Growth-stimulative Effect of Estrogen on Androgen-dependent Shionogi Carcinoma 115

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ABSTRACT

The stimulative effect of 17β-estradiol on the growth of androgen-dependent Shionogi carcinoma 115 and estrogen receptor in the tumor were studied. The incorporation of 17β-[3H]estradiol following a single injection of 17β-[3H]estradiol into tumor-bearing animals was 5- to 20-fold higher in the tumor than in the spleen and blood. Scatchard plot analyses showed that the tumor cytosol possessed a 17β-estradiol-binding site having a high affinity for 17β-estradiol [Kd 1.1 ± 0.1 nM (S.E.)]. Competition experiments demonstrated that the 17β-estradiol binding was specific only for estrogenic compounds. Using sedimentation coefficient obtained by high-salt sucrose gradient (4.0S) and Stokes radius obtained by gel chromatography on Sephadex G-200 (46 Å), the molecular weight of 17β-estradiol-binding component in the tumor cytosol was estimated to be 76,400. In castrated DS mice, a slight but significant increase in growth of s.c. grafted tumors was found by daily s.c. injections of either 17β-estradiol or 10 μg per mouse of testosterone propionate. Growth of the tumor maintained by 10 μg of testosterone propionate was augmented markedly by the addition of 4 μg of 17β-estradiol, and the growth approached the level induced by 100 μg of testosterone propionate. Simultaneous injections of bromocriptine inhibited an increase in 17β-estradiol-induced prolactin secretion but had no effect on the 17β-estradiol-enhanced tumor growth. These results demonstrate for the first time the stimulative effect of estrogen on the growth of androgen-dependent Shionogi carcinoma 115. The tumor contains typical estrogen receptor, which might be able to transmit estrogen signal to tumor cell nuclei with regard to tumor growth.

INTRODUCTION

Androgen-dependent mouse mammary carcinoma SC115 was established in 1964 by Minesita and Yamaguchi (19, 20). The original tumor arose spontaneously as an androgen-independent adenocarcinoma of mammary origin in a female DS mouse and grew equally well when transplanted into male and female mice. After passage in male DS mice for 19 generations, the tumor was found to be androgen dependent, defined by its failure to grow in either female or castrated male mice and by its ability to grow in female or castrated male mice given androgens.

2 To whom requests for reprints should be addressed.
3 The abbreviations used are: SC115, Shionogi carcinoma 115; AR, androgen receptor; ER, estrogen receptor; DHT, 5α-dihydrotestosterone; TP, testosterone propionate; CS-154, bromocriptine; TDM, 10 μM Tris, 1.5 mM EDTA, 0.5 mM dihydrotestosterone, and 10 μM sodium molybdate, pH 7.4 at 20°C; TEDMK, 10 μM Tris, 1.5 mM EDTA, 0.5 mM dihydrotestosterone, 10 μM sodium molybdate and 0.4 mM KCl, pH 7.4 at 20°C; HAP, 5 mM Tris, 5 mM potassium phosphate, and monobasic 50% hydroxypatite, pH 7.4, at 20°C.

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Cells derived from this tumor retain their androgen responsiveness in vivo (3, 4, 18) and in cell culture (6, 9, 10, 28, 29, 36). We (17, 18, 21, 34) and other investigators (2-4, 6, 9, 10, 16, 28, 29, 36) have reported that androgen action on the stimulation of SC115 tumor growth is mediated by a specific AR system in SC115 cells.

We demonstrated in 1969 (21) that the grafted SC115 tumor did not incorporate a significant amount of radioactivity following a s.c. injection of 17β-[3H]estradiol (10 μCi/0.09 μg) into the host animals. On the other hand, Jung-Testas et al. (9) and King et al. (10) in 1976 demonstrated ER in the SC115 cells in culture. We in 1978 (35) and other investigators (24) in 1982 also found the presence of ER in cytosols obtained from s.c.-grafted SC115 tumors. In 1964, Minesita and Yamaguchi (20) found that the growth of s.c.-grafted SC115 tumors in noncastrated male mice was completely suppressed by daily injections of 17β-estradiol (0.3 or 3 mg/kg body weight/day) starting from the day of tumor transplantation. Although Jung-Testas et al. (9) and King et al. (10) found ER in the SC115 cells, they reported that ER and estrogens were unrelated to proliferative response of SC115 cells.

