Activator Protein 2α Transcription Factor Expression Is Associated with Luminal Differentiation and Is Lost in Prostate Cancer1

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ABSTRACT
Purpose: Prostate cancer progression is associated with deregulation of genes like E-cadherin, p21/WAF1, MMP-2, VEGF, and IGF-binding protein, 3 and 5, all of which are target genes for the transcription factor activator protein 2α (AP-2α). We, therefore, hypothesize that the development/progression of prostate cancer is associated with changes in the expression of AP-2α.

Experimental Design: We used immunofluorescent staining to assess the presence of AP-2α in normal, benign, and malignant human prostate tissues and to correlate its expression with tumor grade and stage.

Results: We found that although AP-2α was expressed in normal prostate epithelium, it was not expressed in 30 prostate cancer specimens of different Gleason scores. Moreover, AP-2α protein was present in the luminal cell layer but not in the basal cell layer of the normal epithelium, which indicated that the loss of AP-2α staining in the prostate cancer specimens was not attributable to a lack of AP-2α-expressing cells. Further analysis demonstrated the presence of AP-2α in 2 (40%) of 5 atrophic normal epithelium, in 4 (24%) of 17 cases of benign prostatic hyperplasia, and in 2 (13%) of 13 cases of high-grade prostatic intraepithelial neoplasia. Loss or reduction in AP-2α expression was also observed in LNCaP, LNCaP-LN3, and PC3M-LN4 cell lines.

Conclusions: Our data demonstrate that AP-2α expression is associated with normal luminal differentiation and that a loss of AP-2α expression occurs early in the development of prostate adenocarcinoma. Loss of AP-2α may lead to deregulation in AP-2α target genes that normally regulate cellular growth and differentiation.

INTRODUCTION
The progression from a premalignant to a cancerous epithelium involves deregulation of genes encoding adhesion molecules, proteases, angiogenic molecules, and growth factors and their receptors. Examples of particular interest to us are KAI-1 and E-cadherin, which play an important role in the progression of prostate cancer. Loss of expression of either KAI-1 or E-cadherin is associated with progression to advanced-stage disease (1). Loss of KAI-1, a member of the transmembrane 4 superfamily (2), is a potential marker of metastatic potential for several tumors, but mostly for prostate cancer (2). Introduction of KAI-1 into KAI-1-deficient cells suppresses their metastasis in vivo (2, 3), although the precise mechanism of action is unknown. Similarly, E-cadherin, which mediates cell adhesion and signaling through interactions with α and β catenin, is decreased in poorly differentiated and metastatic prostate cancer cells (4).

Both KAI-1 and E-cadherin genes are targets for regulation by the AP-2α transcription factor (5–7). Other genes that encode important mediators of prostate cancer development/progression, such as MMP-2 (8, 9), p21/WAF1 (10), TGF-α (11), VEGF (12, 13), and the IGF receptor type 1 (14, 15), have been shown to be regulated by AP-2α (16–19) or are potential targets for regulation by AP-2α based on the existence of AP-2-binding sites within their promoter regions (20). We, therefore, hypothesized that the development/progression of prostate cancer is associated with changes in the expression of AP-2α.

AP-2α, first cloned by Williams et al. (21), regulates many aspects of cell proliferation, differentiation, and cell death. AP-2α consists of a family of three isoforms encoded by different genes designated AP-2α, AP-2β, and AP-2γ (21–23). AP-2α knockout mice die perinatally with severe multiple congenital defects involving face, skull, and sensory organs. In situ hybridization showed that mouse embryos express AP-2α specifically in ectoderm-derived tissues, including craniofacial, gonad, kidney, and skin (24, 25). Analysis of AP-2 isoforms in mouse adult tissues demonstrated that AP-2α is the predominant isoform expressed in the adult mouse prostate (26).

