Altered Expression of Androgen Receptor in the Malignant Epithelium and Adjacent Stroma Is Associated with Early Relapse in Prostate Cancer


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Abstract

The molecular basis of androgen-independent prostate cancer is unknown; however, functional androgen receptor (AR) signaling is maintained after the acquisition of hormone-refractory disease. Because normal and malignant prostate epithelial cell proliferation is regulated by androgen stimulation via both the AR-positive stroma and epithelium, we sought to evaluate patterns of AR expression in these cells and to determine any relationships with prostate cancer progression. AR expression in the malignant epithelium and associated peripheripithelial and nonperipheripithelial stroma was measured in a cohort of 96 patients with clinically localized prostate cancer treated with radical prostatectomy. Data were evaluated for disease relapse using the Kaplan-Meier method and in a Cox proportional hazards model with other variables of known clinical relevance, including Gleason score, pathological stage, clinical stage, and pretreatment prostate-specific antigen concentration. Concurrent overexpression of AR (≥70% positive nuclei) in the malignant epithelium and loss of AR immunoreactivity in the adjacent peripheripithelial stroma (≤30%) was associated with higher clinical stage (P = 0.01), higher pretreatment prostate-specific antigen level (P = 0.03), and earlier relapse after radical prostatectomy (log-rank P = 0.009). These data identify a pattern of AR expression in malignant epithelium and adjacent stroma that is associated with a poor clinical outcome in prostate cancer. Equally important, they identify the need to further investigate the mechanistic basis of loss of AR expression in the malignant stroma and its potential role in deregulation of prostate epithelial cell proliferation.

Introduction

Prostate cancer is the most commonly diagnosed male cancer in industrialized societies. A principal clinical problem in prostate cancer is the conversion of hormone-sensitive cancers to hormone-refractory disease after treatment with androgen-deprivation therapy (1). However, unlike the estrogen receptor in breast cancer, where loss of estrogen receptor expression predicts a more aggressive disease course, AR expression in prostate cancer does not provide a similar marker of prognosis and hormonal response (2).

In the normal adult prostate, circulating androgens act via the AR-positive smooth muscle stromal cells to maintain a differentiated, quiescent epithelium (3). The rapid regression of prostate epithelium that follows castration is associated with a progressive dedifferentiation of the smooth muscle cells to relatively undifferentiated fibroblasts. These fibroblasts respond to castrate levels of androgen via the AR to promote mitogenesis of the epithelium. At the same time, the epithelium acts via the AR-positive fibroblasts to facilitate the reversion of the fibroblastic stroma to a fully differentiated smooth muscle phenotype. In prostate cancer, it is hypothesized that altered gene expression in the epithelium results in aberrant epithelial-stromal cell signaling that ultimately leads to epigenetic changes in the stroma and augmentation of uncontrolled proliferation of the epithelium (3). For example, loss or reduced expression of the cellular adhesion molecule, E-cadherin, because of mutations and deletions in the E-cadherin or a-catenin genes is a common feature of malignant prostate epithelial cells (3, 4). In addition, the ability of stromal cells to down-regulate E-cadherin expression has been implied from experiments in vitro where tumor-derived human prostatic stromal cells were cocultured with a nontumorigenic SV40T-immortalized human prostatic epithelial cell line BPH-1, resulting in markedly decreased E-cadherin expression, loss of contact inhibition, and phenotypic changes in the epithelial cells (3). Such data emphasize the importance of stromal-epithelial signaling in the prostate and raise questions on the potential role of stromal AR expression in phenotypic changes associated with prostate tumorigenesis.

The emergence of a “tumor stroma” that facilitates prostate carcinogenesis is not a new concept (3). Thompson et al. (4) demonstrated in an in vivo mouse reconstitution model, the requirement for ras- and myc-induced transformation of both the stromal and epithelial components of the mouse urogenital sinus for carcinoma to develop. In addition, fibroblasts derived from rat urogenital sinus mesenchyme stimulated growth of the prostate cancer cell line, LnCaP, and conversely, LnCaP-conditioned medium stimulated growth of the urogenital sinus mesenchyme (5). However, the role of AR in the “tumor stroma” and any relationship between alterations in stromal AR expression and prostate cancer progression remain unclear. Thus, we sought to determine whether changes in AR expression in the stromal and epithelial components of prostate cancers were associated with disease progression and a poor clinical outcome.

