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Expression and function of androgen receptor coactivators in prostate cancer

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Abstract

Human androgen receptor (AR) associates with coactivator or corepressor proteins that modulate its activation in the presence of ligand. Early studies on AR coactivators in carcinoma of the prostate were hampered because of lack of respective antibodies. Investigations at mRNA level revealed that most benign and malignant prostate cells express common coactivators. AR coactivators SRC-1 and TIF-2 are up-regulated in tissue specimens obtained from patients who failed prostate cancer endocrine therapy. Increased expression of these coactivators is associated with enhanced activation of the AR by the adrenal androgen dehydroepiandrosterone. Similar association between AR coactivator expression and high prostate cancer grade and stage was reported for RAC-3 (SRC-3). The transcriptional integrator CBP was detected in clinical specimens representing organ-confined prostate cancer, lymph node metastases and tumour cell lines. Agonistic effect of the nonsteroidal antiandrogen hydroxyflutamide was strongly potentiated in prostate cells transfected with CBP cDNA. A functional homologue of CBP, p300, is implicated in ligand-independent AR activation by interleukin-6. The AR coactivator Tip60, which is up-regulated by androgen ablation, is recruited to the promoter of the prostate-specific antigen gene in the absence of androgen in androgen-independent prostate cancer sublines. It was proposed that the cofactor ARA70 is a specific enhancer of AR action. However, research from other laboratories has demonstrated interaction between ARA70 and other steroid receptors. Although in some cases dominant-negative coactivator mutants inhibited proliferation of prostate cancer cells in vitro, confirmation from in vivo tumour models is missing. In summary, several abnormalities in AR coactivator expression and function are associated with prostate cancer progression.

Keywords: Androgen receptor; Coactivator; Prostate cancer; Androgen ablation; Protein-protein interaction

1. Introduction

Differences in induction of steroid receptor activity in various cell lines led to the conclusion that, in addition to composition or concentration of serum, there must be cell-specific factors that influence outcome of receptor activation. Nuclear receptors compete for a limited number of transcription factors for activation or repression of specific target genes. Various in vitro and in vivo techniques have been applied to identify nuclear receptor-associated cofactors. Most frequently, yeast two-hybrid assay has been used.

A well-characterized group of coactivators is the p160 family of proteins to which SRC-1, TIF2 and AIB1 protein belong. p160 coactivators interact with both N-(harbours activation function (AF)-1) and C-terminal region (site of AF-2) of the androgen receptor (AR). The coactivator p300 and its functional homologue CBP are transcriptional integrators that may be important for cross-talk with other signaling pathways. There are two major mechanisms by which coactivators modulate functional activity of steroid receptors. p300/CBP, which is a class I coactivator, bridges the transcriptional machinery to nuclear receptors. Class II coactivators, such as p160 proteins, modify chromatin structure through the histone acetyltransferase or ATP-dependent chromatin remodeling activity [1]. SRC coactivators are characterized by NH_2-terminal tandem basic helix–loop–helix and PAS (Per/Arnt/Sim homology) domains, contain three LXXLL motifs in the central portion of the protein and carry a COOH-terminal glutamine-rich region [1]. PIAS (protein inhibitor of activated signal transducer and activator or transcription, STAT) proteins influence the DNA-binding ability

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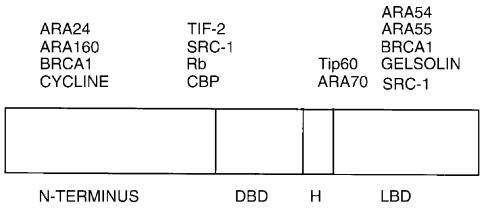

Fig. 1. AR domains implicated in specific interactions with coactivator proteins (DBD, DNA-binding domain; H, hinge region; LBD, ligand-binding domain).

of the STAT transcription factors, a characteristic feature of type I coregulators. PIAS 1 and PIAS 3 are known to enhance transcriptional activity of the AR. An important issue that should be considered in studies with AR coregulators is an interference of some apparent coactivator expression vectors with receptor expression [2]. Therefore, appropriate controls should be included in these experiments to avoid misclassification of AR-interacting proteins. Coactivators from the p160 and p300/CBP protein families are recruited after binding of receptor dimers to the regulatory regions of hormone responsive genes. Interestingly, p300 is recruited to hormone regulatory elements through its interaction with p160 proteins. After coactivator recruitment, the levels of histone acetylation within the promoter region increase. Histone acetylation weakens their interactions with the DNA. This step is followed by an exchange of coactivators at the AF-2 surface of the ligand-binding domain of receptors, recruitment of the RNA polymerase II holoenzyme and the SWI/SNF multiprotein chromatin remodeling complex to the promoter in order to allow binding of the basal transcriptional machinery to the DNA template [3].

