Malignant Transformation in a Nontumorigenic Human Prostatic Epithelial Cell Line

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ABSTRACT

The human prostatic epithelial cell line BPH-1 is normally nontumorigenic in nude mice. The present report demonstrates that this cell line can be permanently transformed by its microenvironment to become tumorigenic. The establishment of a series of tumorigenic sublines based on this parental cell line is described. BPH-1 cells were induced to form tumors either by recombination with human prostatic carcinoma-associated fibroblasts (CAFs) or by exposure to carcinogenic doses of testosterone and estradiol (T+E2) after recombination with rat urogenital sinus mesenchyme. Epithelial cells isolated from these tumors were established as cell strains in culture. When regrafted to nude mice host epithelial cells isolated from CAF- or T+E2-induced tumors were found to be consistently tumorigenic even in the absence of CAF or T+E2. The T+E2-induced cell strains have been designated BPH1TETD-A and -B and the CAF-induced strains are designated BPH1CAFAPTD01 through -08. In vitro, the cells had an epithelial morphology with a less well-defined cobblestone pattern than the parental line. They express SV40 large T antigen, confirming their derivation from the parental BPH-1 line. The BPH1CAFAPTD strains formed colonies in soft agar, whereas the parental BPH-1 cells and the BPH1TETD sublines did not. There was no immunocytochemically detectable expression of androgen (AR), α-estrogen (ERα), or progesterone (PR) receptors by the parental BPH-1 cell line or by any of the tumor-derived cell strains. The cells uniformly coexpressed both basal and luminal cell-type cytokeratins and the basal cell marker p63. When grafted beneath the renal capsule of athymic mouse hosts, all of the tumor-derived cell strains consistently formed tumors. These were predominantly poorly or moderately differentiated squamous or adenocarcinomatous tumors, similar in organization to the primary tumors from which the cell strains were derived. The cell strains continued to express both basal- and luminal-type cytokeratins in vivo. Some of the cell strains also coexpressed vimentin. E-cadherin expression was absent from many of the cells, although patches of cells expressing this marker were seen. The cells continued to express SV40T antigen. These cell strains, which are all derived from a common nontumorigenic progenitor, represent a useful resource for examining genetic and phenotypic changes during carcinogenesis.

INTRODUCTION

The nontumorigenic human prostatic epithelial cell line, BPH-1, can be induced to form tumors either by association with a tumorigenic stromal microenvironment or by treatment with hormonal carcinogens (1–4). This report demonstrates that epithelial cells derived from such tumors have undergone permanent malignant transformation and are tumorigenic in athymic mice. The establishment and characterization of a series of cell strains derived from the nontumorigenic BPH-1 human prostatic epithelial cell line is described.

At present, there are a limited number of models of prostatic carcinogenesis (5). Prostate cancer is a slowly developing disease of aging men and dogs and has an extremely low incidence of spontaneous occurrence in laboratory animals. A variety of methods, including hormonal induction and targeted expression of oncogenes have been used to induce prostate cancer in rats and mice (6–9). In a few cases, it has been possible to examine the range of tumor types derived from a common rodent precursor cell or tumor strain (10, 11).

There is a dearth of model systems to examine the induction of tumors in human prostatic epithelium. Although models that manipulate already malignant human prostatic cells and tissues are available (12), there are few models in which cancer is induced in a previously benign human prostatic epithelium. Baes et al. and Jackson-Cook et al. (13, 14) used repeated cycling of the generally nontumorigenic P69SY40T cell line through nude mouse hosts to produce tumorigenic sublines. Webbet et al. and Bello et al. (5, 15) have used both Ki-ras and the chemical carcinogen methylnitrosourea (MNU) to derive a series of tumorigenic sublines from the nontumorigenic RWPE-1 line. SV40T was introduced into primary cultures of prostatic epithelial cells using the Zipneo viral construct containing a selectable neo cassette to generate the immortalized BPH-1 cell line (16). SV40T interacts with and inactivates both p53 and pRb, thus eliminating these two important tumor suppressor pathways (17). However many SV40T-expressing cells, including the BPH-1 cell line, are not tumorigenic (16, 18). The production of tumors in immuno-incompetent hosts is a clear marker of tumorigenicity and is easily demonstrated. The opposite of tumorigenicity (nontumorigenicity) implies an inability to form tumors. However the mere absence of tumors after transplantation into an immuno-incompetent host does not of itself prove that a cell line or graft is “nontumorigenic.” This terminology requires that the cells or tissues, which were grafted or injected, have the ability to survive at the graft site and not to grow to form a tumor. We have previously demonstrated that parental BPH-1 cells grafted to athymic hosts can be recovered from the graft site for up to 1 year after grafting and that these cells do not form tumors at the site (0/125 attempts; Ref. 4). BPH-1 cells can however be considered to be genetically initiated, in that they have suffered a major genetic insult (attributable to the expression of SV40T), which renders them susceptible to further genetic damage and to progression along a pathway to malignancy.