Materials and Methods

Patient Population. We studied a group of 96 RP specimens from patients treated for clinically localized prostate cancer at St. Vincent’s Hospital, Sydney, between 1989 and 1994 (mean follow-up, 75 months; range, 27–138 months) that are a subset of a cohort described previously (6). The demo-
graphic and clinical features of these patients are listed in Table 1. Relapse was defined by the following criteria: biochemical disease progression with a serum PSA concentration at or above 0.4 ng/ml, rising over a 3-month period; or local recurrence on DRE confirmed by biopsy or by subsequent rise in PSA.

**Tissue Evaluation and Characterization of Antibodies.** Paraffin blocks of formalin-fixed surgical specimens were obtained from the archives of the Department of Anatomical Pathology at St. Vincent’s Hospital and Sugerman Hampson Macquarie Pathology (Sydney, Australia). Pathological evaluation of all blocks from each prostate was performed by one of three histopathologists. Tumor stage was classified according to the TNM staging system and Gleason grade. A block most representative of each cancer was selected for sectioning, and diagnosis of each block was confirmed by examination of a routinely stained H&E section juxtaposed to the section used for AR immunostaining.

**Immunohistochemistry.** Immunohistochemical staining for AR was performed on routinely processed, paraffin-embedded tissue specimens. Four-μm sections of the tissue and control specimens were cut and mounted on Superfrost Plus adhesion slides (Lomb Scientific, Sydney, NSW, Australia). As a positive tissue control, a benign prostatic hyperplasia specimen that had high levels of AR expression was included. In addition, paraffin-embedded cell pellets of the prostate and breast cancer cell lines LncAP and MDA-MB-231 were used as positive and negative controls, respectively. Prior to staining, the sections were dewaxed and rehydrated and then incubated in 0.01 M citrate buffer (pH 6.0). The mouse monoclonal anti-AR antibody (Clone 2F12; Novocastra Laboratories, Newcastle-upon-Tyne, United Kingdom) was applied. An avidin-biotin complex was used as the secondary antibody (Vector Laboratories, Burlington, CA), with 3,3'-diaminobenzidine as substrate. Counterstaining was performed with Whitlock’s hematoxylin, followed by Light Green (BDH Laboratory Supplies, Poole, United Kingdom).

The percentage scores were derived from assessing AR positivity in 500 epithelial cells and 200–250 stromal cells in each tumor specimen by two independent assessors (S. M. H. and D. I. Q.) and by one pathologist (C. S. L.), all of whom were blinded to patient outcome. For each slide, the percentage of nuclear AR immunostaining within areas of stroma and carcinoma was expressed as the ratio of AR-positive cells to the total number of cells counted. Each specimen was categorized by AR nuclear immunoreactivity in the cancer and adjacent peripherioidal stroma so that each tumor was categorized on the basis of < or ≥70% AR expression in the epithelium and ≤ or >30% AR positivity in the peripherioidal stroma.

**Statistical Analysis.** The primary outcome was disease-specific relapse, which was measured from the date of RP. Data were evaluated for disease relapse using the method of Kaplan Meier and log-rank test and by univariate and bivariate analyses in a Cox proportional hazards model for AR status and other clinical and pathologic predictors of outcome. The multivariate model was produced by assessing AR status with other baseline covariates of clinical relevance: Gleason grade, pathological stage, and preoperative PSA, which were modeled as dichotomous or continuous variables as appropriate. Paired t-tests were used to assess the differences in the mean AR immunoreactivity in the peripherioidal stroma compared with the malignant epithelium and the nonperipherioidal stroma in the same specimen. The associations between AR expression and discrete categorical variables were tested using the χ² test. P < 0.05 was required for significance. All reported Ps are two-sided. All statistical analyses were performed using Statview 4.5 software (Abacus Systems, Berkeley, CA).