This review focuses on specific aspects of coactivator action in prostate cancer. Detailed overview of basic aspects of interaction between the AR and coactivators was published elsewhere [1]. AR domains that interact with frequently studied coactivators are depicted in Fig. 1.

Previous research has revealed a role for the AR in advanced carcinoma of the prostate. In contrast to some animal and human prostate cancer cell lines that lack AR expression, the receptor protein is expressed in most carcinoma specimens. Because of point mutations and receptor interaction with signaling pathways of cytokines and peptide hormones, AR activation may increase in therapy-resistant prostate cancer [4]. Better understanding of action of AR-associated proteins may thus facilitate development of new experimental therapies in prostate cancer.

2. General aspects of coactivator research in prostate cancer

Earlier studies on AR coactivators in prostate cancer applied PCR technology to examine contribution of individual coactivators to prostate cancer development and progression. However, little is known about regulation of expression of coactivators in prostate tissue by steroid and peptide hormones. Data obtained in PCR studies are not necessarily representative of protein expression in prostate cancer tissue and those studies could be regarded as the first step in understanding action of cofactors in the prostate. PCR studies confirmed expression of most cofactors in the vast majority of cultured prostate cells [5]. Coactivators' mRNA was detectable in epithelial and stromal primary cell cultures and established cell lines in the prostate. Antibodies for detection of cofactors by Western blot or immunohistochemistry have become available and a number of research studies that report correlation between coactivator expression and various clinical and pathological parameters has increased. Another approach in coactivator research in prostate cancer is based on transient expression of cofactors in prostate cancer cells. In such experiments, the issue of contribution of cofactors to acquisition of agonistic properties of antiandrogenic drugs is frequently addressed. Stable expression of cofactors in prostate cancer cells is a more sophisticated way to investigate their influence on regulation of proliferation and apoptosis. However, there are also difficulties with stable transfection of some prostate cells and amount of data generated by this approach is rather limited.

3. p160 coactivators in carcinoma of the prostate

One of the most frequently investigated cofactors in various diseases is SRC-1. In breast cancer, SRC-1 contributes to acquisition of agonistic properties of the oestrogen receptor antagonist tamoxifen [6]. In prostate cancer samples obtained from patients who failed endocrine therapy, expression of SRC-1 was more intense than in those from patients with benign prostate hyperplasia or androgen-dependent carcinoma of the prostate, as judged by immunohistochemistry or immunoblot [7]. In samples obtained from relapsed tumours, there was a more prominent up-regulation of the cofactor TIF2. Most interestingly, the expression of TIF2 and SRC-1 in the prostate cancer xenograft CWR22 decreased after castration and increased at the time of tumour relapse. Although there is no specific information on contribution of TIF2 or SRC-1 to activation of the AR by receptor antagonists, these data indicate importance of the two p160 coactivators in progression of prostate cancer. In tumour cells that overexpress SRC-1 and TIF2, higher AR activities were measured after treatment with adrenal androgens. In addition to previously described increased activation of the mutated AR by adrenal steroids dehydroepiandrosterone and androstenedione, this might be another mechanism relevant to accelerated tumour growth in the presence of adrenal androgens. Function of SRC-1 in androgen-induced transactivation was also studied with a mutated AR with the substitution of tyrosine for cysteine at codon 619. This mutant is transcriptionally inactive and colocalizes with SRC-1 in aggregates in the nucleus and cytoplasm [8]. Although most studies on AR mutations in prostate cancer led to detection of receptors showing a gain

of function, more recent work revealed a lack of function of some mutated AR. Thus, alterations of localization of SRC-1 may be relevant in a subgroup of prostate cancer patients.

