefur C, Hoff D, Meisner LF, Chang C, Herman JG, Isaacs WB, Nassif N (1998) Methylation of the androgen receptor promoter CpG island is associated with loss of androgen receptor expression in prostate cancer cells. Cancer Res 58: 5310
48. Jeng M-H, Shupnik MA, Bender TP, Westin EH, Badyopadhyay D, Kumar R, Masamura S, Santen RJ (1998) Estrogen receptor expression and function in long-term estrogen-deprived human breast cancer cells. Endocrinology 139: 4164
49. Jenster G, van der Korput HA, van Vroonhoven C, van der Kwast TH, Trapman J, Brinkmann AO (1991) Domains of the human androgen receptor involved in steroid binding, transcriptional activation, and subcellular localization. Mol Endocrinol 5: 1396
50. Joseph IB, Nelson JB, Denmeade SR, Isaacs JT (1997) Androgens regulate vascular endothelial growth factor content in normal and malignant prostatic tissue. Clin Cancer Res 3: 2507
51. Joyce R, Fenton MA, Rode P, Constantine M, Gaynes L, Kolvenbag G, De Wolf W, Balk S, Taplin ME, Bubley GJ (1998) High dose bicalutamide for androgen independent prostate cancer: effect of prior hormonal therapy. J Urol 159: 149
52. Kallio PJ, Jänne OA, Palvimo JJ (1994) Agonists, but not antagonists, alter the conformation of the hormone-binding domain of androgen receptor. Endocrinology 134: 998
53. Kang HY, Yeh S, Fujimoto N, Chang C (1999) Cloning and characterization of human prostate coactivator ARA 54, a novel protein that associates with the androgen receptor J Biol Chem 274: 8570
54. Kim IY, Kim JH, Zelner DJ, Ahn HJ, Sensibar JA, Lee C (1996) Transforming growth factor-beta1 is a mediator of androgen-regulated growth arrest in an androgen-responsive prostatic cancer cell line, LNCaP. Endocrinology 137: 991
55. Knudsen KE, Cavenee WK, Arden KC (1999) D-type cyclins complex with the androgen receptor and inhibit its transcriptional transactivation ability. Cancer Res 59: 2297
56. Kokontis J, Takakura K, Hay N, Liao S (1994) Increased androgen receptor activity and altered c-myc expression in prostate cancer cells after long-term androgen deprivation. Cancer Res 54: 1566
57. Kokontis JM, Hay N, Liao S (1998) Progression of LNCaP prostate tumor cells during androgen deprivation: hormone-independent growth, repression of proliferation by androgen, and role for p27Kip1 in androgen-induced cell cycle arrest. Mol Endocrinol 12: 941
58. Krijnen JL, Janssen PJ, Ruizeveld de Winter JA, van Krimpen H, Schroder FH, van der Kwast TH (1993) Do neuroendocrine cells in human prostate express androgen receptor? Histochemistry 100: 393
59. Krongrad A, Wilson CM, Wilson JD, Allman DR, McPhaul MJ (1991) Androgen increases androgen receptor protein while decreasing receptor mRNA in LNCaP cells. Mol Cell Endocrinol 76: 79
60. Kyprianou N, Isaacs JT (1990) Expression of transforming growth factor-beta in the rat ventral prostate during castration-induced programmed cell death. Mol Endocrinol 3: 1515
61. Lapointe J, Fournier A, Richard V, Labrie C (1999) Androgens down-regulate bcl-2 protooncogene expression in ZR-75–1 human breast cancer cells. Endocrinology 140: 416
62. Lee C, Sutkowski DM, Sensibar JA, Zelner D, Kim I, Amsel I, Shaw N, Prins GS, Kozlowski JM (1995) Regulation of proliferation and production of prostate-specific antigen in androgen-sensitive prostatic cancer cells, LNCaP, by dihydrotestosterone. Endocrinology 136: 796
