Prostate Cancer Progression, Metastasis, and Gene Expression in Transgenic Mice

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ABSTRACT

We previously reported that a transgenic mouse line containing the fetal globin promoter linked to the SV40 T antigen (T Ag) viral oncogene (Gy/T-15) resulted in prostate tumors. In this study, we further explored tumor origin, frequency, invasiveness, androgen sensitivity, and gene expression pattern. T Ag was detected in adult but not fetal and neonatal prostates, suggesting a role for androgens in tumor progression. However, castration shortly after prostate morphogenesis did not prevent tumor development, suggesting an androgen-independent phenotype. Tumors originated within ventral or dorsal prostate lobes and involved intraepithelial neoplasia, rapid growth in the pelvic region, and metastasis to lymph nodes and distant sites. In addition, the primary cancers could be propagated in nude mice or nontransgenic mice. Seventy-five percent of hemizygous and 100% of homozygous transgenic males developed prostate tumors, suggesting a T Ag dosage effect. Biochemical characterization of advanced tumors revealed markers of both neuroendocrine and epithelial phenotypes; markers of terminal differentiation are lost early in tumorigenesis. Tumor suppressor genes (p53 and Rb), normally bound to T Ag, were up-regulated; bcl-2 proto-oncogene, which prevents apoptosis, was slightly up-regulated. Myc, a stimulus to cell cycle progression, was unchanged. We propose the Gy/T-15 transgenic line as a model of highly aggressive androgen-independent metastatic prostate carcinoma with features similar to end-stage prostate cancer in humans.

INTRODUCTION

Prostate cancer is increasingly recognized as a major health problem; it is the most frequently diagnosed cancer in men in the United States and the second leading cause of male cancer deaths. Estimates for 1996 predict that approximately 317,100 men will be diagnosed with prostate cancer and 41,400 will die of the disease (1). Many diagnosed patients undergo surgery or radiation treatment, which is most effective on localized, organ-confined prostate cancer (2, 3). In non-organ-confined and metastatic prostate disease, androgen ablation is effective in 60–80% of the patients, resulting in tumor regression and improved prognosis (4). However, after a period of time, an androgen-independent, or unresponsive, prostate carcinoma occurs in these patients, possibly due to the selection of a small number of androgen-independent cells (5) or to the adaptation of formerly androgen-responsive cells into androgen-independent (6) cells. These tumors, as well as initially androgen-unresponsive prostate tumors, often metastasize to the lymph nodes, lung, and bone, resulting in poor patient prognosis and short survival time (4). Currently, there is no effective treatment for androgen-independent metastatic prostate cancer (reviewed in Ref. 7).

Prostate adenocarcinoma in humans consists predominantly of epithelial cells arranged in acinar structures surrounded by stromal or mesenchymal cells, whereas metastatic or poorly differentiated prostate carcinoma consists of nests of anaplastic epithelial cells separated by bands of fibrovascular stroma (8). Benign prostate hyperplasia consists of a hyperproliferation of epithelial and stromal cells resulting in an enlarged gland (9). Normal prostate, as well as benign and metastatic prostate carcinomas, also contains a few isolated, dispersed neuroendocrine cells (10, 11). Some (10, 12) but not all (11) evidence suggests that androgen-independent metastatic prostate cancer exhibits more neuroendocrine cell characteristics. In addition, a small subset of prostate carcinomas are of the pure neuroendocrine or small cell type (13), similar to small cell lung carcinomas (14). It has been proposed that prostate epithelial (luminal and basal) and neuroendocrine cells originate from the same precursor cell (11, 15–18).

Animal models for prostate cancer have yielded valuable information on the progression of the disease. However, the traditional models [androgen/mutagen induction in rats (19, 20), Dunning rat transplantation (21), xenografts in nude mouse (22), and mouse reconstitution system (23)] share the disadvantage of the lack of a natural microenvironment (24–26), i.e. the prostate compared to s.c. or kidney capsule. Such models may also produce infrequent tumors or require hormone/mutagen treatment for tumor production (19, 20). Recently, these disadvantages have been overcome by models in which targeted expression of SV40 T Ag2 to prostate epithelial cells in transgenic mice results in carcinomas (24, 25). We previously reported that the transgenic mouse line Gy/T-15 expressing T Ag regulated by the human fetal globin promoter results in prostate carcinomas with mixed neuroendocrine and epithelial cell characteristics (26). Here we report on the potential of Gy/T-15 as a model of prostate cancer and present our investigations of tumor origin, frequency, metastasis location, androgen sensitivity, and the expression of a variety of genes.