### Results

The levels of nuclear AR expression were evaluated by immunohistochemistry in 96 RP specimens from patients treated for clinically localized prostate cancer (mean follow-up, 75 months; range, 27–138 months). The distribution of AR immunoreactivity in the stromal and epithelial components is shown in Figs. 1 and 2. Detectable levels of AR were found in 91 of 96 (95%) cancers, with a mean level of 72% AR-positivity. In the NPES, a mean of 76% AR-positive cells was observed in 94 cases (99%) where AR was present. In contrast, in the PES, which was defined as a 10-cell stromal layer surrounding the malignant epithelium, a mean of only 25% AR positivity was observed in 81 cases where AR was detected. This is significantly lower than that observed in the malignant epithelium (P < 0.001) or NPES (P < 0.001).

To determine the potential clinical implications of loss of AR immunoreactivity in the PES associated with prostate cancers, the cohort was stratified on the basis of AR levels in the malignant epithelium and PES in the same specimen. Two distinct groups were identified, based on the mean levels of AR expression detected in areas of stromal and epithelial prostate tissue (Fig. 2). Group B represents 53 of 96 (55%) cases with concurrent high AR expression (≥70%) in the cancer and low (<30%) expression in the PES. Group A represents all those cases in which alternate patterns are present. The combinations represented by Group A are ≤30% AR + PES and ≤70% AR+ tumor cells in 27 of 96 cases (28%); >30% AR+ PES ≥70% AR+ tumor cells in 11 of 96 cases (12%) and >30% AR+ PES ≥70% AR+ tumor cells in 5 (5%) cases. Kaplan-Meier analysis of the data categorized by AR expression demonstrates clearly that the latter three groups cosegregate into a distinct group of patients with a significantly better outcome than the patients in Group B (Fig. 3).

Examination using χ² analysis of the relationship between the patterns of AR expression and other clinicopathological variables showed that concurrent overexpression of the AR (≥70%) in the malignant epithelium and loss of AR in the adjacent PES (<30%); Group B) was associated with higher clinical stage (P = 0.01), higher

### Table 1 Association of altered AR immunoreactivity in carcinoma and adjacent PES with clinicopathological variables (n = 96)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A (%)</th>
<th>Group B (%)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (&lt;65 yr)</td>
<td>52 (57)</td>
<td>40 (46)</td>
<td>0.08</td>
</tr>
<tr>
<td>Pretreatment PSA (≥4 mm)</td>
<td>44 (48)</td>
<td>25 (35)</td>
<td>0.05</td>
</tr>
<tr>
<td>Pretreatment PSA (&gt;4 mm)</td>
<td>53 (56)</td>
<td>34 (35)</td>
<td>0.001</td>
</tr>
<tr>
<td>Pathologic stage**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTNM0</td>
<td>51 (53)</td>
<td>47 (54)</td>
<td>0.09</td>
</tr>
<tr>
<td>PTNM1</td>
<td>35 (37)</td>
<td>24 (37)</td>
<td>0.09</td>
</tr>
<tr>
<td>PTNM2</td>
<td>8 (8)</td>
<td>3 (37)</td>
<td>0.001</td>
</tr>
<tr>
<td>PTNM3</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>PTNM4</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Gleason grade**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4–5</td>
<td>9 (9)</td>
<td>3 (33)</td>
<td>0.54</td>
</tr>
<tr>
<td>6–7</td>
<td>66 (69)</td>
<td>32 (48)</td>
<td>0.01</td>
</tr>
<tr>
<td>8–10</td>
<td>21 (22)</td>
<td>8 (38)</td>
<td>0.70</td>
</tr>
<tr>
<td>Clinical stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>40 (42)</td>
<td>24 (60)</td>
<td>0.01</td>
</tr>
<tr>
<td>T2</td>
<td>49 (51)</td>
<td>39 (49)</td>
<td>0.001</td>
</tr>
<tr>
<td>T3</td>
<td>7 (7)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Hormonal treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NHT</td>
<td>8 (8)</td>
<td>4 (50)</td>
<td>0.76</td>
</tr>
<tr>
<td>No NHT</td>
<td>88 (92)</td>
<td>39 (44)</td>
<td>0.56</td>
</tr>
<tr>
<td>PSA relapse</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td>33 (30)</td>
<td>26 (72)</td>
<td>0.001</td>
</tr>
<tr>
<td>No relapse</td>
<td>60 (62)</td>
<td>33 (55)</td>
<td>0.001</td>
</tr>
<tr>
<td>Clinical relapse**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td>11 (12)</td>
<td>2 (28)</td>
<td>0.01</td>
</tr>
<tr>
<td>No relapse</td>
<td>85 (89)</td>
<td>41 (48)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*The number of patients for whom data were available was 96 unless stated otherwise.