We used SC115 tumors as an animal model for therapy of hormone-dependent tumors and their metastasis (18, 37). During this investigation in 1983, we unexpectedly noticed by almost the same experiment carried out in 1964 (20) that the growth of s.c.-grafted SC115 tumors in noncastrated male mice was only slightly or not significantly suppressed by daily injections of 17β-estradiol (0.4 or 4 mg/kg body weight/day) starting from the day of transplantation, although the 17β-estradiol injections resulted in a reduction of the weight of the seminal vesicles similar to that in castrated mice. Since these findings suggest that the response of SC115 tumor to 17β-estradiol has changed in these 19 years, and since the stimulative effects of estrogens on the growth of androgen-dependent SC115 tumor have not been reported, we studied the growth-stimulative effects of 17β-estradiol and the characteristics of ER in the tumor in detail.

MATERIALS AND METHODS

Animals and Tumors. Two- to 3-month-old male DS mice raised in our laboratory were used. In one experiment, female DS mice were also used. When tumors were grafted onto castrated mice, the castration was carried out at least 1 week in advance. A fragment of tumor (about 1 μl) was inserted beneath the dorsal skin, using a specially devised needle (19). Seed tumors of SC115 were obtained from generations 313 and 28, 29, 36) have reported that androgen action on the stimulation of SC115 tumor growth is mediated by a specific AR system in SC115 cells.

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Chemicals. 17β-[1,2,6,7-3H]Estradiol (92 Ci/mmole) and [1,2-3H]DHT (40 Ci/mmole) were obtained from New England Nuclear (Boston, MA). Nonradioactive steroids were from Steraloids Inc. (Wilton, NH). Sephadex G-200, blue dextran, and marker proteins for gel filtration were purchased from Pharmacia Fine Chemicals (Uppsala, Sweden). Acid-washed char-
injection of 17β-[3H]estradiol. SC115 tumors (1 to 1.5 cm in diameter) were controlled 2 to 3 weeks after the implantation of seed tumors in male mice. Mice were castrated 24 hr before the injection of 17β-[3H]estradiol. 17β-[3H]estradiol (40 μCi; 0.12 μg/mouse) suspended in 0.1 ml of 0.9% NaCl solution (saline) was injected s.c. into the tumor-bearing mice. The mice, 4 in each group, were sacrificed 1, 3, and 9 hr after the injection of 17β-[3H]estradiol, and the tumors, spleens, and blood were obtained. For the estimation of nonspecific retention value, 100 μg of unlabeled 17β-estradiol were injected s.c. into mice at 1 and 2 hr before the injection of 17β-[3H]estradiol.

Radioactivity in homogenates of the tumor, spleen, and blood from each mouse was extracted 3 times with ether:chloriform (4:1, v/v) and backwashed with water. Radioactivity in the extracts was measured using aliquots of the extracts. To other aliquots of the extracts, 100 μg of estrone and 17β-estradiol were added, and 3H-labeled estrogens in the extracts were separated into estrone and 17β-estradiol fractions by paper chromatography using the benzene:formamide system (38). Radioactivity in the estrone and 17β-estradiol fractions was measured using aliquots of eluates. Finally, [3H]estrogens in other aliquots of the estrone and 17β-estradiol fractions were recrystallized with 15 mg of unlabeled estrone and 17β-estradiol, respectively, to constant specific activity, in order to obtain accurately the amount of both estrogens present in all the extracts from the tumor, spleen, and blood was examined 1 to 3 weeks after the implantation of seed tumors in male mice. Mice were castrated 24 hr before sacrifice. All procedures for characterization of ER and AR were carried out at 0–4°, unless noted otherwise. After removal of necrotic and connective tissues, the tumors were minced and homogenized in 6 volumes or 2 volumes (for determination of tumor growth) in 0.05 ml of vehicle (saline, 0.4% Polysorbate 80, 0.5% carboxymethylcellulose, and 0.9% benzyl alcohol) and were injected s.c. One to 10 μg of 17β-estradiol and 10 to 100 μg of TP were used. Control mice were given injections of 0.05 ml of vehicle. CB-154 (200 μg) was suspended in 0.05 ml of sesame oil and was injected s.c.