MATERIALS AND METHODS

Hemizygous and Homozygous Transgenic Mice. Construction of the fetal Gy-globin/SV40 T Ag fusion DNA, developmental regulation, and initial characterization of the subsequent multiple tumors in the Gy/T-15 transgenic line were described previously (26, 27). Transgenic mice were identified by slot blot analysis of neonatal and adult tail or fetal yolk sac DNA using random primed 32P-labeled 2.7-kb SfiI-BamHI T Ag probe. Transgenic hemizygous males were mated with transgenic hemizygous females, and their progeny were identified by slot blot analysis of tail DNA. Adult progeny with 2-fold greater intensity in the T Ag signal (normalized to the single copy mouse vimentin gene; Ref. 28) compared to hemizygous signals were identified as homozygous transgenic mice.

Prostate Tumor Propagation in Nude and Nontransgenic Mice. Small pieces of prostate tumor tissue (1–2 mm3) were transplanted s.c. to the side flanks of several BALB/c-nu/nu nude mice (male and female), and tumor growth was determined weekly. Similar prostate tumor tissue transplantations were done on nontransgenic (CBA × C57) littersmates as hosts.

Histological Sections of Early Prostate Tumors. Histological examination was undertaken for early tumor detection in eight 20–24-week-old transgenic males, seven without visible prostate tumors and one with a small visible...
prostate tumor. The bladder was lifted with forceps, and an incision was made at the mid-urethra, not including the bulbourethra gland. Tissue blocks containing prostate, bladder, seminal vesicles, and coagulating and ampullary glands were laid flat on a small paper, fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned at 5 μm, and stained with H&E.

**Prostate Tumor Formation in Castrated Transgenic Mice.** Eight 4–6-week-old transgenic mice were castrated via the scrotal route under xylazine/ketamine (1:10) anesthesia. After 16 weeks, the animals were examined histologically for the onset of prostate tumors as described above.

**Western Blot Analysis.** Tissues from transgenic and normal mice were prepared for Western blot analysis by mechanical dispersion in hot (70°C) lysis buffer containing 66 mM Tris-HCl (pH 6.8); 2% SDS; 5 mM EDTA; 5 mM EGTA; 10 mM phenylmethylsulfonyl fluoride; 10 mM sodium vanadate; 10 mM sodium fluoride; 10 mM N-ethylmaleimide (29). Samples were boiled for 10 min and centrifuged for 20 min in an Eppendorf microfuge. The supernatant was collected, and protein concentrations were determined with the Bio-Rad protein assay (Bio-Rad Laboratories, Hercules, CA). After separation of 10 μg of protein by SDS-PAGE, proteins were transferred by electrophoresis to Immobilon-P membrane (Millipore, Bedford, MA) and incubated overnight at 4°C in 10% nonfat dry milk, PBS, and 0.1% Tween 20. Primary antibodies specific for epithelial cells (i.e. those expressing cytokeratin 8 (PCK-26; 1/300 dilution; Sigma, St. Louis, MO) and mouse dorsolateral prostate secretory proteins (1/5000 dilution; Ref. 30) were diluted in PBS containing 3% BSA, 2% polyethylene glycol 6000, 1% gelatin, and 0.1% Tween 20, incubated for 1 h at room temperature, and washed in PBS and 0.1% Tween 20. Membranes were then incubated with alkaline phosphatase-conjugated secondary antibody (antirabbit IgG (Sigma); antimouse IgG (Boehringer Mannheim, Indianapolis, IN)) for 1 h at room temperature, washed in PBS and 0.1% Tween 20, and analyzed by exposure to X-ray film (X-Omat; Kodak, Rochester, NY) using Lumi-phos Plus (Boehringer Mannheim).

