WISH-PC2: A Unique Xenograft Model of Human Prostatic Small Cell Carcinoma


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Abstract

Prostatic small cell carcinoma is an aggressive subtype of prostate cancer that usually appears as a progression of the original adenocarcinoma. We describe here the WISH-PC2, a novel neuroendocrine xenograft of small cell carcinoma of the prostate. This xenograft was established from a poorly differentiated prostate adenocarcinoma and is serially transplanted in immune-compromised mice where it grows within the prostate, liver, and bone, inducing osteolytic lesions with foci of osteoblastic activity. It secretes to the mouse Chromogranin A and expresses prostatic plasma carcinoma tumor antigen-1, six-transmembrane epithelial antigen of the prostate, and members of the EGF-receptor family. It does not express prostate-specific antigen, prostate stem cell antigen, prostate-specific membrane antigen, and androgen receptor, and it grows independently of androgen. Altogether, WISH-PC2 provides an unlimited source in which to study the involvement of neuroendocrine cells in the progression of prostatic adenocarcinoma and can serve as a novel model for the testing of new therapeutic strategies for prostatic small cell carcinoma.

Introduction

Primary SCCP is a relatively rare form of NE differentiation of PC. Nevertheless, it is clinically important because it is an extremely aggressive tumor with a very poor prognosis. NE differentiation of PC into SCCP is usually identified at the time of progression or recurrence of tumors that were originally classified as conventional adenocarcinoma of the prostate (1). This heterogeneity can be explained by divergent differentiation from multipotent stem cells (2, 3). Upon diagnosis of a small cell component, the clinical course is aggressive with common local and distant failure and a limited median survival duration of 9.8 months (2). It is therefore important to establish an experimental model of this tumor that will enable the testing and exploitation of potential therapeutic modalities.

The optimal treatment for SCCP has not been determined. The tumor often appears mixed with adenocarcinoma of the prostate, and it is usually treated with chemotherapeutic regimens designed for small cell carcinoma of the lung (1). The possible advantage of hormonal agents combined with chemotherapy remains unproven. Indeed, accelerated proliferation of the NE cells may represent an important step in the development of androgen-independent growth of PC driven by alternative growth signals. di Sant’agene (4) described the NE cells (also known as the endocrine-paracrine cells of the prostate) as intraepithelial regulatory cells displaying hybrid epithelial, neural, and endocrine characteristics. Although devoid of AR (5), the cells are capable of secreting alternative growth factors such as bombesin, serotonin, somatostatin, calcitomin, and parathyroid hormone-related protein (4–6). The prostatic NE cells express the c-erbB-2 growth factor receptors (7, 8). It was suggested that SCCP is composed of an enriched population of androgen-independent cells whose growth is sustained through alternate paracrine and autocrine pathways (6).

Only one model of human SCCP was reported thus far (9, 10). The WISH-PC2 line described here was derived from a PC patient, and expresses novel PC-specific molecular markers. This model should be extremely useful in studies aimed at the elucidation of critical aspects of the NE differentiation of PC, such as the regulatory mechanisms displayed by the NE cells and the interactions between the disseminated tumor and its various metastatic sites. In addition, the effect of various therapies on the primary tumor and on its disseminated form can be further evaluated.

Materials and Methods

Clinical History. The donor of the WISH-PC2 tumor tissue was a 67-year-old Caucasian male. He was diagnosed with T3N1M1 prostatic adenocarcinoma with a Gleason score of 8 (3 + 5). At the time of diagnosis, his serum PSA level was 53 ng/ml. Hormonal ablation was initiated with s.c. injection of 10.8 mg Goseroline every 12 weeks, resulting in a mild decline in serum PSA levels to a nadir of 40 ng/ml. A year later, while continuing this regimen, the patient complained of obstructive voiding symptoms and serum PSA levels rose to 65 ng/ml. Ultrasound demonstrated an enlarged obstructing prostate with a significant post-void residual urine volume. Anti-androgen (bicalutamide 50 mg/day) was added to the luteinizing hormone releasing hormone agonist. However, because of worsening of the obstructive voiding symptoms, the patient underwent a palliative transurethreal resection of the prostate. The WISH-PC2 (Weizmann Institute Sheba Hospital Prostate Cancer) xenograft line was established from tissue samples obtained during this operation. The pathological examination revealed poorly differentiated carcinoma infiltrating the smooth muscle, with a typical NE differentiation (Fig. 1). As the patient’s disease continued to progress, the hormonal therapy was replaced with chemotherapy (cyclophosphamide, doxorubicin, and vinblastine). However, the patient’s condition continued to deteriorate, and he expired a few weeks after the initiation of cytotoxic therapy.

