Prostate cancer is the most frequently diagnosed nonskin cancer in men and the second leading cause of cancer death in North American males (1). The gold standard treatment for localized advanced, recurrent, and metastatic prostate cancer is androgen withdrawal therapy, which blocks the growth-promoting effects of androgens and activates apoptosis (2). After an initial favorable response, progression to a state variably called castration-resistant, hormone refractory, androgen depletion–independent, or androgen-independent is the usual outcome, for which there are currently no curative treatment options (3). Some brief survival extensions can sometimes be achieved using current Taxol-based chemotherapy protocols (4). Despite resistance to androgen withdrawal, progression does not seem to involve loss of the androgen receptor (AR; ref. 5). In over 80% of locally advanced castration-resistant prostate cancers, high levels of nuclear AR have been observed (6), and in bone metastasis, the amount of AR present is often higher than in primary tumors (7). Furthermore, in gene microarray analysis, the most consistent change seen with castration-resistant disease is an increase in AR mRNA (8). It has also been shown that progression of prostate cancer to androgen independence is associated with genetic and epigenetic changes that alter AR function and expression of AR target genes (8–15).

During prostate cancer progression from low-grade to high-grade cancers and, subsequently, to metastasis, there is progressive down-regulation of AR target genes, which inhibit proliferation, induce differentiation, or mediate apoptosis and stress responses (16). Recently, gene fusions of the prostate-specific, androgen-regulated TMPRSS2 and members of the ETS family of transcription factors were found to occur with high frequency in prostate cancer samples and were associated with tumor aggressiveness (17, 18). This may be a mechanism by which androgens can mediate the overexpression of an oncogene. Thus, in hormone refractory prostate cancer, AR may switch its role from promoting differentiation to activating genes involved in proliferation and cell survival.

**Abstract**

**Purpose:** Progression to the castration-resistant state is the incurable and lethal end stage of prostate cancer, and there is strong evidence that androgen receptor (AR) still plays a central role in this process. We hypothesize that knocking down AR will have a major effect on inhibiting growth of castration-resistant tumors.

**Experimental Design:** Castration-resistant C4-2 human prostate cancer cells stably expressing a tetracycline-inducible AR-targeted short hairpin RNA (shRNA) were generated to directly test the effects of AR knockdown in C4-2 human prostate cancer cells and tumors.

**Results:** In vitro expression of AR shRNA resulted in decreased levels of AR mRNA and protein, decreased expression of prostate-specific antigen (PSA), reduced activation of the PSA-luciferase reporter, and growth inhibition of C4-2 cells. Gene microarray analyses revealed that AR knockdown under hormone-deprived conditions resulted in activation of genes involved in apoptosis, cell cycle regulation, protein synthesis, and tumorigenesis. To ensure that tumors were truly castration-resistant in vivo, inducible AR shRNA expressing C4-2 tumors were grown in castrated mice to an average volume of 450 mm³. In all of the animals, serum PSA decreased, and in 50% of them, there was complete tumor regression and disappearance of serum PSA.

**Conclusions:** Whereas castration is ineffective in castration-resistant prostate tumors, knockdown of AR can decrease serum PSA, inhibit tumor growth, and frequently cause tumor regression. This study is the first direct evidence that knockdown of AR is a viable therapeutic strategy for treatment of prostate tumors that have already progressed to the castration-resistant state.
Prostate cancer is the most common lethal malignancy in men. Although androgen withdrawal therapies are used to treat advanced disease, progression to a castration-resistant end stage is the usual outcome. In this study, the tested hypothesis was that the androgen receptor (AR) remains essential for the growth and viability of castration-resistant disease. Knocking down the AR in well-established tumors grown in castrated mice caused growth arrest, decreased serum prostate-specific antigen, and, frequently, regression and total eradication of tumors. Growth control of castration-resistant tumors seemed to be linked to the extent of AR knockdown, which triggers up-regulation of many genes involved in apoptosis, cell cycle arrest, and inhibition of tumorigenesis and protein synthesis. Our findings provide proof of principle that in vivo knockdown of AR is a viable therapeutic strategy to control and possibly eradicate prostate cancers that have progressed to the lethal castration-resistant state.