Expression of the p160 coactivator RAC3 (SRC-3) was studied in prostate carcinoma. Its expression is higher in LNCaP than in PC-3 or DU-145 prostate cancer cells [9]. RAC3 mRNA and protein expression in prostate cancer cells correlate with tumour grade and stage. Notably, increased RAC3 expression is associated with poor patients' survival. Recent results indicate that overexpression of RAC3 leads to steroid-independent activation of the survival Akt pathway [10]. p160 coactivators also interact with several other coactivators and thus enhance AR activity.

4. The role of transcriptional integrators p300 and CBP in malignant prostate disease

p300 and its functional homologue cAMP-response element-binding protein (CREB)-binding protein (CBP) enhance ligand-dependent activation of the AR, although in vitro interaction between the coactivators and the receptor is not altered upon ligand binding. Transcriptional interference between the AR and activator protein-1 complex may be explained by competition for limiting amounts of CBP in cells [11]. AR expression is not altered in cells transfected with CBP cDNA and treated with androgen. Recent study highlighted the importance of p300 in ligand-independent AR activation by interleukin-6 (IL-6) [12]. IL-6 activation of the AR is of interest in prostate cancer because of several reasons [13]. High levels of IL-6 were measured in organ-confined prostate cancer and in sera from patients with metastatic prostate tumour [14,15]. IL-6 receptor, that is also elevated in localized prostate cancer, is composed of the ligand-binding subunit gp80 and the signal-transducing subunit gp130 [14]. Other cytokines of IL-6 family, such as oncostatin M or leukemia inhibitory factor also transmit the signal through the gp130 subunit. IL-6 differentially activates signaling pathway of Janus kinase (JAK)/STAT factors, mitogen-activated protein kinase or phosphatidylinositol 3-kinase in target tissues. This is a basis for its divergent effects in various cell lines. In prostate cancer, stimulatory effects of IL-6 on tumour growth were demonstrated in DU-145 and PC-3 cells, which secrete high cytokine levels into the supernatants [16]. In contrast, parental LNCaP cells do not express IL-6 mRNA and protein. There might be several explanations for down-regulation of IL-6 in LNCaP cells. It is known that androgenic and oestrogenic steroids inhibit IL-6 expression by activation of steroid receptors [17]. The IL-6 gene is repressed by the tumour suppressor retinoblastoma (pRb) [18]. Regulation of growth of LNCaP cells by exogenous IL-6 is a controversial issue. In the authors' laboratory, IL-6 inhibited LNCaP proliferation [13]. However, after prolonged treatment with the cytokine a novel subline of LNCaP cells that acquires a growth advantage in vitro and in vivo was generated [19]. We showed that loss of growth-inhibitory response to exogenous IL-6 is associated with distinct alterations in cell cycle distribution [20]. In the LNCaP-IL-6+ subline, there was a higher expression of cyclin-dependent kinase 2 and loss of p27 and pRb. Interestingly, prolonged treatment with IL-6 in LNCaP cells leads to up-regulation of endogenous IL-6 mRNA and protein. Although the signaling pathway of JAK/STAT3 is relevant to malignant transformation in a variety of human cancers, our studies revealed activation of STAT3 in association with induction of growth arrest and differentiation by IL-6 in parental cells or in a control subline passaged in the absence of IL-6. Tyrosine phoshporylation of STAT3 was not observed in the LNCaP-IL-6+ subline. Instead, cells proliferation was partially inhibited by administration of the inhibitor of MAPK kinase PD 98059.

Activation of the AR by IL-6 was demonstrated in cells transfected with AR cDNA as well as in those that express endogenous receptor. As mentioned before, growth arrest caused by IL-6 is in LNCaP cells associated with AR-mediated induction of prostate-specific antigen [13]. These findings strongly suggest importance of cross-talk between IL-6 and the AR for promotion of differentiation of prostate cancer cells. Debes and associates demostrated that IL-6 activation of the AR is mediated by p300. Overexpression of p300 abrogated inhibition of the AR activation by PD 98059 [12]. Other laboratories provided evidence that signalling pathways of JAK/STAT and protein kinase A and C are also implicated in ligand-independent activation by IL-6 [21]. In addition, IL-6-induced AR activity was suppressed by co-transfection with E1A, a protein which sequesters p300 thus inhibiting its histone acetyltransferase activity. The crucial role of p300 in ligand-independent activation of the AR was confirmed when p300 levels were down-regulated by siRNA. That experimental approach resulted in inhibition of IL-6-induced prostate-specific antigen (PSA) expression. In addition to p300, IL-6-induced activation of the AR is also enhanced by SRC-1, which is phosphorylated by MAPK after IL-6 treatment [22].