63. Levine AC, Liu XH, Greenberg PD, Eliashvili M, Schiff JD, Aaronson SA, Holland JF, Kirschenbaum A (1998) Androgens induce the expression of vascular endothelial growth factor in human fetal prostatic fibroblasts. Endocrinology 139: 4672
64. Lu S, Tsai SY, Tsai MJ (1997) Regulation of androgen-dependent prostatic cancer cell growth: androgen regulation of CDK2, CDK4, and CKI p16 genes. Cancer Res 57: 4511
65. Lu S, Liu M, Epner DE, Tsai SY, Tsai MJ (1999) Androgen regulation of the cyclin-dependent kinase inhibitor p21 gene through an androgen response element in the proximal promoter. Mol Endocrinol 13: 376
66. Lubahn DB, Joseph DR, Sar M, Tan J, Higgs HN, Larson RE, French FS, Wilson EM (1988) The human androgen receptor: complementary deoxyribonucleic acid and cloning, sequence analysis and gene expression in prostate. Mol Endocrinol 2: 1265
67. Miyamoto H, Yeh S, Lardy H, Messing E, Chang C (1998a) Delta 5-androstanediol is a natural hormone with androgenic activity in human prostate cancer cells. Proc Natl Acad Sci USA 95: 11083
68. Miyamoto H, Yeh S, Wilding G, Chang C (1998b) Promotion of agonist activity of antiandrogens by the androgen receptor coactivator, ARA70, in human prostate cancer DU145 cells. Proc Natl Acad Sci USA 95: 7379
69. Mizokami A, Yeh SY, Chang C (1994) Identification of 3′5′-cyclic adenosine monophosphate response element and other cis-acting elements in the human androgen receptor gene promoter. Mol Endocrinol 8: 77
70. Moilanen A, Rouleau N, Ikonen T, Palvimo JJ, Jänne OA (1997) The presence of a transcription activation function in the hormone-binding domain of androgen receptor is revealed by studies in yeast cells. FEBS Lett 412: 355
71. Murtha P, Tindall DJ, Young CY (1993) Androgen induction of a human prostate-specific kallikrein, hKLK2: characterization of an androgen response element in the 5′ promoter region of the gene. Biochemistry 32: 6459
72. Nakhla AM, Romas NA, Rosner W (1997) Estradiol activates the prostate androgen receptor and prostate-specific antigen secretion through the intermediacy of sex hormone-binding globulin. J Biol Chem 272: 6838
73. Nazareth LV, Weigel NL (1996) Activation of the human androgen receptor through a protein kinase A signaling pathway. J Biol Chem 271: 19900
74. Newmark JR, Hardy DO, Tonb DC, et al (1992): Androgen receptor gene mutations in human prostate cancer. Proc Natl Acad Sci USA 89: 6319
75. Nickerson T, Miyake H, Gleave ME, Pollak M (1999) Castration-induced apoptosis of androgen-dependent Shionogi carcinoma is associated with increased expression of genes encoding insulin-like growth factor-binding proteins. Cancer Res 59: 3392
76. Nieh PT (1995) Withdrawal phenomenon with the antiandrogen casodex. J Urol 153: 1070
77. Nordeen SK, Bona BJ, Moyer ML (1993) Latent agonistic activity of the steroid antagonist, RU 486, is unmasked in cells treated with activators of protein kinase A. Mol Endocrinol 7: 731
78. Olapade-Olaopa EO, MacKay EH, Taub NA, Sandhu DP, Terry TR, Habib FK (1999) Malignant transformation of human prostatic epithelium is associated with the loss of androgen receptor immunoreactivity in the surrounding stroma. Clin Cancer Res 5: 569
79. Papandreou CN, Usmani B, Geng Y, Finstad CL, Reuter VE, Powell CT, Scheingerg D, Magill C, Scher HI, Albino AP, Namus DM (1998) Neutral endopeptidase 24.11 loss in metastatic human prostate cancer contributes to androgen-independent progression. Nat Med 4: 50