**RESULTS**

Incorporation of 3H-labeled Estrogens in Tumor following Injection of 17β-[3H]estradiol. Radioactivity in ether:chloriform extracts from the tumor, spleen, and blood was examined 1 to 9 hr after a single s.c. injection of 17β-[3H]estradiol in tumor-bearing animals. A similar experiment carried out in 1969 by us (21) showed that the retention of radioactivity in SC115 tumor was low and was similar to that in estrogen-independent tissues and blood (Chart 1). However, in the present study, radioactivity concentrations in the SC115 tumor (total retention values) were
### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Total Retention (fmol/100 mg tissue)</th>
<th>Nonspecific Retention (fmol/100 mg tissue)</th>
<th>Specific Retention (fmol/100 mg tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>17β-Estradiol</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor</td>
<td>55 ± 6.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9 ± 0.2</td>
<td>46 ± 7.6</td>
</tr>
<tr>
<td>Spleen</td>
<td>13 ± 0.9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5 ± 0.2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>8 ± 1.4&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Blood</td>
<td>4 ± 0.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4 ± 0.2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Estrone</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor</td>
<td>4 ± 0.3</td>
<td>3 ± 0.2</td>
<td>1 ± 0.4</td>
</tr>
<tr>
<td>Spleen</td>
<td>2 ± 0.1</td>
<td>2 ± 0.1</td>
<td>0</td>
</tr>
<tr>
<td>Blood</td>
<td>2 ± 0.2</td>
<td>2 ± 0.1</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup> Mean ± S.E. of 4 mice.

<sup>b</sup> p < 0.01, when compared to the value of tumor.

3- to 10-fold higher than those in the spleen and blood (Chart 1), showing that estrogen retention ability in SC115 tumors has changed in these 14 years. Although the present study used 4 times as much 17β-[<sup>3</sup>H]estradiol with a higher (3-fold) specific activity as did the 1969 study, the conclusion given may not be disturbed by these differences, because detectable radioactivity was found even in 1969 study (Chart 1), and simple experimental procedures were carried out in the same laboratory in 1969 and 1983. Additionally, the specific retention values in the tumor and tissues were examined in the present study. The specific retention values for estrogens were almost undetectable in the blood and were 5- to 10-fold higher in the tumor than in the spleen (data not shown). The specific retention values for estrogens were found to be occupied mostly by 17β-estradiol, and there were no significant differences among the tumor, spleen, and blood in retention of estrone (Table 1). Furthermore, the longer retention of radioactivity (Chart 1) and 17β-[<sup>3</sup>H]estradiol (Table 1) by the tumor could be demonstrated, compared with the spleen and blood.

### Characterization of Estrogen-binding Site in Tumor Cytosol

The characteristics of the estrogen-binding site in the cytosol from SC115 tumor were examined. The characteristics of AR in the tumor cytosol were also examined in comparison. Host male mice were castrated 24 hr before sacrifice. The Scatchard analyses of 17β-estradiol-binding data revealed that the maximum binding sites and K_d were 29 ± 3 (S.E.) fmol per mg of protein and 1.1 ± 0.1 nM, respectively (Table 2), whereas those in cytosol from the rat uterus were found to be 230 ± 25 fmol per mg of protein and 0.5 ± 0.1 nM, respectively.