The NH2 terminus of the AP-2α protein is responsible for transactivation activity, and a basic and helical region in the COOH terminus is responsible for dimerization and DNA binding (27, 28). Agents that induce PKC or cAMP increase AP-2α transactivation activity independently of new protein synthesis (29, 30). In addition, PKA has been shown to phosphorylate and

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3 The abbreviations used are: AP-2α, activator protein 2α; PIN, prostatic intraepithelial neoplasia; BPH, benign prostatic hypertrophy; PZ, peripheral zone; TZ, transition zone; CZ, central zone; HMWK, high-molecular-weight keratin; TBS, Tris-buffered saline; PI, propidium iodide; RT-PCR, reverse transcription-PCR; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; GS, Gleason score; BCH, basal cell hyperplasia; TM, transitional metaplasia.
activate AP-2α, leading to increased transactivation activity (31).

Loss of AP-2α expression seems to play a crucial role in the progression of many different types of cancers, including breast cancer, melanoma, and colorectal cancer. For example, highly metastatic melanoma cell lines do not express AP-2α, whereas nonmetastatic cell lines express high levels of AP-2α (32–34). Reintroduction of full-length AP-2α into highly metastatic melanoma cells greatly reduces their tumorigenicity and metastatic potential (32, 34), and the inactivation of AP-2α in primary cutaneous melanoma results in increased tumor growth in vivo (35). In clinical specimens of melanoma, loss of AP-2α expression correlates with low p21/WAF1 expression and poor survival (36). Moreover, a correlation between low AP-2α expression and disease progression in breast cancer was demonstrated, suggesting a tumor suppressor-like role for AP-2α (37). In colorectal cancer, p21/WAF1 expression correlates with AP-2α expression and poor survival, but not with p53 expression (38). The role of AP-2α in the development/progression of prostate cancer is not yet defined.

Here we analyzed AP-2α expression in prostate cancer and normal prostatic epithelium. We found that AP-2α was lost in primary prostate cancer, whereas it was expressed in normal luminal epithelium. It was absent in the majority of cases of PIN, a precursor of prostate carcinoma, which suggests that the loss of AP-2α is an early event in the development of prostate cancer. Further characterization of the normal prostatic epithelium and benign prostatic conditions demonstrated that AP-2α expression was associated with luminal differentiation. Our results add weight to the hypothesis that the loss of AP-2α expression was associated with luminal differentiation. Our findings also add weight to the hypothesis that the loss of AP-2α expression was associated with luminal differentiation.

**Table 1.** AP-2α immunoreactivity in primary prostate cancer clinical specimen by GS, pathological stage, and zonal origin.

<table>
<thead>
<tr>
<th>GS Pathological stage</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>pT&lt;sub&gt;N&lt;/sub&gt;&lt;sub&gt;0&lt;/sub&gt;</th>
<th>pT&lt;sub&gt;N&lt;/sub&gt;&lt;sub&gt;0&lt;/sub&gt;</th>
<th>pT&lt;sub&gt;N&lt;/sub&gt;&lt;sub&gt;0&lt;/sub&gt;</th>
<th>pT&lt;sub&gt;N&lt;/sub&gt;&lt;sub&gt;0&lt;/sub&gt;</th>
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<td>PZ Ca&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0/4</td>
<td>0/16</td>
<td>0/3</td>
<td>0/4</td>
<td>0/3</td>
<td>0/24</td>
<td>0/1</td>
<td>0/4</td>
<td>0/1</td>
</tr>
<tr>
<td>TZ Ca&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0/4</td>
<td>0/7</td>
<td>0/3</td>
<td>0/4</td>
<td>0/3</td>
<td>0/11</td>
<td>0/1</td>
<td>0/4</td>
<td>0/1</td>
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</table>
| Number of AP-2α positive cases/total number of cases. | 605.0x787.0

**Materials and Methods.**

**Cell Lines.** The LNCaP-FGC (LNCaP) human prostate cancer cell line was obtained from American Type Culture Collection (Rockville, MD). LNCaP is a hormone-responsive cell line isolated from a lymph node metastasis. LNCaP-LN3 and PC3M-LN4 were established and kindly provided by Dr. Curtis Pettaway (M. D. Anderson Cancer Center, Houston, TX; Ref. 39). The HPV-MLC CI3, a nontumorigenic cell line established by immortalization of normal prostate epithelial cells with human papilloma virus (HPV), was kindly provided to us by Dr. Donna Pehel (Stanford University, Palo Alto, CA).