**RNase Protection Analysis.** RNA was isolated from transgenic and non-transgenic animals by the LiCl-urea method (31). T Ag RNA was detected in most fetal and adult tissues of transgenic males using reverse transcription-PCR (data not shown). Thus, we used the less sensitive but more quantitative RNase protection assay to detect low levels of T Ag mRNA with a 32P-labeled SP6 polymerase-synthesized antisense RNA probe as described previously (26, 27). Mouse chromogranin A mRNA levels were measured with 32P-labeled T7 polymerase-synthesized antisense RNA probe from BamHI-digested EcoRI-Stul/Bluescript-SK (32). The following pTRIPLEScript-mouse antisense DNA templates were used to synthesize 32P-labeled antisense RNA probes: p53, retinoblastoma Rb, c-myc, and bcl-2 (Ambion, Austin, TX). Mouse GAPDH mRNA was measured using a 32P-labeled T7 polymerase-synthesized antisense RNA probe from SvuI-digested pTRIPLEScript GAPDH DNA (Ambion). Ten μg of total RNA were hybridized to individual or a combination of antisense RNA probes (p53/Rb/GAPDH and myc/bcl-2/GAPDH) at 37°C for 16–20 h and digested with RNase mixture (Ambion) for 30 min at 37°C. RNase digestion products were analyzed by electrophoresis on polyacrylamide-urea gels and autoradiography.

**T Ag Expression in Fetal, Neonatal, and Adult Prostates.** Transgenic fetal and neonatal males were identified by the position of the testis or ovary during tissue dissection. Tissue from three pooled fetal (16.5 days), four pooled 2.5-day-old neonatal males, one 7.5-day-old neonatal male, four 11-week-old adult males, and four 16–20-week-old adult males was isolated, and RNA was prepared and analyzed for T Ag expression as described above. Fetal prostates were isolated as described previously (33).

**RESULTS**

Previous work with the GyT-15 transgenic line has shown that T Ag is expressed in embryonic tissue (27) but not adult tissue before tumor formation (26); however, transgenic males developed T Ag-expressing prostate tumors by 5–7 months (26). To better understand why these tumors develop, we examined in more detail the T Ag expression pattern in relation to prostate tumor progression.

**T Ag Expression in Adult but not Fetal or Neonatal Prostates.** To determine T Ag expression in transgenic male fetal, neonatal, and adult tissues, including prostate, we used an optimized RNase protection assay with minimal background. We found T Ag expression in fetal tissues (n = 3 pooled 16.5-day), with diminishing or repressed levels in neonatal (n = 4 pooled 2.5-day; n = 1 7.5-day) and adult mice (n = 8, 11–20-week; Fig. 1, A and B). In contrast, T Ag was expressed in adult prostate (seven of eight samples), but not fetal and neonatal prostate (Fig. 1A, compare fetal Lane 13, neonatal Lane 13, and adult Lane 9). Because prostate morphogenesis requires androgens (34, 35), these data point to an androgen-dependent component in tumor progression, similar to that of human prostate cancer.

**Prostate Tumor Development and Metastasis.** Male GyT-15 transgenic mice developed palpable tumors in the urogenital area between 16 and 24 weeks of age (see Fig. 4). These tumors grew very rapidly and resulted in bladder obstruction, possible kidney failure, and a moribund state. Advanced tumors reached 25–30 mm in diameter at a location between the testis and the seminal vesicle, at the base of the bladder (Fig. 2, A and B). The invasive properties of the tumors...
were frequently demonstrated by visible tumor metastasis to the renal lymph node (Fig. 2B; Table 1), adrenal glands, and kidneys.

Before tumor formation, adult transgenic males expressed T Ag only in their prostates (Fig. 1). Therefore, we used the RNase protection assay to identify potential micrometastasis to the lung and bone, which are common metastatic sites in human prostate cancer; our results suggested micrometastasis of prostate tumor cells to the lung, bone, and thymus (Fig. 3, A and B; Table 1). The metastatic phenotype was further confirmed by propagation in nude mice and nontransgenic mice, which resulted in a similar histological tumor pattern (data not shown).