The estrogen-binding site in the tumor cytosol bound 17β-[<sup>3</sup>H]estradiol, and both diethylstilbestrol and 17β-estradiol were efficient inhibitors. DHT was weaker, and testosterone, dexamethasone, and progesterone were much weaker in binding-inhibition activity than estrogens (Chart 2). Competition experiments demonstrated that 17β-estradiol-binding in the tumor cytosol was specific only for estrogenic compounds.

By low- and high-salt sucrose gradient centrifugations, radioactive 8 and 4S peaks were found, respectively, after labeling the cytosol with 17β-[<sup>3</sup>H]estradiol in the presence of DHT. The Stokes radius was estimated by comparing the elution patterns on Sephadex G-200 column with those of standard proteins (26). The tumor cytosol labeled with 17β-[<sup>3</sup>H]estradiol in the presence of DHT prior to gel chromatography contained the 17β-[<sup>3</sup>H]estradiol-binding component with a Stokes radius of 46 ± 1 Å in TEDMK, which could be separated from the [<sup>3</sup>H]DHT-binding component with a Stokes radius of 62 ± 1 Å (Chart 3; Table 2). Using these sedimentation coefficients (4.0 ± 0.1 and 4.1 ± 0.1 s) and Stokes radii (46 ± 1 and 62 ± 1 Å), the molecular weights of ER and AR calculated by the equation of Siegel and Monty (26), with an assumed volume of 0.725 cu cm/g for the partial specific volume, were 76,400 ± 550 and 102,000 ± 1,900, respectively (Table 2). The characteristics of AR in the tumor cytosol shown in Table 2 are quite similar to those reported previously (18, 35). The present findings shown in Charts 2 and 3 and Table 2 clearly indicate the presence of typical ER in the cytosol of SC115 tumor.

### Stimulative Effects of 17β-Estradiol on Tumor Growth

In castrated mice, the SC115 tumors grew rapidly when 100 µg of TP per mouse were injected daily from the day of tumor transplantation, and all animals died within 60 days after the transplantation. In contrast, no castrated animals died within 60 days after the transplantation when only vehicle was injected. Although daily injections of either 10 or 25 µg of TP slightly stimulated the tumor growth, 8 of 10 and 6 of 10 mice survived at the 60th day, respectively (Table 3). Daily injections of 10 µg of 17β-estradiol also slightly stimulated the tumor growth. Addition of 10 µg of 17β-estradiol to either 10 or 25 µg of TP significantly augmented the growth of SC115 tumors. Only 1 of 10 castrated mice survived at the 60th day when 10 µg of TP and 10 µg of 17β-estradiol were injected; no castrated mice survived when 25 µg of TP and 10 µg of 17β-estradiol were injected (Table 3).

The minimum effective dose of 17β-estradiol was determined. Addition of 1 µg of 17β-estradiol per mouse to 10 µg of TP per mouse slightly augmented the tumor growth, but this is not statistically significant (p > 0.05). Addition of 4 µg of 17β-
Table 2

Characteristics of cytosol ER and AR in SC115 tumors

<table>
<thead>
<tr>
<th></th>
<th>ER</th>
<th>AR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max. binding sites (fmol/mg protein)</td>
<td>29 ± 3.0a</td>
<td>42 ± 5.0</td>
</tr>
<tr>
<td>Sedimentation constant (SU)</td>
<td>8.0 ± 0.1</td>
<td>8.0 ± 0.1</td>
</tr>
<tr>
<td>Low salt</td>
<td>4.0 ± 0.1S</td>
<td>4.1 ± 0.1S</td>
</tr>
<tr>
<td>High salt</td>
<td>62 ± 1.0</td>
<td>102,000 ± 1900</td>
</tr>
<tr>
<td>Stokes radius (Å)</td>
<td>46 ± 1.0</td>
<td>76,400 ± 550</td>
</tr>
</tbody>
</table>

* Mean ± S.E. of 3 separate determinations.