Prostatic carcinogenesis involves genetic alterations to epithelial cells including activation of oncogenes (19–22) and inactivation of tumor suppressor genes (23, 24). Alterations in tumor suppressor genes such as the RB and p53 genes have been suggested to play a role in the development of human prostate cancer (23, 25–27). The RB gene encodes a Mr 110,000 nuclear protein involved in cell cycle control (28). RB gene mutations have been reported in 16.4% of primary human prostatic cancers, which suggests that inactivation of

Received 6/4/01; accepted 9/18/01.

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1 Supported by NIH Grants DK52721, DK52708, CA64872, DK47517, CA59831, and CA89520.
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RB may play a role in carcinogenesis in at least a subset of prostatic carcinomas (29–31). Estimates of the levels of p53 mutations in prostate cancer vary widely. Commonly reported figures suggest 20–50% of advanced stage tumors contain these mutations (32). However estimates of p53 mutations as high as 56% in high-grade prostatic intraepithelial neoplasia and 72% in prostatic carcinoma have been made, based on immunohistochemical data (33).

Androgens have long been known to elicit prostatic epithelial differentiation as a result of paracrine actions dependent on receptors located in the urogenital sinus mesenchyme (34). In contrast, differentiated function of prostatic epithelium (expression of secretory markers) is apparently dependent on the presence of ARs located in the epithelial cells (35). More recent data show that ERs in both stromal and epithelial cells play a role in mediating estrogenic effects in the prostate (36). We have previously demonstrated that the nontumorigenic BPH-1 cell line can be induced to form tumors either by the influence of stromal cells that are derived from human prostate tumors (3) or by recombination with rUGM and stimulation with a combination of T+E2, presumably as a result of paracrine interactions (4). This communication describes the isolation and characterization of a series of 10 tumorigenic sublines with various degrees of invasive potential derived from the nontumorigenic parental BPH-1 line. The data presented here demonstrate for the first time that genetically initiated but nontumorigenic human prostatic epithelial cells can undergo permanent malignant transformation as a result of their previous exposure to CAFs. We further demonstrate that cells derived from hormonally induced tumors are likewise tumorigenic. These cell lines will be a useful resource with which to investigate the genetic and phenotypic lesions induced by the in vivo process of carcinogenesis.

**MATERIALS AND METHODS**

Preparation and Processing of Grafts. Two types of cellular recombinants were prepared using previously described methods. Briefly BPH-1 cells were from our own stocks (16). Cells were routinely maintained and passaged in RPMI 1640 with 5% FBS. BPH-1 cells were released from tissue culture plastic with trypsin, washed in growth medium containing 20% FBS, and viable cells were counted using trypan blue exclusion and a hemacytometer.

CAFs were prepared from human prostate tumors as described previously (3). Briefly, tumors were identified using histopathological analysis of stained sections. Five-mm3 tissue fragments immediately adjacent to identified carcinoma were used. Specimens were digested with collagenase and hyaluronidase (37) and placed into culture in RPMI 1640 containing penicillin, streptomycin, and Fungizone supplemented with 10% FBS. After 10 days of growth, the fibroblastic cells were separated from contaminating epithelial and endothelial cells by differential trypsinization. Subsequent immunohistochemical characterization confirmed their fibroblastic nature, as described previously (3).

Pregnant rats were obtained from Simenson (Gilroy, CA). rUGM was prepared from 18-day embryonic fetuses (copulatory plug date denoted as day 0). Urogenital sinuses were dissected from fetuses and separated into epithelial and mesenchymal components by trypsin digestion, as described previously (38). rUGM was then further reduced to single cells by a 90-min digestion at 37°C with 187 units/ml collagenase (Life Technologies, Inc., Grand Island, NY). After digestion, the cells were washed extensively with RPMI 1640 tissue culture medium. Viable cells were then counted using a hemacytometer, and viability was determined by trypan blue exclusion.