**Group B, ≥70% AR+ in cancer and ≥30% AR+ in the PES. Group A represents all cases in which alternate patterns to B are present.

The associations between AR expression and discrete categorical variables were tested using the χ² test. For the purposes of χ² analysis, PTNM0, PTNM1, PTNM2, and PTNM3 were grouped together. P < 0.05 was required for significance and is presented in bold.

**Tumor stage was classified according to the TNM staging system.

*Gleason grade according to Gleason criteria.

*NHT, Neoadjuvant hormonal therapy.

**PSA relapse was defined by the following criteria: biochemical disease progression with a serum PSA concentration at or above 0.4 ng/ml, rising over a 3-month period; or local recurrence on DRE confirmed by biopsy or by subsequent rise in PSA.

Clinical relapse was defined as local recurrence or distant metastases diagnosed by bone scan and/or transrectal biopsy.
pretreatment PSA level \((P = 0.03)\), and early tumor recurrence \((P = 0.009)\). Of the 36 men (35%) who experienced PSA relapse, 26 (76%) demonstrated this altered pattern of stromal-epithelial AR expression (Table 1). In agreement with other published series (7), significant predictors of relapse on univariate analyses in this cohort were pretreatment serum PSA levels, pathological stage, Gleason grade, and clinical stage (Table 2). In addition, elevated expression of AR \((70\%)\) in the malignant epithelium and loss of AR in the adjacent PES \((30\%; \text{Group B})\) was a significant predictor of relapse after radical prostatectomy on univariate analysis \((P = 0.016)\). Concordant with this observation, Kaplan-Meier product limit analysis of disease-free survival in patients stratified on the pattern of stromal-epithelial AR levels demonstrated a significant difference in relapse between the two strata \((\text{log-rank } P = 0.012; \text{Fig. 3})\), with patients exhibiting concurrent overexpression of AR \((70\%)\) in the malignant epithelium and loss of AR immunoreactivity in the PES \((30\%)\) showing an earlier time to relapse after radical prostatectomy. In addition, reanalysis of the data using different cutoffs in AR positivity in the PES at 20 or 25% showed that the relationship of altered AR expression and poor prognosis was maintained \((\text{both log-rank } P = 0.01)\). When stepwise multivariate analyses were constructed with backward elimination, the factors most predictive of relapse were, in descending order: Gleason grade, pathological stage, with pretreatment PSA concentration and AR strata equally predictive in this group.

The role of altered AR expression was also examined in patients who had progressed to advanced prostate cancer after radical prostatectomy. In the cohort of 96 patients, 11 patients had developed local recurrence or distant metastases at the completion of this study. Of these, 9 (82%) cases showed concurrent high AR expression \((70\%)\) in the cancer and low \((30\%)\) expression in the adjacent PES \((P = 0.059; \text{Table 1})\). In addition, 4 of these patients had developed hormone-resistant disease, and of these, three cases (75%) showed this altered pattern of AR expression.

**Discussion**

The combined assessment of AR in epithelial and stromal components of prostate cancers has identified an abnormal pattern of AR expression that is correlated with higher PSA concentration and higher clinical stage and is associated with tumor recurrence. These data provide the first evidence for an association of changes in AR expression in the stromal microenvironment with clinical outcome in prostate cancer.