Table 3

Additive effect of TP and 17β-estradiol on growth of SC115 tumors in castrated male DS mice

<table>
<thead>
<tr>
<th>Dose of steroids</th>
<th>Group</th>
<th>17β-Estradiol</th>
<th>Tumor size at Day 28 (mm)</th>
<th>Survival rate at Day 60</th>
<th>Survival time (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TP</td>
<td>17β-Estradiol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>4 ± 1a</td>
<td>10/10</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>10</td>
<td>13 ± 1b</td>
<td>6/10</td>
<td>56 ± 2</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>10</td>
<td>10 ± 1</td>
<td>8/10</td>
<td>59 ± 1</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>10</td>
<td>24 ± 2b</td>
<td>1/10b</td>
<td>41 ± 3b</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>0</td>
<td>10 ± 1</td>
<td>6/10</td>
<td>57 ± 1</td>
</tr>
<tr>
<td>6</td>
<td>25</td>
<td>10</td>
<td>26 ± 1c</td>
<td>0/10b</td>
<td>36 ± 1b</td>
</tr>
<tr>
<td>7</td>
<td>100</td>
<td>0</td>
<td>35 ± 1c</td>
<td>0/10</td>
<td>27 ± 1</td>
</tr>
</tbody>
</table>

* Mean ± S.E.

Composition of medullary cells when the tumor growth was stimulated by daily injections of 100 µg of TP, whereas the tumors consisted of spindle cells when the hosts were inoculated with only vehicle. When SC115 tumors grew in mice inoculated with 10 µg of TP, 25 µg of TP, or 10 µg of 17β-estradiol, about one-half of tumors were of spindle cell type and another half of mixed type. In contrast, most tumors were composed of medullary type when 17β-estradiol was added to 10 or 25 µg of TP.

Since the administration of 17β-estradiol in animals has been reported to cause an increase in prolactin secretion from the pituitary (33), we investigated whether prolactin is involved in the...
17β-estradiol-induced enhancement of tumor growth. We injected 200 µg of CB-154 every other day in TP- and 17β-estradiol-treated castrated mice starting from the day of transplantation; serum was obtained 28 days after the transplantation. Daily injections of 4 µg of 17β-estradiol were found to elevate serum prolactin to 15.5 ± 4.3 ng/ml (n = 5), while nonestrogenized normal mice showed a lower level (5.6 ± 4.2 ng/ml; n = 5). Although the simultaneous injections of CB-154 to the TP- and 17β-estradiol-treated mice lowered prolactin value to 5.9 ± 3.1 ng/ml (n = 5), administration of CB-154 had no effect on the 17β-estradiol-enhanced tumor growth (Chart 5).

DISCUSSION

The present findings clearly demonstrate the presence of typical ER in SC115 tumor, although the number of binding sites in the tumor is evidently fewer than in typical estrogen-dependent tissues such as the rat uterus. The findings on ER are similar to the previous findings on ER in SC115 tumor reported from 1976 to 1982 (9, 10, 24, 35). Since we reported in 1970 (21) that a significant retention of 3H-labeled estrogen is absent in the s.c.-grafted SC115 tumor, and since Stanley et al. (28) reported in 1977 that a specific estrogen-binding site is not present in SC115 cells in culture, it is concluded that ER in SC115 tumors has increased in the past 14 years.