**Tissue Samples for Immunofluorescent Staining.**

Formalin-fixed, paraffin-embedded radical prostatectomy specimens were selected to include prostate carcinomas of different zonal origins, GSs (40), and pathological stages (41). Normal prostatic epithelium from the PZ, TZ, and CZ, benign prostatic conditions such as BPH, its variant BCH, atrophy, stromal nodules, TM, and high-grade PIN, were also included in the study (Table 1). All of the prostate cancers were androgen-dependent, and the patients had not received therapy prior to the radical prostatectomy. Four-µm sections were used for immunofluorescent staining, and a contiguous section was stained with H&E to determine the histological features of each specimen.

**Immunofluorescent Staining for AP-2α, PSA, and HMWK.** The sections were deparaffinized and steamed in Serotec target unmasking fluid (Serotec Inc., Raleigh, NC) for antigen retrieval. Samples were blocked in blocking solution (1% normal goat serum and 5% normal horse serum in TBS) and incubated overnight with primary antibody diluted in blocking solution. AP-2α was detected using a 1:50 dilution of an anti-AP-2 monoclonal antibody (Serotec Inc.). Similarly, monoclonal antibodies were used to detect HMWK (34812E; DAKO, Inc., Carpinteria, CA) and PSA (DAKO, Inc., Carpinteria, CA). Background staining was determined by staining a contiguous cut with mouse IgG. The primary antibody was washed with TBS and then incubated with FITC-conjugated (AP-2α) or TRITC-conjugated (PSA or HMWK) antimouse antibody. PI was used to counterstain the DNA of the AP-2α stained samples. The slides were mounted using Prolong Anti-Fade kit (Molecular Probes, Eugene, OR) to preserve the fluorophore.

Immunofluorescent microscopy was conducted in an epifluorescence microscope equipped with narrow bandpass excitation filters (Chroma Technology Corp., Brattleboro, VT) to individually select for green and red fluorescence. Images were captured with a C5810 Hamamatsu camera (Hamamatsu Photonics K.K., Japan) mounted on a Zeiss Axiosplan microscope (Carl Zeiss Inc.) using Optimas image analysis software (Media Cybernetics, Silver Spring, MD). Staining of cells grown in culture was detected using a Zeiss confocal laser scanning microscope (upright version) equipped with an argon and HeNe laser. Signals were collected by photomultipliers with 590 nm (PI) long pass filter and a 520–560 nm (FITC) band pass filter, respectively. Digitized images were transmitted to a Macintosh.
based image analysis system through a GPIB interface using BDS-LMS software (Biological Detection Systems, Pittsburgh, PA). Composite images were assembled using Adobe Photoshop (Adobe Systems, Inc., Mountain View, CA).

**Analysis of Immunofluorescent Staining.** Prostate cancer tissue samples were graded according to the Gleason grading system by a single pathologist, who also identified areas containing normal prostate epithelium, BPH, PIN, BCH, stromal nodules, TM, and atrophy. The areas of interest were analyzed under the fluorescent microscope in the sections stained with AP-2/H9251 antisera. Positive AP-2/H9251 staining was recorded if more than 20% of the cells in the gland/lesion demonstrated AP-2/H9251 immunoreactivity. The same areas were also analyzed in the section stained with mouse IgG. If background staining was observed in the areas of interest, the specimen was excluded from the analysis. Statistical analysis was performed using Statistica software (version 6.0, Statsoft, Inc., Tulsa, OK), using the Fisher exact test. Significance was determined at the 95% confidence interval.

**RT-PCR.** Total RNA was isolated using Trizol reagent (Life Technologies, Inc., Rockville, MD) according to the manufacturer’s instructions. One μg of total RNA was reverse transcribed, and GAPDH and AP-2α cDNA were amplified by PCR in the same reaction, as described previously (32). The PCR products were separated on a 3% NuSieve agarose gel, stained with ethidium bromide and visualized with UV light.