Because AR is central in the development of castration-resistant prostate cancer, AR knockdown has been proposed as an additional therapy after failure of androgen ablation (19). The availability of an in vivo tumor model system for AR knockdown is hindered by the failure of cells depleted of the AR protein to grow as xenografts in mice (8). In the present study, we investigated whether AR knockdown could be used as effective therapy to treat prostate cancers that had already progressed to androgen independence. To test this, we used C4-2 cells, a prostate cancer cell line that can grow in the absence of androgens, which, like most castration-resistant clinical prostate cancers, expresses high levels of AR and secretes prostate-specific antigen (PSA) even in an androgen-deprived environment. We found that inducible knockdown of AR with short hairpin RNA (shRNA) in well-established C4-2 xenograft tumors (∼450 mm³), grown in castrated mice, resulted in inhibition of PSA expression and tumor growth in 50% of the animals and complete tumor regression, as well as disappearance of PSA, in the remaining animals. To our knowledge, this is the first demonstration that knocking down AR is an effective therapy to treat prostate cancers that have progressed to the hormonal refractory state.
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Immunohistochemistry for AR and Ki67. Immunohistochemical analyses were done on formalin-fixed, paraffin-embedded tissues, as before (23). Antibodies used were as follows: AR (1:100; Santa Cruz Biotechnology) and Ki67 (1:500; Lab Vision Corporation). Slides were scanned using a BLISS scanner system from Bacus Laboratories, Inc. (24).

Statistical analysis. Microarray data were analyzed statistically using a one-way ANOVA test, with \( P < 0.05 \) considered to indicate significance. Student’s \( t \) test (two-sided) was used to evaluate statistically significant differences in all but the microarray experiments. Results are expressed as mean ± SE with at least three biological replicates. A \( P \) value of \( <0.05 \) was considered significant.

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treatment of scrambled shRNA-expressing cells compared with that in the absence of DOX, whereas DOX-treated AR shRNA-expressing cells exhibited significantly reduced levels of AR mRNA by 67 ± 11% and protein by 63 ± 8% relative to control

<p>| Table 1. Confirmation of microarray findings by real-time RT-PCR |</p>
<table>
<thead>
<tr>
<th>Gene symbol</th>
<th>Genbank accession no.</th>
<th>Description</th>
<th>Fold change ARRAY</th>
<th>Fold change RT-PCR</th>
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<tr>
<td>ATR</td>
<td>Y09077</td>
<td>Ataxia-telangiectasia mutated and Rad3-related, checkpoint function in DNA damage repair</td>
<td>1.9</td>
<td>1.5</td>
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<tr>
<td>Casp6</td>
<td>U20536</td>
<td>Caspase 6, a component of the apoptosis pathway</td>
<td>2.1</td>
<td>1.2</td>
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<tr>
<td>CX3CR1</td>
<td>BC028078</td>
<td>A chemotactic receptor for the CX3C chemokine</td>
<td>3.7</td>
<td>2.2</td>
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<tr>
<td>EAF2/U19</td>
<td>BC014209</td>
<td>ELL (eleven-nineteen lysine-rich leukemia) associated factor 2, also known as U19 (up-regulated gene 19), apoptosis inducer/tumor suppressor</td>
<td>4.4</td>
<td>1.2</td>
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<td>EFNA2</td>
<td>CN408347</td>
<td>Ephrin-A2, ligand for Eph family receptors, EFN/EPH signaling pathway networks with the WNT signaling pathway during embryogenesis, tissue regeneration, and carcinogenesis</td>
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<td>1.6</td>
</tr>
<tr>
<td>EIF2AK3</td>
<td>AF193339</td>
<td>Eukaryotic translation initiation factor 2-α kinase 3</td>
<td>2.6</td>
<td>1.5</td>
</tr>
<tr>
<td>IHPK2</td>
<td>AL117458</td>
<td>Inositol hexaphosphate kinase 2, growth suppressor and apoptosis enhancer during cell stress</td>
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<td>1.8</td>
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<tr>
<td>NFATC1</td>
<td>U80919</td>
<td>Nuclear factor of activated T cells</td>
<td>3.0</td>
<td>1.7</td>
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<tr>
<td>PRKRIR</td>
<td>AF801567</td>
<td>Protein kinase, interferon-inducible double-stranded RNA-dependent inhibitor, 52-kDa repressor of the inhibitor of the protein kinase; also known as death-associated protein 4; inhibits RNA-dependent protein kinase which plays a role in antiviral defense mechanisms</td>
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<td>AF115573</td>
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<td>SH3GLB1/BIF-1</td>
<td>AB007960</td>
<td>SH3-domain GRB2-like endophilin B1; also known as Bif-1 (Bax-interacting factor-1), CGI-61, KIAA0491, dJ612B15.2; a component of the apoptosis pathway as a novel Bax/Bak activator</td>
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<td>2.1</td>
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<tr>
<td>UBE1DC1</td>
<td>AY253672</td>
<td>Ubiquitin-activating enzyme E1-domain containing 1 isoform 1, a member of the E1-like activating family</td>
<td>1.7</td>
<td>1.2</td>
</tr>
</tbody>
</table>

