Development of Androgen-independent Spindle Cell Tumors from Androgen-dependent Medullary Shionogi Carcinoma 115 in Androgen-depleted Nude Mice

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ABSTRACT

When Shionogi carcinoma 115 (SC115, undifferentiated medullary carcinoma showing a compact cell pattern and containing androgen receptor) was transplanted into male and female DS mice, it grew only in males. In contrast to this strict androgen dependency in DS hosts, tumors composed of spindle-shaped cells appeared in more than 80% of cases when SC115 tumor was inoculated into female or castrated male nude athymic (BALB/c-nu/nu) recipients. These spindle cell tumors neither contained cytosol androgen receptor nor showed biologically defined androgen dependency. As spindle cell tumors could be serially transplanted in DS mice but not in BALB/c-+/+ mice and as the original SC115 (medullary carcinoma showing a compact cell pattern) tumor and the spindle cell tumor had many identical chromosome abnormalities, these two types of tumors seem to have a common origin in spite of their morphological, biochemical, and biological differences. Since spindle cells could not be detected histologically in SC115 tumors maintained in intact male DS mice, the present results seem to suggest that SC115 cells may change their morphological, biochemical, and biological characteristics within one passage in androgen-depleted nude athymic mice.

INTRODUCTION

Androgen-dependent mouse mammary carcinoma SC115 was established in 1964 by Minesita and Yamaguchi (22, 23). The original tumor arose spontaneously 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 DS mice and by its ability to grow in female or castrated male DS mice given androgen. We (20, 24, 34–36) and other investigators (2–6, 15, 16, 18, 30, 33) have shown that SC115 cells contain a specific AR system, which has binding properties similar to those of androgen target tissues. It seems that androgen stimulation of SC115 tumor growth is directly or indirectly mediated by AR in SC115 cells. Comparing the results obtained in vivo to those in vitro, Sirbasku (28) recently suggested the possibility that steroid-responsive tumor growth in vivo includes the mechanism of steroid → target tissue → specific target tissue

growth factor → steroid-responsive tumor cells. However, SC115 cells are known to retain their androgen responsiveness even in cell culture (6, 9, 15, 16, 30, 33).

We have recently investigated the fate of SC115 tumors in the presence or absence of androgen (17). The SC115 cells inoculated into androgen-depleted DS mice fell into necrosis within 5 days after implantation. When growth of SC115 cells was initiated by androgen, the fate of SC115 tumors after androgen removal depended on the size of the tumor; small, medium, and large tumors showed complete, temporary, and no regression, respectively. In contrast with both the partial and no androgen dependency of medium and large tumors in situ, tumor seeds taken from the medium and large tumors before androgen removal grew only in females when transplanted into male and female DS mice. The mechanism suggested by Sirbasku (28) would explain why the medium and large tumors, in which critical quantities of growth factors may have been induced, partially or not at all, regress on androgen deprivation of the hosts. On the other hand, tumor seeds taken from about one-half of the regrown tumors after androgen removal grew in both male and female DS hosts. Most of these androgen-independent tumors contained AR and consisted of the original SC115 cells (medullary carcinoma showing a compact cell pattern, AR+) and spindle cells (probably AR−).

Since the development of spindle-shaped cells seemed to be responsible for the modification of the biological characters of SC115 tumors following androgen removal, an attempt was made to clarify the origin and characteristics of these spindle-shaped cells. Although tumors composed of spindle-shaped cells alone are necessary for the study, we obtained only one pure spindle cell tumor, which contained no AR, from among 28 DS mice by androgen removal after initiation of tumor growth, when these mice were used as recipients of SC115 tumors (17). In contrast, by the transplantation of the SC115 tumor into female nude athymic mice, development of tumor was observed in more than 90% of mice in spite of androgen depletion. Furthermore, most of these tumors consisted of pure spindle-shaped cells. Hence, androgen-depleted nude mice were used as hosts of SC115 tumors for the present study, and we found that SC115 cells underwent a morphological change with a loss of AR during one passage in androgen-depleted nude mice.