Establishment of the Xenograft. Animals and Surgical Procedures. Animals used were 4–10-week-old SCID (c.b-17/ScNuBeige or NOD) and nude (BALB/c nu/nu) mice obtained from the pathogen-free animal breeding facilities of the Weizmann Institute of Science. All of the surgical procedures were performed under ketamin + xylazine general anesthesia (127.5 and 4.5 mg/kg, respectively), except for the insertion of s.c. testosterone pellets and s.c. tumor pieces, which was performed under local anesthesia with xylcocaine 10% spray (Astra Sweden). The original surgical samples of the tumor were placed on ice, minced into 3–5-mm pieces, and implanted s.c. into SCID mice. After an initial latency period of 4 months, tumor growth was noticed in 30% of the mice. Thereafter the tumor was serially passed (upon submission of the manu-
script, this line was in its twelfth passage), either s.c. with Matrigel (Becton Dickinson, Bedford MA), as minced tumor pieces, or by direct injection of single-cell suspension into various organs as described below. In some experiments (Fig. 2), a sustained 90-day-release testosterone pellet (12.5 mg/pellet; Innovative Research of America, Sarasota, FL) was implanted s.c. Bilateral transabdominal orchietomy was performed when stated to achieve androgen ablation.

Tumor size was determined by caliper measurements of length, width, and depth, and the tumor volume (mm$^3$) was approximated using the formula: length × width × depth × 0.5236 (11). Doubling time of the tumor growth was calculated during the logarithmic growth phase of subcutaneously growing tumors.

**Injection of Tumors to Various Organs. Orthotopic Injection.** Tumor cell suspensions (20 μl) were injected into the dorsal prostatic lobes through a midline lower abdominal incision as described by Stephenson et al. (12). A well-localized bleb within the injection site was considered to indicate technically satisfactory injection.

**Intraosseous Injection.** Through a skin incision in the medial aspect of the hind limb, the femur and tibia were exposed. A hole was made in the cortical bone of the distal femur or proximal tibia with a 27-gauge needle. Tumor cell suspensions (10 μl) were injected through the duct using a 30-gauge needle.

**Intrahepatic Injection.** A midline abdominal incision was performed to expose the liver. Tumor cell suspensions (10–20 μl) were injected into both hepatic lobes using a 27-gauge needle.

**s.c. Injection.** Mixtures of tumor cell suspensions in various concentrations with 100 μl of Matrigel basement membrane matrix solution (Becton Dickinson) were injected s.c. using a 27-gauge needle.

**Preparation of Single-Cell Suspension.** The xenografted tumor tissue was harvested under sterile conditions and placed immediately in cooled HBSS, (Sigma-Aldrich Co., Ltd.). Cells were dissociated under sterile conditions, first by mincing the tissue with scissors to small fragments and then by gentle mechanical homogenization through a stainless still mesh. Viable cells were separated from debris by layering over Ficoll-Paque 400 (Pharmacia Biotech AB, Uppsala, Sweden) and centrifugation at 500 × g for 20 min. Viable cells at the interface were collected, counted, and resuspended in cooled HBSS to the desired concentrations.