![Fig. 3. Efficiency of AR knockdown in C4-2 xenograft tumors. C4-2 cell lines containing DOX-inducible AR shRNA or scrambled shRNA were s.c. injected into male nude mice. Serum PSA was monitored weekly, and when it reached 50 to 75 ng/mL, 50% of the mice were castrated and all the mice were given DOX in their drinking water (200 μg/mL). Tumor tissues were removed, flash frozen in liquid nitrogen, lysed in radioimmunoprecipitation assay buffer and homogenized with a 2-ml Dounce apparatus. Protein (50 μg) was electrophoresed, blotted, and probed for AR, PSA, and vinculin (for normalization). The results are shown for tumors expressing AR shRNA before treatment (lane 1), from castrated hosts at day 80 (lane 2) or noncastrated hosts at day 94 (lane 3); tumors expressing scrambled shRNA before treatment (lane 4), in castrated hosts at day 52 (lane 5) or noncastrated hosts at day 66 (lane 6).](image-url)
This shows that, although C4-2 cells are castration-resistant, they still contain a functional AR, which is required for PSA activation. Taken together, these findings indicate that C4-2 cells are still dependent on AR for activation of downstream target genes.

To assess the effect of induced AR shRNA expression on the growth of C4-2 cells in vitro, C4-2 cells containing DOX-inducible shRNAs were cultured up to 8 days in the presence of DOX. Induction of AR shRNA resulted in a significant inhibition of growth, such that, by day 8, the number of AR shRNA-expressing cells were reduced by 76\% in the presence of hormone and by 60\% in the absence of hormone relative to the scrambled shRNA control (Fig. 2C), indicating that these castration-resistant cells still require AR for optimal growth.

Effects of AR shRNA on gene expression in androgen-deprived C4-2 cells. The availability of AR shRNA-expressing C4-2 cells afforded us an opportunity to study the influence of AR knockdown on global gene expression using oligonucleotide gene microarrays. To mimic hormone refractory prostate cancer after androgen ablation therapy in the clinic, the shRNA-expressing C4-2 cells were grown in the absence of hormone and in the presence or absence of DOX. AR shRNA-expressing cells + DOX were compared with the controls (see Materials and Methods). A total of 327 genes were found to be differentially expressed at least 1.7-fold greater or 1.7-fold less than those of the controls (P < 0.05) due to AR knockdown (see Supplementary Table S2). Of these, 163 were up-regulated and 164 were down-regulated compared with controls. Based on biological relevance and magnitude of fold changes, we selected 12 genes (Table 1) of the 327 genes that were significantly differentially expressed for evaluation using qRT-PCR. Although the fold change in expression defined by qRT-PCR was different from that observed by gene microarray analysis, the trends were consistent for each respective gene examined (Table 1). The AR and PSA genes were also included as controls and were consistently down-regulated (data not shown). Because AR is known to prevent apoptosis in prostate cells, it is not surprising that some of the genes, such as CASP6, EAF2, IHPK2, and SH3GLB1, which were up-regulated, are involved in apoptosis. Cellular stress induced by loss of AR resulted in increased expression of stress response genes, such as ATR, which encodes a DNA checkpoint kinase, as well as EIF2AK3, encoding a protein that, through its substrate eIF-2\alpha, inhibits protein translation and induces apoptosis. Some of these genes (EAF2, IHPK2) code for proteins that display tumor suppressive functions; hence, increased expression should lead to reductions in cell proliferation and cell survival. Overall, the majority of the genes listed are apoptotic and cell stress response genes that were up-regulated through the loss of AR.