MATERIALS AND METHODS

Animals and Tumors. DS mice were raised in our laboratory. Nude athymic mice (BALB/c-+/-) and their normal control mice (BALB/c-+/-) were kindly supplied by the Institute of Medical Sciences of Tokyo University or were purchased from...
the Japanese Central Laboratory for Experimental Animals (Tokyo, Japan). Nude mice were kept within a filtered-air laminar flow enclosure. Both DS and BALB/c mice were used at 2 to 4 months of age. When castrated animals were used, the operation was carried out at least 1 week in advance. The tumor seeds of SC115 for transplantation were obtained from the 171st to 187th generations. In each experiment, intact male and female DS mice were grafted with the same tumor seeds in order to ensure androgen dependency of the tumor. The transplantation of tumor was done according to the method described previously (22) unless specially mentioned.

Determination of Tumor Growth. Appearance of tumors was observed twice a week for 2 months. After tumor development, mice were kept until death or sacrifice. The length and width of each tumor were determined at least on every 7th day, and the mean of the length and width was used as an index of tumor size.

Assay of Cytosol AR. The assay method was described previously (17). In short, cytosol (3 to 4 mg protein per ml) was incubated with increasing quantities (0.1 to 3.2 pmol per ml) of \[^{3}H\]DHT at 0–4° for 16 hr. To establish the level of nonspecific binding, control cytosols were preincubated with 300 pmol of nonradioactive DHT per ml 20 min prior to the addition of increasing quantities of \[^{3}H\]DHT. Since no significant metabolism of 3.2 pmol of \[^{3}H\]DHT per ml was found in any of the tumor cytosols examined at 0° for 4 hr (more than 96% of \[^{3}H\]DHT remained unchanged), the extent of prior metabolism of the nonradioactive DHT and the metabolism of \[^{3}H\]DHT at 0° seemed to be limited. The number of binding sites and the dissociation constant were calculated according to the procedure of Scatchard (27). A tumor was considered to be AR if it contained less than 3 fmol AR per mg cytosol protein.

Histology. Tumors were fixed in 10% buffered formalin (pH 7.2) and embedded in paraffin; sections were stained with hematoxylin and eosin. Some of the sections were also stained with toluidine blue to demonstrate cartilage cells.

Irradiation. A SC115 tumor was removed and cut in half. One part was kept in a sterilized disposable scalpel in a plastic Petri dish containing about 2 ml McCoy's Medium 5A supplemented with tumor cells 7 days after the last injection.

Immunization. DS mice were given injections of spleen cells from BALB/c-+/+ mice (2 x 10⁷) i.p. twice at 7-day intervals. BALB/c-+/+ mice were immunized by spleen cells from DS mice in the same manner. Immunized mice were inoculated with tumor cells 7 days after the last injection.

Chromosome Analysis. Tumors were removed and minced with a sterilized disposable scalpel in a plastic Petri dish containing about 2 ml McCoy's Medium 5A supplemented with 20% fetal calf serum. The single-cell suspension was prepared by pipetting small pieces of tumors strongly and was centrifuged after 10 min of incubation at 37°. Hypotonic treatment was carried out with 0.075 M KCl containing Colcemid (0.02 to 0.03 μg/ml) for 25 min at 37°. Immediately after the hypotonic treatment, a drop of absolute acetic alcohol (1:3) was mixed into the hypotonic solution, and the suspension was recentrifuged. The cells were washed twice in the absolute acetic alcohol, and the fixed cells were kept for 1 hr at room temperature. Air-dried slides were made by the method described previously (13). Q-bands were obtained by a slight modification of the technique of Caspersson et al. (7). The number of chromosomes was determined by Q-banded slides; karyotypes were made according to the standard karyotype of the mouse recommended by the Committee on Standardized Genetic Nomenclature for Mice (8).

**RESULTS**

Development of "Hard" Tumors in Female Nude Mice. Female and male nude athymic mice were grafted with SC115 tumors. Growth of SC115 tumor (medullary carcinoma showing a compact cell pattern) occurred in 7% of female and 45% of male nude mice (Table 1). Although other types of tumors rarely developed in female or male DS mice, slowly growing tumors were detected in 83% of female and 53% of male nude mice. Thus, in contrast with the marked difference between tumor development in female and male DS mice, there was no statistically significant difference between the total incidences of tumor development in female (90%) and male (98%) nude mice (Table 1). Since these slowly growing tumors were very hard, they were designated as "hard" tumors, whereas tumors with consistency similar to that of original SC115 tumors were designated as "soft" tumors, due to their relative softness. The size of the hard tumors gradually increased in both female and male hosts and killed them mainly by restraining their movement within 5 months after transplantation of original SC115 cells (Chart 1). Histologically, original-type SC115 cells [medullary carcinoma showing a compact cell pattern (Fig. 1A)] were scarcely detected in hard tumors, and spindle-shaped cells were predominant (Fig. 1B). The hardness of the tumor was caused by its remarkable bone formation (Fig. 1C).