Cell recombinants were prepared by mixing 100,000 epithelial (BPH-1) cells with 250,000 rUGM cells or CAFs in suspension. For control grafts, 350,000 cells of each cell type (BPH-1, rUGM, or CAF) were used. Cells were pelleted and resuspended in 50 μl of neutralized rat tail collagen prepared as described previously (39). The recombinants were allowed to set at 37°C for 15 min and were then covered with growth medium (RPMI 1640 + 5% FBS) containing testosterone (10-8 M) and were cultured overnight. Recombinants were then grafted beneath the renal capsule of adult male outbred athymic mice (Simenson). All of the animals were housed in the University of California-San Francisco laboratory animal resource center with food and drinking water ad libitum under controlled conditions (12 h light, 12 h dark, 20°C ± 2°C).

Mice carrying rUGM + BPH-1 recombinants were treated hormonally by surgical implantation of Silastic capsules containing E2 (17-β-estradiol benzoate; Sigma Chemical Co.) and testosterone propionate (Sigma Chemical Co.) as described previously (4). Control animals received empty Silastic tubing. Three months postgrafting, hosts were killed by anesthetic overdose followed by cervical dislocation. Kidneys were excised, and grafts were dissected free of the host kidney, weighed, and then processed for immunohistochemistry and for cell isolation.

**Isolation of Cell Strains.** Grafts, which had formed tumors, were cut into small fragments using forceps and scalpel. Control grafts composed of BPH-1 + rUGM from untreated hosts were treated in the same manner. The resultant tissue fragments were plated overnight in tissue culture flasks in a small volume (1.2 ml in a 25-cm2 flask) of tissue culture medium (RPMI 1640 containing 5% FBS). The following day, the medium and any unattached fragments were aspirated and replaced with 5 ml of fresh medium. After 1 week of growth, the medium was additionally supplemented with 250 μg/ml G418 (Clontech, Palo Alto, CA). G418 selection was applied for 2 weeks, during which time all of the nonresistant cells died. The resulting cell populations were expanded in culture and characterized as described below.

**Regrafting Experiments.** Epithelial cells (350,000 cells) of each of the derived cell strains were suspended in 50 μl of rat tail collagen gel, as described above, and grafted to the kidney capsules of male athymic mouse hosts. After 1 month of growth, the hosts were killed, and the grafts were removed from the kidney, weighed, fixed in formalin, and processed to paraffin. Before fixation, small pieces of the CAFTD grafts were removed and placed in culture as described above to isolate a “second generation” of TD cells. These were again grown in athymic mouse hosts for 1 month, excised and weighed, and fixed for immunohistochemical analysis. The lineage of these cell strains are shown in Fig. 1.

**Immunohistochemistry and Immunocytochemistry.** Formalin-fixed tumor sections were deparaffinized, hydrated, and blocked for 30 min with 0.5% H2O2 in methanol, washed in PBS (pH 7.4), and treated with 5% goat or donkey serum for 30 min. The sections were then incubated with the primary antibodies overnight at 4°C or with nonimmune mouse IgG at the same concentration. In these experiments, rabbit polyclonal anti-AR antibody (PA1–111A; 1:100) was purchased from Affinity BioReagents (Golden, CO). The anti-SV-40 T antibody PaB 101 was a generous gift from Dr. John Lehman (Albany Medical College, Albany, NY). Anticytokeratin antibodies, all mouse monoclonals (LE41, LE61, and LL001 against keratins, 8, 18, and 14, respectively) were generously provided by Dr. E. B. Lane, University of Dundee,