80. Peterziel H, Culig Z, Stober J, Hobisch A, Radmayr C, Bartsch G, Klocker H, Cato ACB (1995) Mutant androgen receptors in prostatic tumors distinguish between amino-acid-

sequence requirements for transactivation and ligand binding Int J Cancer 63: 544
81. Qigley CA, de Bellis A, Marschke KB, elAwady MK, Wilson EM, French FS (1995) Androgen receptor defects: historical, clinical, and molecular perspectives. Endocr Rev 16: 271
82. Quarmby VE, Beckman WCJ, Cooke DB, Lubahn DB, Joseph DR, Wilson EM, French FS (1990) Expression and localization of androgen receptor in the R-3327 Dunning rat prostatic adenocarcinoma. Cancer Res 50: 735
83. Reinikainen P, Palvimo JJ, Janne OA (1996) Effects of mitogens on androgen receptor-mediated transactivation. Endocrinology 137: 4351
84. Sadar MD (1999) Androgen-independent induction of prostate-specific antigen gene expression via cross-talk between the androgen receptor and protein kinase A signal transduction pathways. J Biol Chem 274: 7777
85. Sadi MV, Walsh PC, Barrack ER (1991) Immunohistochemical study of androgen receptors in metastatic prostate cancer-comparison of receptor content and response to hormonal therapy. Cancer 67: 3057
86. Sartorius CA, Tung T, Takimoto GS, Horwitz KB (1993) Antagonist-occupied human progesterone receptors bound to DNA are functionally switched to transcriptional agonists by cAMP. J Biol Chem 268: 9262
87. Schuurmans AL, Bolt J, Veldscholte J, Mulder E (1990) Stimulatory effects of antiandrogens on LNCaP human prostate tumor cell growth, EGF-receptor level and acid phosphatase secretion. J Steroid Biochem Mol Biol 37: 849
88. Small EJ, Carroll PR (1994) Prostate-specific antigen decline after casodex withdrawal: evidence for an antiandrogen withdrawal syndrome. Urology 43: 408
89. Suzuki H, Sato N, Watabe Y, Masai M, Seino S, Shimazaki J (1993) Androgen receptor gene mutations in human prostate cancer. J Steroid Biochem Mol Biol 46: 759
90. Suzuki H, Akakura K, Komiya A, Aida S, Akimoto S, Shimazaki J (1996) Codon 877 mutation in the androgen receptor gene in advanced prostate cancer: Relation to antiandrogen withdrawal syndrome. Prostate 29: 153
91. Swinnen JV, van Veldhoven PP, Esquenet M, Heyns W, Verhoeven G (1996) Androgens markedly stimulate the accumulation of neutral lipids in the human prostatic adenocarcinoma cell line LNCaP. Endocrinology 137: 4468
92. Swinnen JV, Esquenet M, Goossens K, Heyns W, Verhoeven G (1997) Androgens stimulate fatty acid synthase in the human prostate cancer cell line LNCaP. Cancer Res 57: 1086
93. Tan J, Sharief Y, Hamil KG, Gregory CW, Zang DY, Sar M, Gumerlock PH, deVereWhite RW, Pretlow TG, Harris SE, Wilson EM, Mohler JL, French FS (1997) Dehydroepiandrosterone activates mutant androgen receptors expressed in the androgen-dependent human prostate cancer xenograft CWR22 and LNCaP cells. Mol Endocrinol 11: 450
94. Taplin ME, Bubley GJ, Shuster TD, Frantz ME, Spooner AE, Ogata GK, Keer HN, Balk SP (1995) Mutation of the androgen receptor gene in metastatic androgen-independent prostate cancer. New Engl J Med 332: 1393
95. Taplin ME, Bubley GJ, Ko YJ, Small EJ, Upton M, Rajeshkumar B, Balk SP (1999) Selection for androgen receptor mutations in prostate cancers treated with androgen antagonist. Cancer Res 59: 2511
96. Tilley WD, Marcelli M, Wilson JD, McPhaul MJ (1989) Characterization and expression of a cDNA encoding the human androgen receptor. Proc Natl Acad Sci USA 86: 321
97. Tilley WD, Wilson CM, Marcelli M, McPhaul MJ (1990) Androgen receptor gene expression in human prostate carcinoma cell lines. Cancer Res 50: 5382