Table 1

<table>
<thead>
<tr>
<th>Host</th>
<th>No. of mice</th>
<th>Hard</th>
<th>Soft</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female nude</td>
<td>42</td>
<td>35</td>
<td>6</td>
<td>38</td>
</tr>
<tr>
<td>Male nude</td>
<td>38</td>
<td>26</td>
<td>12</td>
<td>38</td>
</tr>
<tr>
<td>Female DS</td>
<td>216</td>
<td>5</td>
<td>17</td>
<td>23</td>
</tr>
<tr>
<td>Male DS</td>
<td>294</td>
<td>226</td>
<td>68</td>
<td>226</td>
</tr>
</tbody>
</table>

* p < 0.01, compared with the value of male mice of the same strain by x² test.

**Development of Soft and Hard Tumors in Nude (BALB/c-+nu/nu) and DS Mice after Inoculation with SC115 Cells**

Values of DS mice are pooled data of controls during the time of the present study (see "Materials and Methods").

Chart 1. Growth of hard and soft tumors in nude (BALB/c-+nu/nu) and DS mice after inoculation with SC115 cells.
As shown in Table 2, AR levels were significantly higher in soft than in hard tumors. AR was not detectable in 6 of the 14 hard tumors examined. Low levels of AR found in 8 of 14 hard tumors seemed to be produced by the original SC115 cells present in these tumors. The dissociation constant for DHT was estimated to be 10^{-10} M in both soft and hard tumors, indicating high-affinity binding.

As the growth of hard tumors was rather slow, and as histological features of hard tumors were quite different from those of the original SC115 tumor, we attempted to determine whether development of hard tumor was induced by grafted SC115 cells or by certain factor(s) released by the cells. Since stabilization of SC115 cells by 5000-rad irradiation resulted in the failure of the induction of hard tumors in female nude mice or production of soft tumors in male DS mice (data not shown), the proliferation of SC115 cells seems to be necessary for the development of the hard tumor.

**Origin of Androgen-independent Hard Tumors.** Nude mice with hard tumors were killed, and the tumors were harvested. Parts showing ossification and necrosis were removed, and the remaining part of the tumor with a cartilage-like consistency was diced into fragments (about 1 cu mm). A fragment was inserted under the dorsal skin of DS and BALB/c-+/+ hosts to determine transplantability. Although hard tumors grew with high incidence in female and male DS mice, the tumors scarcely grew in BALB/c-+/+ mice which are congenic with nude (BALB/c-/-/nu) mice (Table 3). Previous immunization of BALB/c-+/+ mice with spleen cells of DS mice resulted in complete suppression of the growth of the fragments taken from the primary hard tumor. In contrast, immunization of DS mice by spleen cells of BALB+/+ mice did not affect the transplantability of the hard tumor in these DS mice (Table 3). Serial transplantation of hard tumors was possible in intact female and male DS mice and in castrated female and male DS mice. Although bone formation was not detectable after 3 passages in DS mice, the tumors were still composed of spindle-shaped cells.

Since SC115 is a mammary cancer originally developed in female DS mice, XX sex chromosome constitution would be a useful marker for the confirmation of the donor origin of the hard tumor. Accordingly, a hard tumor which developed in a castrated male nude mouse was serially transplanted in castrated male DS mice. The growth of the tumor was accelerated from generation to generation, mitoses of spindle-shaped cells increased, and histological features of the tumor became similar to those of fibrosarcoma (Fig. 1D). The tumor maintained in castrated male DS mice was transplanted into intact female and male DS mice at the 10th and 20th generations. The growth speed of tumors was the same in both female and male DS mice (Table 4). The growth speed at the 10th generation was nearly equal to that of the original SC115 tumors growing in intact male DS mice, and the growth speed at the 20th generation was much faster than that of the latter (Table 4; Chart 1). No AR was detectable in the spindle cell tumors growing in either female or male hosts (Table 4). Chromosome analysis of this line of spindle-cell tumor was carried out at the 14th and 16th generations, as was analysis of the original SC115 tumors growing in intact male DS mice as control.