Fig. 1. a. BPH1CAFTD lineage. BPH-1 cells were recombined with CAFTD and grafted beneath the renal capsule of male athymic mouse hosts to produce tumors. Tissue from these tumors was then put into cell culture, and G418-resistant cells were selected. Cell strains were designated BPH1CAFTD-01, -03, -05, and -07. Each of these cell strains was then grafted beneath the renal capsule of athymic mice to produce tumors. Further cell selection was performed from which BPH1CAFTD-02, -04, -06, and -08 were derived, b. BPH1CAFTD-A lineage. BPH-1 cells were recombined with rUGM and grafted beneath the renal capsule of male athymic mouse hosts. The hosts were treated with T+2E for three months. The resulting tumors were excised; epithelial cells were grown out and selected by resistance to G418.
Dundee, United Kingdom. Mouse anti-E-cadherin monoclonal antibody was purchased from Transduction Laboratories (San Diego, CA). Anti-p63 was purchased from Santa Cruz Biotechnology (Santa Cruz, CA). p63 is a p53 homologue that is essential for regenerative proliferation in epithelial development. We have demonstrated that, in prostate, p63 is coexpressed with cytokeratin 14 and is, thus, a good nuclear marker of basal epithelial cell type (40). Anti-human ERα (clone 1D5) was purchased from Dako (Carpenteria, CA). Anti-Ki67 was purchased from Immunotech (Westbrook, ME). Purified rabbit and mouse IgGs were obtained from Zymed Corp. (South San Francisco, CA). Biotinylated antirabbit and antimouse IgGs were obtained from Zymed Corp. (South San Francisco, CA). Anti-Ki67 was purchased from Immunotech (Westbrook, ME). Purified rabbit and mouse IgGs were obtained from Zymed Corp. (South San Francisco, CA). Biotinylated antirabbit and antimouse IgGs were obtained from Zymed Corp. (South San Francisco, CA). Anti-Ki67 was purchased from Immunotech (Westbrook, ME). Purified rabbit and mouse IgGs were obtained from Zymed Corp. (South San Francisco, CA). Biotinylated antirabbit and antimouse IgGs were obtained from Zymed Corp. (South San Francisco, CA). Anti-Ki67 was purchased from Immunotech (Westbrook, ME). Purified rabbit and mouse IgGs were obtained from Zymed Corp. (South San Francisco, CA). Biotinylated antirabbit and antimouse IgGs were obtained from Zymed Corp. (South San Francisco, CA). Anti-Ki67 was purchased from Immunotech (Westbrook, ME). Purified rabbit and mouse IgGs were obtained from Zymed Corp. (South San Francisco, CA). Biotinylated antirabbit and antimouse IgGs were obtained from Zymed Corp. (South San Francisco, CA). Anti-Ki67 was purchased from Immunotech (Westbrook, ME). Purified rabbit and mouse IgGs were obtained from Zymed Corp. (South San Francisco, CA). Biotinylated antirabbit and antimouse IgGs were obtained from Zymed Corp. (South San Francisco, CA). Anti-Ki67 was purchased from Immunotech (Westbrook, ME). Purified rabbit and mouse IgGs were obtained from Zymed Corp. (South San Francisco, CA).

RESULTS

Grafts of BPH-1 epithelial cells recombined with CAF or recombined with rUGM followed by treatment with T+E2 gave rise to tumors, as described previously (3, 4). ARs and ERs were not detected in the epithelial component of these tumors. However, immunoreactivity to steroid receptors was visualized in both the rUGM and the CAF-derived stromal cells. Grafts of BPH-1 + rUGM in untreated hosts did not form malignant tumors, but gave rise to glandular architecture, as previously described (3, 4). After culture and selection with G418, four cell strains were derived from BPH-1 + CAF tumors (designated BPH1CAFTD₀₁, -₀₃, -₀₅ and -₀₇), and an additional two strains were derived from T+E₂-treated rUGM + BPH₁ tissue recombinants (designated BPH₁TTTT-A and -B). The four BPH₁CAFTD strains were grafted in collagen gel beneath the renal
capsule of athymic mouse hosts, in which they were formed tumors that were used to produce a second generation of BPH1 CAFTD cells (designated BPH1 CAFTD-02, -04, -06 and -08). The lineage derivation of these cell strains is outlined in Fig. 1. In addition to these cell lineages a strain of cells derived from BPH-1 and both of the BPH1 TETD strains (Table 1). Expression was slightly stronger in subconfluent than in confluent cultures. E-cadherin and β-catenin expression was patchy in the tumorigenic sublines, with some cells showing no expression, others expressing poorly, and some demonstrating normal levels of protein. The expression of a range of markers by these cell strains is summarized in Table 1. The BPH1 TETD cells expressed the same markers, had the same morphology, and were plated and allowed to attach in RPMI 1640 supplemented with 5% FBS. Under these conditions, the parental BPH-1 line.