**FACS Analysis.** Single-cell suspensions made from the xenograft were washed and incubated with primary antibody [anti-CD19, anti-CD20, anti-CD22 (a generous gift from Dr. M. Little, DKFZ, Heidelberg, Germany), PA2.6 anti-HLA-ABC (ATCC HB-118), N29 anti-ErbB-2, and L96 anti-ErbB2, no. 105 anti-ErbB-3 and no. 77 anti-ErbB-4, a generous gift from Prof. Y. Yarden (Ref. 13 and references therein), or an irrelevant U76.6, anti-di-nitrophenol monoclonal antibody]. The samples were then washed and incubated with the secondary FITC-labeled antimouse antibody. Stained cells were resuspended in propidium iodide to identify and exclude dead cells. Analysis was performed on the FACScan flow cytometer (Becton Dickinson).

**Immunohistochemistry.** Immunohistochemistry was performed on sections from formalin-fixed, paraffin-embedded blocks as described previously (14).

Antibodies used included mouse monoclonal antibodies to PAP, PSA, NSE, chromogranin and synaptophysin, obtained from DAKO Corp., Carpinteria, CA. Antibodies to human AR were purchased from Innovex Biosciences, USA. Antibody to PSCA was a gift from Dr. Robert Reiter (University of California at Los Angeles). After incubation with monoclonal antibodies, slides were incubated sequentially with peroxidase-conjugated rabbit anti-mouse immunoglobulins, and peroxidase-conjugated swine anti-rabbit immunoglobulins. Antibody localization was visualized with the diaminobenzidine reaction. Negative controls consisted of substitution of the primary antibody with an isotype matched non-cross-reacting antibody of irrelevant specificity.

Immunohistochemical techniques combined with image analysis were used to detect the presence of bcl-2, P glycoprotein (MDR1), and p53. An experienced commercial laboratory performed these pathological evaluations as well as determination of DNA ploidity and proliferation index of the tumor samples (Quantitative Diagnostic Laboratories).

Serum PSA levels were determined by Immulite Third generation PSA kit (Diagnostic Products Corp., Los Angeles, CA). Plasma chromogranin-A levels were quantified using an ELISA kit as recommended by the manufacturer (DAKO Denmark).
not express the B-cell CD19, CD20, and CD22 differentiation antigens (data not shown), excluding the possibility of being an overgrowth of dormant EBV-transformed human B cells (18). The xenografted carcinoma is highly cognate in its gross histological appearance to the donor’s surgical specimen, and it shares the expression of NE tumor markers (Fig. 1): chromogranin A,NSE, and synaptophysin. Notably, chromogranin A is also secreted into the plasma of WISH-PC2-bearing mice, and the plasma concentration of chromogranin A is correlated to the size of the xenograft (data not shown). Hence, chromogranin A can serve as a secreted tumor marker to monitor the growth of this NE SCCP xenograft.

The WISH-PC2 xenograft grows relatively rapidly (Fig. 2) and with a high take rate (visible tumor growth is evident in 90–100% of the animals). Upon s.c. injection of tumor cells or implantation of tumor tissue, growth can be detected within 2–3 weeks. In the presence of Matrigel, the doubling time of the tumor after the s.c. implantation of $3 \times 10^6$ cells, is 11 or 13.5 days for a tumor growing in the presence or absence of androgen, respectively, and 15 and 18 days, respectively, for a tumor that arises from s.c. implantation of tissue (70 mg) with and without androgen supplementation. This pattern of androgen-responsive growth most probably reflects an indirect effect of androgen, inasmuch as the tumor cells do not express ARs as expected for SCCP (1, 3). Because the WISH-PC2 xenograft has been originated from a mixed-type tumor, there is a possibility that it is a mixture of SCCP with some residual adenocarcinoma cells that are hormone-responsive and expand in the presence of androgen. To test this, we stained the WISH-PC2 tissue that grew for more than 80 days in the presence of a continuous supply of testosterone with anti-PSA and anti-AR antibodies. The results did not reveal any staining above background of these tumors. Moreover, RT-PCR analysis of RNA derived from WISH-PC2 that grew in the absence or presence of androgen was completely negative for PSA and AR (data not shown). Similarly, no PSA could be detected in the sera of mice bearing WISH-PC2, regardless of whether they were hormone-supplemented or not. All these data argue against the possibility that the enhanced growth observed in the presence of androgen (Fig. 2) is attributable to residual androgen-responsive adenocarcinoma cells. Apparently, the serial transfer of WISH-PC2 in the absence of an external source of testosterone in the first few generations provided a selective advantage to the SCCP component over the adenocarcinoma. Androgen was demonstrated to have indirect effects on PC via up-regulation of surrounding stromal vascular endothelial growth factor production and angiogenesis (19). The high growth rate is also reflected by the high proliferation index, depicted by staining with the Ki-67 antibody, and directed at a nuclear antigen expressed in proliferating cells (data not shown).