In vivo efficacy of AR shRNA in C4-2 xenografts. To assess the in vivo effect of AR knockdown on AR and PSA proteins, antibiotic-selected DOX-inducible AR shRNA or scrambled shRNA-expressing C4-2 cells were s.c. injected into the flanks of male athymic mice, as described previously (20). When serum PSA levels reached 50 to 75 ng/mL, half of the mice were castrated and all the mice were given DOX (200 \mu g/mL) in their drinking water. Tumors were removed at various time points,
and tissue levels of AR and PSA proteins were assessed by Western blot analyses. Figure 3 shows that tumors expressing scrambled shRNA, in untreated (lane 4), castrated (lane 5), and noncastrated (lane 6) hosts, had readily detectable amounts of AR and PSA proteins. By comparison, in AR shRNA-expressing tumors, barely detectable AR and very low levels of PSA (<30%) were observed (lanes 2 and 3) after extended periods of DOX treatment relative to untreated control (lane 1). These in vivo studies showed that knockdown of AR in xenografts could be sustained for a long period of time (80-94 days) and was more effective than castration alone in reducing PSA protein (lanes 2, 3, and 5). Interestingly, reduction of PSA protein was more pronounced in the castrates than in the noncastrates (lanes 2 and 3), suggesting that residual levels of AR remaining after knockdown can still be activated when there is a large amount of androgen present. On the other hand, a reduced level of androgen after castration is no longer sufficient to activate the low level of AR, indicating that AR knockdown is still crucial for down-regulation of PSA under androgen-deprived conditions.

Effects of AR knockdown on serum PSA and growth of C4-2 tumors in castrated hosts. C4-2 xenograft tumors were grown in castrated hosts to ensure that they were indeed castration-resistant. In the castrates, tumor take was 71% in AR shRNA inducible lines and 93% in scrambled shRNA lines. This is in stark contrast to our finding with LNCaP cells, which showed no tumor take in castrated males, confirming that C4-2 cells are indeed able to grow under androgen-deprived conditions. When serum PSA levels reached 50 to 75 ng/mL, the mice were given DOX in their drinking water. Figure 4A shows serum PSA levels in mice after treatment with DOX to induce AR shRNA or scrambled shRNA. As anticipated, serum PSA for the scrambled shRNA xenograft group continued to increase with DOX treatment and, by day 17, had increased to 344 ± 69% of pretreatment levels. For the AR shRNA xenografts, knockdown of AR resulted in a rapid and sustained decrease in serum PSA, which remained low for >50 days observed in these experiments. Serum PSA reached nadir level at day 17 with an average PSA level of 27 ± 9% of that measured before treatment. After this point, the PSA levels fluctuated slightly but stayed low, such that, by day 52, they were 31 ± 10% of pretreatment levels. These results indicate that suppressing AR protein levels can dramatically reduce PSA production even in castration-resistant C4-2 tumors.

In addition to effects on serum PSA levels, knocking down AR had a major effect on tumor volume. At the time of treatment, the tumors had relatively large volumes averaging 519 mm³ (150-729 mm³/mouse, n = 10) in the scrambled group and 380 mm³ (108-706 mm³/mouse, n = 10) in the AR shRNA group, which were not significantly different (P = 0.13). For the scrambled shRNA tumor group, addition of DOX did not result in any regression. Rather, the tumor volume increased such that, by day 52, tumors had volumes which were 535 ± 145% (mean ± SD, n = 5) of their pretreatment volumes (Fig. 4B). In contrast, the AR shRNA group had volumes averaging only 84 ± 33% of pretreatment sizes at day 52 (Fig. 4B), with the AR shRNA group being 6-fold smaller than the scrambled shRNA group (P < 0.006).

A close inspection of the data revealed two apparent subgroups in the AR shRNA-expressing C4-2 tumors, which could be segregated on the basis of how their tumor volumes changed over time (Fig. 4C). With the first group (nonregressors), tumor volumes were essentially static over the 52-day treatment period.
and growth of castration-resistant C4-2 tumors and that the correlation between the growth of C4-2 cells and the expression of AR and Ki67, implies that AR is necessary for maintenance of tumor volume and serum PSA.