98. Tilley WD, Buchanan G, Hickey TE, Bentel JM (1996) Mutations in the androgen receptor gene are associated with progression of human prostate cancer to androgen independence. Clin Cancer Res 2: 277
99. Trapman J, Klaassen P, Kuiper GG, van der Korput JA, Faber PW, van Rooij HC, Geurts van Kessel A, Voorhorst MM, Mulder E (1988) Cloning, structure and expression of a cDNA encoding the human androgen receptor. Biochem Biophys Res Commun 153: 241
100. Tsukiyama T, Wu C (1997) Chromatin remodeling and transcription. Genes Dev 7: 182
101. Van der Kwast TH, Schalken J, Ruizeveld de Winter JA, van Vroonhoven CCJ, Mulder E, Boersma W, Trapman J (1991) Androgen receptors in endocrine-therapy-resistant human prostate cancer. Int J Cancer 48: 189
102. Veldscholte J, Ris-Stalpers C, Kuiper GGJM, Jenster G, Berrevoets C, Claassen E, van Rooij HCJ, Trapman J, Brinkmann AO (1990a) A mutation in the ligand binding domain of the androgen receptor of human LNCaP cells affects steroid binding characteristics and response to antiandrogens. Biochem Biophys Res Commun 17: 534
103. Veldscholte J, Voorhost-Ogink MM, Bolt-de Vries J, van Rooij HC, Trapman J, Mulder E (1990b) Unusual specificity of the androgen receptor in the human prostate tumor cell line LNCaP: high affinity for progestagenic and estrogenic steroids. Biochim Biophys Acta 1052: 187
104. Veldscholte J, Berrevoets CA, Zegers ND, van der Kwast TH, Grootgoed JA, Mulder E (1992) Hormone-induced dissociation of the androgen receptor-heat-shock protein complex: Use of a new monoclonal antibody to distinguish transformed from nontransformed receptors. Biochemistry 31: 7422
105. Wilding G, Chen M, Gelmann EP (1989) Aberrant response in vitro of hormone-responsive prostate cancer cells to antiandrogens. Prostate 14: 103
106. Wiren KM, Zhang X, Chang C, Keenan E, Orwoll ES (1997) Transcriptional up-regulation of the human androgen receptor by androgen in bone cells. Endocrinology 138: 2291
107. Wong CI, Kelce WR, Sar M, Wilson EM (1995) Androgen receptor antagonist versus agonist activities of the fungicide vinclozolin relative to hydroxyflutamide. J Biol Chem 270: 19998
108. Yan G, Fukabori Y, Nikolaropoulos S, Wang F, McKeehan WL (1992) Heparin-binding keratinocyte growth factor is a candidate stromal-to-epithelial-cell andromedin. Mol Endocrinol 6: 2123
109. Ye D, Mendelsohn J, Fan Z (1999) Androgen and epidermal growth factor down-regulate cyclin-dependent kinase inhibitor p27kip1 and costimulate proliferation of MDA PCa 2a and MDA PCa 2b prostate cancer cells. Clin Cancer Res 5: 2171
110. Yeh S, Chang C (1996) Cloning and characterization of a specific coactivator, ARA70, for the androgen receptor in human prostate cells. Proc Natl Acad Sci USA 93: 5517
111. Yeh S, Miyamoto H, Shima H, Chang C (1998) From estrogen to androgen receptors: a new pathway for sex hormones in prostate. Proc Natl Acad Sci USA 95: 5527
112. Yeh S, Lin HK, Kang HY, Thin TH, Lin MF, Chang C (1999) From HER2/Neu signal cascade to androgen receptor and its coactivators: a novel pathway by induction of androgen target genes through MAP kinase in prostate cancer cells. Proc Natl Acad Sci USA 96: 5458
113. Young CYF, Montgomery BT, Andrews PE, Qiu S, Bilhartz DL, Tindall DJ (1991) Hormonal regulation of prostate-specific antigen messenger RNA in human prostatic adenocarcinoma cell line LNCaP. Cancer Res 51: 3748