The Q-banding analysis revealed that there were metaphases with XX sex chromosome constitution and those with XY constitution in both SC115 and spindle cell tumors. In both cases, most metaphases had 2 X chromosomes and six to 10 structurally abnormal chromosomes. In contrast, metaphases with XY showed no such abnormality, indicating that these male cells were not tumor cells but host cells. Therefore, the number of chromosomes was determined in respective female cells. The modal chromosome number of SC115 cells was 40, whereas that of spindle-shaped cells was 41 and 43. Abnormal chromosomes found in SC115 and spindle-shaped cells were analyzed in detail and shown in Fig. 2. Abnormalities observed in chromosomes 1 (enhanced fluorescent band), 5 (deletion), 11 (additional band), 14 (monosomic), and 19 (monosomic) and in the X chromosome (additional band) were identical in SC115 and spindle-shaped cells.

**DISCUSSION**

When SC115 cells were inoculated into androgen-depleted DS mice, they usually underwent necrosis within 5 days and

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**Table 2**

<table>
<thead>
<tr>
<th>Host</th>
<th>Tumor</th>
<th>AR level (fmol/mg cytosol protein)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female nude</td>
<td>Hard</td>
<td>5.7 ± 2.3(^a) (8) (^d)</td>
</tr>
<tr>
<td></td>
<td>Soft</td>
<td>22.6 ± 5.1 (5)</td>
</tr>
<tr>
<td>Male nude</td>
<td>Hard</td>
<td>6.5 ± 2.2(^a) (6)</td>
</tr>
<tr>
<td></td>
<td>Soft</td>
<td>27.9 ± 4.9 (10)</td>
</tr>
<tr>
<td>Male DS</td>
<td>Soft</td>
<td>37.1 ± 6.1 (9)</td>
</tr>
</tbody>
</table>

\(^a\) Calculated by assuming the number of binding sites of AR-tumor to be 0.  
\(^b\) Mean ± S.E.  
\(^c\) p < 0.01, compared with the value of soft tumors which developed in the same sex and strain.  
\(^d\) Numbers in parentheses, percentages.

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**Table 3**

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Recipients</th>
<th>Transplantability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Female DS</td>
<td>29/45 (^a) (^b)</td>
</tr>
<tr>
<td></td>
<td>Male DS</td>
<td>28/31 (^b)</td>
</tr>
<tr>
<td></td>
<td>Female BALB/c-+/+</td>
<td>1/10</td>
</tr>
<tr>
<td></td>
<td>Male BALB/c-+/+</td>
<td>2/10</td>
</tr>
<tr>
<td>2</td>
<td>Immunized male DS</td>
<td>9/10 (^b)</td>
</tr>
<tr>
<td></td>
<td>Immunized BALB/c-+/+</td>
<td>0/10</td>
</tr>
</tbody>
</table>

\(^a\) No. of mice in which tumors appeared within 2 months per total number of mice given transplants.  
\(^b\) p < 0.01, compared with the value of BALB/c-+/+ mice of the same sex by x^2 test.

---

**Table 4**

<table>
<thead>
<tr>
<th>Generation of tumor</th>
<th>Recipients</th>
<th>Transplantability</th>
<th>Survival time (days)</th>
<th>AR value (fmol/mg cytosol protein)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Female DS</td>
<td>8/9 (^a)</td>
<td>42.7 ± 3.1 (^b) (^d)</td>
<td>&lt;3</td>
</tr>
<tr>
<td></td>
<td>Male DS</td>
<td>8/10</td>
<td>48.1 ± 4.3 (^d)</td>
<td>&lt;3</td>
</tr>
<tr>
<td>20</td>
<td>Female DS</td>
<td>15/15</td>
<td>28.9 ± 1.0 (^b) (^d)</td>
<td>&lt;3</td>
</tr>
<tr>
<td></td>
<td>Male DS</td>
<td>15/15</td>
<td>28.4 ± 0.9</td>
<td>&lt;3</td>
</tr>
</tbody>
</table>

\(^a\) Number of mice in which tumors appeared per total number of mice given transplants.  
\(^b\) Mean ± S.E.  
\(^c\) p > 0.3, compared with the value of male mice by t test.  
\(^d\) p < 0.001, compared with the value at the 20th generation.