Immunohistochemical analysis of AR and Ki67 in C4-2 tumors. Immunohistochemical analysis of the xenograft tissue showed co-occurrence of Ki67 (a marker of cell proliferation) and AR staining for all AR shRNA-expressing xenografts. In the regressing subgroup, a sample that was removed at day 45 showed no AR or Ki67 staining (data not shown). H&E staining of a tumor from the same subgroup, which did not completely regress by day 52, showed that ~50% to 60% of the tissues were tumor tissue, with the remainders being capsular and hemorrhagic tissue (Fig. 5A). Both AR and Ki67 staining were seen to colocalize in the same small (~10%) region of the tumor (Fig. 5A). The absence or occasional appearance of staining for AR in regressing tumors indicates that AR was predominantly lost in this subset of tumors. By comparison, H&E staining of tumors from the nonregressed subgroup showed that ~70% contained tumor tissue with the rest being hemorrhagic, necrotic, and fibrous tissue (Fig. 5B). Both AR and Ki67 staining was seen in all of the tumors (Fig. 5B), indicating that AR was not eliminated in this subgroup. Notably, in the scrambled shRNA-expressing xenografts, there was intense staining of tissue for AR and corresponding Ki67 throughout all of the samples (data not shown). The correlation between the growth of C4-2 cells in vivo and the presence of AR protein, as well as the similar tissue distribution of AR and Ki67, implies that AR is necessary for maintenance and growth of castration-resistant C4-2 tumors and that the relative extent to which it can be knocked down by AR shRNA dictates whether the tumors undergo regression.

Discussion

Progression of prostate cancers to the castration-resistant stage implies that cancer cells have ceased to rely on androgen signaling pathways for maintenance of their growth. However, even after androgen-deprivation therapies, AR may still play a pivotal role. Various approaches, including anti-AR antibodies, hammerhead ribozymes, RNA interference, and chemicals, such as LAQ284 and 3,3′-diindolylmethane, have been tested for their abilities in vitro to reduce the level of AR and have shown associated growth inhibition and, in some cases, apoptosis in androgen-independent prostate cancer cell lines grown in culture (26–31). An indirect approach has been to use 17-allylamino-17-demethoxygeldanamycin to inhibit hsp90 function, which results in AR degradation and delayed growth of the androgen-independent CWRSA6 tumors (32). In the present study, we created a C4-2 castration-resistant human prostate cell line with a tetracycline-inducible shRNA, which directly targets AR and in which we were able to induce 63% to 86% reduction in AR mRNA and protein (Fig. 1A and B). This decrease was accompanied by a reduction in mRNA expression of the AR target gene PSA (Fig. 2A). Furthermore, in transactivation and cell proliferation assays, induction of AR shRNA inhibited activation of the PSA-Luc reporter (Fig. 2B) and growth of the cells (Fig. 2C), demonstrating that, even in castration-resistant prostate cancer cells, AR still activates downstream target genes and is still required for cell growth.

The observation that, in castration-resistant cells, PSA is still dependent on the presence of AR for activation prompted us to examine the status of other AR-regulated genes. To mimic the hormone refractory status of prostate cancer from patients who failed androgen deprivation therapy, we did gene array analysis on RNA isolated from controls and AR knockdown cells in the absence of hormone. Gene expression profiling revealed that 327 genes were differentially expressed. Based on their functional biology and magnitude of change, 12 genes were further validated using qRT-PCR (Table 1). We found that AR knockdown resulted in an up-regulation of a group of genes which play a critical role in apoptosis, such as CASP6, EAF2/ U19, IHPK2, and SH3GLB1/BIFI1 (Table 1). CASP6 is one of the three “executioner caspases” that exerts its action in the late stages of apoptosis (33). Silencing of AR in LNCaP and C4-2 cells using small interfering RNA has been shown to increase CASP6 activation and apoptotic cell death (29). In rat ventral prostate, castration-induced increases in expression level and activation of CASP6 have also been observed (34). Similarly, EAF2/U19 is an AR-regulated (35) apoptosis inducer with tumor suppressive activities and, when overexpressed, markedly induces apoptosis and inhibits prostate tumor growth (36). Its expression has been shown to increase with AR knockdown in LNCaP cells (27). Notably, androgen can inhibit U19-induced apoptosis in LNCaP cells, but not in PC3 prostate cancer cells, which lack a functional AR. Another growth-suppressive and apoptosis-enhancing gene we found to be up-regulated by AR knockdown is IHPK2. IHPK2 protein has many features of a tumor suppressor, and its overexpression has been shown to sensitize ovarian carcinoma cells to the apoptotic effect of cytotoxic drugs, IFN-α2 and IFN-β, as well as radiation (37). We also showed that SH3GLB1/BIFI1 is up-regulated with AR knockdown. This gene is an important component of the mitochondrial pathway for apoptosis as a Bax/Bak activator, and loss of this proapoptotic molecule can contribute to tumorigenesis (38).