**Results and Discussion**

NE differentiation of PC is associated with poor prognosis and resistance to anti-androgen therapy (5, 15). NE differentiation can take several forms, including NE SCCP, carcinoid-like tumor or, most commonly, focal NE differentiation in conventional prostatic adenocarcinoma. In this study, we established a xenograft model that could recapitulate many of the clinical characteristics of SCCP. As such, it enables phenotypic characterization and the development and evaluation of possible therapeutic modalities.

**Growth Pattern of the WISH-PC2 Xenograft.** The patient from whom the WISH-PC2 xenograft was established was initially diagnosed with conventional high-grade adenocarcinoma of the prostate (Fig. 1). The tumor converted to SCCP in parallel to an expeditious clinical course of progression, emphasizing the linkage between the two subtypes of the prostatic tumor (1, 2, 16). Indeed, in the first generation, 20% of the mice into which the tumor pieces were implanted had elevated serum PSA levels. The WISH-PC2 xenograft was established from a tumor-bearing mouse that did not exhibit elevated serum PSA levels. We determined that the WISH-PC2 cells are of human origin and did not result from an overgrowth of the explants by murine cells (17). The xenograft is stained with anti-HLA-A,B,C antibodies (data not shown). In addition, the tumor does not express the B-cell CD19, CD20, and CD22 differentiation antigens (data not shown), excluding the possibility of being an overgrowth of dormant EBV-transformed human B cells (18). The xenografted carcinoma is highly cognate in its gross histological appearance to the donor’s surgical specimen, and it shares the expression of NE tumor markers (Fig. 1): chromogranin A, NSE, and synaptophysin. Notably, chromogranin A is also secreted into the plasma of WISH-PC2-bearing mice, and the plasma concentration of chromogranin A is correlated to the size of the xenograft (data not shown). Hence, chromogranin A can serve as a secreted tumor marker to monitor the growth of this NE SCCP xenograft.

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**Growth of WISH-PC2 in Various Organs.** To establish a valid model in which to test various therapeutic strategies, we developed a xenograft model using WISH-PC2 cells that would closely model human SCCP and its metastasis. The ability of the WISH-PC2 xenograft to grow orthotopically within the murine prostate (Fig. 3) provides such a model. Interestingly, orthotopically transplanted human small cell lung carcinoma displays a different chemosensitivity pattern compared with the s.c. transplanted model (20).

One of the typical clinical features of SCCP, in contrast to adenocarcinoma of the prostate, is its tendency to develop visceral metastasis. The most frequent metastatic sites of SCCP are the bones (55%), regional and distant lymph nodes (52%), and the liver (48%: Ref. 2). Occasionally, liver, lung, and lymph node metastasis can be recovered after s.c. implantation of WISH-PC2. Interestingly, a high incidence of metastasis are found after direct intrahepatic injection of the xenograft cells, especially in surgical wound sites such as that in mice which have undergone bilateral transabdominal orchiectomy for an-