The role of the p300 functional homologue CBP in prostate cancer was addressed in studies in which this coactivator was overexpressed in DU-145 and LNCaP cells [23]. Those studies revealed that CBP potentiates AR activation after treatment with androgen or hydroxyflutamide whereas the effect on enhancement of AR activity by the antiandrogen bicalutamide was either modest (DU-145) or absent (LNCaP). In some patients, flutamide withdrawal or second-line therapy with bicalutamide caused a temporary improvement in their clinical status [24]. On the basis of results obtained after transient overexpression of CBP, one could expect that alterations in expression or recruitment of one or more coactivators are critical for outcome of antiandrogen treatment. CBP is expressed in most organ-confined prostate cancers and in lymph node metastases [23]. Its expression in advanced prostate cancer and regulation by steroid and peptide hormones should be addressed in the future. Taken together, data obtained in studies on p300 and CBP revealed that these structurally similar coactivators are important for regulation

of antagonist/agonist balance of commonly used AR antagonists and nonsteroidal activation of the AR.

5. Tip60 in prostate malignancy

Tip60, a cofactor that directly acetylates the AR, belongs to the MYST protein family and shuttles between cytoplasm and nucleus in response to various peptides [25]. Expression and recruitment of Tip60 were thoroughly studied in prostate cancer clinical samples and experimental models [26]. Tip60 was expressed in all benign tissues studied and the expression in carcinomatous tissue was heterogenous. Some samples showed no Tip60 immunoreactivity whereas in others the coactivator was detected in either nuclei or cytoplasm. Expression of Tip60 correlated inversely with presence of metastasis. Most interestingly, majority of samples obtained from patients with hormone-resistant carcinoma of the prostate showed a strong nuclear immunoreaction. These results are further supported by data obtained with the xenograft CWR22 in which castration resulted in a gradual increase in the coactivator nuclear levels. In addition, in vitro studies with LNCaP or transfected COS cells yielded similar results.

Tip60 function in prostate cancer is altered as revealed in chromatin immunoprecipitation experiments. In parental LNCaP cells, presence of androgen is required for recruitment of Tip60 to the PSA gene promoter. In contrast, in androgen-independent LNCaP sublines Tip60 was recruited to the promoter even in the absence of androgen. Those experiments may provide a mechanistic explanation why AR-regulated genes become expressed when a tumour relapses. Prostate cancer cell sublines developed after androgen ablation represent a clinically relevant model for studies on prostate cancer progression and mimic the conditions in patients. In most of them, AR expression and activity are upregulated and, in some cases, agonistic effects of nonsteroidal AR antagonists are enhanced.

6. Specificity of androgen receptor coactivators

The role of the first AR coactivator discovered, ARA70, has been extensively investigated in carcinoma of the prostate. In 1996, Yeh and Chang postulated that ARA70 (also called RFG or ELE1) interacts specifically with the AR but not with other steroid receptors [27]. They also provided evidence that ARA70 enhances AR activation in the presence of antiandrogens, oestradiol, delta5-androstanediol, or the epidermal growth factor receptor-related molecule HER-2/neu [28–31]. There was no major difference in the extent of coactivation between the antiandrogens hydroxyflutamide and bicalutamide. AR protein stability is also enhanced by ARA70. Increased activation of the AR by oestrogen in the presence of ARA70 may be of interest because of the role of oestrogen receptor (ER)-β in prostate disease. ER-β is, in contrast to ER-α, expressed predominantly in prostate epithelium. It is differentially expressed during prostate carcinogenesis at it could be of interest to determine whether it colocalizes with ARA70 in clinical specimens [32]. Expression of ARA70 in the CWR22 model of relapsed prostate cancer paralled that of other AR-regulated genes; it decreased immediately after androgen deprivation and became elevated during tumour progression [33]. Tekur et al. [34] demonstrated androgenic up-regulation of ARA70 and their results were supported by studies demonstrating down-regulation of ARA70 by the chemopreventive agent resveratrol [35]. Although transient transfection studies suggested involvement of ARA70 in various activation processes, these results do not necessarily mean that the coactivator's effect is proliferative or antiapoptotic. Stable expression of ARA70 cDNA in LNCaP cells yielded inhibition of tumour growth and colony formation [36]. Therefore, the possibility that ARA70 is, in fact, prostate tumour suppressor, deserves further investigation.