---

**Fig. 1**

**Fig. 2**

---

**Chart 1**

**Chart 2**

---

**Fig. 3**

**Fig. 4**

---

**Table 5**

<table>
<thead>
<tr>
<th>Characteristics of spindle cell tumors after serial transplantation in castrated male DS mice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generation of tumor</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>20</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
did not regrow even if androgen was injected into such mice thereafter (17). In contrast, inoculation of SC115 cells into nude mice resulted in the development of tumors even in the absence of androgen. However, morphological features of tumors growing in most female nude mice and in about one-half of those growing in male nude mice were remarkably different from those of the original SC115 tumor. Whereas the original SC115 tumor is a medullary carcinoma showing a compact cell pattern without fibrosis and ossification, the tumors growing in nude mice consisted of fibroblast-like spindle-shaped cells. Because intensive ossification was observed, they were designated as hard tumors. Since the development of such hard tumors was very rare in DS mice (less than 1% in males and about 2% in females), some immune mechanisms seem to inhibit the development of hard tumors in DS mice. Although it has been reported that Moloney sarcoma virus-induced tumors do not regress in nude mice as they usually do in nonnude control mice, there are no reports that show the morphological and biological transformation of inoculated tumor cells during one passage in nude mice, to the best of our knowledge. Therefore, further investigation is necessary to clarify the possible influence of an immune system (absence of the thymus) on the facilitated transformation of SC115 cells.

Although the morphology, androgen dependency, and AR value of the hard tumor were markedly different from those of the original SC115 tumor, these 2 types of tumors seem to have the same origin for the following reasons: (a) the inoculation of 5000-rad irradiated cells did not produce any hard tumors in androgen-depleted nude mice; (b) the hard tumor growing in nude (BALB/c- nu/nu) mice could be transplanted to DS mice but not to normal (+/+ ) BALB/c mice, suggesting that the cells of the hard tumor are of DS mouse origin; (c) the tumor cells which developed in castrated male nude mice had 2 X chromosomes (showing female origin of the cells) and 6 chromosome abnormalities which were identical to those of SC115 cells.

There are 2 possibilities that may explain the development of these androgen-independent spindle-cell tumors. (a) the SC115 tumor is composed of 2 different types of cells, androgen-dependent medullary carcinoma cells and androgen-independent spindle-shaped cells. The latter became predominant in androgen-depleted nude mice; (b) androgen-dependent medullary carcinoma cells change into androgen-independent spindle cells in the absence of androgen. A small population of the latter derived from the inoculated medullary carcinoma cells can survive and proliferate only in nude athymic mice. Although the first possibility cannot be excluded by the present results, the second possibility seems to be more plausible for the following reasons. (a) In our previous experiment in DS mice, spindle-shaped cells appeared in the regrown tumors among originally medullary carcinoma cells following androgen removal from the hosts initially provided with androgen (17). On this occasion, spindle-shaped cells developed by making clusters. Since such spindle cell clusters cannot be detected by intensive histological examination of original SC115 tumors, these tumors do not seem to be composed of 2 types of cells when they are maintained in intact male DS mice. (b) When spindle cell tumors developed in nude mice, their growth was significantly slower than that of original SC115 tumors (Chart 1). Thus, even if spindle cells appeared in original SC115 tumors maintained in intact male DS mice, spindle cells may be selected out during serial passages in the male DS hosts (SC115 tumors used were between the 171st and 187th generations at the time of experiment). (c) By using in vitro culture technique, Desmond et al. (9) and Yates and King (37) recently showed that the shape of SC115 cells changed from fibroblast-like to epithelial when maintained in the absence of androgen. Although the direction of the morphological change induced by androgen depletion seems to be inverse, their results may be an in vitro counterpart of the in vivo phenomenon observed in the present study. Yates and King (37) also found that androgen-dependent SC115 cells in culture lost their androgen responsiveness in the absence of androgen. Since cloning of the cells had been carried out in experiments by both Desmond et al. (9) and Yates and King (37), this in vitro phenomenon was explained as transformation of the cells rather than the selection of one type of cells from mixed cell populations.