**Western Blot.** Fifteen μg of nuclear extract were separated on a 10% SDS/PAGE gel. The proteins were electrophoretically transferred to a PVDF membrane (Millipore Corp., Bedford, MA). The membrane was blocked in blocking solution (5% nonfat dry milk/TBS) and then incubated with primary antibody overnight. For AP-2α detection, a 1:3000 dilution of a

![Fig. 1 Expression of AP-2α in the normal prostate but not in carcinoma. Paraffin-embedded prostate cancers from radical prostatectomy specimens were stained with a monoclonal anti-AP-2 antibody and detected using FITC-conjugated anti-mouse antibody. AP-2α immunoreactivity is absent in moderately differentiated (B) and poorly differentiated (D) prostatic adenocarcinoma and present in adjacent normal epithelium (A and C, respectively). H&E staining of the same samples is shown side by side.](image-url)
A polyclonal antibody against the COOH terminus of AP-2/H9251 (Santa Cruz Biotechnologies, Inc., Santa Cruz, CA) was used. The primary antibody was washed in TTBS (0.1% Tween/TBS) and then incubated in secondary antibody diluted in 0.5% nonfat dry milk/TTBS. Proteins were visualized using enhanced chemiluminescence (ECL) reagent (Amersham Pharmacia Biotech, Arlington Heights, IL) followed by exposure to X-ray film.

**RESULTS**

AP-2/H9251 Is Expressed in Normal Prostate Epithelium but Not in Prostate Adenocarcinoma. Thirty human prostate cancer clinical specimens of different zonal origins, GSs and pathological stages were analyzed by immunofluorescent staining for AP-2α expression. The histological features of the tumor and nonneoplastic prostate tissue were established in an H&E-stained consecutive section of the same block. The GSs of the specimens analyzed were GS 5 (n = 4), GS 6 (n = 16), GS 7 (n = 3), GS 8 (n = 4), and GS 9 (n = 3; Table 1). Twenty-four tumors were organ confined (pT2 N0), one tumor exhibited extraprostatic extension (pT3a N0), four had seminal vesicle invasion (pT3b N0), and one tumor had metastasis to a pelvic lymph node (pT3b N1). AP-2α immunoreactivity was not detected in any prostate cancer, although it was always detected in normal adjacent epithelium. The prostatic stroma was consistently negative. Representative staining is shown in Fig. 1, in which AP-2α protein was not detected in moderately differentiated (Fig. 1B) or in poorly differentiated (Fig. 1D) prostate adenocarcinoma, but positive immunoreactivity was observed in adjacent normal epithelium (Fig. 1, A and C). This contrast is better shown in Fig. 2, in which AP-2α staining was not observed in the infiltrating high-grade carcinoma (GS 9), whereas the normal glands within the tumor (internal control) were positive. Collectively, these results show that AP-2α expression occurs in normal prostate epithelium but is lost in well-to-poorly differentiated prostate cancer specimens.

AP-2α Is Expressed in the Luminal Cell Compartment of the Normal Prostate Epithelium. The epithelial compartment of the normal prostate glands is composed of two major cell populations, basal and luminal cells. Prostate cancer lacks basal cells. Given the striking difference in AP-2α immunoreactivity between normal epithelium and prostate cancer, we wanted to determine which cell population expresses AP-2α and to determine whether the loss of AP-2α expression observed in all cancer cases was attributable to the absence of basal cells in carcinoma. To that end, specimens containing normal epithelium were stained with specific markers for basal or luminal cells. PSA is a marker of luminal differentiation, and it is not present in basal cells. The basal cells are characterized by the expression of HMWKs and do not express PSA. PSA and HMWK staining were compared with AP-2α staining for the same gland in consecutive sections of the same specimen. We observed that AP-2α expression correlated with PSA expression in the luminal cells but not with the expression of HMWK in the basal cell layer (Fig. 3). These results indicate that lack of AP-2α that we observed in carcinomas (Fig. 1 and 2) was not caused by the loss of AP-2α-expressing cells. We conclude that the development of prostate cancer is associated with the loss of AP-2α expression in the luminal cells.