The present findings demonstrate for the first time the stimulative effect of estrogen on the growth of androgen-dependent SC115 tumor. Although most works have shown that the growth of mammary tumors in rats and mice is regulated primarily by prolactin and that estrogen might exert its effect rather indirectly via the secretion of prolactin (33), the present findings rule out the prolactin-mediated 17β-estradiol activity in the growth of mammary tumor SC115. Since we reported in 1965 (20) that daily injections of 17β-estradiol (5 to 10 or 50 to 100 µg/mouse) completely suppress the growth of s.c.-grafted SC115 tumor in noncastrated male mice, it is concluded that the response of SC115 tumors to 17β-estradiol has also changed in these 19 years. The present study shows that estrogen-augmented growth of androgen-dependent SC115 tumor is dose dependent within the range of 1 to 10 µg/mouse/day. Although the effects of higher doses of 17β-estradiol on tumor growth were not examined in the present study, inhibition of the growth at higher doses of 17β-estradiol seems to be ruled out by our recent findings (37). The growth of SC115 tumor in noncastrated male mice was not significantly suppressed by injections of 100 to 130 µg of 17β-estradiol/mouse/day starting from the day of tumor transplantation (37). Suzuki et al. (30) very recently reported that administration of 2 or 200 µg of 17β-estradiol to castrated mice increases the activity of RNA polymerase I and II to a lesser degree than testosterone in SC115 tumor. The findings are not inconsistent with the present findings showing growth-stimulative effect of 17β-estradiol on SC115 tumor.

Our present and previous (20, 21) findings suggest that the response to 17β-estradiol and ER of SC115 tumors have changed in the past 19 years. The SC115 tumor established in 1964 has been serially transplanted from male to male DS mice for 20 years in our laboratory. The SC115 tumors used in the previous and present studies were generations 10 to 15 in the 1965 study (20), generation 89 in the 1970 study (21), and generations 313 to 325 in the present study. Androgen dependency of the SC115 tumor, defined by its failure to grow in female mice and by its ability to grow in male mice, has been examined in all the generations 1 to 325. The androgen dependency, the histological pattern of medullary carcinoma, and the modal chromosome number of 40 were found in all the tumors used in the previous and present studies.

It has been reported that 17β-estradiol can be specifically bound with high and low affinities by ER and AR, respectively, in the cytosol of SC115 tumor, since evidently larger amounts of 17β-estradiol have been shown to compete for the binding of testosterone to AR in SC115 cells (9, 10, 28, 35). At low 17β-estradiol concentration, only ER will be involved, whereas at high 17β-estradiol concentration, AR may also be implicated. The effective dose of 17β-estradiol used in the present study was 4 µg/mouse/day, while the effective dose of TP was 10 µg/mouse/day. Lower doses of 17β-estradiol (1 µg/mouse/day) were ineffective, and daily administration of 10 µg/mouse of TP to tumor-bearing female mice did not significantly augment the growth of SC115. As the minimum effective dose of 17β-estradiol was less than that of androgens, the estrogen action on the stimulation of the growth of SC115 tumor seems to be mediated by ER in the tumor.

Recent studies have shown that the stimulative action of sex steroids such as estrogen and androgen on cell proliferation may be mediated by specific polypeptide growth factor(s) (27). Proliferation of cloned SC115 cells in culture has been shown to be augmented by physiological concentrations of androgens (6, 9, 28). Therefore, if the growth-stimulative action of androgen on SC115 cells is mediated by growth factor(s), the SC115 cells themselves may produce growth factor(s) which are self-stimulatory.

It was reported that estrogen enhances androgen-induced prostate growth in castrated dogs to a degree comparable to that in spontaneous prostate hypertrophy (5, 31). Approximately 2-fold enhancement of cytosal AR by estrogen is demonstrated in dog prostates after 1 to 3 weeks of treatment with 17β-estradiol (23). It was also found that estrogen stimulates the growth of epithelial cells from human metastatic prostate tumor in vitro in the presence of DHT, although DHT alone does not stimulate the growth of the epithelial cells (19). The administration of estrogen increases AR content in human prostate cancer (22). Most of human prostate cancers contain both AR and ER (1). In
contrast with the important roles of androgens, however, the effects of estrogens on the development and growth of prostatic hypertrophy and cancer in humans are not clear. Enhancement by 17β-estradiol of AR content in SC115 tumor and their molecular mechanisms should be examined by future studies. The SC115 tumor seems to be a good model for elucidating the stimulative effect of estrogens on the growth of androgen-dependent tissues and tumors.

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