![Fig. 2. Effect of androgen on the growth of WISH-PC2 xenograft. The volume of s.c. growing WISH-PC2 tumor tissue and dissociated cells grafted s.c. in orchietomized male SCID mice in the absence (solid line) and presence (dotted line) of s.c. implanted slow-release testosterone pellets.](image-url)
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Fig. 3. Growth of WISH-PC2 xenograft in various organs. A, orthotopic growth of WISH-PC2 within the murine prostate, forming a large pelvic tumor mass (41 days after the injection of $2.5 \times 10^6$ tumor cells into the prostate). B, the tumor cells infiltrate the murine prostate microscopically, distorting its normal architecture. (H&E staining; original magnification $\times 400$). C, WISH-PC-2 tumor growth within the murine’s left hepatic lobe (white arrow) 58 days after an intrahepatic injection of $5 \times 10^6$ tumor cells. Black arrows, multiple metastases, including at surgical site of bilateral orchiectomy performed simultaneously with the direct intraprostatic injection. D, histological view of WISH-PC2 tumor nodule within the murine liver. Note the zone of compressed hepatocytes adjacent to the tumor and the high mitotic figure of the tumor cells. Also of note is the NE appearance of the WISH-PC2 tumor composed of clusters and nests of tumor cells interlaced by a delicate reticular connective tissue. (H&E staining; original magnification $\times 100$). E, Tc-99m-MDP bone scan of a mouse 87 days after the injection of $1.5 \times 10^6$ WISH-PC2 cells to the left proximal tibia and PBS to the right one. An increased uptake of the radioisotope indicates osteoblastic activity restricted to the site of tumor injection (arrows) and not in the contralateral control site (TI, site of the tail injection of the radioisotope; UB, urinary bladder; M, marker indicating the location of the right and left legs; T, tumor.) F, plain radiography to the same mouse, demonstrating lytic distraction of the bone only at the site of tumor injection (white arrows) and not in the contralateral tibia. G, histological view of the right proximal tibia of the mouse that was injected with PBS demonstrating normal bone architecture, including epiphysis, bone marrow cells, bone trabeculae. (H&E staining; original magnification $\times 100$). H, bone architecture in the left proximal tibia of the mouse into which the WISH-PC2 cells were injected is distorted by tumor cells (T). Note a bony “plaque” surrounded by abundant osteogenitor cells and osteoblasts (black arrows). On the right upper side of the bony plaque, lytic changes are formed by tumor cells (open arrow; H&E staining; original magnification $\times 200$).

drogen ablation. (Fig. 3). This may represent preferential seeding of the circulating tumor cells in granulating tissue, which is rich in neovascularization and local growth factors. The WISH-PC2 xenograft cells can also grow in the host bones, inducing new bone formation mixed with lytic distraction of the bone, a typical feature of SCCP bone metastasis (21). This is demonstrated both radioisotopically and radiographically (Fig. 3). In contrast with WISH-PC2, the SCCP xenograft UCRU-PR-2, reported previously, failed to grow in the liver (10), and no data are available on the ability of UCRU-PR-2 to grow orthotopically within the prostate or bone.

Malignant Phenotype of the WISH-PC2 Cells. Next we tested WISH-PC2 cells for the expression of several prostate specific markers. Table 1 lists various molecular markers whose expression was evaluated on WISH-PC2. The xenograft does not express PSA, PSMA, PSCA, or PAP. Nevertheless, its prostatic origin is supported by the following molecular markers: (a) expression of cytokeratin 8 and 18 common to PC and prostatic secretory cells (3); (b) expression of PCTA-1, which is a surface marker of PC and its precursor, prostatic intraepithelial neoplasia, but is not found on normal prostate or benign prostatic hyperplasia (22); and (c) expression of the STEAP. This recently described surface marker (23) is highly expressed at all stages of PC and does not seem to be modulated by androgen. Although STEAP is also expressed in multiple cancer cell lines, its expression in normal human tissues is restricted to the prostate and bladder.

Immunostaining of WISH-PC2 xenograft sections demonstrated that the tumor expresses adverse pathological features reflecting the aggressive nature of this tumor. These include aneuploid DNA content, bcl-2 protein, and mutated p53 (Table 1). Although previously prostate NE cells were reported not to express the antiapoptotic bcl-2 marker (24), these cells were terminally differentiated, nonproliferating cells. The WISH-PC2 cells represent malignant prostatic NE cells.