Two common molecular mechanisms potentially responsible for prostate epithelial cell proliferation in the absence of high levels of circulating androgens have been proposed previously. These involve alterations of the signals that activate the AR pathway and deregulation of AR itself (8). Activation of the AR signaling pathway by heregulin and other ligands for receptor tyrosine kinases, e.g., insulin-like growth factor-1, transforming growth factor \(\alpha\), and keratinocyte growth factor, have been implicated recently in disease progression (9–11). During androgen deprivation, growth factors expressed by stromal cells can stimulate epithelial cell proliferation by activating the AR in a ligand-independent manner. For example, signaling via HER-2/neu activates the AR pathway in the absence of androgens and acts synergistically with low concentrations of androgen to activate PSA transcription (11). HER-2/neu activation of PSA transcription is not inhibited by antiandrogen, consistent with an androgen-independent mechanism (11). These findings have important clinical ramifications because they implicate tyrosine kinase receptors as potential...
The AR gene can alter steroid binding specificity and transactivational properties of the AR protein (8). An association between reduced numbers of a polymorphic CAG repeat in the AR gene has been correlated with increased transcriptional activity of the AR and poor clinical outcome (12). In addition, AR protein overexpression as a result of AR gene amplification may contribute to loss of growth control by enabling tumor cells to become hypersensitive to castrate levels of androgen in the prostate (13). The immunohistochemical findings to date have been equivocal with regard to the clinical usefulness of AR levels in predicting prostate cancer outcome. Numerous studies investigating the relationship between AR immunoreactivity and other known markers of clinical significance have reported varying conclusions. In the studies where outcome data are available, AR status was (14, 15) or was not (16–18) prognostic. However, there are no published studies to date that have addressed the relationship between stromal AR levels and clinical progression in this disease.

The data presented in this study support altered AR expression in the tumor-associated stroma as another potential mechanism of achieving androgen-independent prostate epithelial cell proliferation. In agreement with other published series, AR was present in the majority of prostate cancers examined and was not associated with tumor stage or grade (17). However, the loss of AR in the malignant PES implies that the regulation of AR expression in the tumor stroma is altered in prostate cancer. In addition, the recent finding that the stroma surrounding high-grade prostatic intraepithelial neoplasia also lacks AR expression suggests that this alteration in stromal AR expression is an early event in prostate cancer progression (19). Although the mechanisms responsible for this loss of AR expression remain undefined, there is evidence from studies in breast cancer that the estrogen receptor and the epidermal growth factor receptor are reciprocally regulated (20). Thus, loss of AR in the stroma may be associated with up-regulation of receptor tyrosine kinase expression if similar mechanisms are operative in prostate cancer. In addition, growth factors may function synergistically with low concentrations of androgens and low AR expression to activate the AR pathway (11). Hence, identification of factors that can regulate stromal AR expression and activate the AR pathway is a priority. There is increasing evidence that the multistep progression to malignancy involves both genetic alterations to the epithelium and epigenetic effects from the tumor stroma (3). Thus, altered AR expression in the stroma may contribute to uncontrolled epithelial cell proliferation resulting from genetic alterations in the AR itself and in key cell cycle regulatory targets for therapeutic intervention in the management of advanced prostate cancer.

The AR itself is also a target for deregulation. Mutations in the AR gene can alter steroid binding specificity and transactivational prop-

![Graph A](image1)

**Fig. 2.** Histograms demonstrating the distribution of the percentage of AR-positive cells in the stromal-epithelial components in each specimen (n = 96) as determined by immunohistochemistry in areas of malignant epithelium (A), NPES (B), and PES (C) in the same specimen. Paired t tests were used to demonstrate a significant difference in the mean AR immunoreactivity in the PES compared with the malignant epithelium ($P < 0.001$) and the NPES ($P < 0.001$) in the same specimen.

![Graph B](image2)

![Graph C](image3)

**Fig. 3.** Data were evaluated for relapse-free survival using the method of Kaplan Meier and log-rank test ($P = 0.012$) categorized by AR nuclear immunoreactivity in the cancer and adjacent PES into two distinct groups, Groups A and B, as defined in the text.