AP-2α Protein Is Expressed in Benign Lesions and Is Associated with Luminal Differentiation. The absence of AP-2α immunoreactivity in well-differentiated prostate cancer suggests that a loss of AP-2α is an early event in prostate cancer
To further investigate the AP-2 expression pattern in the progression of prostate cancer, we analyzed AP-2 expression in premalignant lesions such as PIN and in benign lesions of the prostate associated with hyperproliferation and alterations in epithelial differentiation. These include BPH, BCH, atrophy, stromal nodules, and TM. Moreover, we characterized AP-2 expression in the normal epithelium of different zones of the prostate, because they differ in their propensity to develop prostate cancer and other (benign) conditions. Prostate cancer and PIN occur most commonly in the PZ, whereas BPH occurs in the TZ. On the other hand, the CZ is highly resistant to cancer. AP-2 staining was detected in the normal glands from all of the zones of the prostate and in the normal epithelium of the PZs (18 of 18, 100%), TZs (13 of 14, 92%), and CZs (3 of 3, 100%; data not shown).

AP-2 staining was also detected in 2 of 5 cases of atrophic normal glands (40%) and in 4 of 17 cases of BPH (24%). All of the lesions that showed AP-2 immunoreactivity were characterized by the presence of a luminal cell compartment. In contrast, lesions in which normal luminal differentiation was absent or altered, such as BCH, TM, and stromal nodules, demonstrated a lack of AP-2 immunoreactivity (Fig. 4). Moreover, AP-2 was detected in only 2 of 13 cases of PIN (15%). Fig. 5 shows representative cases of high-grade PIN that was positive (Fig. 5A) or negative (Fig. 5B) for AP-2 immunoreactivity. A marked and significant reduction in AP-2-positive cases was observed between normal epithelium and PIN (P = 0.0190) and between normal epithelium and prostate cancer (P < 0.0001). Background staining was observed only in prostatic secretions and infiltrating lymphocytes and was minimal in prostatic tissue.
Collectively, these data indicate that AP-2α protein expression is associated with the presence of a luminal cell compartment and that loss of AP-2α expression was observed as early as in the transition from a benign to a premalignant epithelium.

**Expression of AP-2 mRNA and Protein in Prostate Cancer Cell Lines.** We next analyzed AP-2α expression at the mRNA and protein levels in the prostate cancer cell lines most commonly used for preclinical studies. RT-PCR and Western blot analysis demonstrated AP-2α expression in immortalized normal prostate epithelial cells (Fig. 6A and B, Lane 4). The LNCaP cell line and its more metastatic variant LNCaP-LN3 showed no expression of AP-2α mRNA and protein (Fig. 6, A and B, Lanes 5 and 6). The highly metastatic cell line PC3M-LN4 expressed very low levels of AP-2α (Fig. 6A and 6B, Lane 7). AP-2α protein levels were further confirmed by immunofluorescent staining of cells grown in culture. All of the cell lines tested showed similar levels of AP-2α protein as in RT-PCR and Western blot analyses, confirming the specificity of the immunofluorescent technique used to study AP-2α expression in prostate cancer specimens (Fig. 7).
DISCUSSION

This is the first paper to describe the expression of AP-2α in the luminal cell compartment of normal prostate epithelium of all prostatic zones and to demonstrate loss of AP-2α expression in prostate adenocarcinoma. We further characterized the role of AP-2α in the different epithelial and stromal compartments by analyzing AP-2α expression in benign conditions of the prostate, such as atrophy, BPH, stromal nodules, TM, and BCH. AP-2α is detected in those conditions in which a luminal cell layer is present, i.e., atrophy, BPH, and PIN; and absent when the luminal compartment is altered or absent such as in BCH, TM, and stromal nodules, confirming our initial observation that AP-2α is present in the luminal compartment. Our analysis of benign, premalignant, and malignant conditions of the prostate suggests that loss of AP-2α protein is an early event in prostate cancer development, probably occurring in the transition from a normal to a premalignant phenotype.