Other genes that were found to be up-regulated by AR knockdown in our studies include ATR, RASA2/GAP1m, and EIF2AK3. ATR encodes a DNA damage checkpoint kinase. Integrity of the ATR signaling pathway is necessary to maintain genomic stability after cellular assault, and mutations compromising this checkpoint are known to result in cancer progression (39). ATR expression increased 1.9-fold after AR silencing, suggesting that this may be a mechanism through which C4-2 cells defend against cellular stress caused by loss of AR. RASA2/GAP1m is an inhibitor of the Ras signaling pathway (40). Ras is often activated in prostate cancer, and Ras signaling represents a converging point for numerous extra-cellular signaling pathways (41). Up-regulation of GAP1m by AR knockdown may be another means of attenuating Ras signaling, thereby inhibiting growth and cell survival. EIF2AK3 is a stress and cell growth–related gene involved in repression
of global protein synthesis (42). Therefore, in castration-resistant prostate cancer, AR acts like an oncogene, activating genes involved in proliferation and cell survival. Conversely, AR knockdown triggers genes involved in apoptosis and cell cycle arrest and alters genes involved in tumorigenesis and protein translation. Wright and colleagues (43) observed an increase in two of four neuroendocrine markers tested after small interfering RNA knockdown of AR in an androgen-independent LNCaP subtype, which had been selected to survive an in vitro steroid-depleted environment. In our microarray analyses with C4-2 cells, we did not see changes in neuroendocrine markers nor was there any obvious morphologic transdifferentiation of these cells after AR shRNA induction. Presumably, the adaptive strategies used to generate the AR-dependent, castration-resistant C4-2 cells in vivo result in different cells from those generated under in vitro conditions.

Our xenograft tumor studies showed that AR shRNA is very effective in knocking down AR (Fig. 3) and reducing serum PSA, as well as preventing growth of C4-2 tumors (Fig. 4). To ensure that only castration-resistant cancer cells were present, the C4-2 tumors were grown in castrated hosts. Knockdown of AR led to a rapid reduction of serum PSA and tumor growth (Fig. 4A and B). Interestingly, 50% of the tumors underwent complete regression with an accompanying reduction of serum PSA (Fig. 4C and D). Upon immunohistochemical examination of AR and Ki67 for the two subgroups (Fig. 5), it seemed that in the regressing tumors there was either very low levels or complete absence of AR protein, whereas in the nonregressing tumor subgroup there was AR staining, indicating that AR was not eliminated in these tumors. Furthermore, although the cell proliferation marker Ki67 was very low or undetectable in the regressing tumors, in the nonregressing subgroup, it colocalized with AR staining, suggesting that the tumor volume was maintained as a consequence of continued AR stimulation of growth.

One possible explanation for the difference in the two responses can be a technical issue involving the mechanics and site of lentiviral integration, such that some cells lose the AR shRNA cassette more readily than others, particularly when the antibiotic used for selection is no longer present in vivo. A further possibility is that a subpopulation of C4-2 cells in the xenografts is trying to sustain AR expression through adaptive mechanisms, such as AR gene amplification, increased AR protein expression, or enhanced transcriptional activity. Whereas the exact molecular mechanism underlying the two different responses remains to be elucidated, our results do show that even incomplete knockdown of AR is sufficient to inhibit substantial tumor growth whereas complete elimination of AR leads to regression and disappearance of a castration-resistant tumor.

In conclusion, we believe that this is the first study to show that AR knockdown with shRNA in large castration-resistant prostate tumors can result in inhibition of tumor growth and reduction in serum PSA levels, as well as, in some cases, complete tumor regression and disappearance of serum PSA. Furthermore, this is likely the result of up-regulation of genes that promote apoptosis and cell cycle arrest, as well as genes that regulate protein synthesis and tumorigenesis. Our findings indicate that in vivo knockdown of AR is a viable therapeutic strategy to control and possibly eradicate prostate cancers that have progressed to the castration-resistant state.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

We thank Anne Haegert, Mary Bowden, and Estelle Li for technical assistance and Robert H. Bell for statistical analyses.

References

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