<table>
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<tr>
<th>Feature</th>
<th>Expression</th>
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<tr>
<td>DNA ploidy</td>
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<tr>
<td>Proliferative Index (Ki-67)*</td>
<td>High</td>
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<tr>
<td>Bcl-2*</td>
<td>Positive</td>
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<tr>
<td>Mutated p53*</td>
<td>Positive</td>
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<tr>
<td>MDR1 gene product*</td>
<td>Negative</td>
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<td>PSA*</td>
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<td>STEAP*</td>
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<tr>
<td>PCTA-1/galactin-8*</td>
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<td>Synaptophysin*</td>
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* Determined by immunohistochemistry.
* Determined by RT-PCR.
* Determined by Western blot analysis.
* Determined by ELISA of murine host plasma.
* Determined by FACS analysis.
It is therefore intriguing to speculate that both bcl-2 and defective p53 allow these AR-negative cells to survive and overtake the adenocarcinoma cells, which undergo apoptosis in response to androgen deprivation and, potentially, chemotherapy.

FACS analysis using monoclonal antibodies against the epidermal growth factor receptor erb-B family revealed that WISH-PC2 expresses erb-B2, erb-B3, and erb-B4 on its surface. The expression of these growth factor receptors was stable through all of the passages of the tumor (data not shown). Iwamura et al. (7) demonstrated immunostaining of c-erb-B2 on prostatic NE cells using polyclonal antibodies. To the best of our knowledge, no data have been reported to date concerning the coexpression of erb-B3 and/or erb-B4 with erb-B2 on prostatic NE cells, a combination that is necessary for the binding of Neuregulin ligands to these receptors and for their activation (13). The presence of the erb-B set of receptors may provide an alternative pathway of growth signaling for the androgen-independent proliferation of these cells, either directly or by regulating NE peptides that function in an autocrine or paracrine manner.

Potential Application of the WISH-PC2 in Therapeutic Models.

Prostatic small cell carcinoma is a notoriously aggressive malignancy with a very poor prognosis (21). No effective treatment for SCCP has been established, most probably because of the limited patient population and the aggressiveness of the disease. WISH-PC2 provides an in vivo model for the evaluation of different possible therapeutic strategies for SCCP with an inherent plasma tumor marker (chromogranin A).

The issue of whether castration is a justified treatment for SCCP is still unresolved. The progression from adenocarcinoma of the prostate to SCCP usually appears after castration (1). However, based on the evidence that most SCCP are mixed with adenocarcinoma of the prostate, the common practice is to combine hormonal and cytotoxic therapy (21, 25). The fact that androgen supplements somewhat increase WISH-PC2 tumor growth (Fig. 2) suggests that androgens may enhance the growth of the AR-negative xenograft, probably via an indirect effect on the surrounding stroma (19). It is therefore possible that in the case of SCCP, especially in those present as mixed histology (adenocarcinoma and small cell elements), hormonal manipulation may slow tumor progression.

The WISH-PC2 model can serve as a useful model for testing established and novel cytotoxic drugs. Targeted drug delivery to the various anatomical sites of visceral distribution of SCCP, such as liver or bones, may be readily tested in this model system. The WISH-PC2 xenograft, lacking the p-170 multi-drug efflux pump (MDR1; Table 1), that mediates the MDR phenotype, is therefore susceptible to chemotherapy. It has still to be demonstrated however, whether the WISH-PC2, expressing mutated p53 and bcl-2 are susceptible to apoptosis-inducing drugs.

In conclusion, the WISH-PC2 SCCP xenograft is an excellent source for NE prostatic cells and their factors in studies of intercellular interactions that take place during PC progression. Moreover, this novel human xenograft can serve as a model for the exploitation of new therapeutic modalities on this aggressive variant of PC.

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