In the normal prostate epithelium, most of the proliferative activity is present in the basal cell layer, whereas the luminal cell layer is almost completely mitotically inactive (42, 43). PIN is characterized by increased proliferation in the luminal cell compartment and multiple genetic and molecular alterations (44, 45). A novel observation in this study is the loss of AP-2α expression in high-grade PIN, which is considered a precursor of prostate cancer. In PIN, there is increased expression of apoptotic suppressor genes like Bcl-2 (46, 47), which predispose the dysplastic cells for malignant transformation (48). High-grade PIN also shows other molecular changes associated with a malignant phenotype such as increase in microvessel density (49, 50), and increased expression of transforming growth factor (TGF)-α (51), erbB2 (52), and type IV collagenase (53), all of which are regulated by AP-2α. Moreover, there is loss of secretory cell differentiation markers such as PSA, secretory proteins, cytoskeletal proteins, glycoproteins, and neuroendocrine cells. AP-2α expression was lost in the majority of the PIN cases studied, which reflects the loss of terminal differentiation that accompanies the hyperproliferative dysplastic epithelium. Collectively, our data suggest that loss of AP-2α is an early event in prostate cancer progression.

An interesting finding is that a high percentage of BPH cases lose AP-2α expression. In normal epithelium, the basal cell layer is the proliferative compartment that contains stem cells capable of differentiating into luminal cells (45). The luminal population is composed of terminally differentiated epithelial cells and cells with a phenotype intermediate between basal and luminal cells, still capable of proliferation (45, 54, 55). Terminal differentiation is associated with up-regulation of keratin 8 and 18 (56), up-regulation of cell cycle control molecules such as p27/Kip1 (57), and down-regulation of antiapoptotic molecules such as Bcl-2 (46, 58–60). The pathogenesis of BPH is poorly understood, but studies have proposed that it is caused by stromal alterations in the TZ that stimulate growth and modulate differentiation in the epithelial compartments (61–63). Loss of AP-2α in BPH may reflect a failure to complete terminal differentiation in the highly proliferative epithelial cells.
Lipponen et al. (64) studied the correlation between AP-2α expression with p21/WAF1 expression, proliferation markers, and clinical stage in biopsies and transurethral resection specimens (TURP) and concluded that AP-2α is not a good prognostic marker for prostate cancer. They also described cytoplasmic staining in normal prostate epithelium. The use of sections from radical prostatectomy specimens in our studies allowed the characterization of AP-2α expression in all of the prostatic zones, because each zone differs in susceptibility to prostate cancer. The PZ is the most common site for PIN and carcinoma, whereas the CZ is highly resistant to cancer. The TZ has moderate susceptibility to cancer, and it is the site for development of BPH. We confirmed that AP-2α is present in the normal epithelium and further demonstrated that it is equally expressed in all of the prostatic zones. Moreover, by comparing AP-2α expression with markers of luminal (PSA) and basal (HMWK) cells, we found that AP-2α expression is present in the luminal cells of normal prostatic epithelium.

The two studies differ considerably in the patient population and the source of antibody used. Our study focused on hormone-dependent, organ-confined prostate cancer in which the patients have not received previous therapy. Our initial observations that AP-2α expression is lost in prostate cancer led us to focus our attention on low- and intermediate-grade prostate cancer. We did not detect AP-2α expression in any of the prostate cancer specimens studied. Although Kosma’s group [Lipponen et al. (64)] reported mixed expression in primary prostate cancer and reported a subset of high-grade carcinomas with nuclear AP-2α expression with higher propensity to develop metastatic disease, we did not observe AP-2α expression in any of our high-grade carcinomas. However, AP-2α may indeed not be a good prognostic marker because our study showed that AP-2α expression is lost very early in the progression of prostate cancer, before it is clinically significant.

AP-2α is known to regulate genes associated with growth control and differentiation, such as p21/WAF1 (17), c-Myc (65), E-cadherin (5). We, therefore, propose that loss of AP-2α expression is a crucial event in the development of prostate cancer. Furthermore, loss of AP-2α in conjunction with other molecular events can potentially influence later stages in the progression of prostate cancer by deregulating other genes such as VEGF (angiogenesis; Ref. 19), MMP-2 (invasion; Ref. 16), and IGFBP-3 (5 and 5 survival; Refs. 66, 67). To further test this hypothesis, we are currently re-expressing AP-2α in LNCaP-LN3 and PC3M-LN4 cell lines (low or negative AP-2α expression) and analyzing changes in their tumor growth and metastasis in the orthotopic nude mouse model.

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