A comparison of the relative growth rates of the epithelial sublines demonstrated that, in the presence of 5% FBS, all of the cells grew rapidly. In contrast, when the medium was changed to RPMI 1640 supplemented with 2.5% dextran-coated charcoal-stripped, heat-inactivated FBS, the parental BPH-1 cell line became essentially growth-quiescent, whereas the TD strains increased in number between 4- and 8-fold over a 5-day assay (Fig. 3).

The parental BPH-1 and the TETD cell lines grow extremely poorly in vitro in soft agar (Table 2). In contrast the CAFTD sublines all exhibited in vivo tumorigenic ability, whereas the TD strains increased in number between 4- and 8-fold over a 5-day assay (Fig. 3).

Table 2 Colony formation in soft agar

<table>
<thead>
<tr>
<th>Cell strain</th>
<th>Colonies per 10⁵ cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPH-1</td>
<td>0.13</td>
</tr>
<tr>
<td>BPH1 CAFTD-01</td>
<td>8.83</td>
</tr>
<tr>
<td>BPH1 CAFTD-02</td>
<td>4.48</td>
</tr>
<tr>
<td>BPH1 CAFTD-03</td>
<td>19.05</td>
</tr>
<tr>
<td>BPH1 CAFTD-04</td>
<td>0.38</td>
</tr>
<tr>
<td>BPH1 CAFTD-05</td>
<td>2.05</td>
</tr>
<tr>
<td>BPH1 CAFTD-06</td>
<td>4.10</td>
</tr>
<tr>
<td>BPH1 CAFTD-07</td>
<td>6.66</td>
</tr>
<tr>
<td>BPH1 CAFTD-08</td>
<td>9.09</td>
</tr>
<tr>
<td>BPH1 TETD-A</td>
<td>0.38</td>
</tr>
<tr>
<td>BPH1 TETD-B</td>
<td>0.13</td>
</tr>
</tbody>
</table>

* Mean number of colonies from an experiment performed in triplicate.
The article by Phillips et al. describes genetic changes in the cells, a phenomenon described more fully in the tumorigenic behavior, as a result of recombination with CAF, previously shown that human prostate CAFs can induce the BPH-1 cells to elicit permanent malignant transformation in genetically initiated hosts. In some cases, lungs appeared to be abnormally firm, but histological examination revealed that this phenotype is attributable to the deteriorating health of the hosts before being killed.

DISCUSSION

The present communication demonstrates that stromal environment can elicit permanent malignant transformation in genetically initiated but previously nontumorigenic human prostate epithelium. We have previously shown that human prostate CAFs can induce the BPH-1 epithelial cell line to form tumors (3). The present study shows that the tumorigenic behavior, as a result of recombination with CAF, resulted in permanent malignant transformation of the epithelial cells.

Malignant transformation in this model is most likely to be caused by genetic changes in the cells, a phenomenon described more fully in the article by Phillips et al. (41). It is significant that there are characteristic patterns of genetic change that occur in four separate lineages of BPH-1 cells exposed to CAFs, although these were derived from separate experiments using different CAF populations. The BPH1CAPTD lines all share recurrent, and complex (harlequin) chromosomal rearrangements resulting in loss of 8p, 11p, and 20p, and high-level amplification of 1p, 11q, and 20q (41). This type of specific genetic change is an important observation that underlines the concept that stromal microenvironment may play a crucial role in both promoting carcinogenesis and in eliciting genetic changes during malignant progression. The mechanism by which such common genetic changes could be induced by stromal environment is at present unclear, although the changes in cellular adhesion seen in these tumors may provide a clue to the cause of the genetic changes. We previously demonstrated that malignant changes are associated with a reduction or loss of membranous E-cadherin localization in the BPH-1 epithelial cells that form the tumors (3, 4). The cell lines described here likewise have a general tendency toward reduced expression and a loss of membrane localization of adherens junction proteins. Interactions between E-cadherin and p53 have been postulated to result in genomic instability (42). In a broader context, cellular adhesion has been proposed to modulate neoplastic processes by altering the p53 pathways that control genomic stability (43). However, in the present model, the p53 pathway is disrupted in both the benign and malignant phenotypes (because of the presence of SV40T), which suggests that this route may not be involved in progression from the nontumorigenic to the tumorigenic state here.