**Table 2: Univariate analysis for clinicopathological variables and AR immunoreactivity with relapse-free survival (n = 96)**

<table>
<thead>
<tr>
<th>Hazard ratio (95% CI)</th>
<th>$P^*$</th>
</tr>
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<tbody>
<tr>
<td>Pretreatment PSA (n = 94)</td>
<td></td>
</tr>
<tr>
<td>$&lt;10$ vs. $&gt;10$ nm/ml</td>
<td>2.12 (1.04–4.32)</td>
</tr>
<tr>
<td>Pathological stage</td>
<td></td>
</tr>
<tr>
<td>pT2 vs. pT3 or greater</td>
<td>5.36 (2.43–11.79)</td>
</tr>
<tr>
<td>Gleason grade$^a$</td>
<td>1.79 (1.41–2.28)</td>
</tr>
<tr>
<td>Clinical stage $^b$</td>
<td></td>
</tr>
<tr>
<td>T1 and T2 vs. T3</td>
<td>3.22 (1.24–8.33)</td>
</tr>
<tr>
<td>Neoadjuvant therapy</td>
<td>1.02 (0.31–3.32)</td>
</tr>
<tr>
<td>NHT$^c$ plus RP vs. RP alone</td>
<td></td>
</tr>
<tr>
<td>AR status</td>
<td></td>
</tr>
<tr>
<td>Group A vs. Group B$^d$</td>
<td>2.46 (1.99–5.11)</td>
</tr>
</tbody>
</table>

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$^a$ The number of patients for whom data were available was 96 unless stated otherwise.

$^b$ CI, confidence interval.

$^c$ Univariate analysis was performed using a Cox proportional hazards model for AR status and other clinical and pathologic predictors of outcome. $P < 0.05$ was required for significance and is presented in bold.

$^d$ Calculations use Gleason grade as a continuous variable so that for each unit increase in Gleason grade there is a 79% increase in risk of relapse.

$^e$ NHT, Neoadjuvant hormonal therapy.

$^f$ Group B: ≥70% AR+ in cancer and ≤30% AR+ in the PES.
genes, e.g., p53 (6) and p16INK4A (4) leading to a highly aggressive tumor phenotype.

An alternative interpretation of our data is that the epithelial cells in the poor prognosis cohort are overexpressing AR because of AR amplification, so that it only appears that the PES has low expression. However, whereas AR amplification occurs in up to 30% of hormone-refractory local recurrences and metastases of hormone-refractory prostate cancer, it appears to be a rare event in primary prostate cancer, with AR amplification detected in only 1% of 205 primary prostate cancers (21). Furthermore, the data presented here demonstrated similar levels of AR staining intensity in the NPES and in the malignant epithelium (Fig. 1). Thus, it appears unlikely that AR overexpression in the epithelium could explain relative changes in epithelial to AR expression in PES described here.

Although it is clear that metastatic disease ultimately kills the patients, there is increasing evidence that the genetic changes predisposing tumors to an aggressive course may occur early in the carcinogenic process (22). Although our data show that altered AR expression is associated with early biochemical relapse and clinical recurrence, there is insufficient follow-up to determine whether such expression is associated with early development of hormone-refractory disease. Because it is not possible to study relative levels of epithelial-stromal AR expression in metastases, this issue will only be resolved by further follow-up of cohorts with surgically treated localized prostate cancer. However, despite these limitations, of the 4 patients in this cohort that developed hormone-resistant disease coupled with local recurrence or distant metastases, three cases (75%) show this altered pattern of AR expression in the radical prostatectomy specimen. Thus, because an androgen-independent phenotype is an almost inevitable consequence of advanced prostate cancer, the possibility, suggested by this and another study (19), that AR expression in the tumor stroma has a pivotal role early in prostate cancer progression and the subsequent development of androgen independence, may have major clinical implications. The targeting of key paracrine growth factor signaling pathways in locally advanced prostate cancer may be one way of conferring androgen sensitivity to hormone-refractory tumors. Thus, a more detailed understanding of the role of AR signaling mediated by the tumor stroma may provide new insight into the development of androgen-independent disease that will lead ultimately to better clinical management of hormone-refractory prostate cancer and potential new targets for therapeutic intervention.

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References


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