Bruchovsky et al. (5) reported biological and biochemical characteristics of androgen-independent tumors derived from SC115. However, they did not describe how many transplantations they carried out to obtain androgen-independent variants of SC115 tumor. As we could constantly obtain androgen-independent tumors by using female nude mice as recipients, the present experimental system would be useful to investigate mechanisms by which SC115 cells lose androgen dependency.

After serial transplantation of fibroma-like spindle-cell tumor in castrated male DS mice, mitotic figures increased and the tumor had the appearance of fibrosarcoma (Fig. 1D). Since the first description by Ehrlich and Apolant (11), the transformation of adenocarcinoma of the breast (11, 26), lung (31), and prostate (19) into fibrosarcoma-like tumors has been reported by many authors. However, in these reports, the origin of fibrosarcoma cells was not identified. Moreover, the transformation of tumors was attained by chance rather than by experimental induction. As the transformation of SC115 cells can be induced by a simple procedure (i.e., depletion of androgen), inoculation of SC115 cells into androgen-depleted nude mice provides a good system for the investigation of the transformation of transplanted tumors.

Bone formation is frequently observed in the mammary tumor of dogs (1, 29), but rarely in rodents (10, 29, 38) and humans (21). In dogs, cartilage and bone were believed not to be neoplastic but to represent secondary metaplasia of connective tissues surrounding tumor cells (1). Inasmuch as bone formation was not detected after 3 passages of the hard tumor in DS mice, the bone may not be an essential component of the spindle cell tumor. However, the hardness is a useful characteristic for selecting the androgen-independent spindle cell tumors in nude mice grafted with SC115 cells. Although the transformation from the medullary carcinoma to the spindle cell tumor was accompanied by bone formation, the interrelationship between these 2 phenomena is still unclear.

Bruchovsky and Rennie (4) reported that, alone or in combination, the cytosol receptor and nuclear uptake phenotypes did not completely predict for hormonal dependence of various sublines of Shionogi carcinoma, but when screening included a test for displaceable nuclear binding, the criteria were sufficient to predict dependence or autonomy for 100% of 11 variant lines of SC115 tumors. To obtain ideal markers for selecting endocrine-responsive human tumors, the SC115 tumor and its variant lines seem to be a good model system. In
human breast (14, 25) and prostate (12) cancers, the endocrine-responsive tumors are, of course, initially responsive to either surgical ablation or steroid treatments, but eventually regrowth of the tumor tissue occurs. The development of hormone-independent tumors from those initially showing endocrine-therapeutic remission is clinically very important. Our previous (17) and present findings in mice that androgen-dependent cancer cells (AR+) transform into androgen-independent cancer cells (AR−) in the absence of androgen may important leads to future work in this area. Thus, the SC115 tumor seems, again, to be a good model in this area.

ACKNOWLEDGMENTS

We thank Dr. K. Takeda and Dr. H. Otsuka for supporting these studies and Dr. K. J. Mori and Dr. T. Hamako for valuable discussions.

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15. Jung-Testas, I., Desmond, W., and Baulieu, E. E. Two sex steroid receptors in human breast (14, 25) and prostate (12) cancers, the endocrine-responsive tumors are, of course, initially responsive to either surgical ablation or steroid treatments, but eventually regrowth of the tumor tissue occurs. The development of hormone-independent tumors from those initially showing endocrine-therapeutic remission is clinically very important. Our previous (17) and present findings in mice that androgen-dependent cancer cells (AR+) transform into androgen-independent cancer cells (AR−) in the absence of androgen may important leads to future work in this area. Thus, the SC115 tumor seems, again, to be a good model in this area.

Fig. 1. Histological feature of tumors. A. Original SC115 tumor growing in intact male DS mice. Note undifferentiated medullary carcinoma cells showing a compact cell pattern. H & E, × 370. B. Primary hard tumor which developed in female nude mice. H & E, × 370. C. Bone formation in the primary hard tumor. H & E, × 370. D. Spindle cells. H & E, × 370. E. Origin of which was unknown. Abnormalities observed in chromosomes 1, 5, 11, 14, and 19 and the X chromosomes were identical in SC115 and spindle cells.

Fig. 2. A. Chromosomes of a SC115 cell. Arrows, abnormal chromosomes and additional and missing chromosomes. A question-marked chromosome is Marker A, B, and C (left to right), origin of which was unknown. Abnormalities observed in chromosomes 1, 5, 11, 14, and 19 and the X chromosomes were identical in SC115 and spindle cells.

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