Prostate Tumor Frequency in Hemizygous and Homozygous Transgenic Mice. Forty hemizygous transgenic males were necropsied at different ages and examined for the presence of prostate tumors (Fig. 4). We found that prostate tumor development began in these animals between 16 and 20 weeks; by 32 weeks, only 10% of the hemizygous males were free of tumors. Of the 28 transgenic males older than 20 weeks, 21 (75%) developed prostate tumors; individual animals had an adrenal tumor, a hibernoma, and a seminoma, and 4 animals had no visible tumor formation. In transgenic male mice between 16 and 20 weeks, 100% of hemizygotes (n = 8) developed prostate tumors, whereas 50% of hemizygotes (n = 20) developed prostate tumors. These findings suggest that the penetrance of prostate tumor development is complete in the homozygous transgenic males.

Early Prostate Tumor Development. To further confirm the tumor origin site as the prostate and not other accessory glands in the urogenital area, seven transgenic males 16—20 weeks old without a visible tumor and one with a small visible tumor were examined histologically. The ventral and dorsal lobes of the prostate can be distinguished from the bladder, seminal vesicles, coagulating glands, and ampulla based on anatomical location and tissue and cell morphology (34, 35). The ventral lobe of the prostate is located farther from the seminal vesicle, whereas the dorsal lobe of the prostate extends to the backside of the urethra, closer to the seminal vesicle (34, 35). Two males showed early tumor formation, one at the ventral (Fig. 5A) and the other at the dorsal lobe of the prostate (Fig. 5B). Similar results were obtained in additional males. This analysis is important because a previous report of a transgenic mouse model of benign prostate hyperplasia (36) was subsequently determined to be hyperplasia of the ampulla.3

PIN. Higher magnification of the early ventral prostate tumor showed a histological pattern similar to that of the advanced prostate tumors (26), except that prostatic acini or their remnants remained entrapped in the tumor nodule (Fig. 6A), characteristic of prostatic...

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### Table 1 Tissue locations and frequency of prostate tumor metastasis in GyT-15 males (n = 7)

<table>
<thead>
<tr>
<th>Tissue location</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>Visible metastasis</td>
<td></td>
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<tr>
<td>Renal lymph node</td>
<td>7/7</td>
</tr>
<tr>
<td>Adrenal</td>
<td>3/7</td>
</tr>
<tr>
<td>Kidney</td>
<td>3/7</td>
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<tr>
<td>Micrometastasis</td>
<td></td>
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<tr>
<td>Lung</td>
<td>4/7</td>
</tr>
<tr>
<td>Bone</td>
<td>2/7</td>
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<td>Thymus</td>
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3 A. A. Donjacour and G. R. Cunha, personal communication.
Expression of Epithelial and Neuroendocrine Markers in Prostate Tumors. We previously stated that prostate tumors contain mixed epithelial and neuroendocrine cell features based on light and electron micrographs (26). We used Western blot analysis to determine if epithelial markers were expressed in the prostate tumors in our model. We found that advanced prostate tumors expressed cytokeratin 8 (Fig. 7A, Lane 7), similar to the human prostate epithelial cell lines LNCaP and PC3 (Fig. 7A, Lanes 1 and 2; see Ref. 38) and to normal mouse prostate (Fig. 7A, Lane 6). However, tumors did not express mouse dorsolateral prostate secretory protein, which is normally found in well-differentiated mouse prostate epithelial cells (30). In addition, the gap-junction-forming protein connexin 32 gene product expressed in normal human (29) and mouse prostate epithelial cells is lost early in prostate cancer progression (data not shown).

Although we were previously unable to detect the presence of neurosecretory granules in electron micrographs of the prostate tumors (26), we have detected high levels of chromogranin A mRNA in primary, metastatic, and transplanted prostate tumors using RNase protection analysis (Fig. 7B, Lanes 3–10). No differences in cytokeratin 8 protein and chromogranin A RNA were observed in prostate tumors from castrated males (data not shown). In addition, parathyroid hormone-related protein (39, 40) was detected in transplanted prostate tumor by immunohistochemistry (data not shown). These results confirm the original observation that GyTf-15 prostate tumors contain mixed epithelial and neuroendocrine cell features.

Expression of p53, Rb Tumor Suppressor, c-myc, and bcl-2 Proto-Oncogene Products. To begin to explore the molecular changes involved in tumor progression, we used the RNase protection assay to compare the levels of p53, Rb, c-myc, and bcl-2 gene products in prostate tumors and normal mouse tissues including prostate. The p53 and Rb RNA levels were found to be higher than the levels in normal prostate (Fig. 8, compare Lanes 6–8), probably because of the inactivation of p53 and Rb by T Ag (41, 42).