One model, which is in some ways similar, is a study showing that the human prostate cancer cell line LNCaP C4–2, when injected into nude mice, is capable of inducing genetic changes in host stromal cells around the injection site (44). In this instance, genetically damaged and tumorigenic epithelial cells apparently induce "neoplastic transformation in stromal cells of the host organ by some, as yet unknown, epigenetic mechanism(s)" (44). In the present model, the situation is somewhat different in that apparently genetically normal but pheno-
typically modified stromal cells are inducing permanent malignant transformation in genetically initiated but nonmalignant epithelial cells. It is, however, entirely possible that similar epigenetic mechanisms are involved in this process.

Our model of tumorigenesis in the BPH-1 cell line raises the issue of the relative importance and role of genetics versus epigenetic factors in tumorigenesis. CAF-induced tumorigenesis of BPH-1 cell is clearly an epigenetic effect that leads to further genetic alterations in the course of the tumorigenetic process. T\(^{+}\)/E\(^{1001}\)E\(^{2}\)-induced carcinogenesis in BPH-1 cells requires interaction with rUGM as well as treatment with T\(^{+}\)/E\(^{2}\). Hormonal carcinogenesis induced by T\(^{+}\)/E\(^{2}\) in rUGM+BPH-1 recombinants, therefore, is also likely to involve epigenetic as well as genetic mechanisms. Thus, the pathway to hormonal carcinogenesis surely can involve both epigenetic and genetic mechanisms. The dominance of genetic versus epigenetic mechanisms in determining progression to tumorigenesis or the tumorigenic state per se appears to vary on an individual case-by-case basis. There are many instances in which the single addition of a dominant acting oncogene is sufficient to convert a nontumorigenic cell to a fully tumorigenic cell. Such observations emphasize the important genetic change as a key determinant of malignancy. On the other hand, studies with highly malignant teratocarcinoma cells emphasize the dominance of epigenetic factors in the expression of benign versus malignant growth. Small numbers of teratocarcinoma cells trans-
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planted into a host will consistently form tumors that will lead to the demise of the host (45). Such highly malignant cells, when microinjected into mouse blastocysts, will participate in normal development producing a range of benign tissues representing all germ layers. Indeed, because of contribution of teratocarcinoma cells to the germ line, it is possible to derive mouse strains from teratocarcinoma cells (46). Thus, despite the genetic alterations within the parental teratocarcinoma cells, epigenetic factors can elicit reversion of highly malignant cells to benign cells.

The ability of T+2E2 to induce malignancy in BPH-1 cells has been previously demonstrated (4). The original description of these tumors emphasizes that stromal cells are required for sex hormone-induced carcinogenesis. We also demonstrated that transplantable tumors can be established from these T+2E2-induced tumors. The present study demonstrates that epithelial cells that are isolated from these hormone-induced tumors retain their malignant potential. The BPH1/TETD strains shared the 11q and 20q amplifications seen in BPH1/CAPTD but also had high-level amplifications of 7p encompassing the v-erb (epidermal growth factor receptor) region. In addition to the unbalanced translocations seen in the CAFTD cells, TETD cells also had examples of reciprocal translocations, the exact genetic implication of which is currently unclear but may reflect the unique pathways to tumorigenesis induced by TE/UGM (41). Unlike the situation in CAFT-induced carcinogenesis, there are well-established pathways to tumorigenesis induced by TE/UGM (41). Unlike the situation in CAFT-induced carcinogenesis, there are well-established mechanisms by which sex steroid hormones, especially estrogens, can induce genetic change. Metabolism of natural and synthetic estrogens by the unbalanced translocations seen in the CAFTD cells, TETD cells demonstrates that epithelial cells that are isolated from these hormone-induced tumors retain their malignant potential. The BPH1/TETD strains shared the 11q and 20q amplifications seen in BPH1/CAPTD but also had high-level amplifications of 7p encompassing the v-erb (epidermal growth factor receptor) region. In addition to the unbalanced translocations seen in the CAFTD cells, TETD cells also had examples of reciprocal translocations, the exact genetic implication of which is currently unclear but may reflect the unique pathways to tumorigenesis induced by TE/UGM (41). Unlike the situation in CAFT-induced carcinogenesis, there are well-established mechanisms by which sex steroid hormones, especially estrogens, can induce genetic change. Metabolism of natural and synthetic estrogens by the unbalanced translocations seen in the CAFTD cells, TETD cells demonstrates that epithelial cells that are isolated from these hormone-induced tumors retain their malignant potential.

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