In a model of autochthonous mouse prostate cancer (TRAMP), AR mutations were discovered and interactions of these mutants with ARA70 were studied. In comparison with the wild-type AR, activity of the mutated receptor E231G but not K638M or T857A was induced two-fold more strongly by oestradiol in the presence of ARA70 [37].

Although there is no doubt that ARA70 interacts with the AR, its specificity was questioned in subsequent studies. Other investigators demonstrated that this protein potentiates transcriptional activity of the progesterone and glucocorticoid receptors as well [38,39]. In addition, coactivation of the AR by ARA70 was only minor. Thus, the role of ARA70 as a specific AR coactivator has not been confirmed.

The coactivator ARA55 consists of 444 amino acids and has a high homology with hic5, gene induced by transforming growth factor-β [40]. ARA55 potentiates AR activity in the presence of androgen, oestradiol and hydroxyflutamide by interaction with the C-terminal of the AR. Coactivators ARA55 and FHL2 are LIM domain proteins. LIM domains are cysteine- and histidine-rich regions that mediate protein–protein interactions. Interestingly, ARA55 is expressed in AR-negative PC-3 cells, but not in LNCaP or DU-145 cells. This finding implies that ARA55 may also interact with other signaling pathways in prostate cancer cells. In clinical specimens, ARA55 was localized to prostate stroma [36]. Induction of activity of glucocorticoid and progesterone receptors by ARA55 was also reported.

ARA54 is a coactivator of 474 amino acids with a molecular mass of 54 kDa which particularly enhances activation of the mutated LNCaP AR in response to oestradiol or hydroxyflutamide [41]. Dominant-negative mutants of ARA54 inhibited proliferation of LNCaP cells [42]. This is an interesting finding that deserves further studies with other androgen-responsive tumor models. At present, there are no in vivo data confirming that down-regulation of an AR coactivator inhibits tumour growth.

In contrast to ARA70 or ARA54, the N-terminal-associated coactivator ARA160 does not potentiate AR activation by oestradiol [43]. ARA267 is a coactivator with exceptionally large molecular mass and does not significantly influence the interaction between the N- and C-terminal of the AR [44]. Its expression does not significantly change in samples obtained from prostate cancer patients.

7. Spectrum of androgen receptor coactivators

The tumour suppressor pRb is inactivated in a subgroup of prostate cancers cells due to point mutations. Because of inactivation of pRb, there is a loss of cell cycle control at the G1/S checkpoint. There is a bidirectional communication between androgenic hormones and pRb; low doses of androgens induce phosphorylation of pRb thus allowing the transcription factor E2F to up-regulate target genes and stimulate proliferation [45]. Higher androgen doses, in contrast, do not increase pRb phosphorylation. On the other hand, pRb enhanced AR transcriptional activity four-fold in DU-145 cells in the presence of dihydrotestosterone and acted with ARA70 in an additive manner [46]. One could speculate that Rb is involved in differentiation of prostate cells through the AR pathway. AR activity is also potentiated by BRCA-1, as evidenced by increased expression of its target gene p21 [47]. This mechanism lead to increased cell death in PC-3 cells that stably express the AR. In contrast, coactivation of the AR by cyclin E may be associated with stimulation of proliferation of prostate cancer cells [48]. Cyclin E binds to the N-terminal region of the AR thus stimulating AF-1. Another example of an AR coactivator that is most likely involved in induction of proliferation is cdc25B [49]. This phosphatase mediates activation of cyclin-dependent kinases and is overexpressed in prostate cancer, especially in high grade Gleason tumours. Coactivation of the AR by TGF-β is a matter of debate. Activity of mutated AR 877 is enhanced by Smad3, an intermediary moledule in TGF-β signaling [50]. In contrast, Hayes and associates reported on inhibtion of AR activity by Smad3 [51]. TGF-β is an inhibitor of mitogenic signaling caused by epidermal growth factor and its signaling is frequently altered in prostate cancer. TGF-beta promotes angiogenesis and suppresses immune response thus facilitating tumour growth in vivo. Variances in outcome of interaction between TGF-β and the AR might be explained by differences in cell culture conditions between laboratories where the studies were performed.