The levels of bcl-2 RNA, an inhibitor of apoptosis previously shown to be expressed in androgen-independent prostate cancer (43, 44), were slightly up-regulated compared to the level in normal prostate.
p53 and Rb and the expression of the antiapoptosis bcl-2 gene may play important roles in the formation of Gy/T-15 prostate tumors. We propose that Gy/T-15 can be used as a model of androgen-independent metastatic prostate carcinoma, with similarities to human end-stage prostate cancer.

The progression of the Gy/T-15 prostate tumor resembles the development of human prostate cancer [i.e. from PIN to adenocarcinoma (early tumor) and metastatic prostate carcinoma (advanced tumor)]. However, unlike human prostate cancer, which progresses slowly over a long period of time, the Gy/T-15 prostate tumor progresses very quickly from PIN to metastatic undifferentiated carcinoma. In addition, visible metastatic prostate cells are located primarily in the adrenal gland and kidney, although there is some micrometastasis to the lung and bone, similar to that found in human prostate cancer.

The expression of T Ag in the adult but not fetal and neonatal prostate suggests that androgen-dependent prostate morphogenesis may be necessary for tumor progression. However, castrated Gy/T-15 males still developed prostate tumors, suggesting that the tumors are androgen-independent. It is possible that the males used for castration already had enough androgen stimulation of prostate morphogenesis to initiate tumorigenesis; however, at this age, neither tumors nor abnormal histology was ever observed. Castration at 1–2 weeks (or before androgen stimulation of prostate morphogenesis) would better clarify the role of androgens in tumor progression in young adult males. Thus, unlike most human prostate cancers, which are initially androgen-dependent and then progress to androgen independence, the Gy/T-15 prostate tumor seems to start at or to progress very quickly to an androgen-independent phenotype.

SV40 T Ag is a well-characterized viral oncogene known to bind and inactivate the p53 and Rb tumor suppressor gene products as well as other factors (45, 46). It is likely that increased expression of T Ag in adult prostate leads to tumor progression. p53 and Rb RNA levels in primary (Fig. 8) and metastatic tumors (data not shown) are higher compared to those of normal prostate, recalling previous observations in cell lines and transgenic mice expressing T Ag (41, 42). Thus, tumor progression probably involves the inactivation of p53 and Rb proteins by T Ag. Several reports suggest an important role for numerous tumor suppressor genes including p53 and Rb in the progression of prostate cancer from benign to metastatic carcinoma (reviewed in Refs. 47 and 48). Inactivation of p53 is more common in androgen-independent prostate cancer and seems to be a late-stage event in the progression pathway (49).

Besides removing a block in cell cycle progression, the loss of p53 gene function also probably removes a block to apoptosis (50), prostate (Fig. 8, compare Lanes 6–8). The levels of c-myc RNA, a stimulus to cell cycle progression, were similar in normal prostate and prostate tumor (Fig. 8, Lanes 6–8). In contrast, adrenocortical tumors from transgenic females showed lower levels of Rb and bcl-2 and higher levels of c-myc (Fig. 8, compare Lanes 7–9). These results suggest that the inactivation of tumor suppressor gene products like p53 and Rb and the expression of the antiapoptosis bcl-2 gene may play important roles in the formation of Gy/T-15 prostate tumors.
In summary, we characterized GyfT-15 prostate tumors by analyzing early tumor formation and frequency, metastatic behavior, androgen sensitivity, and gene expression patterns. We propose to use this transgenic line as a model of androgen-independent metastatic prostate carcinoma, with demonstrated similarities to advanced human prostate cancer, or end-stage disease. These transgenic mice should be useful test subjects for chemotherapeutics for the treatment and prevention of androgen-independent metastatic prostate cancer and for a variety of studies of the molecular mechanisms of transformation in the development of prostate carcinoma.

ACKNOWLEDGMENTS

We thank Annemarie Donjacour and Gerald Cunha for generously providing antibodies against mouse dorsolateral prostate secretory proteins, demonstrating to C. P.-S. the dissection of mouse ventral and dorsolateral prostate lobes, and confirming prostate lobes by analysis of light micrographs of early tumors; Alicia De Las Pozas for excellent technical assistance; Carolyn Cray for nude mouse tumor transplants; Douglas Burton for parathyroid hormone-related protein immunostaining; Daniel O’Connor for mouse chromogranin A cDNA; Don Tindall for mouse androgen receptor cDNA; and Semie Capetanaki for mouse vimentin cDNA.

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| p53/Rb tumor suppressor and bcl-2/myc proto-oncogene expression in G-yfT-15 prostate tumors (PT, Lanes 7 and 8) compared to expression in mouse brain (Br, Lane 1), lung (La, Lane 2), liver (Li, Lane 3), kidney (Ki, Lane 4), spleen (Sp, Lane 5), prostate (Pr, Lane 6), and adrenal tumor (AT, Lane 9). GAPDH RNA varies widely in different tissues and is not reflective of the equal amounts (10 µg) of RNA loaded onto the gels. Similar results were obtained in two other experiments from additional tumor samples. Sizes of the protected fragments are 327 nt (Rb), 265 nt (p53), 326 nt (myc), 191 nt (bcl-2), and 135 nt (GAPDH). Autoradiograms were exposed for 17 h (p53, Rb, GAPDH) or 3 days (myc and bcl-2) using two intensifying screens.

Fig. 8. Tumor suppressor and proto-oncogene expression. RNase protection analysis of p53/Rb tumor suppressor and bcl-2/myc proto-oncogene expression in G-yfT-15 prostate tumors (PT, Lanes 7 and 8) compared to expression in mouse brain (Br, Lane 1), lung (La, Lane 2), liver (Li, Lane 3), kidney (Ki, Lane 4), spleen (Sp, Lane 5), prostate (Pr, Lane 6), and adrenal tumor (AT, Lane 9). GAPDH RNA varies widely in different tissues and is not reflective of the equal amounts (10 µg) of RNA loaded onto the gels. Similar results were obtained in two other experiments from additional tumor samples. Sizes of the protected fragments are 327 nt (Rb), 265 nt (p53), 326 nt (myc), 191 nt (bcl-2), and 135 nt (GAPDH). Autoradiograms were exposed for 17 h (p53, Rb, GAPDH) or 3 days (myc and bcl-2) using two intensifying screens.

thereby facilitating cell survival. Higher expression of the antiapoptosis bcl-2 gene in prostate tumors also suggests an important role for apoptosis in tumorigenesis. In contrast, the cell cycle stimulus c-myc was expressed at levels similar to the levels in normal prostate. These results share similarities with observations of metastatic androgen-independent human prostate carcinoma (47, 48).

It has been proposed that androgen ablation therapy of an initially responsive prostate tumor results in a subsequent selection or adaptation to an androgen-independent state (5, 6). Because there is currently no effective treatment for androgen-independent prostate cancer, better understanding of the evolution of this phenotype is critical. Neuroendocrine cells may offer one example of an androgen-independent phenotype, but controversy exists over whether they are more prominent in metastatic prostate cancer (10–12). The identification of intermediate cell phenotypes (i.e. luminal/basal, basal/neuroendocrine, and luminal/neuroendocrine) in normal and neoplastic prostate suggests a plasticity between these cell types and their possible origin from a common stem cell (11, 18). Prostate tumors in the GyfT-15 transgenic line express luminal epithelial cytokeratin 8 protein and neuroendocrine chromogranin A RNA (Fig. 7) and may be similar to a highly metastatic subline of PC3 (16). These mice may offer a better in vivo system for studying the relationships among the multiple epithelial cell phenotypes present in normal and neoplastic prostate.

Two recently published transgenic mouse models of prostate cancer use the androgen-dependent epithelial cell-specific promoters C3 (24) and probasin (25) to target T Ag to the prostate. The resulting prostate carcinomas are also similar to human adenocarcinomas and undifferentiated carcinomas. These promoters presumably target T Ag to mature luminal epithelial cells of the prostate duct, suggesting that these cells can dedifferentiate to form tumors. Because prostate tumors in GyfT-15 mice develop after castration and express cytokeratin 8 and chromogranin A, the target cell expressing T Ag is probably an androgen-independent luminal epithelial cell with neuroendocrine features. Together, these transgenic models should provide insight into the mechanisms of prostate cancer development and the role of androgen-dependent and -independent cell phenotypes.


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