AR activity could be also enhanced by gelsolin, an actin severing protein that regulates cytoskeleton reorganization and cellular motility [52]. Gelsolin COOH-terminal interacts with the DNA- and ligand-binding domains of the AR. Importantly, gelsolin and AR colocalize in prostate cancer cells. In LNCaP cells, expression of gelsolin increased after bicalutamide treatment. Clinical studies revealed a similar phenomenon in specimens obtained from patients treated who received androgen ablation therapy. Ability of hydroxyflutamide to antagonize androgen effect on receptor transactivation is reduced by overexpression of gelsolin. Reduced antagonistic properties of another antiandrogen, cyproterone acetate, were observed in cells transfected with BAG-1 cDNA [53]. BAG-1 is a regulator of heat-shock protein 70. Interaction between the largest member of BAG family, BAG-1L, and the AR occurs through both NH_2- and COOH-termini of the receptor. FHL2 is an AR coactivator which selectively enhances activation of the AR, but not that of other steroid receptors. It is translocated to the nucleus by the Rho signaling pathway [54].

In several studies, interaction between β-catenin and the AR was addressed. β-Catenin is a downstream effector of the Wnt signaling pathway that regulates a number of cellular processes including differentiation, proliferation and migration. However, it has not yet been determined whether the coactivator function of β-catenin for AR occurs in response to Wnt signaling or other extracellular stimuli. β-Catenin caused AR hypersensitivity in the presence of other steroids and diminished antagonistic properties of bicalutamide [55]. Coactivation of the AR by β-catenin may be reduced by overexpression of E-cadherin, cell adhesion molecule whose alterations commonly occur in carcinoma of the prostate.

8. Summary

Most important alterations in expression and function of AR coactivators in prostate cancer are summarized in Table 1. From research on AR cofactors in prostate cancer, it could be concluded that most of them are widely expressed in tumour cells. The fact that the expression of some coregulators increases after androgen ablation is intriguing. Prostate cancer cells are able to adapt to an environment with low androgen supply by several mechanisms; in previous studies, it was demonstrated that AR levels increase during long-term androgen ablation. It should be kept in mind that some coactivators are implicated in regulation of AR cross-talk with other signaling pathways.

From several studies, it is evident that antagonistic properties of antiandrogens are substantially reduced when a coactivator is overexpressed. Inappropriate action of nonsteroidal and steroidal antiandrogens was observed in various prostate

Table 1
Alterations in AR cofactor expression or function in prostate cancer

Coactivator	Expression and function in prostate cancer
SRC-1	Increased expression in recurrent cancer colocalization with AR in aggregates (mutated AR)
TIF-2	Increased expression in recurrent cancer
CBP	Potentiates agonistic effect of hydroxyflutamide
Tip60	Increased nuclear localization in therapy-resistant disease
ARA70	Potentiates various AR activations, reduced expression in cancer tissues, inhibition of growth of prostate cancer cells
ARA55	Potentiates agonistic effect of hydroxyflutamide
ARA54	Potentiates agonistic effect of hydroxyflutamide
RAC3	Expression correlates with high tumour grade and stage

cancer models and it could be explained if more data on specific interaction with coactivators will become available. For this reason, studies on expression of coactivators in advanced prostate cancer are of interest and there is an evidence that some coactivators are overexpressed in therapy-resistant carcinoma of the prostate. Because of their overexpression and potentiation of activation of the AR by antiandrogens, coactivators could be considered targets for novel experimental therapies. At present, it is not clear whether redundant action of some of these coregulatory proteins hampers development of new experimental therapy approaches.

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